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Editors: **Longmore, Murray; Wilkinson, Ian B; Turmezei, Tom; Cheung, Chee Kay**
Title: ***Oxford Handbook of Clinical Medicine, 7th Edition***

From the preface to the first edition

This book, written by junior doctors, is intended principally for medical students and house officers. The student becomes, imperceptibly, the house officer. For him we wrote this book not because we know so much, but because we know we remember so little. For the student the problem is not simply the quantity of information, but the diversity of places from which it is dispensed. Trailing eagerly behind the surgeon, the student is admonished never to forget alcohol withdrawal as a cause of post-operative confusion. The scrap of paper on which this is written spends a month in the white coat pocket before being lost for ever in the laundry. At different times, and in inconvenient places, a number of other causes may be presented to the student. Not only are these causes and aphorisms never brought together, but when, as a surgical house officer, the former student faces a confused patient, none is to hand.

We aim to encourage the doctor to enjoy his patients: in doing so we believe he will prosper in the practice of medicine. For a long time now, house officers have been encouraged to adopt monstrous proportions in order to straddle simultaneously the diverse pinnacles of clinical science and clinical experience. We hope that this book will make this endeavour a little easier by moving a cumulative memory burden from the mind into the pocket, and by removing some of the fears that are naturally felt when starting a career in medicine, thereby freely allowing the doctor's clinical acumen to grow by the slow accretion of many, many days and nights.

R.A.H. & J.M.L. 1985

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Preface to the seventh edition

Who needs handbooks? With so many wonderful guidelines emanating from national institutions and Royal Colleges, and so much evidence-based medicine on the web, the idea of a handbook might appear redundant. But just how wonderful are all these guidelines? Let us look at the evidence: in one study of a quiet day on call, 18 patients were seen by one doctor, who made 44 diagnoses. The guidelines advising on these conditions ran to 3679 pages.[1] All these guidelines no doubt needed to be read carefully and in full. Carefully! In full!! Just what planet are we on if we expect this to happen? Pluto, it turns out. Each day on Pluto lasts 153.36 hours.[2] Allowing 2 minutes a page and a few seconds for reflection, this is just long enough to digest the necessary guidelines. From this we conclude that every junior doctor should be provided with breathing apparatus to survive in the rarefied atmosphere which gives rise to guidelines, as well as a team of readers to give advice as he or she works at the bedside. Pie in the sky? Not quite. Here on Earth, the answer lies in your own hands as you read this, and OUP put it there in the hope and certain knowledge that this bird in your hand is worth *at least* two on Pluto.

We welcome Tom Turmezei and Chee Kay Cheung, who breathe new life into this edition—which goes to press 21 years after our first edition. We are aware that by being 21 we may be regarded as being almost established: we would far rather continue to enjoy the fate of our first edition, which was banned from two medical schools—so far as we could tell for making learning medicine too easy. Or perhaps it was for saying that we should work for our patients, not our consultants. To revive this sense of the subversive we have run comments orthogonal to the text (sometimes literally and sometimes metaphorically)—to act as a counter to our more Panglossian sentiments, which might otherwise fatuously indicate that everything is for the best in the best of all possible wards. Voltaire, the creator Panglos, like all true saprophytes (*Candida* included), fed for ever off decaying matter (the effete French Court)—whereas we take our nourishment from the living wells of knowledge embodied in Medline, the BMJ, and the *New England Journal of Medicine*.

This edition embodies countless changes—the most obvious being the addition of a Radiology chapter—and the introduction of colour images throughout the text. But the main thing we bring to our readers is a friend in the pocket—wearing bright new underclothes, and freshly recommitted to the task of being your champion, your mentor, and your fond support—come what may.

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Conflicts of interest

This volume has been critically appraised by two doctors (JML & JABC) who have no contact with commercial interests such as pharmaceutical companies. In order to reassure readers, and in the light of recent studies which have shown that writers of guidelines often have overt and covert connections with drug companies,[3] we wish to place on record that there has been no covert pressure to exclude or include certain drugs in this text, they have adhered to a policy of not seeing representatives from any such commercial company, and neither are they in receipt of any gifts, grants, or hospitality from such companies.

Drugs (and how to keep abreast of changes)

While every effort has been made to check this text, it is still possible that errors have been missed. Also, dosage schedules are continually being revised and new side-effects recognized. Oxford University Press makes no representation, expressed or implied, that drug dosages in this book are correct. For these reasons, the reader is strongly urged to consult the most recently published *British National Formulary*, and the pharmaceutical company's *data sheet* (summaries of product characteristics/SPC; www.Medicines.org.uk) before administering any of the drugs recommended in this book. Unless stated otherwise, drug doses and recommendations are for the *non-pregnant adult* who is *not breast-feeding*.

Corrections are posted on the web at www.oup.com/OHCM. See also the *What's new* section of www.bnf.org.

Readers are also reminded of the need to keep up to date, and that this need can only ever be partly addressed by printed texts such as this.

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Acknowledgements

We would like to record our heartfelt thanks to our advisers on specific sectionsâ each is acknowledged on chapter's first page.

For checking the text we thank, and admire the fortitude of, Judith Collier, David Knight, Ahmad Mafi and Thomas Jaconelli. We particularly thank our drug reader, Dr Steve Emmett, for his painstaking work checking drug dosages.

IBW would like to acknowledge his clinical mentors Jim Holt and John Cockcroft. We also thank Dr P Scally and Dr J Harper for providing x-ray plates, as well as for many thoughtful comments on the whole text. For further help we thank Dr J Burke, Dr Omid Zarghom, and Professor J McCormack.

The British Lending Library and staff at the Cairns Library, Oxford, and at Worthing Postgraduate Library have been most helpful in tracing references.

We would like to thank the staff of OUP for their help and support. It is a particular pleasure to document here the enormous contribution made to this and many other Oxford Handbooks by Alison Langton, whose steadfast support since OHCM's conception in 1981 has been a model of fair and creative publishing.

Readers' comments These have formed a vital part of our endeavour to provide an accurate, comprehensive, and up-to-date text. We sincerely thank the many student, doctors and other health professionals who have found the time and the generosity to write to us on our Reader's Comments Cards (enclosed) or via the web. These have now become so numerous that they cannot all be listed here.

3rd-party web addresses We disclaim any responsibility for 3rd-party content.

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Prologue to clinical medicine: *Dag Hammarskjöld on teamwork*

Good doctors are good team players, because health care is complex, and nobody knows everything; and nobody knows how to relate to every patient and his or her unique needs. Because we are all fallible, we all see many examples of poor teams, where bad communication, power struggles, and personality clashes lead to poor outcomes. Stress, overwork, and resource restrictions contribute to this, but not inevitably. So it is worthwhile, at the outset of this journey through clinical medicine, to commit oneself to being a good team member. 3 rules help: (1) All members are valuable; none is irreplaceable, and members are valued for who they are, not just for the resources they bring. (2) 'Innocence is no excuse'—ie you may not be 'to blame' for a group's malfunction but in the end each member is responsible for everything. (3) Every member needs encouragement. Just how important this is, is shown by this comment from a well-known statesman:[1]

'He was impossible. It wasn't that he didn't attend to his work. But his manner brought him into conflict with everybody … When the crisis came, and the whole truth had to come out, he laid the blame on us: in his conduct there was nothing, absolutely nothing to reproach. His self-esteem was so strongly bound up, apparently, with the idea of his innocence, that one felt a brute as one demonstrated, step by step, the contradictions in his defence, and, bit by bit, stripped him naked before his own eyes. But justice to others demanded it.

When the last rag of a lie had been taken from him, and we thought there was nothing more to be said, out it came with stifled sobs.

"But why did you never help me? You knew that I always felt you were against me. And fear and insecurity drove me further and further along the course for which you now condemn me. It's been so hard—everything. One day, I remember, I was so happy: one of you said that something I had produced was quite good—"

So, in the end, we were, in fact, to blame. We had not voiced our criticisms, but we had allowed them to stop us from giving him a single word of acknowledgement, and in this way had barred every road to improvement. It is always the stronger one who is to blame.'

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Dedication

This work is dedicated to doctors everywhere, especially to those who are just starting out, or who are in the thick of it, or who are at the sharp end of a difficult decision.

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Common reference intervals

Common haematology values *If outside this range, consult:*

Haemoglobin	men:	13-18g/dL	p310
	women:	11.5-16g/dL	p310
Mean cell volume, MCV	76-96fL		↓p312; ↑p318
Platelets	150-400 × 10^9/L		p348
White cells (total)	4-11 × 10^9/L		p316
neutrophils	40-75%		p316
lymphocytes	20-45%		p316
eosinophils	1-6%		p316

Blood gases

	kPa	*mmHg*	
pH 7.35-7.45			p173, p658

P_aO_2	>10.6	75-100	p173, p658
P_aCO_2	4.7-6	35-45	p173, p658
Base excess ±2mmol/L			p173, p658

U&E etc (urea and electrolytes) ***If outside this range, consult:***

sodium	135-145mmol/	p666
potassium	3.5-5mmol/L	p668
creatinine	70-150µol/L	p292 & p294
urea	2.5-6.7mmol/L	p292 & p294, p661 (eGFR)
calcium	2.12-2.65mmol/L	p670
albumin	35-50g/L	p678
proteins	60-80g/L	p678

LFTs (liver function tests)

bilirubin	3-17µol/L	p242

alanine aminotransferase, ALT	3-35iu/L	
aspartate transaminase, AST	3-35iu/L	p242
alkaline phosphatase	30-35iu/L (*adults*)	p242

'Cardiac enzymes' For troponins, see p81 & p104.

creatine kinase	25-195iu/L	p104 (p538)
lactate dehydrogenase, LDH	70-250iu/L	p104

Lipids and other biochemical values

cholesterol	<6mmol/L *desired*	p682
triglycerides	0.5-1.9mmol/L " "	p682
amylase	0-180*somorgyi* u/dL	p584
C-reactive protein, CRP	<10mg/L	p679
glucose, fasting	3.5-5.5mmol/L	p190
prostate specific antigen, PSA	0-4ng/mL	p681

T4 (total thyroxine)	70-140mmol/L	p200
TSH	0.5-~5mu/L	p200

For all other reference intervals, see p741

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Symbols and abbreviations

Symbols and abbreviations

▸ ▸▸
this fact or idea is important. ▸▸don't dawdle!—prompt action saves lives

incendiary (controversial) topic

[ ]
non-BNF drug dose

reference available on our website www.oup.com/OHCM

♂ : ♀
male-to-female ratio. û:ý=2:1 means twice as common in males

@1234567
search Medline (pubmed.gov) with '1234567' to get an abstract (omit the '@')

∵ ~
on account of (Ì means *therefore*; ~ means *approximately*)

-ve +ve
negative and positive, respectively

↑ ↓ ↔
increased, decreased, and normal, respectively (eg serum level)

△; △△
diagnosis; δδ means differential diagnosis (list of possibilities)

A_2
aortic component of the second heart sound

A2A
angiotensin-2 receptor antagonist **(**p28**3**; = AT-2, A2R, and AIIR)

Ab
antibody

ABC
airway, breathing, and circulation: basic life support (see inside back cover)

ABG
arterial blood gas (P_aO_2, P_aCO_2, pH, HCO_3^-)

ABPA
allergic bronchopulmonary aspergillosis

Ac
ante cibum (before food)

ACE(i)
angiotensin-converting enzyme (inhibitors)

ACTH
adrenocorticotrophic hormone

ADH
antidiuretic hormone

ad lib
ad libitum; as much/as often as wanted (Latin for *at pleasure*)

AF
atrial fibrillation

AFB
acid-fast bacillus

AFP or α-FP

alpha-fetoprotein

Ag

antigen

AIDS

acquired immunodeficiency syndrome

Alk phos

alkaline phosphatase (also ALP)

ALL

acute lymphoblastic leukaemia

AMA

antimitochondrial antibody

AMP

adenosine monophosphate

ANA

antinuclear antibody

ANCA

antineutrophil cytoplasmic antibody

APTT

activated partial thromboplastin time

AR

aortic regurgitation

ARA

angiotensin receptor antagonist (p301; also AT-2, A2R, and AIIR)

ARDS

acute respiratory distress syndrome

ARF

acute renal failure

AS

aortic stenosis

ASD

atrial septal defect

ASO(T)

antistreptolysin O (titre)

AST

aspartate transaminase

AT-2

angiotensin-2 receptor blocker **(**p28**3**; also AT-2, A2R, and AIIR)

ATN

acute tubular necrosis

ATP

adenosine triphosphate

AV

atrioventricular

AVM

arteriovenous malformation(s)

AXR

abdominal x-ray (plain)

Ba

barium

BAL

bronchoalveolar lavage

Bd

bis die (twice a day)

BKA

below-knee amputation

***BMJ*/BMA**

British Medical Journal/British Medical Association

BNF

British National Formulary

BP

blood pressure

bpm

beats per minute (eg pulse)

Ca

cancer

CABG

coronary artery bypass graft

cAMP

cyclic adenosine monophosphate (AMP)

CAPD

continuous ambulatory peritoneal dialysis

CBD

common bile duct

CC

creatinine clearance (also CrCl)

CCF

congestive cardiac failure (ie left and right heart failure)

CCU

coronary care unit

CHB

complete heart block

CHD

coronary heart disease (related to ischaemia and atheroma)

CI

contraindications

CK

creatine (phospho)kinase (also CPK)

CLL/CML

chronic lymphocytic leukaemia/chronic myeloid leukaemia

CMV

cytomegalovirus

CNS

central nervous system

COC

combined oral contraceptive, ie (o)estrogen + progesterone

COPD

chronic obstructive pulmonary disease

CPAP

continuous positive airways pressure

CPR

cardiopulmonary resuscitation

CRF

chronic renal failure

CRP

c-reactive protein

CSF

cerebrospinal fluid

CT

computer tomography

CVP

central venous pressure

CVS

cardiovascular system

CXR
chest x-ray

d
day(s) (also expressed as /7)

DC
direct current

DIC
disseminated intravascular coagulation

DIP
distal interphalangeal

dl
decilitre

DoH (or DH)
department of health (UK)

DM
diabetes mellitus

DU
duodenal ulcer

D&V
diarrhoea and vomiting

DVT
deep venous thrombosis

DXT
deep radiotherapy

E-BM
evidence-based medicine and its journal published by the BMA

EBV
Epstein-Barr virus

ECG
electrocardiogram

Echo
echocardiogram

EDTA
ethylene diamine tetraacetic acid (eg in FBC bottle)

EEG
electroencephalogram

ELISA
enzyme linked immunosorbant assay

EM
electron microscope

EMG
electromyogram

ENT
ear, nose, and throat

ERCP
endoscopic retrograde cholangiopancreatography; see also MRCP

ESR
erythrocyte sedimentation rate

ESRF
end-stage renal failure

EUA
examination under anaesthesia

FB
foreign body

FBC
full blood count

FDP

fibrin degradation products

FEV_1; F_iO_2

forced expiratory volume in 1st sec; F_iO_2: partial pressure of O_2 in inspired air

FFP

fresh frozen plasma

FroM

full range of movements

FSH

follicle-stimulating hormone

FVC

forced vital capacity

g

gram

GA

general anaesthetic

GAT(Sanford)

Sanford *guide to antimicrobial therapy* www.sanfordguide.com

GB

gall bladder

GC

gonococcus

GCS

Glasgow coma scale

GFR

glomerular filtration rate eGFR, p661

GGT

gamma glutamyl transpeptidase

GH

growth hormone

GI

gastrointestinal

GP

general practitioner

G6PD

glucose-6-phosphate dehydrogenase

GTN

glyceryl trinitrate

GTT

glucose tolerance test (also OGTT: oral GTT)

GU(M)

genitourinary (medicine)

h

hour

HAV

hepatitis A virus

Hb

haemoglobin

HBsAg/HBV

hepatitis B surface antigen/hepatitis B virus

HCC

hepatocellular cancer

Hct

haematocrit

HCV (HDV)

hepatitis C virus (HDV is hepatitis D virus)

HDL
high-density lipoprotein, p683

HHT
hereditary haemorrhagic telangiectasia

HIDA
hepatic immunodiacetic acid

HIV
human immunodeficiency virus

HOCM
hypertrophic obstructive cardiomyopathy

HONK
hyperosmolar nonketotic (diabetic coma)

HRT
hormone replacement therapy

HSV
herpes simplex virus

IBD
inflammatory bowel disease

IBW
ideal body weight, p434

ICP
intracranial pressure

IDA
iron-deficiency anaemia

IDDM
insulin-dependent diabetes mellitus

IFN-α
alpha interferon

IE
infective endocarditis

Ig
immunoglobulin

IHD
ischaemic heart disease

IM
intramuscular

INR
international normalized ratio (prothrombin ratio)

IP
interphalangeal

IPPV
intermittent positive pressure ventilation

ITP
idiopathic thrombocytopenic purpura

ITU
intensive therapy unit

iu
international unit

IVC
inferior vena cava

IV(I)
intravenous (infusion)

IVU
intravenous urography

JAMA
Journal of the American Medical Association

JVP
jugular venous pressure

K
potassium

KCCT
kaolin cephalin clotting time

Kg
kilogram

Kpa
kiloPascal

L
litre

LAD
left axis deviation on the ECG; also left anterior descending coronary artery

LBBB
left bundle branch block

LDH
lactate dehydrogenase

LDL
low-density lipoprotein, p683

LBW
lean body weight, p434

LFT
liver function test

LH
luteinizing hormone

LIF
left iliac fossa

LKKS
liver, kidney (R), kidney (L), spleen

LMN
lower motor neurone

LP
lumbar puncture

LUQ
left upper quadrant

LV
left ventricle of the heart

LVF; LVH
left ventricular failure; left ventricular hypertrophy

µg
microgram

MAI
Mycobacterium avium intracellulare

MAOI
monoamine oxidase inhibitors

mane
morning (from Latin; the 'e' may be written 'é', but purists frown on this)

MC & S
microscopy, culture and sensitivity

MCP
metacarpo-pharangeal

MCV
mean cell volume

MDMA
3,4-methylenedioxymethamphetamine

ME

myalgic encephalomyelitis

MET

meta-analysis

mg

milligram

MI

myocardial infarction

min(s)

minute(s)

mL

millilitre

mmHg

millimetres of mercury

MND

motor neurone disease

MRCP

magnetic imaging cholangiopancreatography (also Member of Royal College of Physicians)

MRI

magnetic resonance imaging

MRSA

methicillin-resistant *Staphylococcus aureus* (p408)

MS

multiple sclerosis (do not confuse with mitral stenosis)

MSU

midstream urine

NAD

nothing abnormal detected

NBM

nil by mouth

ND

notifiable disease

NEJM

New England Journal of Medicine

ng

nanogram

NG(T)

nasogastric (tube)

NHS

National Health Service (UK)

NICE

National Institute for Health and Clinical Excellence www.nice.org.uk

NIDDM

non-insulin-dependent diabetes mellitus

NMDA

N-methyl-*D*-aspartate

NNT

number needed to treat, for 1 extra satisfactory result (p650)

Nocte

at night

NR

normal range—the same as reference interval

NSAIDs

non-steroidal anti-inflammatory drugs

N&V

nausea and/or vomiting

od

omni die (once daily)

OD

overdose

OGD

oesophagogastroduodenoscopy

OGS

oxogenic steroids

OGTT

oral glucose tolerance test

OHCS

Oxford Handbook of Clinical Specialties, 7e OUP, Collier & Longmore

om; on

omni mane (in the morning); *omni* nocte (at night)

OPD

out-patients department

ORh-

blood group O, Rh negative

OT

occupational therapist

OTM/S

Oxford Textbook of Medicine (OUP 4e, 2003)/*Surgery* (2000)

P_2

pulmonary component of second heart sound

P_aCO_2

partial pressure of carbon dioxide in arterial blood

PAN

polyarteritis nodosa

P_aO_2

partial pressure of oxygen in arterial blood

PBC

primary biliary cirrhosis

PCP

Pneumocystis carinii (*jiroveci*) pneumonia

PCR

polymerase chain reaction (DNA diagnosis)

PCV

packed cell volume

PE

pulmonary embolism

PEEP

positive end-expiratory pressure

PERLA

pupils equal and reactive to light and accommodation

PEF(R)

peak expiratory flow (rate)

PID

pelvic inflammatory disease

PIP

proximal interphalangeal (joint)

PMH

past medical history

PND

paroxysmal nocturnal dyspnoea

PO

per os (by mouth)

PPF

purified plasma fraction (albumin)

PPI

proton pump inhibitor, eg omeprazole, lansoprazole, etc.

PR

per rectum (by the rectum)

PRL

prolactin

PRN

pro re nata (as required)

PRV

polycythaemia rubra vera

PSA

prostate specific antigen

PTH

parathyroid hormone

PTT

prothrombin time

PUO

pyrexia of unknown origin

PV

per vaginam (by the vagina; the route for pessaries)

PVD

peripheral vascular disease

qds; qqh

quater die sumendus (to be taken 4xdaily); qqh *quarta quaque hora:* every 4h

R

right

RA

rheumatoid arthritis

RAD

right axis deviation on the ECG

RBBB

right bundle branch block

RBC

red blood cell

RCT

randomized control trial

RFT

respiratory function tests

Rh

Rh; not an abbreviation, but derived from the rhesus monkey

RIF

right iliac fossa

RUQ

right upper quadrant

RV

right ventricle of heart

RVF

right ventricular failure

RVH

right ventricular hypertrophy

[prescription take]

recipe (treat with)

S or sec

second(s)

S1, S2

first and second heart sounds

SBE

subacute bacterial endocarditis (IE is *infective endocarditis*)

SC

subcutaneous

sd

standard deviation

SE

side-effect(s)

SL

Sublingual

SLE

systemic lupus erythematosus

SOB

short of breath (SOB(O)E: short of breath on exercise)

SPC

summary of product characteristics (SPC; www.medicines.org.uk)

SpO_2

peripheral oxygen saturation (%)

SR

slow-release (also called MR, modified-release)

Stat

statim (immediately; as initial dose)

STD/STI

sexually-transmitted disease or sexually-transmitted infection

SVC

superior vena cava

Sy(n)

syndrome

T°

temperature

$T_{½}$

biological half-life

T3; T4

triiodothyronine; T4 is thyroxine

TB

tuberculosis

tds

ter die sumendus (to be taken 3 times a day)

TFTs

thyroid function tests (eg TSH)

TIA

transient ischaemic attack

TIBC

total iron binding capacity

tid

ter in die (3 times a day)

TPR

temperature, pulse, and respirations count

TRH; TSH

thyroid-releasing hormone; TSH means thyroid-stimulating hormone

U

units

UC

ulcerative colitis

U&E

urea and electrolytes and creatinine—in plasma, unless stated otherwise

UMN
upper motor neurone

URT(I)
upper respiratory tract (infection)

US(S)
ultrasound (scan)

UTI
urinary tract infection

VDRL
venereal diseases research laboratory (syphilis serology)

VE
ventricular extrasystole

VF
ventricular fibrillation

VMA
vanillyl mandelic acid (HMMA)

[V with dot above]/[Q with dot above]
ventilation/perfusion ratio

VSD
ventriculo-septal defect

VT
ventricular tachycardia

WBC; WCC
white blood cell; white blood cell count

wk(s)
week(s)

WR
Wassermann reaction

yr(s)
year(s)

ZN
Ziehl-Neelsen (stain for acid-fast bacilli, eg mycobacteria)

Other abbreviations are given on pages where they occur: also, consult the *index*.

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1

Thinking About Medicine

The Old Hippocratic oath ~425$_{BC}$

I swear by Apollo the physician, and Aesculapius and Health and All-heal, and all the gods and goddesses, that, according to my ability and judgment, I will keep this oath and stipulation—to reckon him who taught me this Art equally dear to me as my parents, to share my substance with him, and relieve his necessities if required; to look upon his offspring in the same footing as my own brothers, and to teach them this Art, if they shall wish to learn it, without fee or stipulation, and that by percept, lecture, and every other mode of instruction, I will impart a knowledge of the Art to my own sons, and those of my teachers, and to disciples bound by a stipulation and oath according to the law of medicine, but to none other.

I will follow that system of regimen, which, according to my ability and judgment, I consider for the benefit of my patients, and abstain from whatever is deleterious and mischievous.

I will give no deadly medicine to anyone if asked, nor suggest any such counsel; and in like manner I will not give to a woman a pessary to produce abortion. With purity and with holiness I will pass my life and practice my Art.

I will not cut persons labouring under the stone, but will leave this work to be done by men who are practitioners of this work.

Into whatever houses I enter, I will go into them for the benefit of the sick, and will abstain from every voluntary act of mischief and corruption; and, further, from the seduction of females, or males, of freemen or slaves.

Whatever, in connection with my professional practice, I see or hear, in the life of men, which ought not to be spoken of abroad, I will not divulge, as reckoning that all such should be kept secret.

While I continue to keep this oath unviolated, may it be granted to me to enjoy life and practice this Art, respected by all men, in all times. Should I violate this Oath, may the reverse be my lot.

A New Hippocratic oath ~2004$_{AD}$

I promise that my medical knowledge will be used to benefit people's health; patients are my first concern. I will listen to them, and provide the best care I can. I will be honest, respectful, and compassionate towards all.

I will do my best to help anyone in medical need, in emergencies. I will make every effort to ensure the rights of all patients are respected, including vulnerable groups who lack means of making their needs known.

I will exercise my professional judgment as independently as possible, uninfluenced by political pressure or the social standing of my patient. I will not put personal profit or advancement above my duty to my patient.

I recognize the special value of human life, but I also know that prolonging life is not the only aim of health care. If I agree to perform abortion,[1] I agree it should take place only within an ethical and legal context.

I will not provide treatments that are pointless or harmful, or which an informed and competent patient refuses. I will help[2] patients find the information and support they want to make decisions on their care.

I will answer as truthfully as I can, and respect patients' decisions, unless that puts others at risk of substantial[3] harm. If I cannot agree with their requests, I will explain why.

If my patients have limited mental awareness, I will still encourage them to participate in decisions as much as they feel able. I will do my best to maintain confidentiality about all patients.

If there are overriding reasons preventing my keeping a patient's confidentiality I will explain them. I will recognize the limits of my knowledge and seek advice from colleagues as needed. I will acknowledge my mistakes.

I will do my best to keep myself and my colleagues informed of new developments, and ensure that poor standards or bad practices are exposed to those who can improve them.

I will show respect for all those with whom I work and be ready to share my knowledge by teaching others what I know. I will use my training and professional standing to improve the community in which I work.

I will treat patients equitably and support a fair and humane distribution of health resources. I will try to influence positively authorities whose policies harm public health.

I will oppose policies which breach internationally accepted standards of human rights. I will strive to change laws that are contrary to patients' interests or to my professional ethics.

While I continue to keep this Oath unviolated, may it be granted to me to enjoy life and the practice of the Art, respected by all, in all times.

Ideals

Decision and *intervention* are the essence of action: *reflection* and *conjecture* are the essence of thought: the essence of medicine is combining these realms in the service of others. We offer these ideals to stimulate both thought and action: like the stars, ideals are hard to reach, but they serve for navigation during the night. We choose Orion (**fig 1**) as our emblem for this navigation as he had miraculous sight (a gift from his immortal lover, Eos, to help him in his task of hunting down all dangerous things)—and, as his constellation is visible in the Northern *and* the Southern hemispheres (being at the celestial equator), he links our readers everywhere.

- Do not blame the sick for being sick.
- If the patient's wishes are known, comply with them.
- Work for your patients, not your consultant.
- Ward staff are usually right; respect their opinions.
- Treat the whole patient, not the disease, or the nurses.
- Admit people—not ‘strokes’, ‘infarcts’, or ‘crumble’.
- Spend time with the bereaved; help them to shed tears.
- Give the patient (and yourself) time: time for questions, to reflect, to allow healing, and time to gain autonomy.
- Give patients the benefit of the doubt. Be optimistic. Optimistic patients who feel in charge, live longer.[2]
- Use ward rounds to boost patients' morale, not your own.
- Be kind to yourself: you are not an inexhaustible resource.
- Question your conscience—however strongly it tells you to act.

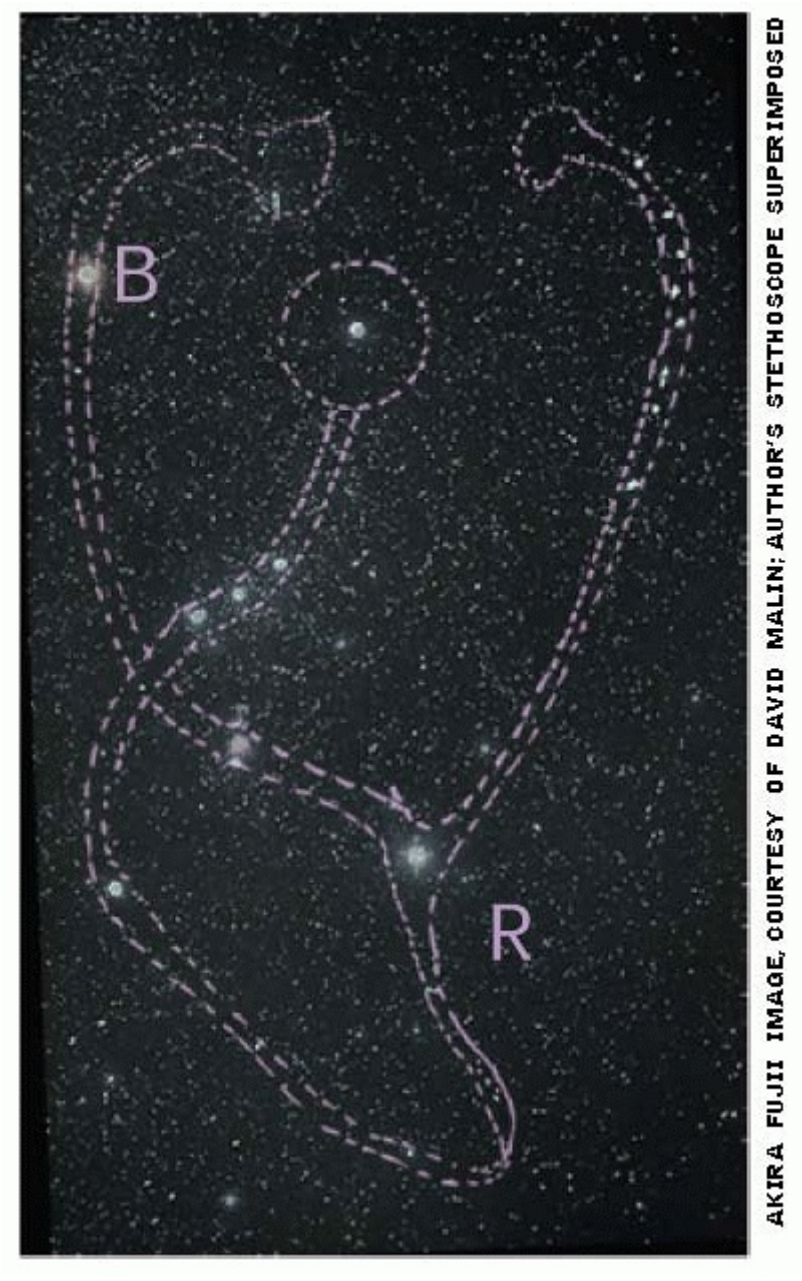


Fig 1. The constellation of Orion has 3 superb stars: *Bellatrix* (the bell of the stethoscope), *Betelgeuse* (**B**) and *Rigel* (**R**). The 3 stars near the crossover (Orion's belt) are Alnitak, Alnilam, and Mintaka.[1]

Ideal and less than ideal methods of care

A story illustrates the options: a man cut his hand and went round to his neighbour for help. This neighbour happened to be a doctor, but it was not the doctor but his 3-year-old daughter who opened the door. Seeing that he was hurt and bleeding, she took him in, pressed her handkerchief over his wound, and reclined him, feet up, in the nearest chair. She stroked his head and patted his hand, and told him about her marigolds, and then about her frogs, and, after some time, was starting to tell him about her father—when her father eventually appeared. He quickly turned the neighbour into a patient, and then into a bleeding biohazard, and then dispatched him to Casualty 'for suturing'. (The neighbour had no idea what this was.) He waited 3 hours in Casualty, had 2 desultory stitches, and 1 interview, with a medical student who suggested a tetanus vaccination (to which he unfortunately developed an allergic reaction). He returned to his doctor next door a few days later, praising his young carer, but not the doctor (who had turned him into a patient), nor the hospital (who had turned him into an item on a conveyor belt), nor the student who turned him into a question mark (does a 50-year-old man with a full series of tetanus vaccinations need a booster at the time of injury?).

It was the 3-year-old who was his true nurse-cum-physician and universal health worker, who took him in on his own terms, cared for him, and gave him time and dignity. Question her instinct for care as you will: point out that it could have led to harm, and is, in any case, inadequate for scientific medicine, and that the hospital was just a victim of its own success. But remember that the story shows that *there is*, as TS Eliot said, *at best, only a limited value in the knowledge derived from experience*, eg the knowledge encompassed in this book. The child had the innate understanding and the natural compassion that we all too easily lose amid the science, the knowledge, and our stainless-steel universe of organized health care.

The bedside manner and communication skills

Our bedside manner matters as it shows patients if they can *trust* us. Where there is no trust there is little healing. A good bedside manner is not static. It develops in the light of patients' needs. And it is grounded in the timeless virtues of honesty, humour, and humility in the presence of human weakness and human suffering.

The following are examples from an endless variety of phenomena which arise whenever doctors meet patients. One of the great skills (and pleasures) in medicine is to learn how our actions and attitudes influence patients, and how to take this knowledge into account when assessing the validity and significance of the signs and symptoms we elicit. What we receive from our patients is not 'hard evidence', but a much more plastic commodity, moulded as much by the doctor's attitude and the hospital or consulting room environment as by the patient's own hopes and fears. It is our job to adjust our attitudes and environment so that these hidden hopes and fears become manifest and the channels of communication are always open.

Anxiety reduction or intensification

Simple explanation of what you are going to do often defuses what can be a highly charged affair. With children, try more subtle techniques, such as examining the abdomen using the child's own hands, or examining his teddy bear first (see p601).

Pain reduction or intensification

Compare: 'I'm going to press your stomach. If it hurts, cry out' with 'I'm going to touch your stomach. Let me know what you feel' and 'Now I'll lay a hand on your stomach. Sing out if you feel anything.' The examination can be made to sound frightening, neutral, or joyful, and the patient will relax or tense up accordingly.

The tactful or clumsy invasion of personal space

During ophthalmoscopy, eg we must get much nearer to the patient than is acceptable in normal social intercourse. Both doctor and patient may end up holding their breath, which helps neither the patient keep his eyes perfectly still, nor the doctor to carry out a full examination. Simply explain 'I need to get very close to your eyes for this.' (Not 'We need to get very close for this'—one of the authors was kissed repeatedly while conducting ophthalmoscopy by a patient with frontal lobe signs.)

Inducing trance-like states

Watch a skilful practitioner at work palpating the abdomen: the right hand rests idly on the abdomen, far away from the part which hurts. He meets the patient's gaze: 'Have you ever been to the seaside?' His hand caresses rather than penetrates. 'Imagine you are back on the beach now, perfectly at ease, gazing at the blue, blue sky.' He presses as hard as he needs. 'Tell me now, where were you born and bred?' If he stops talking and frowns only during palpation of the epigastrium, something possibly quite useful has been discovered.

Communication

All ideas are useless unless we communicate them. Be simple and direct. Avoid jargon; even words such as 'remission' and 'jaundice' are often misunderstood. In one study, 10% of patients said jaundice meant yellow vomit; see www.psychooncology.org. Give the most important details first. Check on retention and understanding. Be specific. 'Drink 6 cups of water daily' is better than 'Drink more fluids'. Give videos or written material with easy readability. Flesch's formula quantifies this: ***F***=206.835-(1.015 × ASL)-(84.6 × ASW) where ASL=average sentence length (number of words ÷ number of sentences) and ASW=average number of syllables/word. 100 is very easy; aim for >70. ***F*** for the first paragraph of this page is 71 but our second paragraph is much more complex: ***F***=39, as calculated by Microsoft Word's® automated Flesch score. It is sobering to display readability statistics for patient information leaflets imported into Word®, and then fun to see if you can re-edit to get a score of >70. ▸Don't assume all patients can read: naming the pictures but not the words on our test chart (p51) reveals this tactfully.

Ensure harmonization between your view of what should be done and your patient's. We often talk of ***compliance*** with our regimens, when what we should talk of is ***concordance***, for concordance recognizes the central role of patient participation in all good plans of care.

Asking questions

No class of questions is 'correct'. Sometimes you need to ask one type of question; sometimes another. Get good at shifting from one kind to another, and you will soon learn to judge the most effective questions for the patient in front of you. The aim of asking questions is to *describe*, not from the point of view of intellectual imperialism ('If you can describe the world, you can have it'), but from the point of view of practical help: what cannot be described cannot be cured, and what is described but still cannot be cured can, at least, be shared, mitigated, and so partially overcome. Different kinds of questions either throw light on this issue, or obscure it, as in the 2 examples below.

Leading questions

On seeing a bloodstained handkerchief you ask: 'How long have you been coughing up blood?' '6 weeks, doctor', so you assume haemoptysis for 6 weeks. In fact, the stain could be due to an infected finger, or to epistaxis (nose bleed). On finding this out later (and perhaps after expensive and unpleasant investigations), you will be annoyed with your patient for misleading you—whereas he was trying to be polite by giving the sort of answer you were obviously expecting. With such leading questions as these, the patient is not given an opportunity to deny your assumptions.

Questions suggesting the answer

'Was the vomit red, yellow, or black—like coffee grounds?'—the classic description of vomited blood. 'Yes, like coffee grounds, doctor.' The doctor's expectations and hurry to get the evidence into a pre-decided format have so tarnished the story as to make it useless.

Open questions

The most open question is 'How are you?' This suggests no particular answer, so the direction a patient chooses offers valuable information. Other examples are gentle imperatives such as 'Tell me about the vomit' 'It was dark' 'How dark?' 'Dark bits in it' 'Like...?' 'Like bits of soil in it.' This information is gold, although it is not cast in the form of 'coffee grounds'.

Patient-centred questions

'What do you think is wrong?' 'Are there any other aspects of this we might explore?' 'Are there any questions you want to ask?' (a closed question). Better still, try 'What are the other things on your mind?[3] How does having this affect you? What is the worst thing? It makes you feel...' (The doctor is silent.) ▸Unless you become patient-centred your patient may never be fully satisfied with you, or fully cooperative.

Casting your questions over the whole family

This is most useful in revealing if symptoms are caused or perpetuated by psychological mechanisms. They probe the network of causes and enabling conditions which allow nebulous symptoms to flourish in family life. 'Who else is important in your life? ... Are they worried about you? Who really understands you?' Until this sort of question is asked, illness may be refractory to treatment. Eg 'Who is present when your headache starts? Who notices it first—you or your wife? Who worries about it most (or least)? What does your wife do when (or before) you get it?' Think to yourself: *Who* is his headache? We note with fascination research showing that in clusters of hard-todiagnose symptoms, it is the spouse's view of them that is the best predictor of outcome: if the spouse is determined that symptoms must be physical, the outcome is worse than if the spouse allows that some symptoms may be psychological.

Echoes

Try repeating the last words said as a route to new intimacies, otherwise inaccessible, as you fade into the distance, and the patient soliloquizes '...I've always been suspicious of my wife.' 'Wife ...' 'My wife ... and her father together.' 'Together...' 'I've never trusted them together.' 'Trusted them together...' 'No, well, I've always felt I've known who my son's real father was... I can never trust those two together.' Without any questions you may unearth the unexpected, important clue which throws a new light on the history.

▸*If you only ask questions, you will only receive answers in reply.* If you interrogate a robin, he will fly away: treelike silence may bring him to your hand.

What is the mechanism? Finding narrative answers

Like toddlers, we should always be asking '*Why*?'—not just to find ultimate causes, but to enable us to choose the simplest level for intervention. Some simple change early on in a chain of events may be sufficient to bring about a cure, whereas later on in the chain such opportunities may not arise.

For example, it is not enough for you to diagnose heart failure in your breathless patient. Ask: '*Why is there heart failure*?' If you do not, you will be satisfied with giving the patient an anti-failure drug—and any side-effects from this, such as uraemia or incontinence induced by diuretic-associated polyuria, will be attributed to an unavoidable consequence of necessary therapy.

If only you had asked '*What is the mechanism of the heart failure*?' you might have found a cause, eg anaemia coupled with ischaemic heart disease. You cannot cure the latter, but treating the anaemia may be all that is required to cure the patient's breathlessness. But do not stop there. Ask: '*What is the mechanism of the anaemia*?' You find a low MCV and a correspondingly low serum ferritin (p312)— and you might be tempted to say to yourself, I have the prime cause.

Wrong! Put aside the idea of prime causes, and go on asking '*What is the mechanism*?' Retaking the history (often the best 'investigation') shows a very poor diet. '*Why is the patient eating a poor diet*?' Is he ignorant or too poor to eat properly? You may find the patient's wife died a year ago, he is sinking into a depression, and cannot be bothered to eat. He would not care if he died tomorrow.

You come to realize that simply treating the patient's anaemia may not be of much help—so go on asking '*Why*?': 'Why did you bother to go to the doctor if you aren't interested in getting better?' It turns out he only went to see you to please his daughter. He is unlikely to take your drugs unless you really get to the bottom of what he cares about. His daughter is what matters and, unless you include her, all your initiatives may fail. Talk to her, offer help for the depression, teach her about iron-rich foods and, with luck, your patient's breathlessness may gradually begin to disappear. Even if it does *not* start to disappear, you are learning to stand in your patient's shoes and you may discover what will enable him to accept help. And this dialogue may help you to be a kinder doctor, particularly if you are worn out by endless lists of technical tasks which you must somehow fit into impossibly overcrowded days and nights. You never really know a man until you stand in his shoes and walk around in them. Harper Lee; *To Kill a Mockingbird*

Constructing imaginative narratives yielding new meanings

Doctors are often thought of as being reductionist or mechanistic—but the above shows that asking '*Why?*' can enlarge the scope of our enquires into holistic realms. Another way to do this is to ask '***What does this symptom mean?***'—for this person, his family, and our world. A limp might mean a neuropathy, or falling behind with the mortgage, if you are a dancer; or it may represent a medically unexplained symptom which subtly alters family hierarchies both literally (on family walks) and metaphorically. Science is about clarity, objectivity, and theory in modelling reality. But there is another way of modelling the external world which involves subjectivity, emotion, ambiguity, and arcane relationships between apparently unrelated phenomena. The medical humanities (p19) explore this—and have burgeoned recently[4] —leading to the existence of two camps: humanities and science. If, while reading this you are getting impatient to get to the real nuts and bolts of technological medicine, you are in the latter camp. We are not suggesting that you leave it, only that you learn to operate out of both. If you do not, your professional life will be full of failures which you may deny or remain in ignorance of. If you *do* straddle both camps, there will also be failures, but you will realize what these failures *mean*, and you will know how to *transform* them. This

transformation happens through dialogue and reflection. We would achieve more if we did less: every hospital should have a department of reflection and it should be visited as often as the radiology department. In fact every hospital has many such departments, carved out of our own minds—it's just that their entrances are blocked by piles of events, tasks and happenings.

Death: diagnosis and management

Death is Nature's master stroke, albeit a cruel one, because it allows genotypes space and opportunity to try on new phenotypes. The time comes in the life of any organ or person when it is better to start again from scratch rather than carry on with the weight and muddle of endless accretions. Our bodies and minds are these perishable phenotypes—the froth, which always turns to scum, on the wave of our genes. These genes are not really *our* genes. It is we who belong to them for a few decades. It is one of Nature's great insults that she should prefer to put *all* her eggs in the basket of a defenceless, incompetent neonate rather than in the tried and tested custody of our own superb minds. But as our neurofibrils begin to tangle, and that neonate walks to a wisdom that eludes us, we are forced to give Nature credit for her daring idea. Of course, Nature, in her careless way, can get it wrong: people often die in the wrong order (one of our chief roles is to prevent this misordering of deaths, not the phenomenon of death itself).

So we must admit that, on reflection, dying *is* a brilliant idea, and one that it is most unlikely we could ever have thought of ourselves.

Causes of death

Homicide, suicide, misadventure, or natural causes.

Diagnosing death

Apnoea with no pulse[1] and no heart sounds, and fixed pupils.[2] If on a ventilator, brain death may be diagnosed even if the heart is still beating, via the ***UK brain death criteria*** which state that brain death is death of the brainstem, recognized by establishing:

- Deep coma with absent respirations (hence on a ventilator).
- The absence of drug intoxication and hypothermia (<35°C).
- The absence of hypoglycaemia, acidosis, and U&E imbalance.

Tests:

All brainstem reflexes should be absent.

- Unreactive pupils. Absent corneal response (no blink to a cotton-wool touch).
- No vestibulo-ocular reflexes, ie no eye movement occurs after or during slow injection of 20mL of ice-cold water into each external auditory meatus in turn. Visualize the ear-drum first to eliminate false negative tests, eg due to wax.
- No motor response within the cranial nerve distribution should be elicited by adequate stimulation.
- No gag reflex or response to bronchial stimulation, and no respiratory effort on stopping the ventilator and allowing P_aCO_2 to rise to 6.7kPa.

Other considerations:

Repeat tests after a suitable interval, eg 24h. Spinal reflexes are not relevant to diagnosing brain death; EEG is not required, nor is a neurologist. The doctor diagnosing brain death must be a consultant (or his deputy registered for >5yrs). The opinion of one other doctor (any) should also be sought.

US criteria

for brain death are different: an EEG must confirm absence of cerebral activity if brain death is to be diagnosed within 6h of apparent cessation of brain activity. Diagnosis is allowed in cases of intoxication if isotope angiography shows absent cerebral circulation, or if the intoxicant has been metabolized.

Organ donation:

The point of diagnosing brain death is partly that this allows organs (kidney, liver, cornea, heart, or lungs) to be donated and removed with as little hypoxic damage as possible. Don't avoid the topic with relatives. Many are glad to consent and to know that good can come after the death of a relative, that some part of the relative will go on living, giving a new life to another person.

After death

Inform GP and the consultant. See the relatives. Sign death certificates promptly. If the cause is violence, injury, neglect, surgery, anaesthesia, alcohol, suicide, or poisoning, or is unknown, inform the Coroner/Procurator Fiscal.

Facing death

People imagine that they are not afraid of death when they think of it while they are in good health (Marcel Proust). So, to get into the mood, as a thought experiment, place a finger in your left supraclavicular fossa, and feel there the craggy node of Virchow, telling of some distant gastric malignancy, as if it were a death warrant. Perhaps you have just 4 months left. Live with this 'knowledge' for a day or two, and see how it changes your attitude to family and friends on the one hand, and the million irrelevances which clutter our minds on the other.

As the week unfolds, you may experience thoughts and feelings that are new to you, but all too familiar to your patients. And as the months and years roll

by, and you find yourself sitting opposite certain patients, put that finger once more on that metaphorical node and turn it over in your mind, and it will turn you, so you are sitting not opposite your patient but beside him. But there is only so much comfort you can bring in this way, as, in the end, you cannot tame death.

Whenever you find yourself thinking *it is better for him not to know*, suspect that you mean: *it is easier for me not to tell*. We find it hard to tell for many reasons: it distresses patients; it may hold up a ward round; we do not like acknowledging our impotence; telling reminds us of our own mortality and may unlock our previous griefs. We use many tricks to minimize the pain: *rationalization* ('He would not want to know'); *intellectualization* ('Research shows that 37% of people at stage 3 survive 2 years…'); *brusque honesty* ('You are unlikely to survive 1 month' and, so saying, the doctor rushes off to more vital things); *inappropriate delegation* ('Sister will explain it all to you when you are calmer'). Telling may help because:

- He already half knows but everyone shies away so he cannot discuss his fears (of pain, or that his family will not cope).
- There may be many affairs for the patient to put in order.
- To enable him to judge if unpleasant therapy is worthwhile.

▸*Most patients are told less than they would like to know.*[5]

What are his worries likely to be?

Put yourself in the patient's place.

- Give some information, and then the opportunity to ask for more.
- Be sensitive to hints that he may be ready to learn more. 'I'm worried about my son.' 'What is worrying you most?' 'Well, it will be a difficult time for him, (pause) starting school next year.' Silence, broken by the doctor, 'I get the impression there are other things worrying you.' The patient now has the opportunity to proceed further, or to stop.
- Ensure that the GP and the nurses know what you have and have not said. Also make sure that this is written in the notes.

Stages of acceptance

Accepting death takes time, and may involve passing through 'stages' on a path. It helps to know where your patient is on this path (but progress is rarely orderly and need not always be forwards: the same ground often needs to be recovered). At first there may be *shock* and *numbness*, then *denial* (which reduces anxiety), then *anger* (which may lead you to dislike your patient, but anger can have positive attributes, eg in energizing people—and it can trump fear and pain; it is different from mere hostility), then *grief*, and then, perhaps, *acceptance*.[6] Finally there may be intense longing for death as the patient moves beyond the reach of worldly cares.[1]

Living wills and advance directives

If a patient's views are known, comply with them. But these views change, are ambiguous, or hard to interpret, even if a *living will* exists. In one study of a will stating '*… with the development of any life threatening medical situation I should not be given active treatment such as antibiotics or ventilation …*', 6 out of 12 health professionals said they would give antibiotics for pneumonia, as the will was not clear enough (eg had quality of life deteriorated enough to trigger the will?).[7] Assume that living wills *do* have legal status; get help from colleagues or a judge if in doubt.

Prescribing drugs

▸Consult the BNF or BNF *for children* or your local equivalent before giving any drug with which you are not thoroughly familiar; check interactions meticulously.

Before prescribing, ask if the patient is allergic to anything. The answer is often 'Yes'—but do not stop here. Characterize the reaction, or else you risk denying a possibly life-saving, and very safe, drug such as penicillin because of a mild reaction, eg nausea. Is the reaction a ***true allergy*** (anaphylaxis, p780, or a rash?), a ***toxic effect*** (eg ataxia is inevitable if given large doses of phenytoin), or a ***predictable adverse reaction*** (eg GI bleeding from aspirin), or an ***idiosyncratic reaction***?

Remember *primum non nocere*: first do no harm (p746). The more minor the complaint, the more weight this dictum carries. The more serious the complaint, the more its antithesis comes into play: *nothing ventured, nothing gained.*

Prescribing in renal failure

See p295. In liver failure, see p251.

Ten commandments

▸These should be written on every tablet.

1. Explore alternatives to drugs—which often lead to doctor-dependency, paternalism, and medicalization of life. Drugs are also expensive: >£11 billion/yr[UK]; prices increase much faster than general inflation. There are 3 places to look: ***The larder:*** lemon and honey for sore throats, rather than penicillin. ***The blackboard:*** eg education about the self-inflicted causes of oesophagitis. Rather than giving expensive drugs, advise raising the head of the bed, and avoiding tight garments, too many big meals, smoking, and alcohol excess. ***Lastly, look to yourself:*** giving a piece of yourself, some real sympathy, is worth more than all the drugs in your pharmacopoeia to patients who are frightened, bereaved, or weary of life. One of us (JML) for many years looked after a lady who was paranoid: monthly visits comprised an injection and a hug, no doubt always chaperoned, until one day mental health nurses took over her care. She was seen by a different nurse each month. They didn't know about hugging, so after a while she stopped cooperating, and soon it fell to me to certify her death.
2. Are you prescribing for a minor illness because you want to solve all problems? Patients may be happy just to know the illness *is* minor. Knowing this may

make it acceptable. Some people do not believe in drugs, and you must find this out.

3. Decide if the patient is responsible. If he now swallows *all* the quinine pills you have so attentively prescribed for his cramps, death will be swift.
4. Know of other ways your prescription may be misused. Perhaps the patient whose 'insomnia' you so kindly treated is even now selling it on the black market or grinding up your prescription prior to injecting himself, desperate for a fix. Will you be suspicious when he returns to say he has lost his drugs?
5. Address these questions when prescribing off the ward:
    - How many daily doses are there? 1-2 is *much* better than 4. Good doctors spend much time harmonizing complex regimens: the more you know about practical therapeutics the better for your patient. One reason for 'failure' of HIV drugs, for example, is that regimens are too complex. Drug companies know this, so keep abreast of new modified release (MR) preparations.
    - The bottle/box: can the patient read the instructions—and can he open it?
    - How will you know if the patient forgets to return (follow-up)?
    - If the patient agrees, enlist the spouse's help in ensuring that he remembers to take the pills. Check, eg by counting the remaining pills at the next visit.
6. List the risks (side-effects, contraindications, interactions, risk of allergy). Of any new problem, always ask yourself: *Is this a side-effect?*
7. Agree with the patient on the risk : benefit ratio's favourability. Try to ensure there is true concordance (p3) between you and your patient.
8. Record how you will review the patient's need for each drug.
9. Quantify progress towards specified, agreed goals, eg pulse rate to mark degree of Ò-blockade; or peak flow to guide steroid use in asthma.
10. List benefits of *this* drug to *this* patient for *all* drugs taken. Specify what each drug is for—and co-operate with national computer schemes (eg the 'NHS spine') which aggregate drugs prescribed for your patient from *all* sources.

Prevention

Two mottoes: *The only good medicine is preventive medicine* and *If preventable … why not prevented?* During life on the wards you will have many opportunities for preventive medicine, and unconsciously you will pass most of them over, in favour of more glamorous tasks such as diagnosis, and clever interventions, involving probes, scalpels, and imaging. But if we imagine a ward where scalpels remain sheathed and the only thing being probed is our commitment to health, then preventive medicine comes to the fore, and it is our contention that such a ward might produce more health than some entire hospitals. The first step is to motivate your patient to take steps to benefit their own health by asking Socratic questions. 'Do you want to smoke?' 'What does your family think about smoking' 'Do you want your children to smoke?' 'Would there be any advantages in giving up?' 'Why is your health important to you?' 'Is there anything more important we can help with?' 'How would you spend the money you might save?' These types of questions along with specific strategies in prevention (p79) are more likely to produce change than withering looks and lectures on lung cancer or legs dropping off. In summary: in any preventive activity, get the patient on your side: make him *want* to change. Once you have done this, address the topics in the BOX (among others). Sometimes referral to other agencies is needed—eg for genetic counselling, contraception, and preconception advice (OHCS p2).

Examples of prevention

Primary prevention: (preventing occurrence)

Vaccination
Quit smoking advice
Binge drinking advice
Healthy eating advice
Safe(r) sex advice (HIV)
Screening for hypertension
Preconception folic acid to prevent spina bifida
Fluoride in water (caries)

Secondary prevention: (screening for 1st stages)

Cervical cytology
Mammography
Proteinuria in pre-eclampsia
Microalbuminuria in DM
Colonoscopy for polyps
Densitometry (osteoporosis)
Diet advice in impaired fasting glycaemia

Tertiary prevention: (preventing complications)

Aspirin after a stroke
Statins in angina
Retinal photography in DM
Hip protectors after falls
'Don't go barefoot' in those with diabetic neuropathy
Vitamin D in osteoporosis

The law of unintended consequences (Sod's law, p646)

decrees that those whom you have to persuade the hardest to accept prevention by screening will be those to whom a complication befalls—such as colon perforation during colonoscopy to prevent cancers in those with UC or polyps. Or endoscopy will find an area of possible cancer in someone with Barrett's oesophagus (p686)—and a fit person dies of a post-op complication (oesophagectomy is dangerous). With this in mind, concentrate on those preventive activities which are simple, cheap, and have a complication rate approaching zero.

Individualized risk communication

Risk communication which is done thoughtlessly and only dwelling on positive aspects can lead to bitterness, anger, and litigation.[8] If communication is based on a person's individual risk factors for a condition (eg age, family history, smoking status, cholesterol level, eg using formulae such as that on p642), is risk communicated in ways that change behaviour? A 2003 Cochrane meta-analysis[9] suggests 'not necessarily' (although uptake of screening tests *is* improved). At least this technique promotes dialogue, and dialogue opens doors, minds, and possibilities for choice. ***Informed participation*** is the aim, not passive acceptance of advice. It does not make much difference whether information is given as an absolute risk, or as a risk score, or categorized as high, medium, or low risk. See also 'Consent' p554.

Is this new drug any good? Analysis & meta-analysis

Research is a booming enterprise as seen from the inside (publications, impact factors, citations, grant income, large teams etc)[1]—but $billions go in and not much comes out. Very occasionally we recommend a new drug: on what grounds?

1. Does the research paper give a clear, clinically significant answer as well as a statistically significant answer in patients similar to those I treat?
2. Is the journal peer reviewed? Experts vet the paper before release (an imperfect process, as they have unknown axes to grind ± competing interests).
3. Are the statistical analyses valid? Much must be taken on trust as many analyses depend on sophisticated computing. Few papers, unfortunately, present 'raw' data. Look out for obvious faults by asking questions such as:
   - Is the sample large enough to detect a clinically important difference, say a 20% drop in deaths from disease X? If the sample is small, the chance of missing such a difference is high. In order to reduce this chance to less than 5%, and if disease X has a mortality of 10%, >10,000 patients would need to be randomized. If a small trial which lacks power (the ability to detect true differences) *does* give 'positive' results, the size of the difference between the groups is likely to be exaggerated. (This is type I error; a type II error applies to results which indicate that there is no effect, when in fact there is.) ▸So beware even quite big trials which purport to show that a new drug is as effective as an established treatment.
   - Were the compared groups chosen randomly? Did randomization produce groups that were well matched? Were the treatments being compared carried out by practitioners equally skilled in each treatment?
   - Was the study 'double blind' (both patient and doctor are unaware of which treatment the patient is having)? Could either have told which was given, eg by the metabolic effects of the drug?
   - Was the study placebo- controlled? Good research can go on outside the realm of double-blind, randomized trials, but you need to be more careful in drawing conclusions—eg for intermittent symptoms, a bad time (prompting a consultation) is followed by a good time, making any treatment given in the bad phase appear effective. ***Regression towards the mean*** occurs in many areas, eg repeated BP measurement: because of transitory or random effects, most people having a high value today will have a less high value tomorrow— and most of those having a low value today will have a less extreme value tomorrow. This concept works at the bedside: if someone who is drowsy after a head injury has a high BP, and the next measurements are *higher still*, ie no regression to the mean, then this suggests a 'real' effect, such as ICP↑.
   - Has time been allowed for criticism of the research to appear in the correspondence columns of the journal in question?
4. If I were the patient, would I want the new treatment?
5. What has the *National Institute for Clinical Excellence*[UK] (NICE) said? Note that NICE quite often changes its mind—a problem with all intelligent organizations.

Meta-analyses

Systematic merging of similar trials *may* explain data inconsistencies. It is quicker and cheaper than doing new studies, and can establish generalizability of research.[10] *Be cautious!* In one study looking at recommendations of meta-analyses where there was a later 'definitive' big trial, it turned out that meta-analyses got it wrong 30% of the time, and 20% of good meta-analyses fail to avoid bias.[11] Don't assume that all meta-analyses, even those from the best stables, such as Cochrane, are free of bias owing to pharmaceutical funding.[12]

▸A big well-planned trial may be worth centuries of uncritical medical practice; but a week's experience on the wards may be more valuable than years reading journals. This is the paradox in medical education: how can we trust our own experiences knowing they are all anecdotal; how can we be open to novel ideas but avoid being merely fashionable? A stance of wary open-mindedness may serve us best.

[1] Charlton 2006 *Med Hypotheses* 66 1 *Is medical research a good way of spending money?* Possibly not.

Surviving house jobs

If some fool or visionary were to say that our aim should be to produce the greatest health and happiness for the greatest number of our patients, we would not expect to hear cheering from the tattered ranks of midnight house officers: rather, our ears are detecting a decimated groan—because these men and women know that there is something at stake in house-officership far more elemental than health or happiness: namely survival. Here we are talking about our own survival, not that of our patients. It is hard to think of a greater peacetime challenge than these first months on the wards. Within the first weeks, however brightly your armour shone, it will now be smeared and splattered if not with blood, then with the fallout from very many decisions which were taken without sufficient care and attention. Not that you were lazy, but *force majeure* on the part of Nature and the exigencies of ward life have, we are suddenly stunned to realize, taught us to be second-rate: for to insist on being first-rate in all areas is to sign a kind of death warrant for many of our patients, and, more pertinently for this page, for ourselves. Perfectionism cannot survive in our clinical world. To cope with this fact, or, to

put it less depressingly, to flourish in this new world, don't keep re-polishing your armour (what are the 10 causes of atrial fibrillation—or are there 11?), rather furnish your mind—and nourish your body (regular food and drink make those midnight groans of yours less intrusive). Do not voluntarily deny yourself the restorative power of sleep. A good nap is the order of the day—and for the nights, sleep for as long as possible. Remember that sleep is our natural state in which we were first created, and we only wake to feed our dreams.

We cannot prepare you for finding out that you do not much like the person you are becoming, and neither would we dream of imposing on our readers a recommended regimen of exercise, diet, and mental fitness. Finding out what can lead you through adversity is the art of living. What will you choose: physical fitness, martial arts, poetry, karate, the sermon on the mount, juggling, meditation, yoga, a love affair—or will you make an art form out of the ironic observation of your contemporaries?

Many nourish their inner person through a religious belief, and attend mosque, church, synagogue, or temple. A multicultural society provides diversity and room for all branches of expression. Bear in mind not to compare yourself with your contemporaries. Those who make the most noise are often *not waving but drowning*. Plan recreation in advance. Start thinking about senior house officer jobs, and speak to the Regional Postgraduate Advisor in the specialty you select. Such enquiries supply energy to get you through the darker hours of house jobs, and may motivate you if the going gets tough. Not that this is any guarantee that the plans will work, but if your yoga, your sermons, and your fitness regimens turn to ashes in your mouth, then at least you will know the direction in which to spit. House jobs are not just a phase to get through and to enjoy where possible (there are often *many* such possibilities); they are also the anvil on which we are beaten into a new and perhaps rather uncomfortable shape. Luckily not all of us are made of iron and steel so there is a fair chance that, in due course, we will spring back into something resembling our normal shape, and, in so doing, we may come to realize that it was our weaknesses, not our strengths, which served us best.

House jobs can encompass tremendous up-and-down swings in energy, motivation, and mood, which can be precipitated by small incidents. If you are depressed for more than a day, speak to a sympathetic friend, partner, or counsellor to help you put it in perspective. ▸When in doubt, communicate.

Quality, QALYs, and the interpretation of dreams

Resource allocation: who gets what

Resource allocation is about cutting the health cake—whose size is *given*. What slice should go to transplants, new joints, and services for dementia? Cynics would say that this depends on how vociferous each group of patients (or doctors) is. Others try to find a rational way to allocate resources. Health economists (econocrats) have invented the QALY for this purpose. NB: Focusing on how to cut the cake diverts attention from how large the cake should be (is it better to spend money on space exploration or incontinence pads?)

How much is a life worth?

Some countries will spend $2-10 million to find a man on a life-raft; others will spend nothing ('he's just one more mouth to feed').[13] [14] Totalitarian capitalist states (eg China) will take a different view to liberal democracies. In France, one life is worth a hundred cherry trees, if the blossom is fine.[15]

What is a QALY?

The essence of a QALY (Quality Adjusted Life Year) is that it takes a year of healthy life expectancy to be worth 1, but regards a year of unhealthy life expectancy to be worth <1. Its exact value is lower the worse the quality of life of the unhealthy person.[16] If a patient is likely to live for 8yrs in perfect health on an old drug, he gains 8 QALYs; if a new drug would give him 16yrs but at a quality of life rated by him at only 25% of the maximum, he would gain only 4 QALYs. The dream of a health economist is to buy most QALYs for his budget. As a rule of thumb, some heath assessment organizations (NICE[UK], controversially) *sometimes* keep an arbitrary figure in their head (such as £30,000/QALY).[17] If an intervention costs more than this, the reasons for recommending it have to be all the more explicit.

Cost per QALY In various studies, with undeclared assumptions, this was (£):

GP advice to stop smoking	220	Kidney transplant	4710
Preventing stroke by BP treatment	940	Breast cancer screening	5780
Pacemaker implantation	1100	Infliximab in Crohn's [18]	6700
Valve replaced		Heart transplant	7840

	(eg for aortic stenosis)		1140	Home dialysis	17,260
Hip replacement (♀ aged 60-69) [19]			1470	Brain tumour surgery	107,780
CABG for LAD stenosis (p135)	2090	Interferon in MS (p488)		834,000	

QALYs *do* help in rationing, but problems include pricing and invidiousness in choosing between the health of different people; a *huge* snag is that if we accept that the quality of our life is the quality of our relationships (Anthony Robbins), and that the value of relationships is unquantifiable (1 wife is good, but 2 wives are not *exactly* twice as good),[1] then we can see why bodies such as NICE get excoriated over issues such as dementia drugs, when apparently small objective improvements can cause disproportionate joy, as when a demented man becomes able to recall his son's name.[20] [21]

The inverse care law and distributive justice

> ***'Availability of good medical care tends to vary inversely with the need for it in the population served. This operates more completely where medical care is most exposed to market forces … The market distribution of medical care exaggerates maldistribution of medical resources.'***

There is much evidence in support of this famous thesis formulated by Tudor Hart,[22] and there is no doubt that if one wants to make a positive contribution to health, it is no good just discovering pathways, blocking receptors, and inventing drugs. The more this is done, the more urgent the need for distributive justice—that unyielding and perpetually problematic benchmark against which we are all judged.

If those who shout loudest get heard first, we need to know when to train our ears to be deaf—eg when deciding who to put on urgent and non-urgent operating lists. Unconsciously, we calibrate our lives to reduce stress. If we can learn the art of selective deafness, this need for the stressless life becomes less pressing, and, in the silence, we may come to know our professional values a little better.

Psychiatry on medical and surgical wards

▸Psychopathology is common in colleagues, patients, and relatives. ▸Seek help for your own problems. Find a sympathetic GP and register with her. You are not the best person to plan your assessment, treatment, and referral.

Current mental state

▸OHCS p324. 'Move gently through her thoughts, as one might explore a new garden.[1] [23] What is in bloom now? Where do those paths lead? What is under that stone? ***Focus on:*** Appearance; behaviour (anxious? suspicious?); speech (rate; content); mood; beliefs; hallucinations; orientation; memory (current affairs recall, monarch's name); concentration. Note the patient's insight and degree of rapport. Non-verbal behaviour often gives more valid clues than words alone.

Depression

This is common, and often ignored, at great cost to wellbeing. Thinking 'I would be depressed in her situation' may sap our will to help, and as biological features (early waking, ↓appetite, ↓weight, loss of interest in sex and hobbies) are common on all wards, we may not realize just how bad things have got. ***The 2 'best questions' are:***[24] *'Have you been bothered by feeling down, depressed, or hopeless in the last month?*' If so, ask '*Have you been bothered by lack of interest or pleasure in doing things?*' If 'yes', depression is likely. There may also be guilt and feelings of worthlessness. ▸*Don't think it's not your job to recognize and treat depression*. It is as important as pain. Try to arrange activities to boost the patient's morale and confidence, and keep him in touch with his fellows. Communicate your thoughts to other team members: nurses, physio- and occupational therapists, as well as relatives, if the patient wishes. Among these, your patient may find a kindred spirit who can give insight and support. ▸If in doubt, try an antidepressant, and see if it helps, eg dosulepin 25-75mg at night, or lofepramine[2] 70mg/8-12h PO, if no hepatic or severe renal impairment. For *selective serotonin reuptake inhibitors* (eg fluoxetine, 20mg/24h), see OHCS p340. Remember that cognitive interventions are just as important as drugs (OHCS p370), so liaise with the patient's GP before discharge.

Alcohol

This is a common cause of problems on the ward (both the results of abuse and the effects of withdrawal). See p274.

The violent patient

Recognize early warning signs: tachypnoea, clenched fists, shouting, chanting, restlessness, repetitive movements, pacing, gesticulations. Your own intuition may be helpful here. At the first hint of violence, get help. If alone, make sure you are nearer the door than the patient.

- Do not be alone with the patient; summon the police or porters if needed.
- Try calming and talking with the patient. Do not touch him. Use your body language to reassure (sitting back, open palms, attentive).
- Get his consent; if unforthcoming, emergency treatment can still be given to save life, or serious deterioration. Enlist the help of nurses who know the patient.
- Use minimum force to achieve his welfare (but this may entail 6 strong men).

Causes: *anger*, *alcohol intoxication*, *drugs* (recreational; prescribed), *hypoglycaemia*, *delirium* (p476), *psychosis*. Do blood glucose, or give IV dextrose stat (p816). Before further tests, haloperidol may be needed: ~2mg IM (up to 10 or, rarely, 18mg stat; monitor pulse, T°, and BP every 15min-4h); maximum daily dose: 18mg.

If a rational adult refuses vital treatment, it may be as well to respect this decision, provided he is 'competent', ie he understands the consequences of his actions, and what you are telling him, is able to retain this information, and form the belief that it is true. Competence is rarely all or nothing, so don't hesitate to get the opinion of others. Enlist the persuasive powers of someone the patient respects.

Mental Health Acts

Familiarize yourself with local procedures and laws pertaining to your country before your period of duty starts (OHCS p402). In England, Common Law allows restraining a patient who is being violent on the ward.

The elderly patient in hospital

▸Only in the past 3 centuries has life-expectancy risen much above 40 years. *An ageing population is a sign of successful social, health, and economic policies*.[25]

Healthy ageing

is not a contradiction as health is not just 'complete mental and physical wellbeing (WHO) but also a process of adaptation, to changing environments, to growing up and ageing, to healing when damaged, to suffering, and death. Health embraces the future so includes anguish and the inner resources to live with it' (Illich, OHCS p470). ▸Ageing is a continuum and is malleable, representing cumulative effects of stressors (eg free radicals) and acquired mechanisms for dealing with them (as important as genetic effects).

Beware ageism! Old age is associated with disease but doesn't cause it *per se*.[26] Any deterioration is from treatable disease *until proved otherwise*.

1. Contrary to stereotype, most old people are fit.[27] 80% of those over 85yrs old do not live in institutions (95% if aged ~65yrs); 70% manage stairs and can bathe without help. Number of years in education and the number of co-morbidities correlate inversely with difficulties in the activities of daily living.[1]
2. With any problem, find the cause; don't always be thinking: *this is simply ageing*. Look (within reason) for treatable disease, ↓fitness, and social factors.
3. Do not restrict treatment simply because of age. Old people vary. Age alone is a poor predictor of outcome and should not be used as a substitute for careful assessment of each patient's potential for benefit and risk.[28]

Characteristics of disease in old age

There are differences of emphasis in the approach to old people compared with young people.[29]

1. ***Multiple pathology:*** Several disease processes may coincide: find out which impinge on each complaint (eg senile cataract + arthritis = falls).
2. ***Multiple causes:*** One problem may have several causes. Treating each alone may do little good; treating all may be of much benefit.[30]
3. ***Non-specific presentations:*** Some presentations are common in old people—eg the 'geriatric giants':[31] incontinence (p604);[32] immobility; instability (falls); and dementia/confusion (p476 & p478). Any disease may present with these. Also, typical signs and symptoms may be absent (myocardial infarction without chest pain; pneumonia, but no cough, fever, or sputum).
4. ***Rapid worsening if treatment is delayed:*** Complications are common.
5. ***More time is required for recovery:*** Points 4-6 reflect impairment in homeostatic mechanisms and loss of 'physiological reserve'.
6. ***Impaired metabolism and excretion of drugs:*** Doses may need lowering, not least because there is often less tolerance to side-effects.
7. ***Social factors:*** These are central in aiding recovery and return to home.

Special points

Assess all disabilities; get home details, eg stairs; access to toilet.

- Drug concordance (p3): how many different tablets can he cope with? Probably not many more than 2. So which are the most important drugs? You may have to ignore other desirable remedies, or enlist the help of a friend, a spouse, or a pharmacist (who can batch morning, noon, and night doses in compartmentalized containers so complex regimens may be reduced to 'take the morning compartment when you get up, the noon compartment before lunch, etc').
- Social network (regular visitors; family and friends).

- Care details: what services are in operation?—meals delivered; community psychiatric or district nurse—who else is involved in the care?
- Speak to others (relatives; neighbours; carers; GP).
- Make a ***careplan***. Include nutrition. If food is dumped beside a blind man, and no one helps cut it up, he may starve. A passing doctor may arrange a CT 'for cachexia', when what he needs is food and cataract surgery.

On examination:

Do BP lying and standing (postural drop >20/10mmHg " falls). Rectal exam: impaction " overflow incontinence. Detailed CNS exam may be needed if presentation is non-specific. This tires patients, so consider doing in batches.

Beyond the hospital: planning successful discharges (How to live and be frail in the community)

▸*Start planning discharge from day 1.* A very common question on ward-rounds is: 'Will this patient get on OK at home?—we've got him as good as we can, but is discharge safe?' In answering this take into account:

- Does the patient live alone? Does any carer have support? Is he/she already exhausted by other duties (eg a handicapped toddler)?
- Is your patient in fact a carer for someone else even more frail?
- Most patients want to go home promptly. If not, find out why.
- Is the accommodation suitable? Stairs? Toilet on same floor?
- If toilet access is difficult, can he transfer from chair to commode?
- Can he open a tin, use the phone, plug in a kettle, cook soup?
- Is the family supportive—in theory or in practice?
- Are the neighbours friendly? 'But I would not trouble them'. Explore the validity of this sentiment by asking if they would want to know if they were reasonably fit, and a neighbour were in need.
- Are social services and community geriatric services well integrated? Or will the person who provides the lunch ignore the patient if she cannot gain access? Proper *case management programmes* with defined responsibilities, entailing integration of social and geriatric services really can help *and* save money (~20%).[33] Such integration is rare[34] but is possible in the UK thanks partly to the advent of Primary Care Trusts with overarching responsibilities for *both* medical *and* social care.

UK NHS national service framework (NSF) for older people

There are 8 standards of care

http://bmj.com/cgi/content/full/326/7402/1300

1. *Rooting out age discrimination:* NHS services are to be provided regardless of age, on the basis of need alone. Social services will not use age in eligibility criteria or policies, to restrict access to available services.
2. *Person-centred care:* NHS services treat older people as individuals and enable them to make choices about their own care
3. *Intermediate care:* Older people will have access to intermediate care services at home or in designated care settings, to promote their independence by providing enhanced services from the NHS and councils to prevent unnecessary hospital admission. Rehabilitation services will enable early discharge from hospital and prevent premature or unnecessary admission to long-term residential care.
4. *General hospital care:* Older people's care in hospital is delivered through appropriate specialist care and by hospital staff who have the right set of skills to meet their needs.
5. *Stroke:* People who are thought to have had a stroke must have access to diagnostic services, and be treated appropriately by a specialist stroke service, and subsequently, with their carers, participate in a multi-disciplinary programme of secondary prevention and rehabilitation.
6. *Falls:* The NHS, working in partnership with councils, is required to take action to prevent falls and reduce fractures in older people and provide advice on fall prevention, through a specialist falls service.
7. *Mental health in older people* is to be promoted by access to integrated mental health services (from the NHS or councils) to ensure effective diagnosis, treatment, and support, for them and their carers.
8. *The promotion of health and active life in older age:* The health and well-being of older people are promoted through a coordinated programme of action led by the NHS with support from councils.

NSFS ATTEMPT TO IMPROVE SERVICES BY CENTRAL COMMAND AND CONTROL: THE LEAST SUBTLE AND EFFECTIVE METHOO

On being busy: Corrigan's secret door

Unstoppable demands, increasing expectations as to what medical care should bring, the rising number of elderly patients, coupled with the introduction of new and complex treatments all conspire, it might be thought, to make doctors ever busier. In fact, doctors have always been busy people. Sir James Paget, for example, would regularly see more than 60 patients each day, sometimes travelling many miles to their bedside. Sir Dominic Corrigan was so busy 160 years ago that he had to have a secret door made in his consulting room so that he could escape from the ever-growing queue of eager patients.

We are all familiar with the phenomenon of being hopelessly over-stretched, and of wanting Corrigan's secret door. Competing, urgent, and simultaneous demands make carrying out any task all but impossible: the house officer is trying to put up an intravenous infusion on a shocked patient when his 'bleep' sounds. On his way to the phone a patient is falling out of bed, being held in, apparently, only by his visibly lengthening catheter (which had taken the house officer an hour to insert). He knows he should stop to help but, instead, as he picks up the phone, he starts to tell Sister about 'this man dangling from his catheter' (knowing in his heart that the worst will have already happened). But he is interrupted by a thud coming from the bed of the lady who has just had her varicose veins attended to: however, it is not her, but her visiting husband who has collapsed and is now having a seizure. At this moment his cardiac arrest 'bleep' goes off, summoning him to some other patient. In despair, he turns to Sister and groans: 'There must be some way out of here!'

At times like this we all need Corrigan to take us by the shadow of our hand, and walk with us through a metaphorical secret door, into a calm inner world. To enable this to happen, make things as easy as possible for yourself.

First, however lonely you feel, you are not usually alone. Do not pride yourself on not asking for help. If a decision is a hard one, share it with a colleague. Second, take any chance you get to sit down and rest. Have a cup of coffee with other members of staff, or with a friendly patient (patients are sources of renewal, not just devourers of your energies). Third, do not miss meals. If there is no time to go to the canteen, ensure that food is put aside for you to eat when you can: hard work and sleeplessness are twice as bad when you are hungry. Fourth, avoid making work for yourself. It is too easy for junior doctors, trapped in their image of excessive work and blackmailed by misplaced guilt, to remain on the wards reclerking patients, rewriting notes, or rechecking results at an hour when the priority should be caring for themselves. Fifth, when a bad part of the rota is looming, plan a good time for when you are off duty, to look forward to during the long nights.

However busy the 'on take', your period of duty will end. For you, as for Macbeth:

> *Come what come may, Time and the hour runs through the roughest day.*

Riding the wave

In *Macbeth*, toil and trouble go hand in hand, but sometimes we work best when we are busy. This is recognized in the aphorism that *if you want a job done quickly, give it to a busy (wo)man*. Observe your colleagues and yourself during a busy day. Sometimes our energy achieves nothing but our own inundation. At other times, by jettisoning everything non-essential, we get airborne, and accomplish marvellous feats. But note that what keeps us riding the wave of a busy day is not what we jettison but what we retain: humour, courtesy, and an ability to twinkle. A smile causes no delays, and reaches far beyond our lips.

Health and medical ethics

In our public medical personas, we often act as though morality consisted only in following society's conventions: we do this not so much out of laziness but because we recognize that it is better that the public think of doctors as old-fashioned or stupid, than that they should think us evil. But in the silences of our consultations, when it is we ourselves who are under the microscope, then, wriggle as we may, we cannot escape our destiny, which is to lead as often as to follow, in the sphere of ethics. To do this, we need to return to first principles, and not go with the flow of society's expectations. To give us courage in this enterprise, we can recall the aviator's and the seagull's law: it is only by *facing* the prevailing wind that we can become airborne, and achieve a new vantage point from which to survey our world.

Our analysis

starts with our aim: to do good by making people healthy. *Good*[1] is the most general term of commendation, and entails four cardinal duties:

1. Not doing harm. We owe this duty to all people, not just our patients.[35]
2. Doing good by positive actions. We particularly owe this to our patients.
3. Promoting justice—ie distributing scarce resources fairly (p12) and respecting rights: legal rights, rights to confidentiality, rights to be informed, to be offered all the options, and to be told the truth.
4. Promoting autonomy. This is not universally recognized; in some cultures facing starvation, for example, it may be irrelevant, or even be considered subversive.

Health

entails being sound in body and mind, and having powers of growth, development, healing, and regeneration. *How many people have you made healthy (or at least healthier) today?* And in achieving this, *how many cardinal duties have you ignored?* Herein lies a central feature of medicine. We cannot spend long on the wards or in our surgeries trying to 'make people healthy' before we have breached every cardinal duty—particularly (3) and (4). Does it matter? What is the point of having principles if they are regularly ignored? The point of having them is to provide a context for our negotiations with patients. If we want to be better doctors, there are many worse places to start than by trying to put these principles into action. Inevitably, when we try to, there are times when they conflict with each other. What should guide us when these principles conflict? It is not just a case of deciding off the top of one's head on the basis of the above analysis. It may be worthwhile aspiring to a synthesis—if you have the time (time will so often be what you do *not* have; but so often, in retrospect, when things have gone wrong, you realize that they would not have done so if you had *made* time).

Synthesis

When we must act in the face of two conflicting duties, one of the duties is *not* a duty. How do we tell which one? Trying to find out involves getting to know our patients, and asking some questions:

- Are the patient's wishes being complied with?
- What do your colleagues think? What do the relatives think? Ask the patient's permission first. Have they his or her best interests at heart?
- Is it desirable that the reason for an action be universalizable? (That is, if I say this person is too old for such-and-such an operation, am I happy to make this a general rule for everyone?—Kant's 'law'.)[2]
- If an investigative journalist were to sit on a sulcus of mine, having full knowledge of my thoughts and actions, would she be bored or would she be composing vitriol for tomorrow's newspapers? If so, can I answer her, point for point? Am I happy with my answers? Or are they merely tactical devices?
- What would a patient's representative think—eg the elected chairman of a patient's participation group (OHCS p496)? These opinions are valuable as they are readily available (if a local group exists) and they can stop decision-making from becoming dangerously medicalized.

[1] Don't think of good and evil as forever opposite; good can come out of evil, and vice versa: this fundamental mix-up explains why we learn more from our

dissolute patients than we do from saints.

[2] There are problems with universalizability: only intuition can suggest how to resolve conflicts between competing universalizable principles. Also, there is a sense in which all ethical dilemmas are unique, so no moral rules are possible or required—so they *cannot* be universal (Sartre, Nietzsche).

Difficult patients

'Unless both the doctor and the patient become a problem to each other, no solution is found.'[1] Jung's aphorism is untrue for half our waking lives: for an anaesthetist eg there is no need for the patient to become a problem in order for the anaesthetic to work. But, as with all the best aphorisms, being untrue is the least of the problems they cause us. Great aphorisms signify because they unsettle. Our settled and smug satisfaction at finishing a period of duty without any problems is so often a sign of failure. We have kept the chaos at bay, whereas, if we were greater men or women, we would have embraced it. Half our waking professional lives we spend as if asleep, on automatic, following protocols or guidelines to some trite destination—or else we are dreaming of what we could do if we had more time, proper resources, and perhaps a different set of colleagues. But if we had Jung in our pockets he would be shaking us awake, derailing our guidelines, and saluting our attempts to risk genuine interactions with our patients, however much of a mess we make of it, and however much pain we cause and receive. (Pain, after all, is the inevitable companion to lives led authentically.[2]) To the unreflective doctor, and to all average minds, this interaction is anathema, to be avoided at all costs, because it leads us away from anaesthesia, to the unpredictable, and to destinations which are unknown.

So, every so often, try being pleased to have difficult patients: those who question us, those who do not respond to our treatments, or who complain when these treatments *do* work. Very often, it will seem that whatever you say it is wrong: misunderstood, misquoted, and mangled by the mind you are confronting— perhaps because of fear, loneliness, or past experiences which you can only guess at. If this is happening, *shut up*—but don't *give up*. Stick with your patient. Listen to what he or she is saying and not saying. And when you have understood your patient a bit more, negotiate, cajole, and even argue—but don't bully or blackmail ('If you do not let your daughter have the operation she needs, I'll tell her just what sort of a mother you are …'). When you find yourself turning to walk away from your patient, turn back and say 'This is not going very well, is it? Can we start again?' And don't hesitate to call in your colleagues' help: not to win by force of numbers, but to see if a different approach might bear fruit. By this process, you and your patient may grow in stature. You may even end up with a truly satisfied patient. And a satisfied patient is worth a thousand protocols.

Medicine, art, and the humanities

Let us start with an elementary observation: *there are no justly famous living doctors*; indeed *there are no famous dead doctors*. The most famous doctors are either villains or those immortalized in literature—eg Dr Watson, Dr Frankenstein, and Dr Faustus.[1] Hereby we demonstrate the power of the written word. And it *is* an extraordinary power. When we curl up in an armchair and read for pleasure, we open the portals of our minds because we are alone. While we are reading, there is no point in dissembling. We confront our subject matter with a steady eye because we believe, that, while reading to ourselves, we cannot be judged. Then, suddenly, when we are at our most open and defenceless, literature takes us by the throat— and that eye which was so steady and confident a few minutes ago is now perhaps misting over, or our heart is missing a beat, or our skin is covered in a goose-flesh more papular than ever a Siberian winter produced. Once we have been on earth for a few decades, not much in our mundane world sends shivers down our spines, but the power of worlds of literature and art to do this ever grows.

There are, of course, doctors who are quite well known: Arthur Conan Doyle, William Carlos Williams, Somerset Maugham, and Anton Chekhov, and they are all artists. What about Sigmund Freud? Here is the exception which proves the rule— proves in the sense of testing, for he is not really an exception. We can accept him among the great only in so far as we view his oeuvre as an artistic oeuvre, rather than as a scientific one. Science has progressed for years without Freud, but, as art, his work and insights (such as the subconscious, which he 'invented') will survive: and survival, as Bernard Shaw pointed out, is the only test of greatness.

The reason for the ascendancy of art over science is simple. We scientists, in our humble way, are only interested in explaining reality. Artists are good at explaining reality too: but they also *create* it. Our most powerful impressions are produced in our minds not by simple sensations but by the association of ideas. It is a preeminent feature of the human mind that it revels in seeing something as, or through, something else: life refracted through experience, light refracted through jewels, or a walk through the woods transmuted into a Pastoral Symphony. Ours is a world of metaphor, fantasy, and deceit.

What has all this to do with the day-to-day practice of medicine? The answer lies in the word 'defenceless' above. When we read alone and for pleasure, our defences are down—and we hide nothing from the great characters of fiction. In our consulting rooms, and on the ward, we so often do our best to hide everything, beneath the white coat, or the avuncular bedside manner. So often, a professional detachment is all that is left after all those years inured to the foibles, fallacies, and frictions of our patients' tragic lives. It is at the point where art and medicine collide, that doctors can re-attach themselves to the human race and re-feel those emotions which motivate or terrify our patients. We all have an Achilles heel: that part of our inner self which was not rendered forever invulnerable to mortal cares when we were dipped in the waters of the river Styx as it flowed down the wards of our first disillusion. Art and literature, among other things, may enable this Achilles heel to be the means of our survival as thinking, sentient beings, capable of maintaining a sympathetic sensibility to our patients.

The American approach is to create Professors of Literature-in-Medicine and to conjure with concepts such as *the patient as text*, and most American medical schools do courses in literature in an attempt to inculcate ethical reasoning and speculation. Here, we simply intend to demonstrate, albeit imperfectly, in our writings and in our practice of medicine, that *every* contact with patients has an ethical and artistic dimension, as well as a technical one.

Editors: Longmore, Murray; Wilkinson, Ian B; Turmezei, Tom; Cheung, Chee Kay
Title: *Oxford Handbook of Clinical Medicine, 7th Edition*

2

Clinical Skills

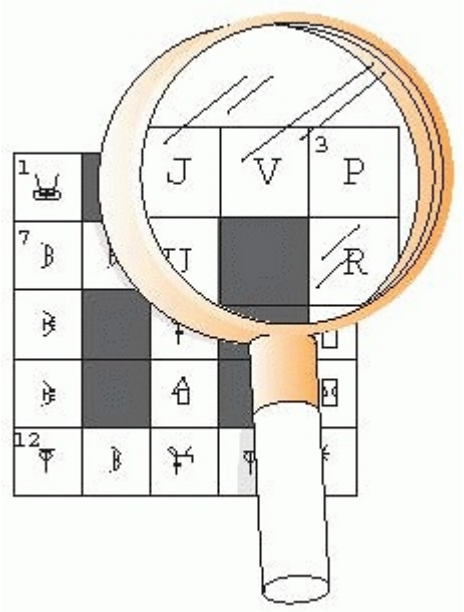


Fig 1. Skills acquired over years of training help us to unravel the clues that we pick up during history-taking and clinical examination. However, the clues are rarely straight: most are cryptic (eg clubbing, p56, caused by several underlying processes). Just as with crosswords, the satisfaction of completing the whole puzzle comes only after having put together the network of solved clues successfully. With practice we get quicker, slicker and better, just like the veteran solver. No wonder our elders seem to make such easy work of it all—see BOX opposite, *The patient now waiting for you …*

Advice and experience

▸The way to learn physical signs is at the bedside, with guidance from an experienced colleague. This chapter is not intended as a substitute for this process: it is simply an *aide-mémoire*.

▸We ask questions to get information to help with differential diagnosis. But we also ask questions to find out about the inner life and past exploits of our patients, so that they do not bore us, and so that we can respect them as individuals. The patient is likely to notice and reciprocate this respect, and this reciprocation is the foundation of most of our therapeutic endeavours. Our challenge is to identify with as broad a range of humanity as possible, without getting exhausted by the scale of this enterprise.

▸'Truth lies not only in what is said, but also in who says it, to whom, why, how, and under what circumstances.'

Vaclav Havel *Letters To Olga* (138)

The patient now waiting for you in cubicle 9 …

The first news of your next patient will often be via a phone call: 'There's an MI on the way in'—or 'There's someone dementing in cubicle 9'—or 'Can you take the overdose in resus?' On hearing such sanitized, dehumanized descriptions, our minds will start painting pictures, and the tone of these messages tends to colour these pictures. So when we arrive at the bedside, our mind is far from a *tabula rasa* or blank canvas on which the patient can paint his woes.

The mind is always painting pictures, filling in gaps, and falling into traps. Perception is an active process, for, as Marcel Proust, that life-long all-knowing patient, observed:[1]

> *We never see the people who are dear to us save in the animated system, the perpetual motion of our incessant love for them, which before allowing the images that their faces present to reach us catches them in its vortex, flings them back upon the idea that we have always had of them, makes them adhere to it, coincide with it.*

So if you want to know your patient, take snapshots of him from various angles, and briefly contemplate him in the round before Proust's vortex whisks you off track. Divest yourself of those prejudices and expectations which all good diagnosticians somehow ignore, and you will be all set for a Gestalt recognition (p188) of incipient myxoedema (the cause of the dementia in cubicle 9—see p189), jaundice, anaemia, or, perhaps more important, the recognition that the person in front of you is frightened, failing, or dying.

Embracing the oral tradition

The written word has been with us only for a few thousand years. Even during this phase in history, epics, stories, methods, and teaching have still been passed on by word of mouth through the practice of oral tradition. It may be surprising, therefore, that we rely so much on the written word, given that so many important nuances can be missed.

In a working culture that has shifted from continuing care by multi-talented individuals towards an ever-changing team in a string of handovers, we might do well to uphold this oral tradition. So to keep the chain strong and the care continuous, we should in the first instance strive to communicate face to face, at least when practical. In the least, to remain politic, we should continue to talk to each other—see MINIBOX.

Encourage 'The good…'

- Face to face handover
- Clear histories
- Civility

Avoid '…the bad…'

- Written handover
- Hurrying
- Abruptness

Prevent '…the ugly'

- Mismanagement
- Missed investigations, results and procedures
- Upset patients, carers and relatives

Taking a history

Taking (or receiving) histories is what most of us spend most of our professional life doing, and it is worth doing well. A good history is the biggest step towards the correct diagnosis. History-taking, examination, and treatment of a patient begin the moment one reaches the bedside. (The divisions imposed by our page titles are somewhat misleading). Try to put the patient at ease: a good rapport may relieve distress on its own. It often helps to shake hands. Always introduce yourself and check whether the patient is comfortable. Be conversational rather than interrogative in tone. General questions (age, occupation, marital status) help break the ice and assess mental functions—sometimes important to establish early on.

Presenting complaint (PC)

'What has been the trouble recently?' Record the patient's own words rather than eg 'dyspnoea'.

History of presenting complaint (HPC)

When did it start? What was the first thing noticed? Progress since then. Ever had it before? '**SOCRATES**' questions: **s**ite; **o**nset (gradual, sudden); **c**haracter; **r**adiation; **a**ssociations (eg nausea, sweating); **t**iming of pain/duration; **e**xacerbating and alleviating factors; **s**everity (eg scale of 1-10, compared with childbirth, or with worst ever previous pain).

Direct questioning (DQ)

Specific questions about the diagnosis you have in mind (+ its risk factors, eg travel—p378) and a review of the relevant system.

Past medical history (PMH)

Ever in hospital? Illnesses? Operations? Ask specifically about diabetes, asthma, bronchitis, TB, jaundice, rheumatic fever, high BP, heart disease, stroke, epilepsy, peptic ulcer disease, anaesthetic problems.

Drug history (DH)

Any tablets, injections? Any 'off-the-shelf' or 'over-the-counter' drugs? Herbal remedies, the Pill? Ask the features of allergies: it may not have been one, but on the other hand it may have been a minor reaction of sensitization (if any warning is given at all) before full-blown anaphylaxis.

Social history (SH)

Probe without prying. 'Who else is there at home?' Job. Marital status. Spouse's job and health. Housing—any stairs at home? Who visits— relatives, neighbours, GP, nurse? Are there any dependents at home? Mobility—any walking aids needed? Who does the cooking and shopping? What can the patient not do because of the illness? The social history is all too often seen as a dispensable adjunct, eg while the patient is being rushed to theatre, but vital clues may be missed about the quality of life and it is too late to ask when the surgeon's hand is deep in the belly and she is wondering how radical a procedure to perform. It is worth cultivating the skill of asking a few searching questions of the admitting family doctor while you are conversing on the phone. If you are both busy, do not waste time on things you will shortly verify yourself but tap his knowledge of the patient and his 'significant others'. Remember: the GP is likely to be a specialist in his patients, whom he may have known for decades. He may even hold a 'living will' or advance directive to reveal your patient's wishes if he cannot speak for himself.

Alcohol, tobacco, recreational drugs

How much? How long? When stopped? The CAGE questionnaire is useful as a screening test for alcoholism (p274). Quantify smoking in terms of **pack-years**: 20 cigarettes/day for 1 year equals 1 pack-year. Smoking is forbidden among Sikhs, so be tactful. We all like to present ourselves well, so be inclined to double any stated quantities (**Holt's 'law'**).

Family history (FH)

Areas of the family history may need detailed questioning, eg to determine if there is a significant family history of heart disease you need to ask about the health of the patient's grandfathers and male siblings, smoking, tendency to hypertension, hyperlipidaemia, and claudication before they were 60 years old, as well as ascertaining the cause of death. Ask about TB, diabetes, and other relevant diseases. See BOX. ▸**Be tactful when asking about a family history of malignancy.**

Functional enquiry

(p24) helps uncover undeclared symptoms. Some of this may already have been incorporated into the history.

▸Don't hesitate to retake the history after a few days: recollections change.

Drawing family trees to reveal dominantly inherited disease[1]

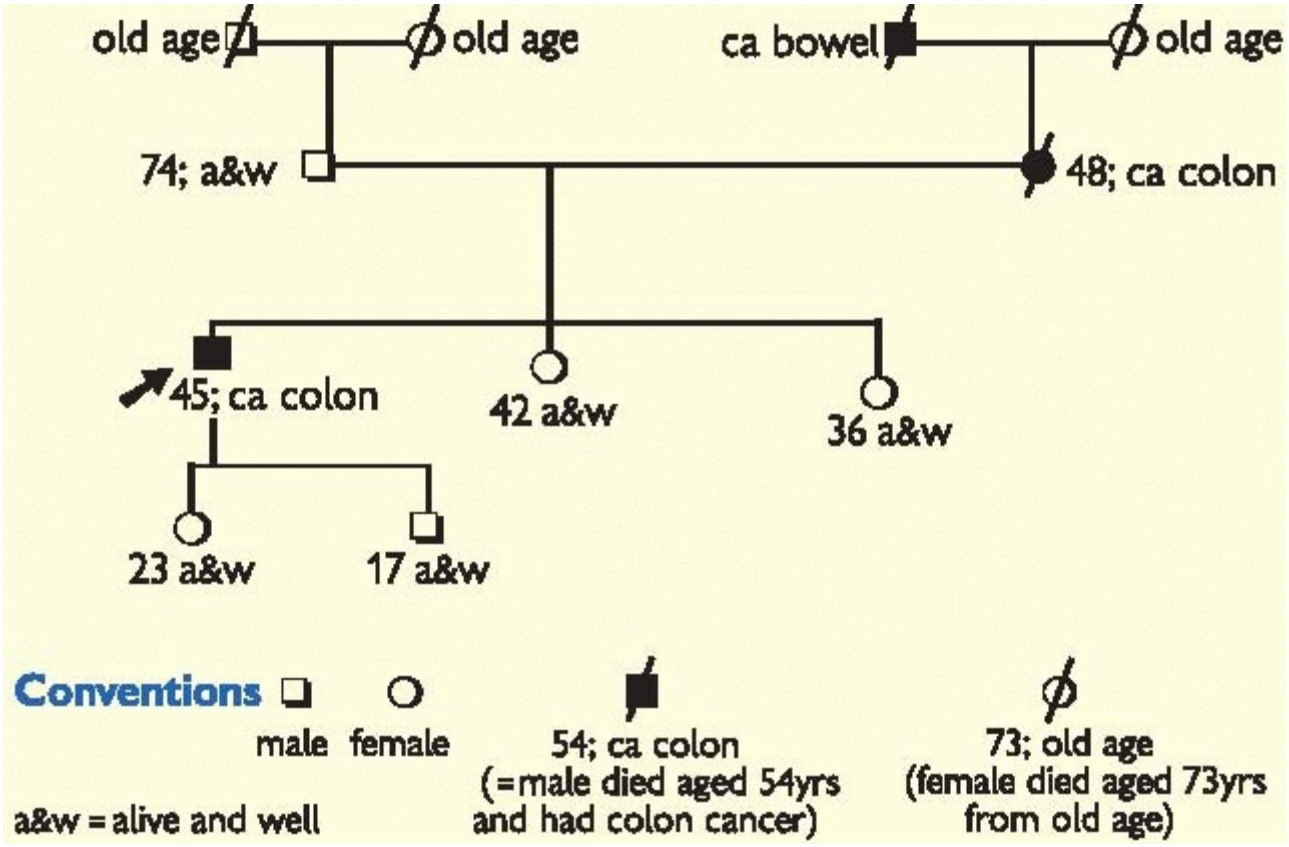
Advances in genetics are touching all branches of medicine. It is increasingly important for doctors to identify patients at high risk of genetic disease, and to make appropriate referrals. The key skill is drawing a family tree to help you structure a family history as follows:

1. Start with your patient. Draw a square for a male and a circle for a female. Add a small arrow (↗, see below) to show that this person is the *propositus* (the person through whom the family tree is ascertained).
2. Add your patient's parents, brothers, and sisters. Record basic information only, eg age, and if alive and well (a&w). If dead, note age and cause of

death, and pass an oblique stroke through that person's symbol.

3. Ask the key question 'Has anybody else in your family had a similar problem as yourself?', eg heart attack/angina/stroke/cancer. Ask only about the family of diseases that relate to your patient's main problem. Do not record a potted medical history for each family member: time is too short.
4. Extend the family tree upwards to include grandparents. If you haven't revealed a problem by now, go no further—you are unlikely to miss important familial disease. If your patient is elderly it may be impossible to obtain good information about grandparents. If so, fill out the family tree with your patient's uncles and aunts on both the mother's and father's sides.
5. Shade those in the family tree affected by the disease. • = an affected female; ▪= an affected male. This helps to show any genetic problem and, if there is one, will help demonstrate the pattern of inheritance.
6. If you have identified a familial susceptibility, or your patient has a recognized genetic disease, extend the family tree down to include children, to identify others who may be at risk, and who may benefit from screening. ▸You must find out who is pregnant in the family, or may soon be, and arrange appropriate genetic counselling (OHCS p154).

The family tree below shows these ideas at work and indicates that there is evidence for genetic risk of colon cancer, meriting referral to a geneticist.



THIS PAGE OWES MUCH TO DR HELEN FIRTH, WHO WE THANK.

Functional enquiry

Just as skilled acrobats are happy to work without safety nets, so also older clinicians may operate without the functional enquiry. But to do this you must be experienced enough to understand all the nuances of the presenting complaint.

General questions

may be the most significant, eg in TB, endocrine problems, or cancer: • Weight loss • Night sweats • Any lumps • Fatigue/malaise/lethargy • Sleeping pattern[1] • Appetite • Fevers • Itch or rash • Recent trauma[2]

Cardio-respiratory symptoms

Chest pain (p80). Exertional dyspnoea (=breathlessness): quantify exercise tolerance **and how it has changed**, eg stairs climbed, or distance walked, before onset of breathlessness. Paroxysmal nocturnal dyspnoea (PND). Orthopnoea, ie breathlessness on lying flat (a symptom of left ventricular failure): quantify in terms of number of pillows the patient must sleep on to prevent dyspnoea. Oedema. Palpitations (awareness of heartbeats). Cough. Sputum. Haemoptysis (coughing up blood). Wheeze.

Gut symptoms

Abdominal pain (constant or colicky, sharp or dull; site; radiation; duration; onset; severity; relationship to eating and bowel action; alleviating or exacerbating, or associated features). Other questions—think of symptoms throughout the GI tract, from mouth to anus:

- Swallowing (p232)
- Indigestion (p234)

- Nausea/vomiting (p232)
- Bowel habit (p238 & p240)
- Stool:
  - colour, consistency, blood, slime
  - difficulty flushing away (p272)
  - tenesmus or urgency

Tenesmus is the feeling of incomplete evacuation of the bowels (eg due to a tumour or irritable bowel syndrome). **Haematemesis** is vomiting blood. **Melaena** is altered (black) blood passed PR (p244), with a characteristic smell.

Genitourinary symptoms

Incontinence (stress or urge, p604). Dysuria (painful micturition). Haematuria (bloody micturition). Nocturia (needing to micturate at night). Frequency (frequent micturition) or polyuria (the frequent passing of large volumes of urine). Hesitancy (difficulty starting micturition). Terminal dribbling.

Vaginal discharge (p406). Menses: frequency, regularity, heavy or light, duration, painful. First day of last menstrual period (LMP). Number of pregnancies and births. Menarche. Menopause. Any chance of pregnancy now?

Neurological symptoms

Special senses:

Sight, hearing, smell, and taste. Seizures, faints, 'funny turns'. Headache. 'Pins and needles' (paraesthesiae) or numbness. Limb weakness ('Are your arms and legs weaker than normal?'), poor balance. Speech problems (p46). Sphincter disturbance. Higher mental function and psychiatric symptoms (p46-p49). The important thing is to assess function: what the patient can and cannot do at home, work, etc.

Musculoskeletal symptoms

Pain, stiffness, swelling of joints. Diurnal variation in symptoms (ie with time of day). Functional deficit.

Thyroid symptoms

Hyperthyroidism:

Prefers cold weather, bad tempered, sweaty, diarrhoea, oligomenorrhoea, weight↓ (though often ↑ appetite), tremor, palpitations, visual problems.

Hypothyroidism:

Depressed, slow, tired, thin hair, croaky voice, heavy periods, constipation, dry skin, prefers warm weather.

▸History-taking may seem deceptively easy, as if the patient knew the hard facts and the only problem was extracting them; but what a patient says is a mixture of hearsay ('she said I looked very pale'), innuendo ('you know, doctor, down below'), legend ('I suppose I bit my tongue; it was a real fit, you know'), exaggeration ('I didn't sleep a wink'), and improbabilities ('The Pope put a transmitter in my brain'). The great skill (and pleasure) in taking a history lies not in ignoring these garbled messages, but in making sense of them.

Presenting your findings—and the role of jargon [1]

We are forever presenting patients to our colleagues, almost never questioning the mechanisms and motivations which permeate these oral exchanges—and sometimes send them awry. By some ancient right we assume authority to retell the patient's story at the bedside—not in our own words but in highly stylized medical code: 'Mr Hunt is a 19-year-old **Caucasian male**, a **known case of** Down's syndrome with little intelligible speech and an IQ of 60, **who complains of** paraesthesiae and weakness in his right **upper limb** … He **admits to drinking 21 units per week** and **other problems** are …'

Do not comfort yourself by supposing this ritualistic reinterpretation arises out of the need for brevity. If this were the reason, and we are speaking in front of the patient, all that is in bold above could be omitted, or drastically curtailed. The next easy conclusion to confront is that we purposely use this jargon to confuse or deceive the patient. This is only sometimes the case, and we must look for deeper reasons for why we are wedded to these medicalisms.

We get nearer to the truth when we realize that these medicalisms are used to sanitize and tame the raw data of our face-to-face encounters with patients—to make them bearable to us—so that we can **think** about the patient rather than having to **feel** for him or her. This is quite right and proper—but only sometimes. Usually what our patients need is sympathy, and this does not spring from cerebration. These medicalisms insulate us from the unpredictability of experiential phenomena. We need the illusion that we are treading on wellmarked- out territory when we are describing someone's pain—a problematic enterprise, not least because if the description is objective it is invalid (pain is, *par excellence*, subjective), and if it is subjective, it is partly incommunicable.

These medicalisms enroll us into a half-proud, half-guilty brotherhood, cemented by what some call patronage and others call fear. This fear can manifest itself as intense loyalty so that, err as we may, we cling to our medical loyalties unto death (that of the patient, not our own). Language is the tool unwittingly used to defend this autocracy of fear. The modulations of our voice, the stylized vocabulary, and the casual neglect of logic and narrative order ensure, in the above example, that we take on board so little of our patient that we remain upright and afloat, above the whirlpools of our patients' lives. In this case, not a case at all, but a child, a family, a mother worried sick about what will happen to her son when she dies: a son who has never **complained** of anything, has never **admitted** to anything, expresses no **problems**—it is our problem that his hand is weak, and his mother's that he can no longer attend riding for the disabled, because she can no longer be away from home and do her part-time job. So when you next hear yourself declaim in one breath that 'Mr Smith is a 50-year-old Caucasian male with crushing central chest pain radiating down his left arm', take heed—what you may be communicating is that you have stopped thinking about this person—and pause for a moment. Look into your patient's eyes: confront the whirlpool.

Footnotes in History: Osler

One of the keys to enjoying medicine is an enthusiasm for involvement, which can be rewarded with the pleasure of sharing in the success of a treatment with a patient and colleagues alike. One outstanding man of medicine and shaper of medical history with such an enthusiasm was William Osler. He held the attitude that promoting equanimity and courtesy among patients and colleagues was an essential part of practice—he himself was a constant inspiration to his students and fellow teachers and also to his patients at a time when prognoses were generally poor. So if you are ever short of inspiration consider what may have been his, because aside from his many scientific contributions, Osler also wrote on the modern philosophies of medical education and patient care. For further insights, see www.whonamedit.com.[2]

Physical examination

With a few exceptions (eg BP), physical examination is not a good screening test for detecting disease. Plan your examination to emphasize the areas that the history suggests may be abnormal. A few well-directed, problem-oriented minutes can save hours of fruitless physical examination. You will still be expected to examine all 4 major systems (cardiovascular, respiratory, abdominal, and neurological), but with time you will be adept at excluding any major pathology. Establish your own comprehensive routine—practice is the key.

Look at your patient as a whole to decide how sick he seems to be. Is he well or *in extremis*? Try to decide **why** you think so. Is he in pain? Does it make him lie still (eg peritonitis) or writhe about (eg colic)? What is the pattern of breathing: laboured; rapid; shallow; irregular; distressed? Is he obese or cachectic? Is his behaviour appropriate? Can you detect any unusual ***smell*** eg hepatic fetor (p250), cigarettes, alcohol? Also take a moment to look around the bed for other clues, eg inhalers, insulin administration kit, walking aids etc.

Specific diagnoses can often be made from ***the face and body habitus*** and these may be missed unless you stop and consider them: eg acromegaly, thyrotoxicosis, myxoedema, Cushing's syndrome, or hypopituitarism, see p188. Is there an abnormal distribution of body hair (eg bearded ♀, or hairless ♂) suggestive of endocrine disease? Is there anything about him to trigger thoughts about Paget's disease, Marfan's, myotonia, and Parkinson's syndrome? Look for rashes, eg the malar flush of mitral disease and the butterfly rash of SLE.

Assess the degree of ***hydration*** by examining the skin turgor (see BOX), the axillae, and mucous membranes. Sunken orbits may also occur in dehydration. Check peripheral perfusion: eg press the nose/finger and time capillary return (CR)—it should be <2s in a well-hydrated individual. Record the temperature, and BP (lying and standing may be compared to postural hypotension, a sign of shock).

Check for ***cyanosis*** (central and peripheral, p56). Is the patient ***jaundiced***? Yellow skin is unreliable and may be produced by the lemon tinge of uraemia, pernicious anaemia, carotenaemia (in all these cases the sclerae are not yellow), or caecal carcinoma. The sign of jaundice is yellow sclerae seen in good daylight. ***Pallor*** is a nonspecific sign and may be racial, familial, or cosmetic. ***Anaemia*** is assessed from the palmar skin creases (when spread) and conjunctivae (**fig 1**, p311)—usually pale if Hb <8-9g/dL: you cannot conclude anything from **normal** conjunctival colour; but if they are pale, the patient is probably anaemic. Koilonychia and stomatitis (sore, dry, inflamed skin around the mouth, particularly at its lateral edge) suggest iron deficiency. Anaemia with jaundice suggests malignancy or haemolysis. Pathological ***hyperpigmentation*** is seen in Addison's, haemochromatosis (slate-grey) and ***amiodarone***, ***gold***, ***silver***, and ***minocycline*** therapy.

Palpate for ***lymph nodes*** in the neck (from behind), axillae, groins, and epitrochlear region (rarely palpable, but significant if present)—see p64 for causes. Any ***subcutaneous nodules*** (p64, p617)?

Don't forget to look at the results of ***urinalysis*** and ***urine output charts*** where indicated. Look at the ***temperature chart***. Average temperature values are 36.8°C (mouth), 36.4°C (axilla), 37.3°C (rectum).[1] **Hypothermia** is defined as a core temperature <35°C; special thermometers may be needed to measure temperatures below this level. A morning temperature ≥37.3°C (mouth) or >37.7°C (rectum) constitutes a **fever**.[2] Note the periodicity of any fever (p376). Do not always believe the temperature chart—if you suspect that the patient has a fever (eg by back-of-the-hand on the forehead), take the temperature yourself.

Don't feel downheartened if you miss a clinical sign—inter-observer variation is a fact of life! Embrace the opportunity to ingrain what you have missed into your own subconscious routine, building up your skills with time and practice.

The hands

A wealth of information can be gained from shaking hands and rapidly examining the hands of the patient. Is there a palsy or deformity—eg the patient may offer the other hand? Are they warm and well-perfused? Warm, sweaty hands signal hyperthyroidism while cold, moist hands may be due to anxiety. Are the rings tight with oedema? Lightly pinch the dorsum of the hand—persisting ridging of the skin means loss of tissue turgor (dehydration, or lack of connective tissue support from ageing). Are there any tar stains from tobacco use? Does the patient have difficulty releasing your hand after shaking it (dystrophia myotonica, p502)? Reluctance to let go is also a sign of loneliness.

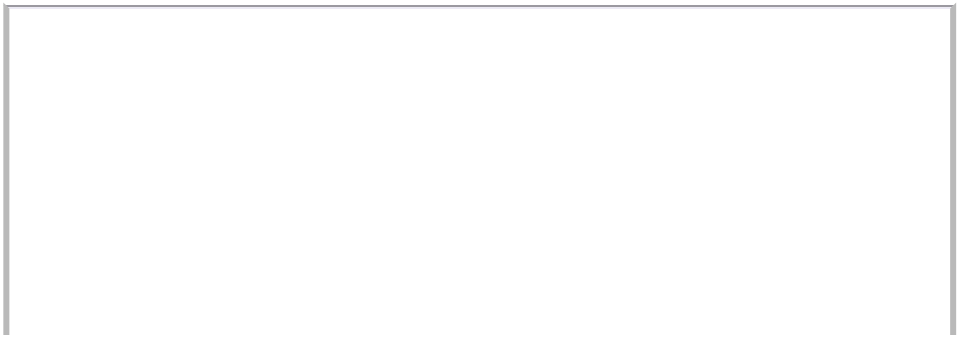
Nails

Koilonychia

(spoon-shaped nails) suggests iron deficiency, fungal nail infection or Raynaud's. ***Onycholysis*** (nail destruction) is seen with hyperthyroidism, fungal infection, and psoriasis. ***Beau's lines*** (**fig 1**) are transverse furrows from temporary arrest of nail growth at times of ↑biological stress: malaria, typhus, rheumatic fever, Kawasaki disease, myocardial infarct, chemotherapy, Guillain-Barré & Raynaud's syndrome, trauma, high-altitude climbing, and deep sea diving.[3] As nails grow at ~0.1mm/d, the furrow's distance from the cuticle allows dating of the stress. ***Mees' lines*** are single white, transverse bands seen in arsenic poisoning or renal failure. ***Muehrcke's lines*** are paired white, parallel transverse bands (*without* furrowing)[4] seen eg in hypoalbuminaemia.

Terry's nails:

Proximal portion of nail is white/pink, nail tip is red/brown (causes: cirrhosis, chronic renal failure). ***Pitting*** is seen in psoriasis and alopecia areata.



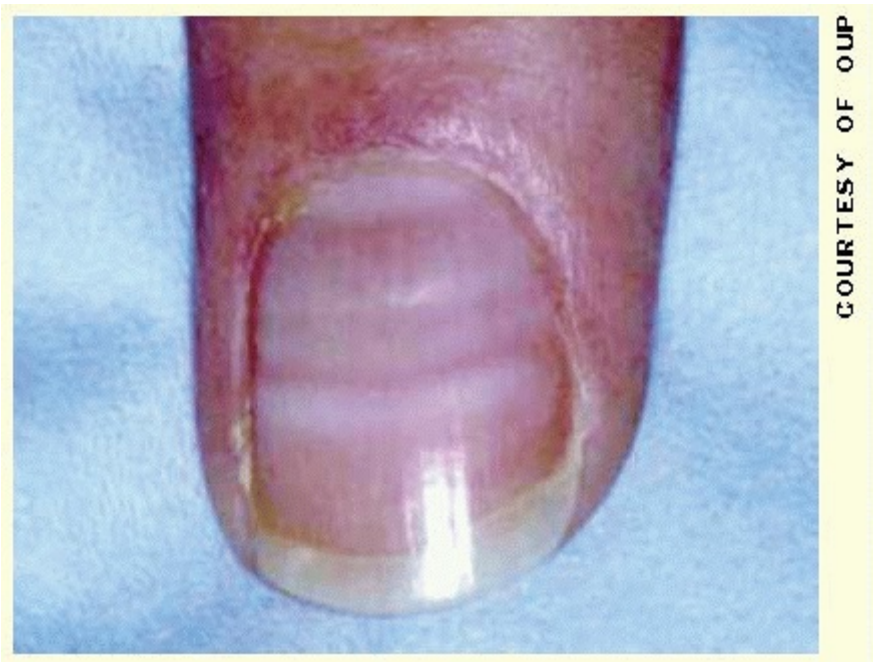


Fig 1. Beau's lines

Splinter haemorrhages

are fine longitudinal haemorrhagic streaks (under nails), which in the febrile patient may suggest infective endocarditis. They may be normal—being caused, eg by gardening. ***Nail-fold infarcts*** are characteristically seen in vasculitic disorders.

Clubbing

of the nails occurs with many disorders (p56). There is an exaggerated longitudinal curvature and loss of the angle between nail and nail-fold (ie no dip). Also the nail feels 'boggy'. The cause is unknown but may be due to ↑blood flow through multiple arteriovenous shunts in the distal phalanges.

Chronic paronychia

is a chronic infection of the nail-fold and presents as a painful swollen nail with intermittent discharge. Treatment: keep nails dry; antibiotics, eg ***erythromycin*** 250mg/6h PO and ***nystatin*** ointment.

The hands

Changes occur in many diseases. ***Palmar erythema*** is associated with cirrhosis, pregnancy, and polycythaemia. ***Pallor*** of the palmar creases suggests anaemia; ***pigmentation*** of the palmar creases (**fig 2**) is normal in Asians and blacks but is also seen in Addison's disease and Nelson's syndrome (↑ACTH after removal of the adrenal glands in Cushing's disease).[5] An odd rash on the knuckles (Gottren's papules) with dilated end-capillary loops at the nail-fold suggests dermatomyositis (p538). ***Dupuytren's contracture*** (fibrosis and contracture of palmar fascia, p690) is seen in liver disease, trauma, epilepsy, and ageing.[6] Swollen proximal interphalangeal (PIP) joints with distal (DIP) joints spared suggests rheumatoid arthritis; swollen DIP joints suggests osteoarthritis, gout, or psoriasis. Look for ***Heberden's*** (DIP, **fig 3**) and ***Bouchard's*** (PIP) 'nodes'—osteophytes (bone over-growth at a joint) seen with osteoarthritis.

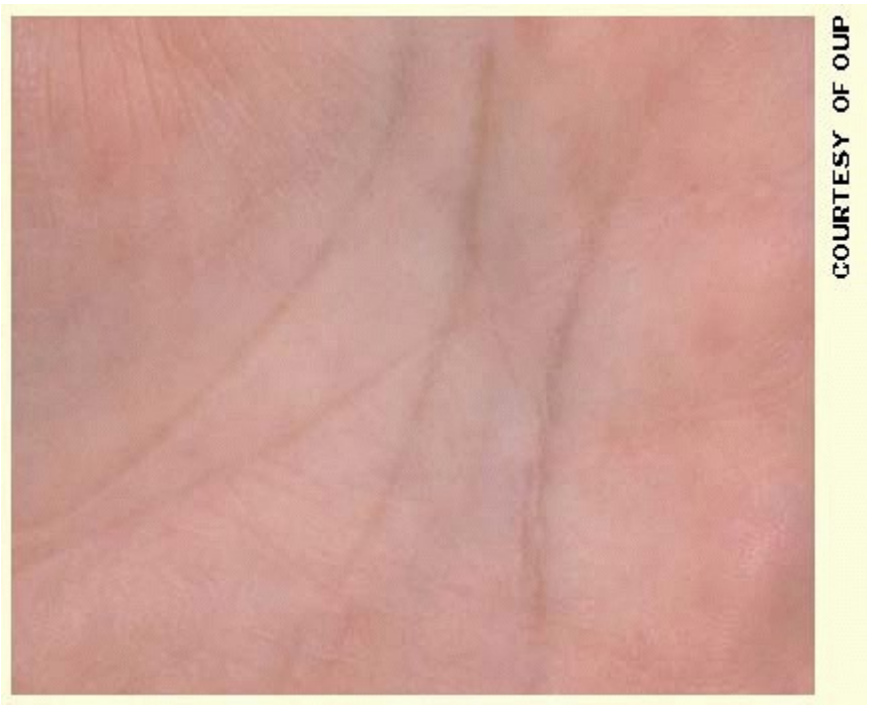


Fig 2. Hyperpigmented palmar creases.

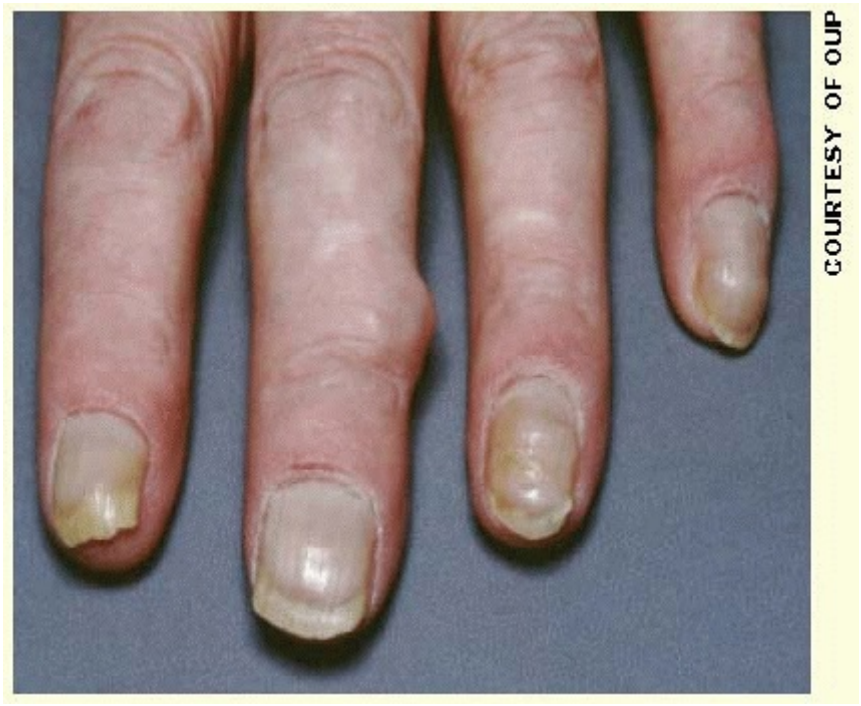


Fig 3. Heberden's node

[1] The accuracy of different non-invasive methods for measuring temperature is continually being assessed.

[2] The nadir is at 6 AM, with a zenith at 6 PM; the mean amplitude of variability is 0.5°C.

The cardiovascular system

History

Ask about age, occupation, hobbies, sport, exercise and ethnic origin.

Presenting symptoms

- Chest pain (p80 & p772)
- Palpitations; dizziness; blackouts
- Ankle swelling
- Dyspnoea (p58)—exertional? orthopnoea? PND?

Past history

- Angina or MI
- Rheumatic fever
- Intermittent claudication

Ischaemic heart disease (IHD) risk factors

- Smoking
- Diabetes mellitus

- Family history (Ist degree relative <60yrs old with IHD.)
- Hypertension
- Hyperlipidaemia

Drug history

- Previous and current regimens

Past tests and procedures:

- ECG
- Angiograms
- Angioplasty/stents
- Echocardiography
- Cardiac scintigraphy
- CABG (bypass grafts)

Appearance

Ill or well? In pain? Dyspnoeic? Are they pale, cold, and clammy? Is there corneal arcus or xanthelasma (hyperlipidaemia (p682))? Is there a malar flush (mitral stenosis, low cardiac output)? Are there signs of Graves' disease (bulging eyes, goitre—p202)? Is the face dysmorphic, eg Down's syndrome, Marfan's syndrome (p698)—or Turner's, Noonan's, or William's syndromes (p139)? Can you hear the click of a prosthetic valve?

Hands

Finger clubbing occurs in congenital cyanotic heart disease and endocarditis. Splinter haemorrhages, Osler's nodes (tender nodules in finger pulps) and Janeway lesions (red macules on palms) are signs of infective endocarditis. If found, examine the fundi for Roth's spots (retinal infarcts p376, **fig 1**). Are there nail-fold infarcts (vasculitis, p542) or nailbed capillary pulsation (Quincke's sign in aortic regurgitation)? Is there arachnodactyly (Marfan's) or polydactyly (ASD)? Are there tendon xanthomata (hyperlipdaemia)? **Pulse** See p30.

Blood pressure

(see BOX) **Systolic BP** is the pressure at which the pulse is first heard as on cuff deflation; the **diastolic** is when the heart sounds disappear (Korotkov sound, K5) or become muffled (K4—use eg in the young, who often have no K5; state which you use). The ***pulse pressure*** is the difference between systolic and diastolic pressures. It is narrow in aortic stenosis and wide in aortic regurgitation. It also narrows in hypovolaemia and widens in septic shock. Defining hypertension is problematic: see p124. Examine the fundi for hypertensive changes (p125). **Shock** may occur if systolic <100mmHg (p778). ***Postural hypotension*** is defined as a drop in systolic >20mmHg or diastolic >10mmHg on standing (p68).

Jugular venous pressure

See p30.

Praecordium

Inspect for ***scars*****:** median sternotomy (CABG; valve replacement; congenital heart disease). Inspect for any pacemakers. Palpate the ***apex beat***. Normal position: 5th intercostal space in the mid-clavicular line. Is it displaced laterally? Is it abnormal in nature: **heaving** (caused by outflow obstruction, eg aortic stenosis or systemic hypertension), **thrusting** (caused by volume overload, eg mitral or aortic incompetence), **tapping** (mitral stenosis, essentially a palpable 1st heart sound), **diffuse** (LV failure, dilated cardiomyopathy) or **double impulse** (HOCM)? Is there dextrocardia? Feel for ***left parasternal heave*** (RV enlargement eg in pulmonary stenosis, cor pulmonale, ASD) or ***thrills*** (transmitted murmurs).

Auscultating the heart

See BOX.

Lungs

Examine the bases for creps & pleural effusions, indicative of cardiac failure.

Oedema

Examine the ankles, legs, sacrum, torso for pitting oedema.

Abdomen

Hepatomegaly and ascites in right-sided heart failure; pulsatile hepatomegaly with tricuspid regurgitation; splenomegaly with infective endocarditis.

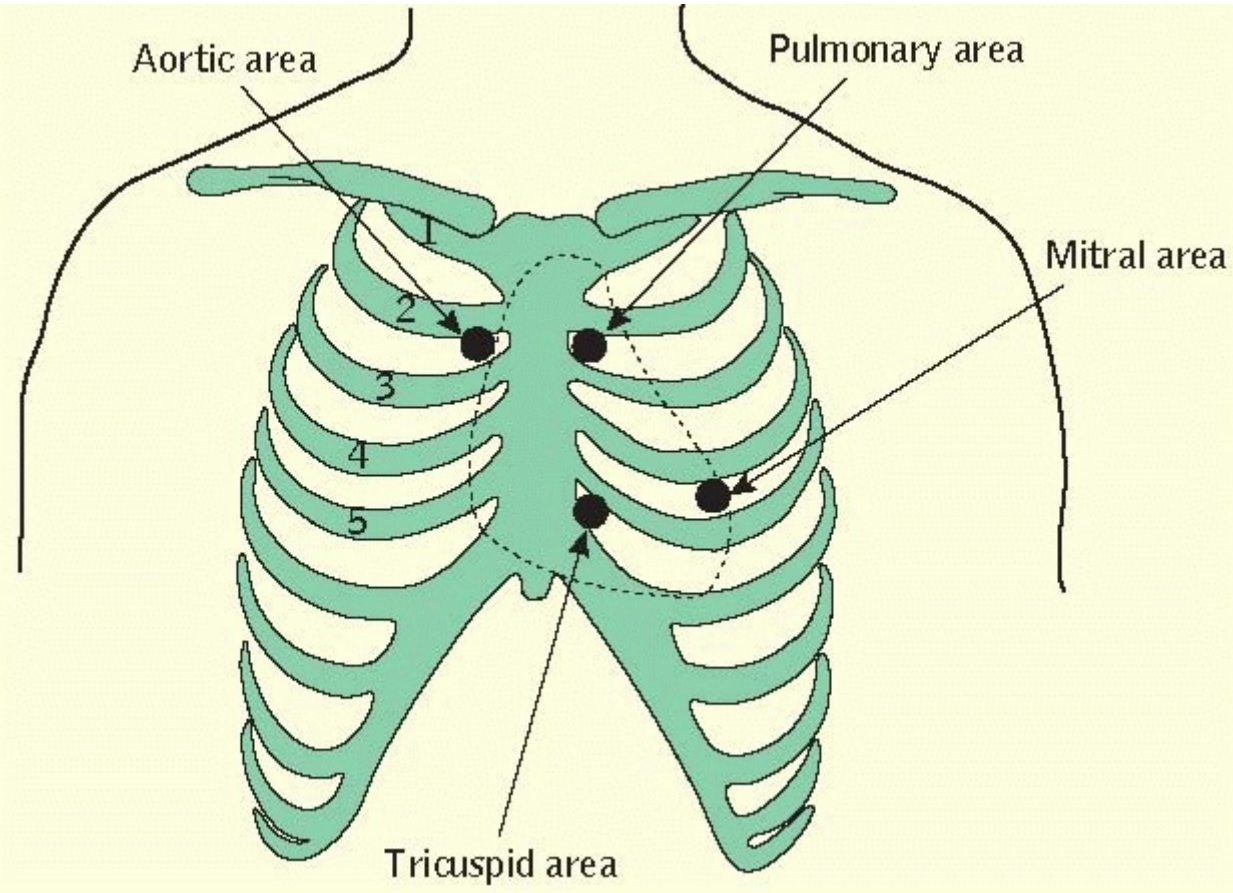
Peripheral pulses

Palpate radial, brachial, carotid, femoral, popliteal, dorsalis pedis, and posterior tibial pulses. Feel for ***radio-femoral delay*** (coarctation of the aorta) and ***radio-radial delay*** (eg from aortic arch aneurysm). Auscultate for ***bruits*** over the carotids and elsewhere, particularly if there is inequality between pulses or absence of a pulse. Causes: atherosclerosis (elderly), vasculitis (young, p542).

Auscultating the heart

▸If you spend time listening to the history, and feeling pulses, auscultation will hold few surprises: you will often already know the diagnosis. Feel for the pulse at the same time as you listen, either at the apex or in the carotid artery.

- Listen with bell and diaphragm at the apex (mitral area). Identify ***1st*** and ***2nd heart sounds***: are they normal? Listen for ***added sounds*** (p32) and ***murmurs*** (p34). Repeat at lower left sternal edge and in aortic and pulmonary areas (right and left of manubrium in the 2nd intercostal space)—and in both the left axilla (radiation of mitral incompetence) and over the carotids (radiation of aortic stenosis).
- Reposition the patient in the left lateral position: again feel the apex beat (is it tapping, as in mitral stenosis?) and listen specifically for a diastolic rumble of mitral stenosis. Sit the patient up and listen at the lower left sternal edge for the blowing diastolic sound of aortic regurgitation—accentuated at the end of expiration.



After Clinical Examination; N Talley, Blackwell

An unusual BP measurement

It is always important not to interpret a BP measurement in isolation (p124). We cannot be certain to diagnose hypertension (or hypotension) in isolation, as there may be many confounding factors such as pain, the 'white coat' effect, and the equipment used.[7] Getting the cuff size right is very important, as too small will give an elevated reading and too large will give a low reading—the optimal cuff width is 40% of the arm circumference. If you suspect a BP reading to be anomalous check the equipment and review the observation chart for previous readings and other vital signs. Consider taking a manual reading with a different set yourself! Mercury sphygmomanometers are the type least likely to go wrong. See *regression towards the mean*, p10. Often a quiet chat with the patient will bring the BP down (both yours and your patient's)—and if you keep your ears open, the patient may reveal some new tangential but vital fact which the official history glossed over.

The jugular venous pressure

The internal jugular vein acts as a capricious manometer of right atrial pressure. Observe 2 features: the **height** (jugular venous pressure, JVP) and the **waveform** of the pulse. JVP observations are often difficult. Do not be downhearted if the skill seems to elude you. Keep on watching necks, and the patterns you see may slowly start to make sense—see BOX for the local venous anatomy. Relating the waveform to the arterial pulse (by concomitant palpation) will help to decipher patterns.

The height

Observe the patient at 45°, with his head turned slightly to the left— good lighting and correct positioning makes the examination a lot easier. Look for

the right internal jugular vein, which passes just medial to the clavicular head of sternocleidomastoid up behind the angle of the jaw to the ear lobes. The JVP is the vertical height of the pulse above the sternal angle. It is raised if >4cm. Pressing on the abdomen normally produces a transient rise in the JVP. If the rise persists throughout a 15s compression, it is a **positive abdominojugular reflux sign**.[1] This is a sign of right ventricular failure, reflecting inability to eject the increased venous return.[8]

[1] This sign was first described by W Pasteur in 1885, in the context of tricuspid incompetence. The term 'hepatojugular reflux' later arose, but was replaced by 'abdominojugular reflux' (not *reflex*!),[8] as pressure over the middle of the abdomen, as well as over the liver, can be used to elicit the sign.

The waveform

See BOX.

Abnormalities of the JVP

- ***Raised* JVP *with normal waveform:*** Fluid overload, right heart failure.
- ***Raised* JVP *with absent pulsation:*** svc obstruction.
- ***Large a wave:*** Pulmonary hypertension, pulmonary stenosis.
- ***Cannon a wave:*** When the right atrium contracts against a closed tricuspid valve, large 'cannon' a waves result. ***Causes:*** complete heart block, single chamber ventricular pacing, ventricular arrhythmias/ectopics.
- ***Absent a wave:*** Atrial fibrillation.
- ***Large systolic v waves:*** Tricuspid regurgitation—look for earlobe movement.
- ***Constrictive pericarditis:*** High plateau of JVP (which rises on inspiration— Kussmaul's sign) with deep × and y descents.
- ***Absent* JVP:** When lying flat, the jugular vein should be filled. If there is reduced circulatory volume (eg dehydration, haemorrhage) the JVP may be absent.

Pulses

▸Assess the radial pulse to determine rate and rhythm. **Character** and **volume** are best assessed at the brachial or carotid arteries. A **collapsing pulse** may also be felt at the radial artery when the patient's arm is elevated above his head.

Rate

Is the pulse fast ($\gtrsim$100bpm, p112) or slow ($\lesssim$60bpm, p110)?

Rhythm

An irregularly irregular pulse occurs in AF or multiple ectopics. A regularly irregular pulse occurs in 2° heart block and ventricular bigeminus.

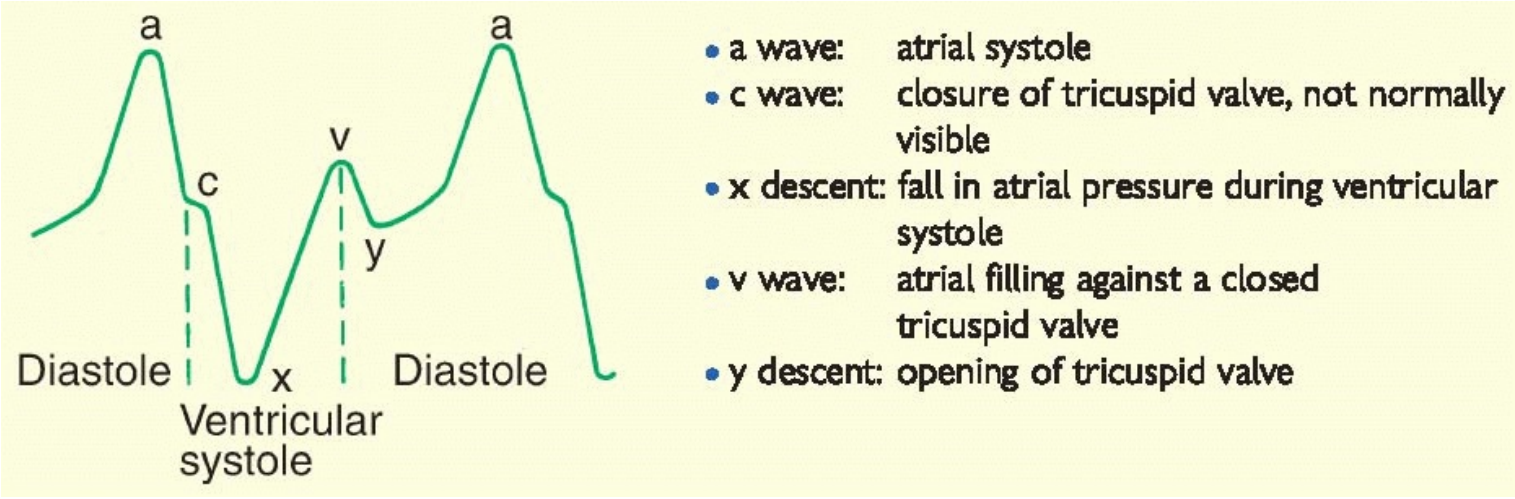
Character and volume

- ***Bounding pulses*** are caused by CO_2 retention, liver failure, and sepsis.
- ***Small volume pulses*** occur in aortic stenosis, shock, and pericardial effusion.
- ***Collapsing ('waterhammer') pulses*** are caused by aortic incompetence, AV malformations, and a patent ductus arteriosus.
- ***Anacrotic (slow-rising) pulses*** occur in aortic stenosis.
- ***Bisferiens pulses*** occur in combined aortic stenosis and regurgitation
- ***Pulsus alternans*** (alternating strong and weak beats) suggests LVF, cardiomyopathy, or aortic stenosis.
- ***Jerky pulses*** occur in HOCM.
- ***Pulsus paradoxus*** (systolic pressure weakens in inspiration by >10mmHg) occurs in severe asthma, pericardial constriction, or cardiac tamponade.

Peripheral pulses

(See p28.) See p759 for ABG sampling.

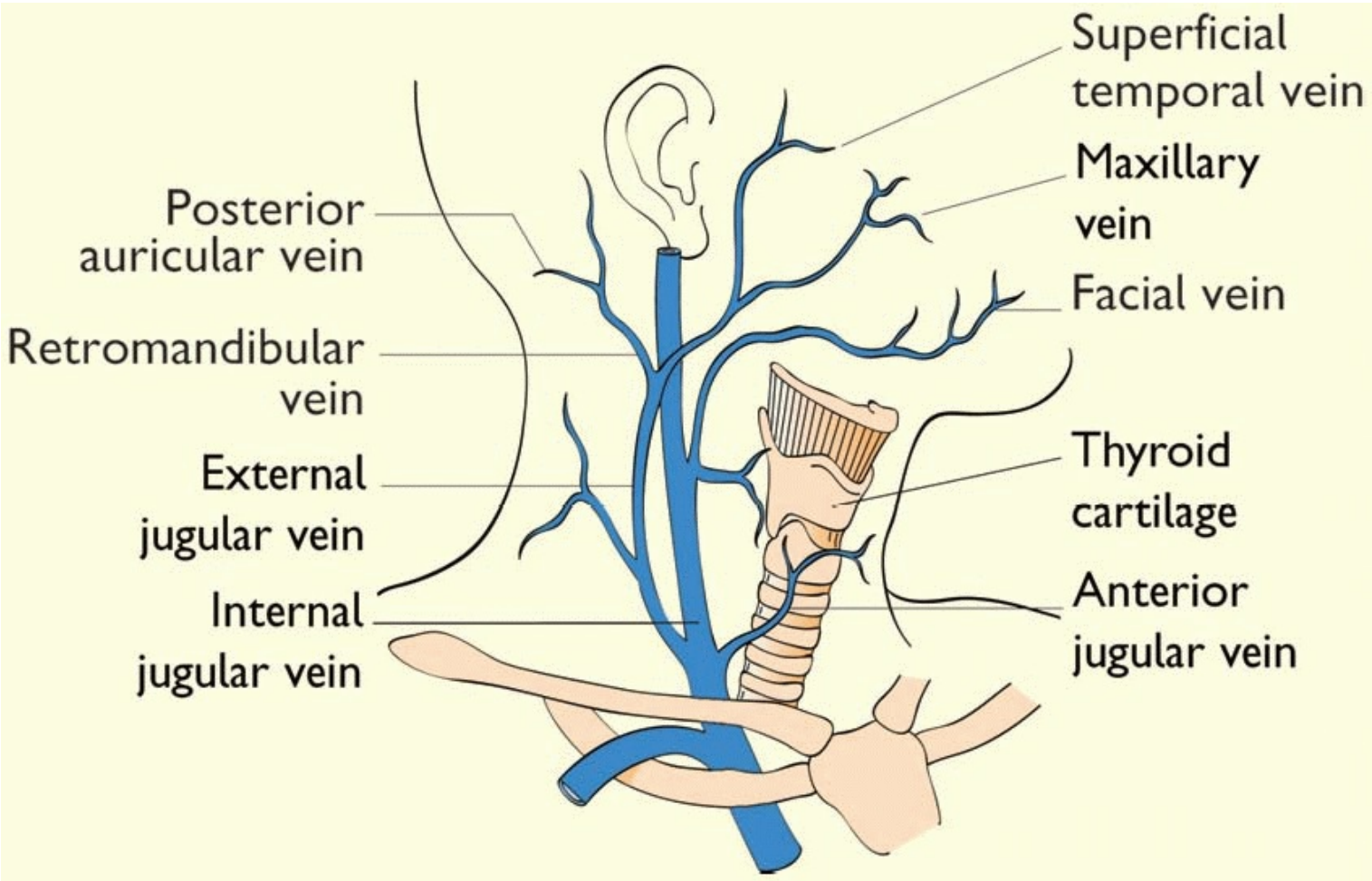
The jugular venous pressure wave



AFTER CLINICAL EXAMINATION, MACLEOD, CHURCHILL

The JVP drops as the × descent during ventricular systole because the right atrium is no longer contracting and the tricuspid valve is closed. This means that the pressure in the right atrium is dropping and this is reflected by the JVP.

The jugular venous systems



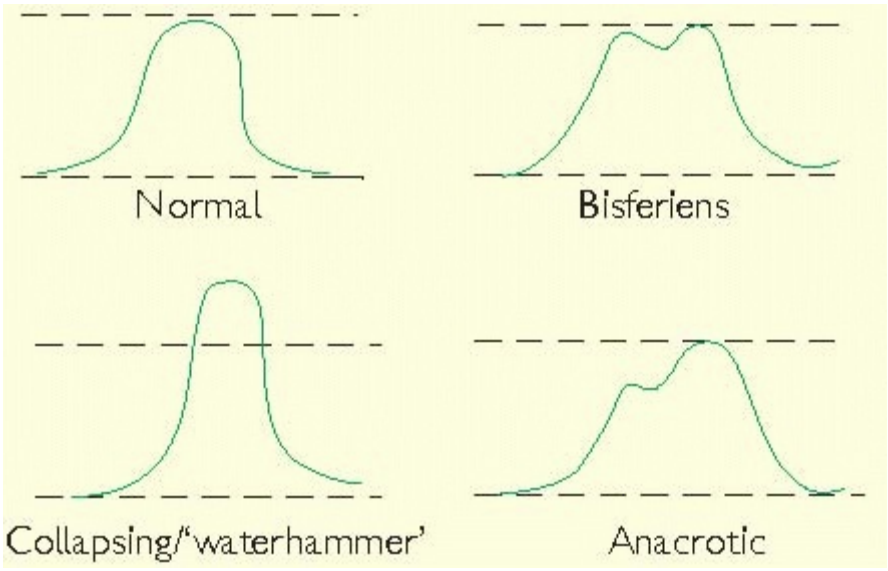
AFTER CLINICAL ANATOMY PRINCIPLES, L.H. MATHERS ISBN 0815189265

Is a pulse arterial or venous?

A venous pulse:

- Is not usually palpable.
- Is obliterated by finger pressure on the vessel.
- Rises transiently with pressure on abdomen (**abdominojugular reflux**) or on liver (**hepatojugular reflux**).
- Alters with posture and respiration.
- Usually has a double pulse for every arterial pulse.

Arterial pulse waveforms



AFTER AIDS TO UNDERGRADUATE MEDICINE, J BURTON, CHURCHILL

Inside the waterhammer

Before the age of video games, the waterhammer was a popular toy that consisted of a vacuum tube half-filled with water. On inversion, the whoosh of water produced an intriguing hammer-blow as it rushed from end to end. This is the alternative name for Corrigan's (collapsing) pulse—ie one in which the upstroke is abrupt and steep, whose peak is reached early and with abnormal force—before a rapid downstroke (as blood whooshes back into the left ventricle through an incompetent aortic valve).[9] Sometimes events conspire to put ***us*** in the waterhammer— rushing about in a vacuum tilted for the malicious pleasure of an unseen child. To let some air in, take a deep breath, and read all about Corrigan (p16).

The heart sounds

▸Listen systematically: sounds then murmurs. While listening, palpate the carotid artery: S_1 is synchronous with the upstroke.

Heart sounds

The 1st and 2nd sounds are usually clear. Confident pronouncements about other sounds and soft murmurs may be difficult. Even senior colleagues disagree with one another about the more difficult sounds and murmurs.

The 1st heart sound

(S_1) represents closure of mitral (M_1) and tricuspid (T_1) valves. Splitting in inspiration may be heard and is normal.

In mitral stenosis, because the narrowed valve orifice limits ventricular filling, there is no gradual decrease in flow towards the end of diastole. The valves are therefore at their maximum excursion at the end of diastole, and so shut rapidly leading to a loud S_1 (the 'tapping' apex). S_1 is also loud if diastolic filling time is shortened eg if the P-R interval is short, and in tachycardia.

S_1 is soft if the diastolic filling time is prolonged eg if the P-R interval is long, or if the mitral valve leaflets fail to close properly (ie mitral incompetence).

The intensity of S_1 is variable in AV block, AF, and nodal or ventricular tachycardia.

The 2nd heart sound

(S_2) represents aortic (A_2) and pulmonary valve (P_2) closure. The most important abnormality of A_2 is softening in aortic stenosis.

A_2 is said to be loud in tachycardia, hypertension, and transposition, but a loud A_2 is probably not a useful clinical entity.

P_2 is loud in pulmonary hypertension and soft in pulmonary stenosis. **Splitting** in inspiration is normal and is mainly due to the variation with respiration of right heart venous return, causing the pulmonary component to be delayed. **Wide splitting** occurs in right bundle branch block, pulmonary stenosis, deep inspiration, mitral regurgitation, and VSD. **Wide fixed splitting** occurs in ASD. **Reversed splitting** (ie A_2 following P_2, with splitting increasing on expiration) occurs in left bundle branch block, aortic stenosis, PDA (patent ductus arteriosus), and right ventricular pacing. A single S_2 occurs in Fallot's tetralogy, severe aortic or pulmonary stenosis, pulmonary atresia, Eisenmenger's syndrome (p143), large VSD, hypertension. **NB:** splitting and P_2 are heard best in the pulmonary area.

A 3rd heart sound

(S_3) may occur just after S_2. It is low pitched and best heard with the bell of the stethoscope. S_3 is pathological over the age of 30yrs. A loud S_3 occurs in a dilated left ventricle with rapid ventricular filling (mitral regurgitation, VSD) or poor LV function (post MI, dilated cardiomyopathy). In constrictive pericarditis or restrictive cardiomyopathy it occurs early and is more high pitched ('pericardial knock').

A 4th heart sound

(S_4) occurs just before S_1. Always abnormal, it represents atrial contraction against a ventricle made stiff by any cause, eg aortic stenosis, or hypertensive heart disease.

Triple and gallop rhythms

A 3rd or 4th heart sound occurring with a sinus tachycardia may give the impression of galloping hooves. An S_3 gallop has the same rhythm as '**Ken**-tucky', whereas an S_4 gallop has the same rhythm as 'Tenne**ssee**'. When S_3 and S_4 occur in a tachycardia, eg with pulmonary embolism, they may summate and appear as a single sound, a summation gallop.

An ejection systolic click

is heard early in systole with bicuspid aortic valves, and if BP↑. The right heart equivalent lesions may also cause clicks.

Mid-systolic clicks

occur in mitral valve prolapse (p130).

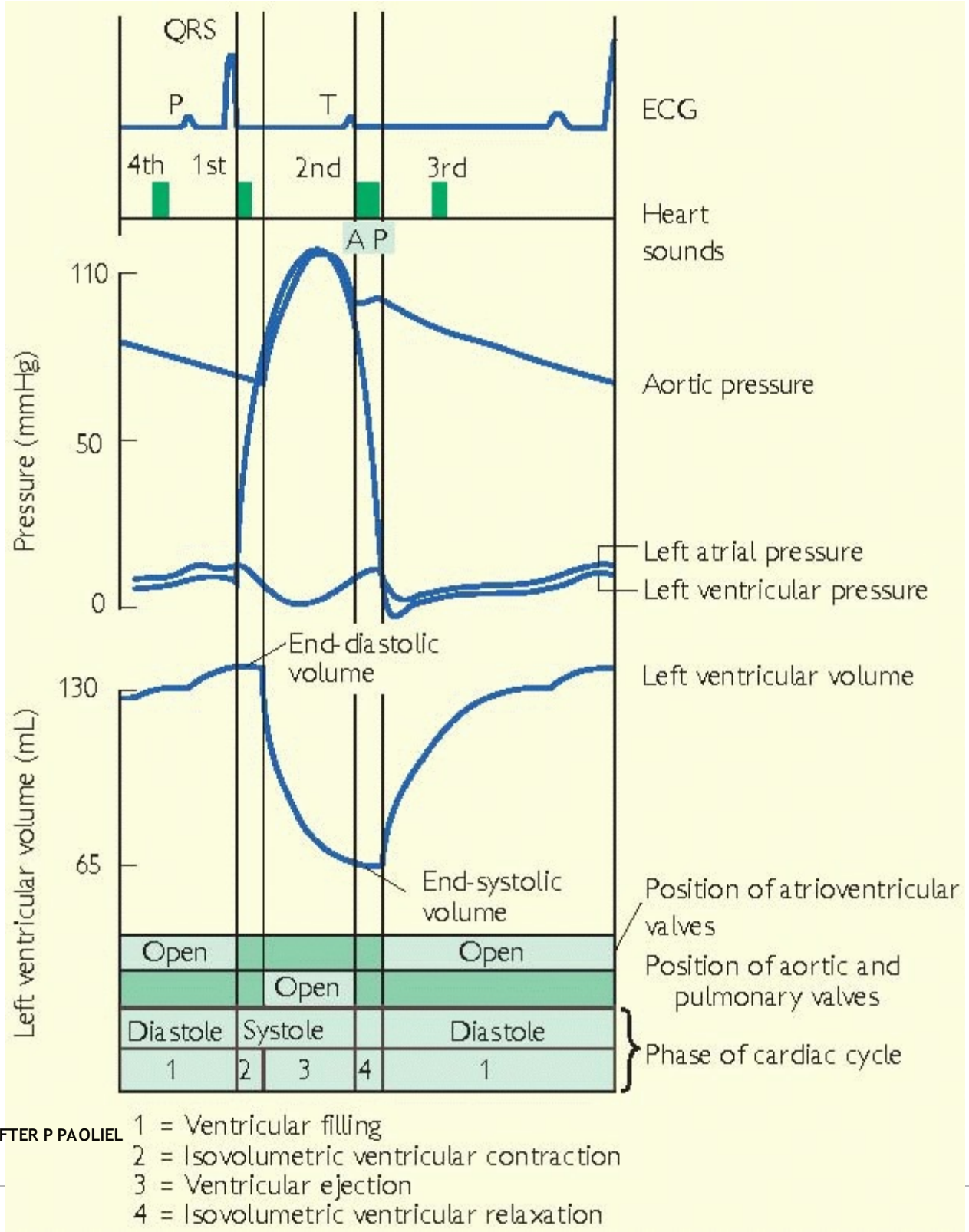
An opening snap

precedes the mid-diastolic murmur of mitral stenosis. It indicates a pliable (noncalcified) valve.

Prosthetic sounds

are caused by nonbiological valves, on opening and closing: **rumbling sounds** ≈ ball and cage valves (eg Starr-Edwards); **single clicks** ≈ tilting disc valve (eg single disc: Bjork Shiley; bileaflet: St Jude—often quieter). Prosthetic mitral valve clicks occur in time with S_1, aortic valve clicks in time with S_2.

The cardiac cycle



AFTER P PAOLIEL

Cardiac murmurs[1]

▸ Always consider other symptoms and signs before auscultation and think: what do I expect to hear? But don't let your expectations determine what you hear.

▸ Use the stethoscope correctly: remember that the bell is good for low-pitched sounds (eg mitral stenosis) and should be applied **gently**. The diaphragm filters out low pitches, making higher pitched murmurs easier to detect (eg aortic regurgitation). **NB:** a bell applied tightly to the skin becomes a diaphragm.

▸ Consider any murmur in terms of **character**, **timing**, **loudness**, **area where loudest**, **radiation**, and **accentuating manoeuvres**.

▸ When in doubt, rely on echocardiography rather than disputed sounds. (But still enjoy trying to figure out the clinical conundrum!)

Character and timing

- ***An ejection-systolic murmur*** (***ESM***, crescendo-decrescendo) usually originates from the outflow tract and waxes and wanes with the intraventricular pressures. ESMs may be innocent and are common in children and high output states (eg tachycardia, pregnancy). Organic causes include aortic stenosis and sclerosis, pulmonary stenosis, and HOCM.
- ***A pansystolic murmur (PSM)*** is of uniform intensity and merges with S_2. It is usually organic and occurs in mitral or tricuspid regurgitation (S_1 may also

be soft in these), or a ventricular septal defect (p142). Mitral valve prolapse may produce a late systolic murmur ± midsystolic click.

- ***Early diastolic murmurs (EDM)*** are high pitched and easily missed: listen for the 'absence of silence' in early diastole. An EDM occurs in aortic and, though rare, pulmonary regurgitation. If the pulmonary regurgitation is secondary to pulmonary hypertension resulting from mitral stenosis, then the EDM is called a Graham Steell murmur.
- ***Mid-diastolic murmurs (MDM)*** are low pitched and rumbling. They occur in mitral stenosis (accentuated presystolically if heart still in sinus rhythm), rheumatic fever (Carey Coombs' murmur: due to thickening of the mitral valve leaflets), and aortic regurgitation (Austin Flint murmur: due to the fluttering of the anterior mitral valve cusp caused by the regurgitant stream).

Intensity

All murmurs are graded on a scale of 1-6 (see TABLE), though in practice diastolic murmurs, being less loud, are only graded 1-4. Intensity is a poor guide to the severity of a lesion—an ESM may be inaudible in severe aortic stenosis.

Area where loudest

Though an unreliable sign, mitral murmurs tend to be loudest over the apex, in contrast to the area of greatest intensity from lesions of the aortic (right 2nd intercostal space), pulmonary (left 2nd intercostal space) and tricuspid (lower left sternal edge) valves.

Radiation

The ESM of aortic stenosis classically radiates to the carotids, in contrast to the PSM of mitral regurgitation, which radiates to the axilla.

Accentuating manoeuvres

- ***Movements*** that bring the relevant part of the heart closer to the stethoscope accentuate murmurs (eg leaning forward for aortic regurgitation, left lateral position for mitral stenosis).
- ***Expiration*** increases blood flow to the left side of the heart and therefore accentuates left sided murmurs. ***Inspiration*** has the opposite effect.
- ***Valsalva manoeuvre*** (forced expiration against a closed glottis) decreases systemic venous return, accentuating mitral valve prolapse and HOCM, but softening mitral regurgitation and aortic stenosis. ***Squatting*** has exactly the opposite effects. ***Exercise*** accentuates the murmur of mitral stenosis.

Non-valvular murmurs

A pericardial friction rub may be heard in pericarditis. It is a superficial scratching sound, not confined to systole or diastole. ***Continuous murmurs*** are present throughout the cardiac cycle and may occur with a patent ductus arteriosus, arteriovenous fistula, or ruptured sinus of Valsalva.

Typical waveforms of common heart murmurs

After Clinical Examination, N Talley, Blackwell

Grading intensity of heart murmurs

▸The following grading is commonly used for murmurs—systolic murmurs from 1 to 6 and diastolic murmurs from 1 to 4, never being clinically >4/6.

Grade	Description
1/6	Very soft, only heard after listening for a while
2/6	Soft, but detectable immediately
3/6	Clearly audible, but no thrill palpable
4/6	Clearly audible, palpable thrill
5/6	Audible with stethoscope only partially touching chest
6/6	Can be heard without placing stethoscope on chest

Prosthetic valve murmurs[10]

Prosthetic aortic valves:

All types produce a degree of outflow obstruction and thus have an ESM. Tilting single disc (eg Bjork Shiley) and bileaflet (eg St Jude) valves do not completely close and allow a regurgitant stream during diastole, hence they have a low-intensity diastolic murmur. The intensity of this murmur increases as the valve fails. Ball and cage valves (eg Starr-Edwards) and tissue valves **do** close completely in diastole and so any diastolic murmur implies valve failure.

Prosthetic mitral valves:

Ball and cage valves project into the left ventricle and can cause a low-intensity ESM as they interfere with the ejected stream. Tissue valves and bileaflet valves can have a low-intensity diastolic murmur. Consider any systolic murmur of loud intensity to be a sign of regurgitation and ∴ failure.

The respiratory system

History

Age, race, occupation. **Presenting symptoms**—as follows:

- ***Cough:*** (see BOX)

  Duration? Character (eg brassy/barking/hollow)? Nocturnal (≈asthma)? Exacerbating factors? Sputum/haemoptysis?
- ***Dyspnoea:*** (p58 & p770)

  Duration? Steps climbed/distance walked before onset? NYHA classification (p121)? Diurnal variation (≈asthma)?
- ***Hoarseness:*** (OHCS p568)

  eg due to laryngitis, recurrent laryngeal nerve palsy, Singer's nodules, or laryngeal tumour.
- ***Wheeze*** (p38)
- ***Fever/night sweats*** (p60)
- ***Chest pain*** (p80)
- ***Stridor*** (p72)

Past history

Ask about: Pneumonia/bronchitis; TB; atopy[1] (asthma/eczema/hay fever); previous CXR abnormalities; lung surgery; myopathy; neurological disorders.

Family history

Atopy?[1] Emphysema? TB?

Social history

Quantify smoking in terms of **pack-years** (20 cigarettes/day for 1 year = 1 pack-year). Occupational exposure (farming, mining, asbestos exposure) has possible serious compensatory implications? Animals at home (eg birds)? Recent travel/TB contacts?

Drug history

Respiratory drugs (eg steroids, bronchodilators)? Any other drugs, especially with respiratory SEs (eg ACE inhibitors, cytotoxics, ß-blockers, amiodarone)?

Examination

Undress to the waist, and sit him on the edge of the bed.

Inspection

Assess **general health**: is he unwell? Cachectic? Using accessory muscles of respiration, eg sternocleidomastoids, platysma, and strap muscles of the neck (infrahyoid)? Are there signs of respiratory distress (see below)? Is there stridor (p72)? Count the **respiratory rate** and note **breathing pattern**. Is there Kussmaul's (rapid, deep respiration, p62) or Cheyne-Stokes (apnoea alternating with hyperpnoea, p54) breathing? Look for **chest wall deformities** (p54). Inspect the chest for scars of past surgery, chest drains, or radiotherapy (skin thickening and tattoos demarcating the field of irradiation). Note **chest wall movement**: is it symmetrical? If not, pathology is on the restricted side. Is there paradoxical respiration (abdomen sucked in with inspiration; seen in diaphragmatic paralysis)?

Examine the hands

for clubbing (p56), peripheral cyanosis (p56), tar staining, and wasting/weakness of the intrinsic muscles—seen in T1 lesions (eg Pancoast's tumour, p700). Palpate the wrist for tenderness (hypertrophic pulmonary osteoarthropathy, HPOA, from lung cancer). Check for asterixis (CO_2 retention flap). Palpate the pulse for a paradoxical character (weakens in inspiration; quantify in mmHg by measuring BP in inspiration and expiration, p30).

Regard the face

Check for ptosis and a constricted pupil (Horner's syndrome, eg Pancoast's tumour, p700). Are the tongue and lips bluish (central cyanosis, p56)?

Feel the trachea

in the sternal notch (it should pass just to the right). If deviated, concentrate on the upper lobes for pathology. Note the presence of **tracheal tug** (descent of trachea with inspiration, meaning severe airflow limitation). Palpate for **cervical lymphadenopathy** from behind, with the patient sitting forward.

Examining the chest

(See p38.) If an abnormality is detected, try to localize it to the likely **segment** (see BOX). If this is not possible, state the **zone** of the findings.

Further examination

Look at the **JVP** (p30) and examine the heart for signs of **cor pulmonale** (p186). Look at **temperature charts**. Inspect the **sputum** (See BOX). Test peripheral **O_2 saturation** and **PEFR** at the bedside (p148).

Respiratory distress

occurs if high negative intrapleural pressures are needed to generate air entry. Signs: tachypnoea, nasal flaring, tracheal tug (pulling of thyroid cartilage towards sternal notch in inspiration), the use of accessory muscles of respiration, intercostal, subcostal, and sternal recession, and pulsus paradoxus (p30).

Characteristic coughs

Coughing is a relatively nonspecific symptom, resulting from irritation anywhere from the pharynx to the lungs. The character of a patient's cough may, however, give some clues as to the underlying cause:

- ***Loud, brassy coughing*** suggests pressure on the trachea eg by a tumour.
- ***Hollow, 'bovine' coughing*** is associated with recurrent laryngeal nerve palsy.
- ***Barking coughs*** occur in acute epiglottitis.
- ***Chronic cough:*** Think of pertussis, TB, foreign body, asthma (eg nocturnal).
- ***Dry, chronic coughing*** may occur following acid irritation of the lungs in oesophageal reflux, and as a side-effect of ACE inhibitors.

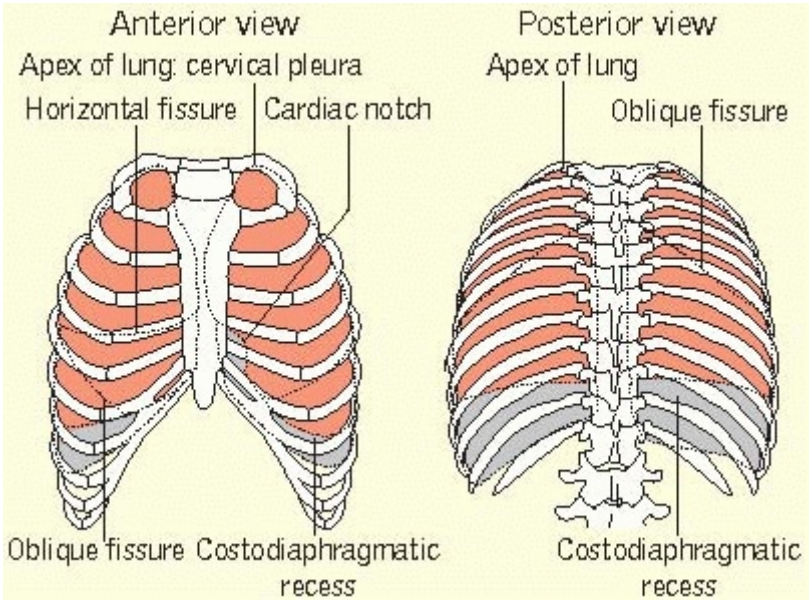
▸Do not ignore a change in character of a chronic cough; it may signify a new problem eg infection, malignancy.

Sputum examination

Always inspect any sputum produced, however unpleasant this task may be. Send suspicious sputum for microscopy (Gram stain and auramine/ZN stain, if indicated), culture, and cytology.

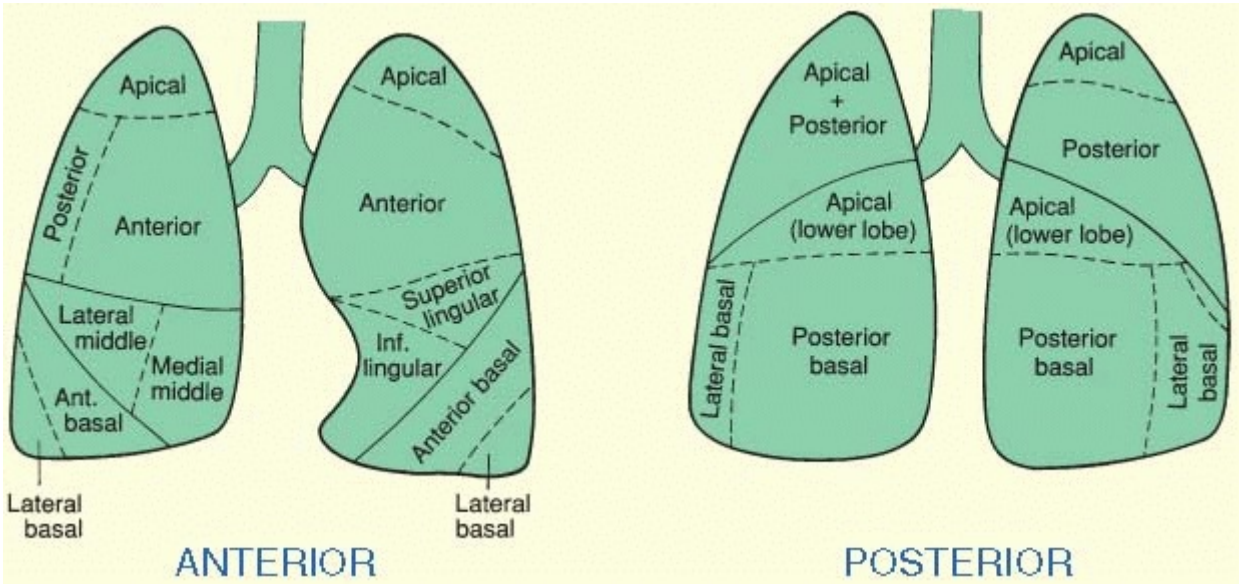
- ***Black carbon specks*** in the sputum suggests smoking, the most common cause of increased sputum production.
- ***Yellow/green sputum*** suggests infection eg bronchiectasis, pneumonia.
- ***Pink frothy sputum*** suggests pulmonary oedema.
- ***Bloody sputum (haemoptysis)*** may be due to malignancy, TB, infection, or trauma, and requires investigation for these causes. See p62.
- ***Clear sputum*** is probably saliva.

Surface pleural, lung and fissure markings



AFTER RCSI WWW.RCSI.IE

The respiratory segments supplied by the segmental bronchi



Examining the chest

Inspection

General—see p36. Look for deformities of the spine (kyphoscoliosis) or chest wall (*pectus excavatum* or *carinatum*, p54), or scars from surgery.

Palpation

Lymphadenopathy:

Check for cervical lymphadenopathy from behind, with the patient sitting forward.

Tracheal position:

Is it central or displaced to one side (towards an area of collapse, away from a large pleural effusion or tension pneumothorax; slight deviation to the right is normal).

Expansion:

Use both hands to compare chest expansion on both sides; expansion <5cm on deep inspiration is abnormal. Reduced expansion implies pathology on that side. Test ***tactile vocal fremitus*** by asking the patient to repeat '99' while palpating the chest wall with the ulnar border of your hands over different respiratory segments, comparing similar positions over each lung in turn. Increased vocal fremitus implies consolidation, but is less sensitive than vocal resonance (see p76).

Percussion

Percuss symmetrical areas of the anterior, posterior, and axillary regions of the chest wall. When percussing posteriorly, move the scapulae out of the way by asking the patient to move his elbows forward across his chest. Do not forget to percuss the supraclavicular fossae (lung apices).

Causes of a dull percussion note:

collapse, consolidation, fibrosis, pleural thickening, or pleural effusion (classically stony dull). The **cardiac dullness** is usually detectable over the left side of the chest. The **liver dullness** usually extends up to the fifth rib, right mid-clavicular line; if the chest is resonant below this level, it is a sign of lung hyperexpansion (eg asthma, emphysema).

Causes of a hyperresonant percussion note:

pneumothorax or hyperinflation (COPD).

Auscultation

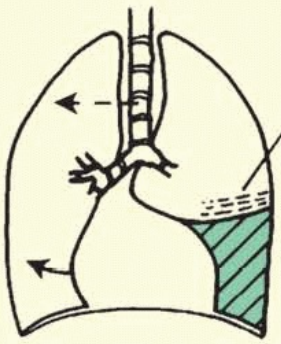
Listen with the diaphragm over symmetrical areas of the anterior, posterior, and axillary regions of the chest wall, and use the bell to auscultate over the supraclavicular fossae. ▸Consider breath sounds in terms of **quality**, **intensity**, and the **presence of additional sounds**.

- ***Quality and intensity*** Normal breath sounds have a rustling quality and are described as vesicular. **Bronchial breathing** has a hollow quality; there is a gap between inspiration and expiration. Bronchial breath sounds occur where normal lung tissue has become firm or solid, eg consolidation, localized fibrosis, above a pleural effusion, or next to a large pericardial effusion (Ewart's sign, p140). It may be associated with increased tactile vocal fremitus, vocal resonance, and whispering pectoriloquy (p76). **Diminished breath sounds** occur with pleural effusions, pleural thickening, pneumothorax (**fig 1**, p735), bronchial obstruction, asthma, or COPD. The **silent chest** occurs in life-threatening asthma and is due to severe bronchospasm which prevents adequate air entry into the chest.
- ***Added sounds*** **Wheezes (rhonchi)** are caused by air passing through narrowed airways. They may be monophonic (a single note, signifying a partial obstruction of one airway, eg tumour) or polyphonic ('My chest sounds like a load of cats'— multiple notes, signifying widespread narrowing of airways of differing calibre, eg asthma, COPD). Wheezes may also be heard in left ventricular failure ('cardiac asthma'). **Crackles (crepitations)** are caused by the re-opening, during inspiration, of the small airways which have become occluded during expiration. They may be fine and high pitched if coming from distal air spaces (eg pulmonary oedema, fibrosing alveolitis) or coarse and low pitched if they originate more proximally (eg bronchiectasis). The timing of crackles is important; early inspiratory crackles suggest small airways disease (eg COPD), whereas late/pan-inspiratory crackles suggest disease confined to the alveoli. Crackles that disappear on coughing are insignificant. **Pleural rubs** are caused by movement of the visceral pleura over the parietal pleura, when both surfaces are roughened, eg by an inflammatory exudate. Causes include adjacent pneumonia or pulmonary infarction. **Pneumothorax click** is produced by a shallow left pneumothorax between the 2 layers of parietal pleura over-lying the heart and is heard during cardiac systole.

▸Clinical examination has only a 50% sensitivity for picking up pneumonia (specificity 60-75%).

Physical signs on chest examination

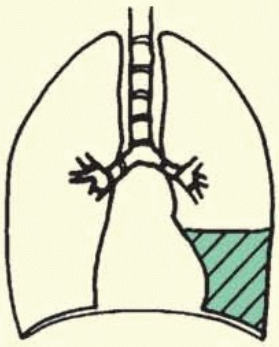
Some physical signs



(There may be bronchial breathing at the top of an effusion)

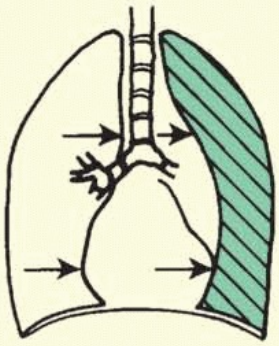
PLEURAL EFFUSION

Expansion: ↓
Percussion: Stony dull ↓
Air entry: ↓
Vocal resonance: ↓



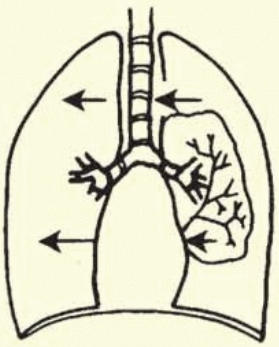
Trachea + mediastium central
Expansion ↓
Percussion note ↓
Vocal resonance ↑
Bronchial breathing ± coarse crackles (with whispering pectoriloquy)

CONSOLIDATION



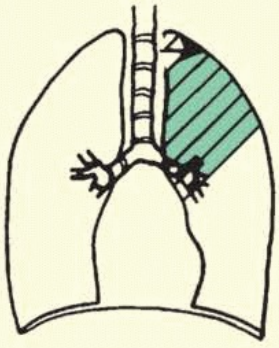
Expansion ↓
Percussion note ↓
Breath sounds ↓

EXTENSIVE COLLAPSE PNEUMONECTOMY/ LOBECTOMY



Expansion ↓
Percussion note ↑
Breath sounds ↓

PNEUMOTHORAX



Expansion ↓
Percussion note ↓
Breath sounds bronchial ± crackles

FIBROSIS

Gastrointestinal history

Presenting symptoms

Abdominal pain (p52), distension

Nausea, vomiting, haematemesis

Dysphagia (p232)

Indigestion (dyspepsia, p58)

Recent change in bowel habit

Diarrhoea or constipation (p240)

Rectal bleeding (p70) or melaena (p244)

Appetite, weight change

Mouth ulcers (p230); Jaundice (p242)

Pruritus; Dark urine, pale stools

Social history

Smoking, alcohol, recreational drug use

Overseas travel, tropical illnesses

Contact with jaundiced persons

Occupational exposures

Sexual orientation

Past history

Peptic ulcer disease

Carcinoma

Jaundice, hepatitis

Blood transfusions, tattoos

Previous operations

Last menstrual period (LMP)

Past treatment

Steroids, the Pill

NSAIDs; antibiotics

Dietary changes

Family history

Irritable bowel syndrome (IBS)

Inflammatory bowel disease (IBD)

Peptic ulcer disease

Polyps, cancer

Jaundice

Examining the gastrointestinal system

Inspect

(and smell) for signs of chronic liver disease:

- Hepatic fetor on breath (p250)
- Purpura (purple stained skin, p330)

- Spider naevi (**fig 1**, p253)
- Liver flap (asterixis, a coarse irregular tremor seen in hepatic failure)
- Leuconychia (hypoalbuminaemia)
- Gynaecomastia
- Scratch marks
- Palmar erythema
- Clubbing (rare)
- Muscle wasting
- Jaundice

Inspect for signs of malignancy, anaemia, jaundice, hard Virchow's node in left supraclavicular fossa (p614). Look at the abdomen. Note:

- Visible pulsation (aneurysm, p586)
- Striae (stretch marks, eg pregnancy)
- Peristalsis
- Distension
- Scars
- Genitalia
- Masses
- Herniae

If abdominal wall veins look dilated, assess **direction of flow**. In inferior vena caval (IVC) obstruction, flow below the umbilicus is up; in portal hypertension (*caput medusae*), flow radiates out from the umbilicus.

The cough test:

While looking at the face, ask the patient to cough. If this causes abdominal pain, flinching, or a protective movement of hands towards the abdomen, suspect peritonitis. (See BOX).

Genitourinary history

Presenting symptoms

Fever, loin/scrotal pain, dysuria, haematuria

Urethral/vaginal discharge (p406)

Sex—any problems? Painful intercourse (dyspareunia, OHCS p310)?

Menses: menarche, menopause, length of periods, amount, pain? Intermenstrual loss?

1st day of last menstrual period (LMP)?

Past history

Urinary tract infection

Renal colic

DM, BP↑, gout, analgesic use

Previous operations

Social history

Smoking

Sexual orientation

Detecting outflow obstruction

(eg from prostatic hypertrophy). Ask:

- On wanting to pass water, is there delay before you start? (**Hesitancy**)
- Does the flow stop and start? Do you go on dribbling when you think you've stopped, even after giving it a good shake? (**Terminal dribbling**)

- Is your stream getting weaker? Can you hit the wall OK? (**Poor stream**)
- Do you ever pass water when you do not want to? (**Incontinence**—p604)
- Do you feel the bladder is not empty after passing water?[i]
- On feeling an urge to pass water, do you have to go at once? (**Urgency**)[i]
- Do you urinate often at night? (**Nocturia**)[i] In the day? How often? (**Frequency**)[i]

Palpating and percussing the abdomen ▸**See also p52**

Adjust the patient so that he is lying flat, with his head resting on only 1 pillow, and his arms at his side. Expose from 'nipples to knees', but remember to consider modesty. Make sure that the patient and your hands are warm.

Inspection

See OPPOSITE. Is the abdomen moving with respiration? Count the respiratory rate (may be a marker of intra-abdominal disease); eg ↑ with **1** splinting of the diaphragm from distension; **2** fast, shallow breaths to avoid painful deeper inspiration; **3** respiratory compensation of metabolic acidosis; **4** shock.

Palpation

While palpating, be looking at his face to assess any pain. First palpate gently through each quadrant, starting away from the site of the pain—otherwise everywhere may be uncomfortable! Note tenderness, guarding (involuntary tensing of abdominal muscles because of pain or fear of it), and rebound tenderness (greater pain on removing hand than on gently depressing abdomen: it is a sign of peritoneal inflammation); Rovsing's sign (appendicitis, p582);[11] Murphy's sign (cholecystitis, p590).

Palpating the liver:

Begin in the right iliac fossa with the patient breathing deeply. Use the radial border of the index finger to feel the liver edge, moving up 2cm at a time at each breath in. Assess its size (causes of hepatomegaly—p63), regularity, smoothness, and tenderness. Is it pulsatile (tricuspid regurgitation)? Confirm the lower border and define the upper border by percussion (normal upper limit is in 5th intercostal space): it may be pushed down by emphysema. Listen for an overlying bruit. ***The scratch test*** is an another way to find the lower liver edge: start with the diaphragm of the stethoscope over the right costal margin. Gently scratch the abdominal wall, starting in the right lower quadrant and working up towards the liver edge. A sharp increase in transmission of the scratch is heard when the lower border of the liver is reached.

Palpating the spleen:

Start in the RIF, moving towards the left upper quadrant with each breath. **Features of the spleen differentiating it from kidney:** cannot get above it (ribs overlie its top); overlying percussion note is dull; it moves more with inspiration—towards the RIF; it may have a palpable notch on its medial side. If you suspect splenomegaly but cannot detect it, assess the patient in the right lateral position with your left hand pulling forwards from behind the rib cage. Is the percussion note dull in the mid-axillary line in the 10th intercostal space?

Palpating the kidneys:

Try bimanually with the left hand under the patient to push it up in the renal angle. Attempt to ballot the kidney (ie bounce it gently but decisively between a hand applied to the loin and the other applied opposite, anteriorly). It moves only slightly with respiration.

Percussion

If this induces pain, there may be peritoneal inflammation below (eg an inflamed appendix).[12] Some experts use percussion first, before palpation, because even anxious patients do not expect this to hurt—so, if it does hurt, this is a very valuable sign. Percuss for the shifting dullness of ascites (p624): the level of right-sided flank dullness increases by lying on the right, and vice versa for lying on the left. Ultrasound is a more reliable way of detecting ascites.

Auscultation

Bowel sounds: absence implies ileus; they are enhanced and tinkling in bowel obstruction. Listen for bruits in the aorta, renal and femoral arteries.

Examine

Mouth, tongue, rectum (p627), genitalia, and urine as appropriate.

Ordering the examination during clinical exams:

It can be useful to auscultate before palpation/percussion, as bowel sounds induced by palpation may mask vascular bruits (you should not palpate deeply in the vicinity of bruits lest you damage an aneurysm)—and this is the preferred order in many places. In the UK you may be expected to auscultate last, especially during finals examinations. If you don't, you might need to explain, 'I am auscultating now to detect bruits which might be dangerous to palpate.'

The neurological system

History

This should be taken from the patient and if possible, from a close friend or relative as well for corroboration/discrepancies. The patient's memory, perception, or speech may be affected by the disorder making the history difficult to obtain. Note the progression of the symptoms and signs: gradual deterioration (eg tumour) *vs* intermittent exacerbations (eg multiple sclerosis) vs rapid onset (eg stroke). Ask about age, occupation and ethnic origin. Right- or left-hand dominant?

Presenting symptoms

- ***Headache:*** (p448 & p768) Different to usual headaches? Acute/chronic? Speed of onset? Single/recurrent? Unilateral/bilateral? Associated aura (migraine, p450)? Any meningism (p806)? Worse on waking (↑ICP)? Decreased conscious level? ▸Take a 'worst-ever' headache very seriously. (See p735)
- ***Weakness:*** (p458) Speed of onset? Muscle groups affected? Sensory loss? Any sphincter disturbance? Loss of balance? Associated spinal/root pain?
- ***Visual disturbance:*** (OHCS p410) eg blurring, double vision (diplopia), photophobia, visual loss. Speed of onset? Any preceding symptoms? Pain in eye?

- ***Special senses:*** Hearing (p456), smell, taste.
- ***Dizziness:*** (p454) Illusion of surroundings moving (vertigo)? Hearing loss/tinnitus? Any loss of consciousness? Positional?
- ***Speech disturbance:*** (p46) Difficulty in expression, articulation, or comprehension (can be difficult to determine)? Sudden onset or gradual?
- ***Dysphagia:*** (p232) Solids and/or liquids? Intermittent or constant? Difficulty in coordination? Painful (odynophagia)?
- ***Fits/faints/'funny turns'/involuntary movements:*** (p452) Frequency? Duration? Mode of onset? Preceding aura? Loss of consciousness? Tongue biting? Incontinence? Any residual weakness/confusion? Family history?
- ***Skin sensation disturbance:*** Eg numbness, 'pins & needles' (paraesthesiae), pain, odd sensations. Distribution? Speed of onset? Associated weakness?
- ***Tremor:*** (p72) Rapid or slow tremor? Present at rest? Worse on deliberate movement? Taking Ò-agonists? Any thyroid problems? Any family history?

Cognitive state

If there is any doubt about the patient's cognition, an objective measure is a cognitive test—guessing has been shown to be inaccurate![13] The following 10 questions comprise the abbreviated mental test score (AMTS), a commonly used screening questionnaire for cognitive impairment:[14]

1. Tell patient an address to recall at the end (eg 42 West Street, Gateshead)
2. Age
3. Time (to nearest hour)
4. What year is it?
5. Recognize 2 people (eg doctor & nurse)
6. Date of birth
7. Dates of the Second World War
8. Name of present monarch
9. Name of hospital/institution
10. Count backwards from 20 to 1

A score of ≤6 suggests poor cognition, acute (delirium), or chronic (dementia). AMTS correlates well with the more detailed mini-mental state examination (MMSE™). **NB:** deaf, dysphasic, depressed, and un-cooperative patients, as well as those who do not understand English, will also get low scores.[15] See TABLE, p47 for a longer dementia score test.

Past medical history

Ask about meningitis/encephalitis, head/spine trauma, seizures, previous operations, risk factors for vascular disease (p462, AF, hypertension, hyperlipidaemia, diabetes mellitus, smoking), and recent travel. Is there any chance that the patient is pregnant (eclampsia, OHCS p48)?

Drug history

Any anticonvulsant/antipsychotic/antidepressant medication? Any psychotropic drugs (eg ecstasy)? Any medication with neurological side-effects (eg ***isoniazid*** which can cause a peripheral neuropathy)?

Social and family history

What can the patient do and not do, ie activities of daily living (ADLs)? What is the Barthel Index score?[16] Any neurological or psychiatric disease in the family? Any consanguinity?

Examining the neurological system

▸The neurological system is usually the most daunting examination to learn, but the most satisfying once perfected. Learn at the bedside from a senior colleague, preferably a neurologist, and there is no substitute for practice. Be aware that books present ideal situations: often one or more signs are equivocal or even contrary to expectation; don't be put off, consider the whole picture, including the history; try re-examining the patient.

Higher mental function

Conscious level (Glasgow coma scale, p776), orientation in time, place, and person, memory (short and long term). See opposite for the AMTS and p47 for the full mental test score (MTS).

Speech

Is there alteration in voice sound (**dysphonia** eg in laryngitis, recurrent laryngeal nerve palsy, or vocal cord tumour)? **Dysphasia** & **dysarthria**: see p46?

Skull and spine

Malformation. Signs of injury. Palpate scalp. If there is any question of spinal injury, **do not move the spine**: in-line immobilisation is required. Is there meningism (p806)? Auscultate for carotid/cranial bruits. Screening by listening for carotid bruits has a high specificity (91%) but a low sensitivity (56%), so if stenosis is suspected arrange a carotid ultrasound scan.[17]

Motor system

(upper or lower limb) ▸It is essential to discriminate whether weakness is upper (UMN) or lower (LMN) motor neurone (p439).

Inspect

for posture abnormality (eg 'pyramidal' posture of UMN lesions, p439), or involuntary movement, wasting, or fasciculation (muscle twitching, not moving the limb)?

Drift:

Patient sitting, arms outstretched, eyes closed. Do arms drift downwards? Unequal drift is a valuable sign of subtle focal motor deficits, occurring in UMN weakness, cerebellar disease, and loss of proprioception (=**pseudoathetosis**).

Tone:

Look for **hypotonia** (floppy) or **spasticity** (pressure fails to move a joint until it gives way, like a clasp-knife), rigidity (lead pipe), rigidity + tremor = cogwheeling. Is there **clonus** (rhythmic muscle 'beats' on sudden stretching, eg gastrocnemius on ankle dorsiflexion) at wrist, patella, or ankle?

Power:

(See p438) Oppose each movement. Ascertain the distribution of any weakness—which movements/nerve roots are affected (myotomes, p444)? Quantify strength of each movement eg using UK MRC scale (p439).

Reflexes:

Brisk in UMN lesions, reduced/absent in LMN lesions. Biceps reflex: (C5-6), triceps (C7-8), supinator (C5-6), knee (L3-4 ± L2), ankle (S1-2), abdominals (lost in UMN lesions), plantars (up-going in UMN lesions). **Hoffman's reflex:** flexion of thumb and index finger on flicking the middle finger's pulp (p439).

Coordination:

Finger-nose (touch nose with a finger), rub heel up and down shin, rapid alternating movements (eg rapidly pronate and supinate hand on dorsum of other hand; clumsiness in this (=**dysdiadochokinesis**) occurs in cerebellar lesions). Is there dyspraxia (p46)?

Gait:

(See p459) Ask the patient to walk: normally; heel-to-toe; on heels; then on toes. Observe standing feet together ± squatting. If balance is worse on shutting the eyes, **Romberg's test** is +ve, implying abnormal joint position sense. If he cannot perform this even with eyes open, this may be cerebellar ataxia, but is not Romberg's +ve.

Sensation

Dorsal column:

Light touch (cotton wool), vibration (128Hz tuning fork), joint position sense (=**proprioception**).

Spinothalamic:

pain (pin-prick) and temperature. Testing temperature sensation is not usually required, but can be performed with test tubes filled with hot and cold water. Determine if any sensory loss is below a spinal cord level (eg cord compression), or in a glove and stocking distribution (eg peripheral neuropathy)? See dermatomes on p446.

Cranial nerves

See p44.

Cranial nerve examination

Approach to examining the cranial nerves

Where is the lesion? Think systematically. Is it in the brainstem (eg MS), or outside, pressing on the brainstem? Is it the neuromuscular junction (myasthenia) or the muscles (eg a dystrophy)? Cranial nerves may be affected singly or in groups. ▸Face the patient (helps spot asymmetry). For causes of lesions, see BOX. For names of the nerves, see BOX, p49.

I	***Smell:*** Test ability of each nostril to distinguish familiar smells, eg peppermint.
II	***Acuity*** in each eye separately, and its correctability with glasses or pin-hole; use chart on p51. ***Visual fields:*** Compare during confrontation with your own fields or formally. Any losses/inattention? Sites of lesions: *OHCS* p428. *Pupils:* (p68) Size, shape, symmetry, reaction to light (direct and consensual), and accommodation if reaction to light is poor. ***Ophthalmoscopy:*** (*OHCS*, p412) Darken the room. Instil ***tropicamide*** 0.5%, 1 drop, if needed (▸check for history of glaucoma beforehand). Select the focusing lens for the best view of the optic disc (pale? swollen?). This is found when the ophthalmoscope's dot of light is reflected from the cornea at 9 o'clock (right disc) or 3 o'clock (left disc). Follow vessels outwards to view each quadrant; rack back through the lenses to inspect lens and cornea. If the view is obscured, examine the red reflex, with your focus on the margin of the pupil, to look for a cataract. You will get a view of the fovea if you ask the patient to look at the ophthalmoscope's finest beam (after drops)—this is the sacred place: the **only** place with 6/6 vision. ▸Pathology here merits prompt ophthalmic referral.
IV & VI	Eye movements. ***III palsy:*** Ptosis, large pupil, eye down and out. ***IV palsy:*** diplopia on

III^{P},	looking down and in (often noticed on descending stairs)— head tilting compensates for this (ocular torticollis). ***VI nerve palsy:*** Horizontal diplopia on looking out. ***Nystagmus*** is involuntary, often jerky, eye oscillations. Horizontal nystagmus is often due to a vestibular lesion (acute: nystagmus away from lesion; chronic: towards lesion), or cerebellar lesion (unilateral lesions cause nystagmus towards the affected side). If it is more in whichever eye is abducting, MS may be the cause (internuclear ophthalmoplegia, p64). If also deafness/tinnitus, suspect a peripheral cause (eg VIII lesion, barotrauma, Ménière's, p454). If it varies with head position, suspect benign positional vertigo (p454). If it is up-and-down, ask a neurologist to explain what is going on—upbeat nystagmus classically occurs with lesions in the midbrain or at the base of the 4th ventricle, downbeat nystagmus in foramen magnum lesions. Nystagmus lasting <2 beats is normal, as is nystagmus at the extremes of gaze.
V	***Motor palsy:*** 'Open your mouth': jaw deviates to side of lesion. ***Sensory:*** Corneal reflex lost first; check all 3 divisions.
VII^{P}	***Facial nerve lesions*** cause droop and weakness. As the forehead has bilateral representation in the brain, only the lower two-thirds is affected in UMN lesions, but all of one side of the face in LMN lesions. Ask to 'raise your eyebrows'; 'show me your teeth'; 'puff out your cheeks'. Taste can be tested (though rarely done) with salt/sweet solutions.
VIII	***Hearing:*** p456. Ask to repeat a number whispered in an ear while you block the other. Perform Weber's and Rinne's tests (p456). ***Balance/vertigo:*** p454.
IX^{P}	**& X^{P}** ***Gag reflex:*** Touch the back of the palate with a spatula to elicit a reflex contraction. The afferent arm of the reflex involves IX; the efferent arm involves X. X lesions also cause the palate to be pulled to the normal side on saying 'Ah'.
XI	***Trapezii:*** 'Shrug your shoulders' against resistance. ***Sternocleidomastoid:*** 'Turn your head to the left/right' against resistance.
XII	***Tongue movement:*** The tongue deviates to the side of the lesion.

Causes of cranial nerve lesions

Any cranial nerve may be affected by diabetes mellitus; stroke; MS; tumours; sarcoidosis; vasculitis, p542, eg PAN (p543), SLE (p540); syphilis. Chronic meningitis (malignant, TB, or fungal) tends to pick off the lower cranial nerves one by one.

I	Trauma; respiratory tract infection; frontal lobe tumour; meningitis.

	Field defects may start as small areas of visual loss (scotomas, eg in glaucoma). ***Monocular blindness:*** Lesions of one eye or optic nerve, eg MS, giant cell arteritis. ***Bilateral blindness:*** Methanol, tobacco amblyopia; neurosyphilis. **Field defects— *Bitemporal hemianopia:*** Optic chiasm compression, eg pituitary adenoma, craniopharyngioma, internal carotid artery aneurysm (**fig 1**, p440). ***Homonymous hemianopia:*** Affects half the visual field contralateral to the lesion in each eye. Lesions lie beyond the chiasm in the tracts, radiation, or occipital cortex, eg stroke, abscess, tumour.
II	***Optic neuritis*** (pain on moving eye, loss of central vision, afferent pupillary defect, disc swelling from papillitis). **Causes:** Demyelination (eg MS); rarely sinusitis, syphilis, collagen vascular disorders. ***Ischaemic papillopathy:*** Swelling of optic disc due to ischaemia of the posterior ciliary artery (eg in giant cell arteritis). ***Papilloedema (swollen discs):*** **1** ↑ICP (tumour, abscess, encephalitis, hydrocephalus, benign intracranial hypertension); **2** retro-orbital lesion (eg cavernous sinus thrombosis, p472). ***Optic atrophy*** (pale optic discs and reduced acuity): MS; frontal tumours; Friedreich's ataxia; retinitis pigmentosa; syphilis; glaucoma; Leber's optic atrophy; optic nerve compression.[18]
III[C]	**alone** Diabetes; giant cell arteritis; syphilis; posterior communicating artery aneurysm (+ surgery);[19] idiopathic; ↑ICP (if uncal herniation through the tentorium compresses the nerve). 3rd nerve palsies without a dilated pupil are typically 'medical' (eg diabetes; BP↑). Early dilatation of a pupil implies a compressive lesion, from a 'surgical' cause (tumour; aneurysm) because the parasympathetic fibres run on the outer aspect of the nerve.
IV[C]	**alone** Rare and usually due to trauma to the orbit.[20]
VI[C]	**alone** MS, Wernicke's encephalopathy, false localizing sign in ↑ICP, pontine stroke (presents with fixed small pupils ± quadriparesis).[21]
V[C]	***Sensory:*** Trigeminal neuralgia (pain but no sensory loss, p449), herpes zoster, nasopharyngeal cancer, acoustic neuroma (p454). *Motor:* Rare.
VII	***LMN:*** Bell's palsy (p492), polio, otitis media, skull fracture, cerebello-pontine angle tumours eg acoustic neuroma, malignant parotid tumours, herpes zoster (Ramsay Hunt syndrome *OHCS* p652). *UMN:* (spares the forehead, because of its bilateral innervation) Stroke, tumour.
VIII	(p454 & p456) Noise, Paget's disease, Ménière's disease, herpes zoster, acoustic neuroma, brainstem CVA, drugs (eg aminoglycosides).

IX, X, XII	Trauma, brainstem lesions, neck tumours.[22]
XI	Rare. Polio, syringomyelia, tumour, stroke, bulbar palsy, trauma, TB.

P Remember that these cranial nerves carry parasympathetic fibres. Sympathetic fibres originate from the thoracic chain and run with the arterial supply to distribute about the body.

C=structures passing through the cavernous sinus; see BOX, p49. **NB: V_a** is the only division of **V** to do so.

Groups of cranial nerves

VIII, then V ± VI: Cerebellopontine angle tumours, eg acoustic neuroma (p454; facial weakness is, surprisingly, not a prominent sign). **V & VI** (Gradenigo's syndrome): Lesion (eg a complication of otitis media) at the apex of the petrous temporal bone ('petroapicitis' on MRI).[23] **III, IV & VI:** Stroke, tumours, Wernicke's encephalopathy, aneurysms, MS.[24] **III, IV, V_a & VI:** Cavernous sinus thrombosis, superior orbital fissure lesions (Tolosa-Hunt syndrome, OHCS p654). **IX, X & XI:** Jugular foramen lesion. △△: Myasthenia gravis, muscular dystrophy, myotonic dystrophy, mononeuritis multiplex (p494).

Speech and higher mental function

▸Have mercy on those with dysphasia: they are suffocating because language is the oxygen of the mind.[1]

Dysphasia

(Impairment of language caused by brain damage) ***Assessment:***

1. If speech is fluent, grammatical and meaningful, dysphasia is unlikely.
2. **Comprehension:** Can the patient follow one, two, and several step commands? (touch your ear, stand up then close the door).
3. **Repetition:** Can the patient repeat a sentence?
4. **Naming:** Can he name common and uncommon things (eg parts of a watch)?
5. **Reading and writing:** Normal? They are usually affected like speech in dysphasia. If normal, the patient is unlikely to be aphasic—is he mute?

Classification:

- ***Broca's (expressive) anterior dysphasia:*** Non-fluent speech produced with effort and frustration with malformed words, eg 'spoot' for 'spoon' (or 'that thing'). Reading and writing are impaired but comprehension is relatively intact. Patients understand questions and attempt to convey meaningful answers. **Site of lesion:** infero-lateral dominant frontal lobe (see **fig 1**).
- ***Wernicke's (receptive) posterior dysphasia:*** Empty, fluent speech, like talking ragtime with phonemic (*flush* for *brush*) and semantic (*comb* for *brush*) paraphasias/neologisms (may be mistaken for psychotic speech). He is oblivious of errors. Reading, writing, **and** comprehension are impaired (replies are inappropriate). **Site of lesion:** posterior superior dominant temporal lobe.
- ***Conduction aphasia:*** (Traffic between Broca's and Wernicke's area is interrupted.) Repetition is impaired; comprehension and fluency less so.
- ***Nominal dysphasia:*** Naming is affected in all dysphasias, but in nominal dysphasia, objects cannot be named but other aspects of speech are normal. This occurs with posterior dominant temporoparietal lesions.

▸Mixed dysphasias are common. Discriminating features take time to emerge after an acute brain injury (**fig 1**). Consider speech therapy (of variable use).

Dysarthria

Difficulty with articulation due to incoordination or weakness of the musculature of speech. Language is normal (see above).

Assessment:

Ask to repeat ‘British constitution’ or ‘baby hippopotamus’.

- ***Cerebellar disease:*** Ataxia speech muscles cause slurring (as if drunk) and speech irregular in volume and scanning or staccato in quality.
- ***Extrapyramidal disease:*** Soft, indistinct, and monotonous speech.
- ***Pseudobulbar palsy:*** (p498) Spastic dysarthria (**upper motor neurone**). Speech is slow, indistinct, and effortful (‘Donald Duck’ or ‘hot potato’ voice from bilateral hemispheric lesions, MND (p498), or severe MS).
- ***Bulbar palsy:*** **Lower motor neurone** (eg facial nerve palsy, Guillain-Barré, MND, p498)—any associated palatal paralysis gives speech a nasal character.

Dysphonia

Difficulty with speech volume due to weakness of respiratory muscles or vocal cords (Myasthenia, p504; Guillain-Barré syndrome, p694). It may be precipitated in myasthenia by asking the patient to count to 100. Parkinson's gives a mixed picture of dysarthria and dysphonia.

Dyspraxia

(Poor performance of complex movements despite ability to do each individual component). Test by asking the patient to copy unfamiliar hand positions, or mime an object's use, eg a comb. The term ‘dyspraxia’ is used in 3 other ways:

- ***Dressing dyspraxia:*** The patient is unsure of the orientation of clothes on his body. Test by pulling one sleeve of a sweater inside out before asking the patient to put it back on (mostly nondominant hemisphere lesions).
- ***Constructional dyspraxia:*** Difficulty in assembling objects or drawing—a 5-pointed star (nondominant hemisphere lesions, hepatic encephalopathy).
- ***Gait dyspraxia:*** More common in the elderly; seen with bilateral frontal lesions, lesions in the posterior temporal region, and hydrocephalus.

Problems with classifying dysphasias

The classical model of language comprehension occurring in Wernicke's area and language expression in Broca's area is too simple. Functional MRI studies show that the old idea that the processing of abstract words is confined to the left hemisphere, whereas concrete words are processed on the right is too simplistic.[1] It may be better to think of a mosaic of language centres in the brain with more or less specialized functions. There is evidence that tool-naming is handled differently and in a different area to fruit-naming.[25] There are also individual differences in the anatomy of these mosaics.[26] This is depressing for those who want a rigid classification of aphasia, but a source of hope to those who have had a stroke: recovery may be better than neuroimaging leads us to believe.[27] So, where possible, be optimistic.

[1] While abstract words activate a sub-region of the left inferior frontal gyrus more strongly than concrete words, specific activity for concrete words can also be observed in the left basal temporal cortex.

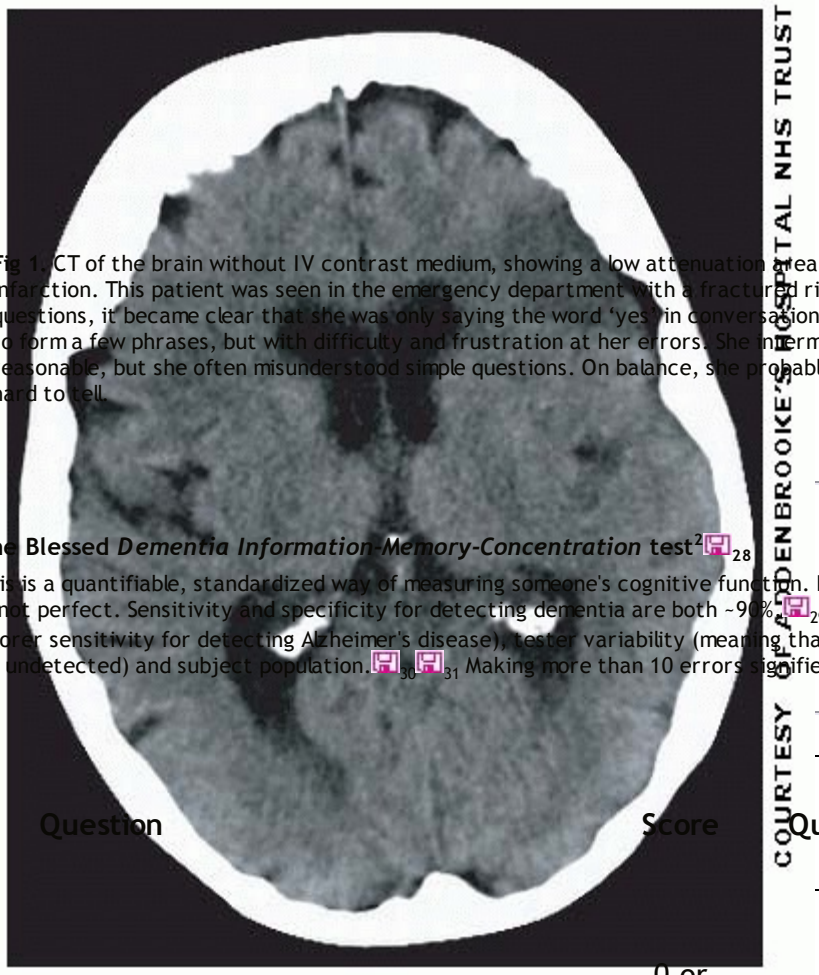


Fig 1. CT of the brain without IV contrast medium, showing a low attenuation area in the frontal lobe, corresponding to an area of acute infarction. This patient was seen in the emergency department with a fractured right neck of femur: she had fallen on to her right side. After a few questions, it became clear that she was only saying the word 'yes' in conversation. Further assessment of her speech revealed that she was able to form a few phrases, but with difficulty and frustration at her errors. She intermittently understood 3-stage commands and repetition was reasonable, but she often misunderstood simple questions. On balance, she probably had an expressive dysphasia, but in the acute setting it was hard to tell.

The Blessed *Dementia Information-Memory-Concentration* test[2][28]

This is a quantifiable, standardized way of measuring someone's cognitive function. It is most useful for serial measurements, but like all such scores it is not perfect. Sensitivity and specificity for detecting dementia are both ~90%[29] though scores will varying according to underlying diagnosis (eg poorer sensitivity for detecting Alzheimer's disease), tester variability (meaning that a 2-3 point improvement eg on starting some new treatment may go undetected) and subject population.[30][31] Making more than 10 errors signifies cognitive impairment:

Question	Score	Question	Score
Know his name	0 or 1	Type of place eg hospital	0 or 1
Know his age	0 or 1	Name of hospital	0 or 1
Time (to nearest hour is OK)	0 or 1	Name of ward	0 or 1
Time of day	0 or 1	Name of town	0 or 1
Day of the week	0 or 1	School	0 or 1
Date of month	0 or 1	(Former) occupation	0 or 1
Season	0 or 1	(Former) employer	0 or 1

Current year	0 or 1	Former town of work or home	0 or 1
Teach name and address and test recall after 5min:		Prime minister or head of government name	0 or 1
Mr. John Brown		Years of World War I	0 or 1
42 West Street	0 to 5	Years of World War II	0 or 1
Gateshead		Monarch/head of state's name	0 or 1
Recognises 2 people	0, 1 or 2	Months of year backwards	0, 1 or 2
Birthday	0 or 1	Count from 1 to 20	0, 1 or 2
Town of birth	0 or 1	Count from 20 to 1	0, 1 or 2
Name of spouse or sibling	0 or 1	**Maximum score**	**36**

NB: Including an 'informant report questionnaire' improves the efficiency of the mental test score as a screening tool for dementia.[32] Another score that can be used to assess cognitive function is the mini-mental state examination (MMSE™), though recent copyright means that its use has become more restricted.[33] See also the AMTS, p42.

[2] Kafka's law: *In youth we take examinations to get into institutions. In old age to keep out of them.*

Psychiatric assessment

Introduce yourself, ask a few factual questions (precise name, age, marital status, job, and who is at home). These will help your patient to relax.

Presenting problem

Then ask for the main problems which have led to this consultation. Sit back and listen. Don't worry whether the information is in a convenient form or not—this is an opportunity for the patient to come out with his worries unsullied by your expectations. After 3–5min you should have a list of all the problems (each sketched only briefly). Read them back to the patient and ask if there are any more. Then ask about:

History of presenting problem

For each problem obtain details, both current state and history of onset, precipitating factors, and effects on life.

Check of major psychiatric symptoms

Check those which have not yet been covered: **depression**—low mood, anhedonia (inability to feel pleasure), thoughts of worthlessness/hopelessness, sleep disturbance with early morning waking, loss of weight and appetite. Ask specifically about **suicidal thoughts and plans:** 'Have you ever been so low that you thought of harming yourself?', 'What thoughts have you had?' **Hallucinations** ('Have you ever heard voices when there hasn't been anyone there, or seen visions?'), and **delusions** ('Have you ever had any thoughts or beliefs which have struck you afterwards as bizarre?'); **anxiety** and **avoidance behaviour** (eg avoiding shopping because of anxiety or phobias); **obsessional thoughts** and **compulsive behaviour, eating disorders**, **alcohol** (see p274 for alcohol screening tests) and **other drugs.**

Present circumstances

Housing, finance, work, marriage, friends.

Family history

Ask about health, personality, and occupation of parents and siblings, and the **family's medical and psychiatric history.**

Background history

Try to understand the presenting problem.

- ***Biography*** (relationships with family and peers as a child; school and work record; sexual relationships and current relationships; and family). Previous ways of dealing with stress and whether there have been problems and symptoms similar to the presenting ones.
- ***Premorbid personality*** (mood, character, hobbies, attitudes, and beliefs).

Past medical and psychiatric history

Mental state examination

This is the state **now**, at the time of interview.

- ***Appearance:*** Clothing, glasses, headwear? Unkempt/meticulous?
- ***Observable behaviour:*** Eg excessive slowness, signs of anxiety.
- ***Mode of speech:*** Include the rate of speech, eg retarded or gabbling (pressure of speech). Note its content. Flight of ideas? Knight's move? (See BOX)
- ***Mood:*** Note thoughts about harming self or others. Gauge your own responses to the patient. The laughter and grand ideas of manic patients are contagious, as to a lesser extent is the expression of thoughts from a depressed person.
- ***Beliefs:*** Eg about himself, his own body, about other people, and the future. Note abnormal beliefs (delusions), eg that thoughts are overheard, and abnormal ideas (eg persecutory, grandiose).
- ***Unusual experiences or hallucinations:*** Note modality, eg visual, auditory.
- ***Orientation:*** In time, place, and person. What is the date? What time of day is it? Where are you? What is your name?
- ***Short-term memory:*** Give a name and address and test recall after 5min. Make sure that he has got the address clear in his head before waiting the 5min.
- ***Long-term memory:*** Current affairs recall. Name of current political leaders (p47). This tests many other CNS functions, not just memory.
- ***Concentration:*** Months of the year backwards.
- Note the degree of your ***rapport*** and the patient's ***insight*** into his current state.

Nonverbal behaviour

Gesture, gaze and mutual gaze, expressions, tears, laughter, pauses (while listening to voices?), attitude (eg withdrawn).

Psychiatric symptoms

There are many different ways to think about psychiatric symptoms. One simple approach can be to consider negative and positive symptoms. ***Negative symptoms*** involve the absence of a behaviour, thought, feeling or sensation (eg lack of appetite, apathy, and blunted emotions in depression), whereas ***positive symptoms*** involve their presence when not normally expected (eg thought insertion, ie 'someone is putting thoughts into my head'). Understanding the difference between psychosis and neurosis is vital. ***Psychosis*** entails a thought disorder (eg thought insertion, thought broadcasting) ± delusions (abnormal beliefs which are held to despite all reasoning, and which run counter to the patient's culture) and abnormal perceptions (eg hallucinations), ***neurosis*** entails insight—if there are intrusive ideas or odd experiential phenomena the person knows that they are false or illusory (and may be triggered by stress etc).

Interesting abnormalities of speech include ***flight of ideas***, in which the speech races through themes, switching whimsically or through associations eg 'clang' association: 'Yesterday I went down to the local shop. I didn't hop (*clang*), but I walked. Kangaroos hop, don't they. My friend Joey wasn't there, though …'. ***Knight's move*** is an unexpected change in the direction of speech or conversation (akin to the lateral component of the move of the knight's piece in chess) and ***neologism*** is the formation of new words. They may be normal or indicate an organic brain condition or a psychosis.

Many psychiatric symptoms in isolation, to a lesser degree of severity, or even in a different culture, may well be considered part of 'normal' behaviour. For example, where would we be without language embracing brave new words?[34] As with so many aspects of medicine, in psychiatry there is a vast spectrum of behaviour, thought and perception, at least one extreme of which is considered to be 'abnormal'. It is in part our challenge to attempt to interpret these symptoms with relevance, insight and impartiality so that we may best benefit our patients and not form opinions that are set in stone. On acute medical wards psychiatric symptoms are usually due to stress, drug or alcohol withdrawal, U&E imbalance, or medication. When in doubt, ask a psychiatrist to help. **NB:** it is normal for the bereaved to hear the voice of the person who has died.

▸Beware of simplistic formulations, eg *If you talk to God, you are praying. If God talks to you, you have schizophrenia* (Dr Thomas Szasz). It is not the auditory phenomenon which makes the diagnosis of psychosis: what matters is what the patient believes about the phenomenon, and whether they are associated with a thought disorder or a delusion.

The contents of the cavernous sinus and the cranial nerve names

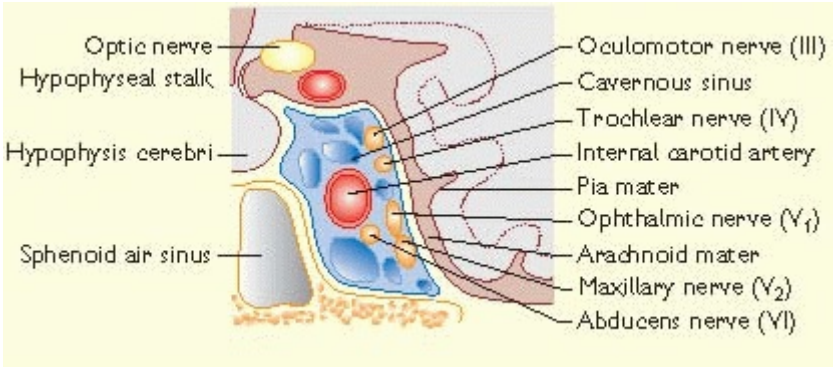


Image after RSCI website

Cranial nerve names	
I	olfactory
II	optic
III	oculomotor
IV	trochlear
V	trigeminal

V_1	ophthalmic division
V_2	maxillary division
V_3	mandibular division
VI	abducens
VII	facial
VIII	vestibulocochlear
XI	glossopharyngeal
X	vagus
XI	accessory
XII	hypoglossal

Method and order for routine examination

We all have our own system, sometimes based on these lines, but sometimes containing elements unique to each doctor, arising from his or her own interaction with countless past patients and their eccentricities. This fact is one reason why it is often so helpful to ask for second opinions: the same field may be ploughed again but yield quite a different harvest.

1. Look at the patient. Healthy, unwell, or *in extremis*? This vital skill improves with practice. ▸Beware those who are sicker than they look, eg cardiogenic shock; cord compression; nonaccidental injury.
2. Pulse, BP; T°; infrared tympanic^{IRT} & liquid crystal^{LC} devices avoid mercury.[1]
3. Examine nails, hands, conjunctivae (anaemia), and sclerae (Þjaundice). Consider: Paget's, acromegaly, endocrine disease (thyroid, pituitary, or adrenal hypo/ hyperfunction), body hair, abnormal pigmentation, skin.
4. Examine mouth and tongue (cyanosed; smooth; furred; beefy, eg rhomboid area denuded of papillae by *Candida*, after prolonged steroid inhaler use).

5. Examine the neck from behind: nodes, goitre.
6. Make sure the patient is at 45° to begin CVS examination in the neck: JVP; feel for character and volume of carotid pulse.
7. The praecordium. Look for abnormal pulsations. Feel the apex beat (character; position). Any parasternal heave or thrill? Auscultate (bell & diaphragm) apex in the left lateral position, then the other 3 areas (p29) and carotids. Sit the patient forward: listen during expiration.
8. Whilst sitting forward, look for sacral oedema.
9. Begin the respiratory examination with the patient at 90°. Observe (and count) respirations; note posterior chest wall movement. Assess expansion, then percuss and auscultate the chest with the bell.
10. Sit the patient back. Feel the trachea. Inspect again. Assess expansion of the anterior chest. Percuss and auscultate again.
11. Examine the breasts* (if indicated) and axillary nodes (p610).
12. Lie the patient flat with only one pillow. Inspect, palpate, percuss, and auscultate the abdomen.
13. Look at the legs: any swellings, perfusion, pulses, or oedema?
14. CNS exam: *Cranial nerves:* pupil responses; fundi; visual fields; visual acuity. Do corneal reflexes. 'Open your mouth; stick your tongue out; screw up your eyes; show me your teeth; raise your eyebrows.' *Peripheral nerves:* Look for wasting and fasciculation. Test tone in all limbs. 'Hold your hands out with your palms towards the ceiling and fingers wide. Now shut your eyes.' Watch for pronator drift. 'Keep your eyes shut and touch your nose with each index finger.' 'Lift your leg straight in the air. Keep it there. Put your heel on the opposite knee (eyes shut) and run it up your own shin.' You have now tested power, coordination, and joint position sense. Tuning fork on toes and index fingers to assess vibration sense.
15. Examine the gait and the speech.
16. Any abnormalities of higher mental function to pursue?
17. Consider rectal and vaginal examination.*
18. Examine the urine with dipstick and microscope if appropriate.

▸***Remember the need for a chaperone for all intimate examinations.**

▸**In general, go into detail where you find (or suspect) something to be wrong.**

He moved N. 48

all the brightest gems N. 24

faster and faster towards the N.18

ever-growing bucket of lost hopes; had there been just one more year N. 14

of peace the battalion would have made a floating system of perpetual drainage. N. 12

A silent fall of immense snow came near oily remains of the recently eaten supper on the table. N. 10

We drove on in our old sunless walnut. Presently classical eggs ticked in the new afternoon shadows. N. 8

We were instructed by my cousin Jasper not to exercise by country house visiting unless accompanied by thirteen geese or gangsters. N. 6

The modern American did not prevail over the pair of redundant bronze puppies. The worn-out principle is a bad omen which I am never glad to ransom in August. N. 5

Record the smallest type (eg N. 12 left eye, N.6 right eye, spectacles worn) or object accurately read or named at 30cm

Acknowledgements

Principle sources: *Clinical Examination*, 4e, NJ Talley and S O'Connor, Blackwell Science, ISBN 0729537420; *Aids to Undergraduate Medicine*, 6e, JL Burton *et al*, Churchill, ISBN 0443056927.

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Title: *Oxford Handbook of Clinical Medicine, 7th Edition*

3

Signs and Symptoms

Symptoms are features which patients report. ***Physical signs*** are elicited at the bedside. Together, they constitute the features of the condition in that patient. Their evolution over time, and interaction with the physical, psychological, and social spheres comprise the natural history of any disease. Here, we discuss symptoms in isolation. This is unnatural—but a good first step in learning how to diagnose. All doctors have to know about symptoms and their relief: this is what doctors are for. This chapter is disappointing in trying to explain *combinations* of symptoms, as illnesses often do not fit into the 80-or-so features given below. It was this disappointment which was our stimulus to produce our electronic system, where over 20,000 signs, symptoms, and test results can be sifted in devious and diverse ways to help with difficult problems in differential diagnosis. See www.webmentorlibrary.com. So do not expect too much from this chapter: just a few common causes of common symptoms and signs.

Abdominal distension

Causes:

The famous five **FS (see BOX)**. Specific groups: *Air* is resonant on percussion. *Ascites* is free fluid in the peritoneal cavity. Signs: shifting dullness and fluid thrill (p41). The characteristic feature of *pelvic masses* is that you cannot get below them (ie their lower border is undefined). Causes of *right iliac fossa masses:* Appendix mass/abscess (p582), kidney mass, caecal cancer, a Crohn's or TB mass, intussusception, amoebic abscess or any pelvic mass.

Also see causes of *ascites with portal hypertension* (p624), *hepatomegaly* (p62), *splenomegaly*, and *other abdominal masses* (p624).

Abdominal pain

varies depending on the underlying cause. Examples: irritation of the mucosa (acute gastritis), smooth muscle spasm (acute enterocolitis), capsular stretching (liver congestion in CCF), peritoneal inflammation (acute appendicitis) and direct splanchnic nerve stimulation (retroperitoneal extension of tumour). The *character* (constant or colicky, sharp or dull), *duration,* and *frequency* depend on the mechanism of production. The *location* and *distribution* of referred pain depend on the anatomical site. *Time of occurrence* and *aggravating* or *relieving factors* such as meals, defecation, and sleep also have special significance related to the underlying disease process. ▸Evaluation of the acute abdomen is considered on p580. The site of the pain may provide a clue as to the cause:

- Epigastric pain Pancreatitis, gastritis or duodenitis, peptic ulcer, gall bladder disease, aortic aneurysm.
- Left upper quadrant pain Peptic ulcer, gastric or colonic (splenic flexure) ca, splenic rupture, subphrenic or perinephric abscess, renal (colic, pyelonephritis).
- Right upper quadrant pain Cholecystitis, biliary colic, hepatitis, peptic ulcer, colonic cancer (hepatic flexure), renal (colic, pyelonephritis), subphrenic or perinephric abscess.
- Loin pain Renal colic, pyelonephritis, renal tumour, perinephric abscess, pain referred from vertebral column.
- Left iliac fossa pain Diverticulitis, volvulus, colon cancer, pelvic abscess, inflammatory bowel disease, hip pathology, renal colic, urinary tract infection (UTI), cancer in undescended testis. *Gynae:* Torsion of ovarian cyst, salpingitis, ectopic pregnancy. Right iliac fossa pain All causes of left iliac fossa pain plus appendicitis and Crohn's ileitis, but usually excluding diverticulitis.
- Pelvic pain *Urological:* Urinary tract infection (UTI), urinary retention, bladder stones. *Gynae:* Menstruation, pregnancy, endometriosis (OHCS p288), salpingitis, endometritis (OHCS p274), torsion of ovarian cyst.
- Generalised: Gastroenteritis, irritable bowel syndrome, peritonitis, constipation.
- Central: Mesenteric ischaemia, abdominal aneurysm, pancreatitis.
- *Remember referred pain:* Myocardial infarct ?epigastrium; pleural pathology.

Amaurosis fugax

See p468.

Abdominal distension: the *Famous Five* Fs: Fat, flatus, fluid, faeces, and fetus

Air	Ascites	Solid masses	Pelvic masses
	Malignancy[1]	Malignancy[1]	Bladder: full

			or Ca
Intestinal obstruction (incl. faecal)	Cirrhosis	Lymph nodes	Fibroids; fetus
	Right heart failure	Aortic aneurysm	Ovarian cyst
Aerophagy (air swallowing)	Hypoproteinaemia (eg nephrotic)	Cysts: renal, pancreatic	Ovarian cancer Uterine cancer

[1] Any intra-abdominal organ, eg colon, stomach, pancreas, liver, kidney.

Enid Blyton's *Famous Five* characters can generally solve any crime or diagnostic problem using 1950s methodologies steeped in endless school holidays, copious midnight feasts (always confection laden), and lashings of homemade ginger beer.

The one insoluble problem was (and is) abdominal distension. The methods used by the Famous Five actually *contribute* to each of its causes: fat, fluid, faeces, flatus, and fetus. If you think it far-fetched to implicate ginger-beer in the genesis of fetuses, note that because it was home-made, like the fun, there was no limit to its intoxicating powers in those long-gone vintage summers.

Enid Blyton did her best to minimize the risks of unwanted pregnancies by gender reassignment (George) and by making one of her characters a dog (Timmy)—but accidents *must* have happened. The point is to remember to ask 'when was your last period' *whenever* confronted by a distended abdomen.

Anaemia

is haemoglobin concentration below the normal range (see p310). It may be assessed from the conjunctivae and skin creases. Koilonychia and stomatitis (p26) suggest iron deficiency. Anaemia with jaundice suggests haemolysis.

Athetosis

This is due to a lesion in the putamen, causing slow sinuous writhing movements in the hands, which are present at rest.

Pseudoathetosis

refers to athetoid movements in patients with severe proprioceptive loss.

Backache

p528.

Blackouts

p452.

Breathlessness

(dyspnoea) p58.

Breast pain

Often this is premenstrual (*cyclical mastalgia*, OHCS p254)—but the patient may be worried that she has breast cancer. So examine carefully (p610), and refer eg for mammography as appropriate. If there is no sign of breast pathology, and it is not cyclical, think of:

- Tietze's syndrome
- Bornholm disease[1]
- Gallstones
- Lung disease
- Angina
- Thoracic outlet syndrome
- Oestrogens (HRT)

If none of the above, *wearing a firm bra* all day may help, as may NSAIDs.

Cachexia

Severe generalized muscle wasting implying malnutrition, neoplasia, CCF, Alzheimer's disease, prolonged inanition, or infection—eg TB, enteropathic AIDS ('slim disease', eg from *Cryptosporidium*, p380).

Carotid bruits

may signify stenosis (>30%) caused by atheroma, often near the internal carotid origin. Heard best behind the angle of jaw. The key question is: *is he/she symptomatic?* If symptomatic (ie has had a TIA or carotid artery territory stroke) and the disability is not too severe, do a doppler ultrasound of the carotid arteries, and consider surgery if stenosis $\gtrsim$70%, and *possibly* if $\gtrsim$50% (p468).[2] Surgery for asymptomatic patients is debatable.[3] In anyone with a carotid bruit, consider aspirin prophylaxis. Ask a neurologist's advice.

[2] 21% reduction in 5yr risk of stroke or surgical death if stenosis $\gtrsim$70%; 5.7% reduction if 50-70% stenosis; below 50% stenosis surgery is unhelpful/harmful. See PM Rothwell 2003 *Stroke* **34** 514.

Chest deformity

• *Barrel chest:* AP diameter↑, tracheal descent and chest expansion↓, seen in chronic hyperinflation (eg asthma/COPD). • *Pigeon chest (pectus carinatum):* Prominent sternum with a flat chest, seen with lung hyperinflation while bony thorax is still developing eg in chronic childhood asthma. Often seen with *Harrison's sulcus*, a groove deformity caused by indrawing of the lower ribs at the diaphragm attachment site. • *Funnel chest (pectus excavatum):* Developmental defect involving local sternum depression (lower end). • *Kyphosis:* 'Humpback' from ↑ AP thoracic spine curvature. • *Scoliosis:* Lateral curvature (OHCS p672); both of these may cause a restrictive ventilatory defect.

Chest pain

See p80 & p772.

Cheyne-Stokes respiration

Breathing becomes progressively deeper and then shallower (±episodic apnoea) in cycles.

Causes:

Brainstem lesions or compression (stroke, ICP↑). If the cycle is long (eg 3min), the cause may be a long lung-to-brain circulation time (eg in chronic pulmonary oedema or poor cardiac output). It is enhanced by opioids.

Chorea

means dance—a continuous flow of jerky movements, flitting from one limb or part to another. Each movement looks like a fragment of a normal movement. It should be distinguished from athetosis/pseudoathetosis (above), and hemiballismus (see p460).

Causes:

Basal ganglia lesion: Huntington's disease (p694), post-infective: Sydenham's chorea (St Vitus' dance—p128), SLE (p540), Wilson's disease (p257), kernicterus, polycythaemia (p350), neuroacanthocytosis (a familial association of acanthocytes in peripheral blood with chorea, oro-facial dyskinesia, and axonal neuropathy), hyperthyroidism (p202), drugs (L-dopa, contraceptive steroids, chlorpromazine). Early stages of chorea may be detected by feeling fluctuations in muscle tension while the patient grips your finger. Treat with dopamine antagonists, eg tetrabenazine 12.5mg/12h (/24h if elderly) PO; increase, eg to 25mg/8h PO; max 200mg/d.

Chvostek's sign

Tapping on the facial nerve over the parotid gland causes a facial twitch in hypocalcaemia, due to nerve hyperexcitability. See Trousseau's sign.

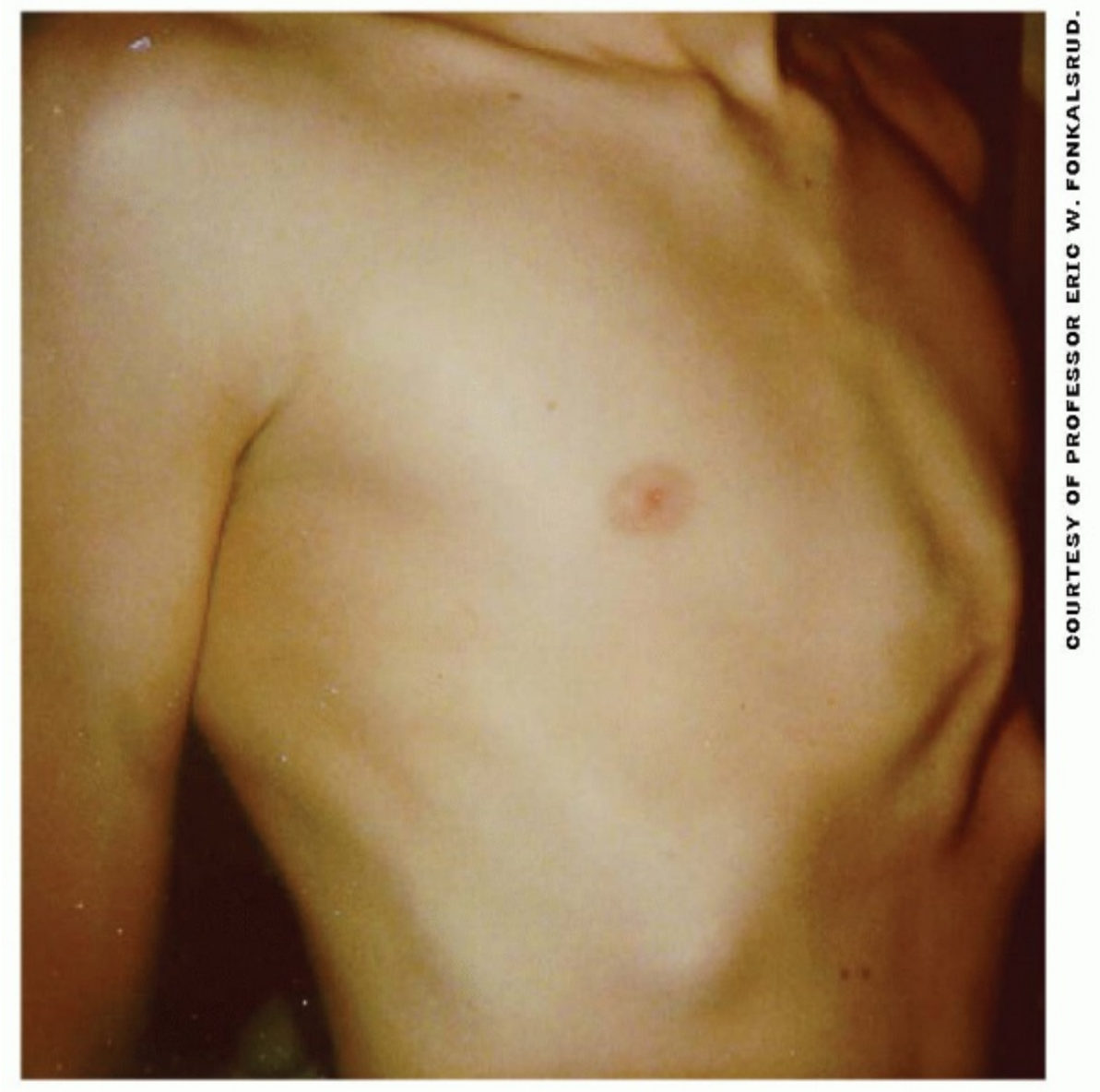


Fig 1. Pectus carinatum (pigeon chest).[1]

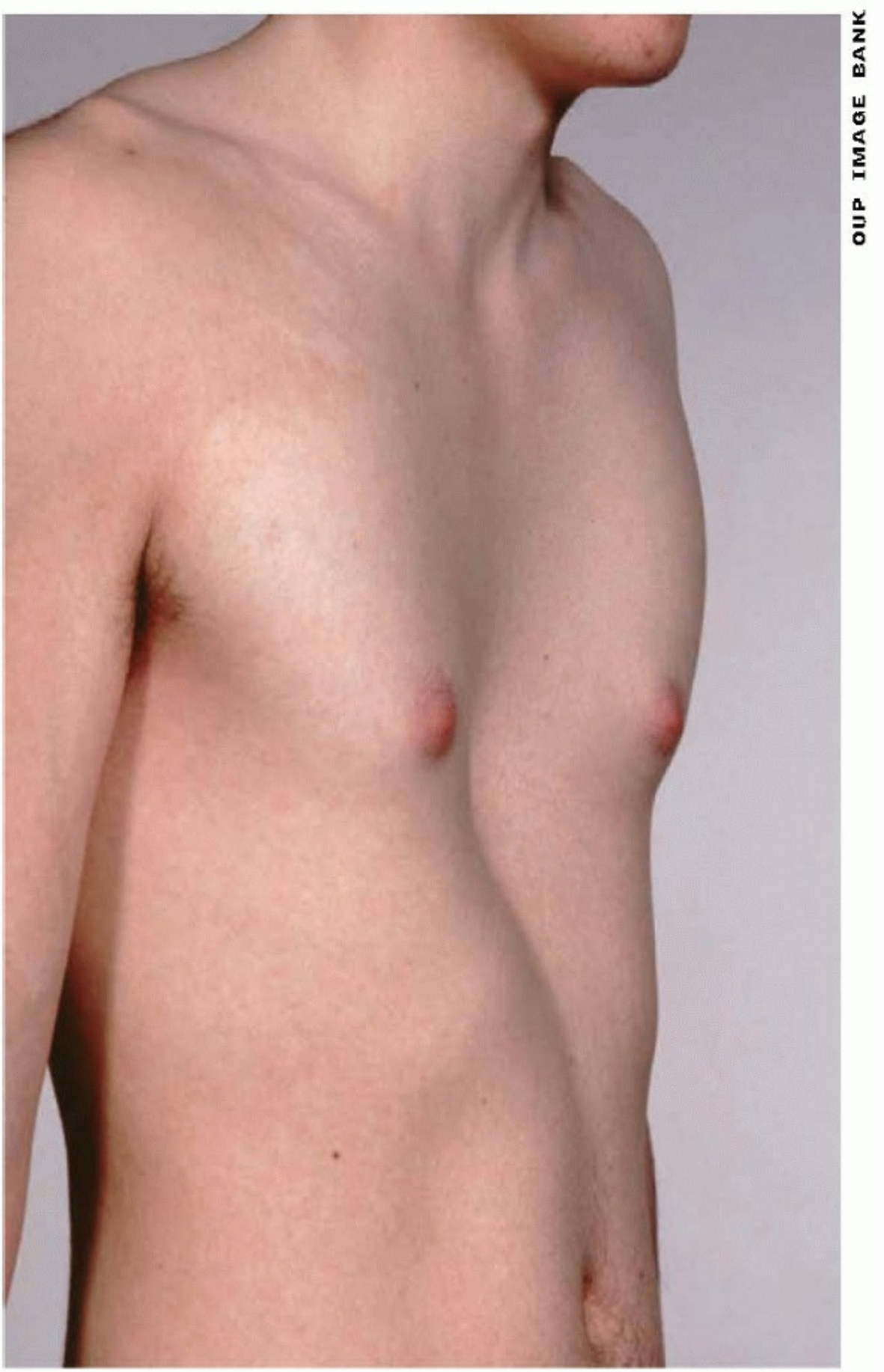


Fig 2. Pectus excavatum. The medical term for funnel or sunken chest. It is usually asymptomatic, but may cause displacement of the heart to the left, and restricted ventilatory capacity. Associations: Scoliosis, Marfan's, and Ehlers-Danlos syndromes.

Clubbing

Finger nails (±toenails) have exaggerated curvature in all directions. There is a loss of the angle between nail and nail-fold, and the nail-fold feels boggy. There are changes in local blood flow, but the exact mechanism is unclear.

Thoracic causes:

- Bronchial carcinoma (usually *not* small cell)
- Chronic lung suppuration
  - empyema, abscess
  - bronchiectasis
  - cystic fibrosis
- Fibrosing alveolitis
- Mesothelioma

GI causes:

- Inflammatory bowel disease (especially Crohn's)
- Cirrhosis
- GI lymphoma
- Malabsorption, eg coeliac

Rare:

- Familial
- Thyroid acropachy (p546)
- Unilateral clubbing, from:
  - axillary artery aneurysm
  - brachial arteriovenous malformations

Cardiac causes:

- Cyanotic congenital heart disease
- Endocarditis
- Atrial myxoma

Confusion

This common phenomenon is often multifactorial (p476). Remember alcohol withdrawal as a cause, classically occurring 48 hours after admission with vivid hallucinations.

Constipation

See p240.

Cough

See p37. See also Haemoptysis (p63).

Cramp

(Painful muscle spasm). Cramp in the legs is common, especially at night or after exercise. It only occasionally indicates disease, in particular: salt depletion, muscle ischaemia, or myopathy. Forearm cramps suggest motor neurone disease. Night cramps may respond to passive exercises or quinine bisulfate 300mg at night PO. Writer's cramp is a focal dystonia causing difficulty with the motor act of writing. The pen is gripped firmly, with excessive flexion of the thumb and index finger (± tremor). There is normally no CNS deficit. Oral drugs or psychotherapy rarely work, but botulinum toxin (OHCS p460) often helps, sometimes dramatically (it has side-effects). Similar specific dystonias may apply to other muscle groups.

Cyanosis

Dusky blue skin (*peripheral*—of the fingers) or mucosae (*central*—of the tongue), representing ≥2.5g/dL of Hb in its reduced form, hence it occurs more readily in polycythaemia than anaemia.

Causes:

- ***Lung disease*** with inadequate oxygen transfer eg luminal obstruction, asthma, COPD, pneumonia, PE, pulmonary oedema—may be correctable by ↑ inspired O2.
- ***Cyanotic congenital heart disease***, where there is shunting from pulmonary to systemic circulation bypassing the lungs, eg patent ductus arteriosus, transposition of the great arteries, VSD with right to left shunting (Eisenmenger's syndrome, see p143)—cyanosis is *not* reversed by increasing inspired oxygen.
- Rare cause: methaemoglobinaemia, a congenital or acquired red cell disorder.

▸Acute cyanosis is a sign of impending emergency. Is there asthma, an inhaled foreign body, a pneumothorax (p735, fig 1) or pulmonary oedema? See p798.

Peripheral cyanosis

will occur in causes of central cyanosis, but may also be induced by changes in the peripheral and cutaneous vascular systems in patients with normal oxygen saturations. It occurs in the cold, in hypovolaemia, and in arterial disease, and is therefore not a specific sign.

How to test for finger clubbing

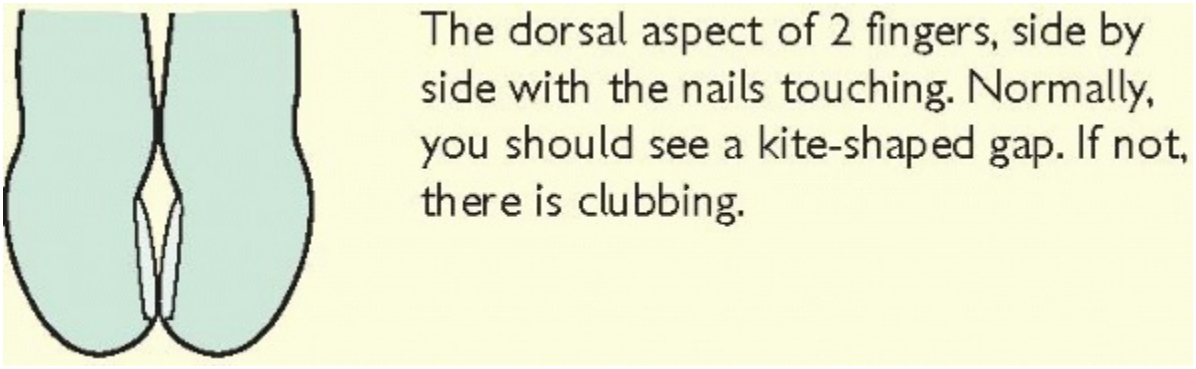


Fig. 1a

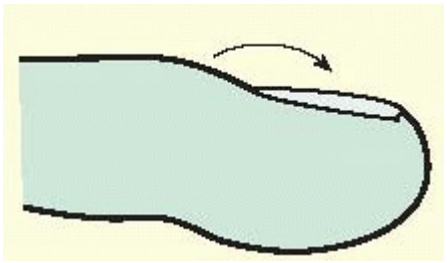


Fig. 1b

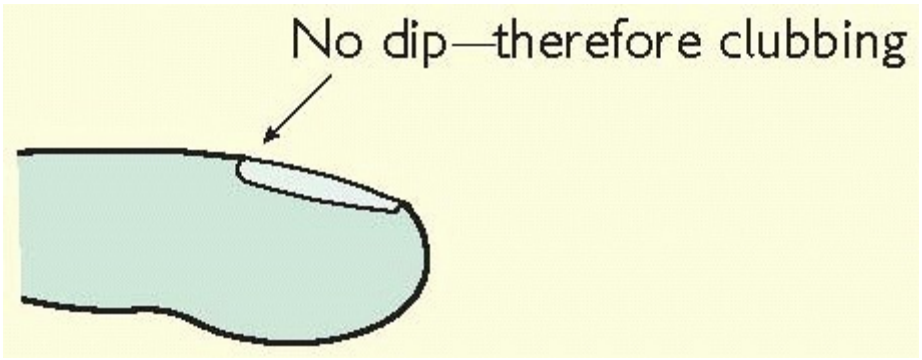


Fig. 1c

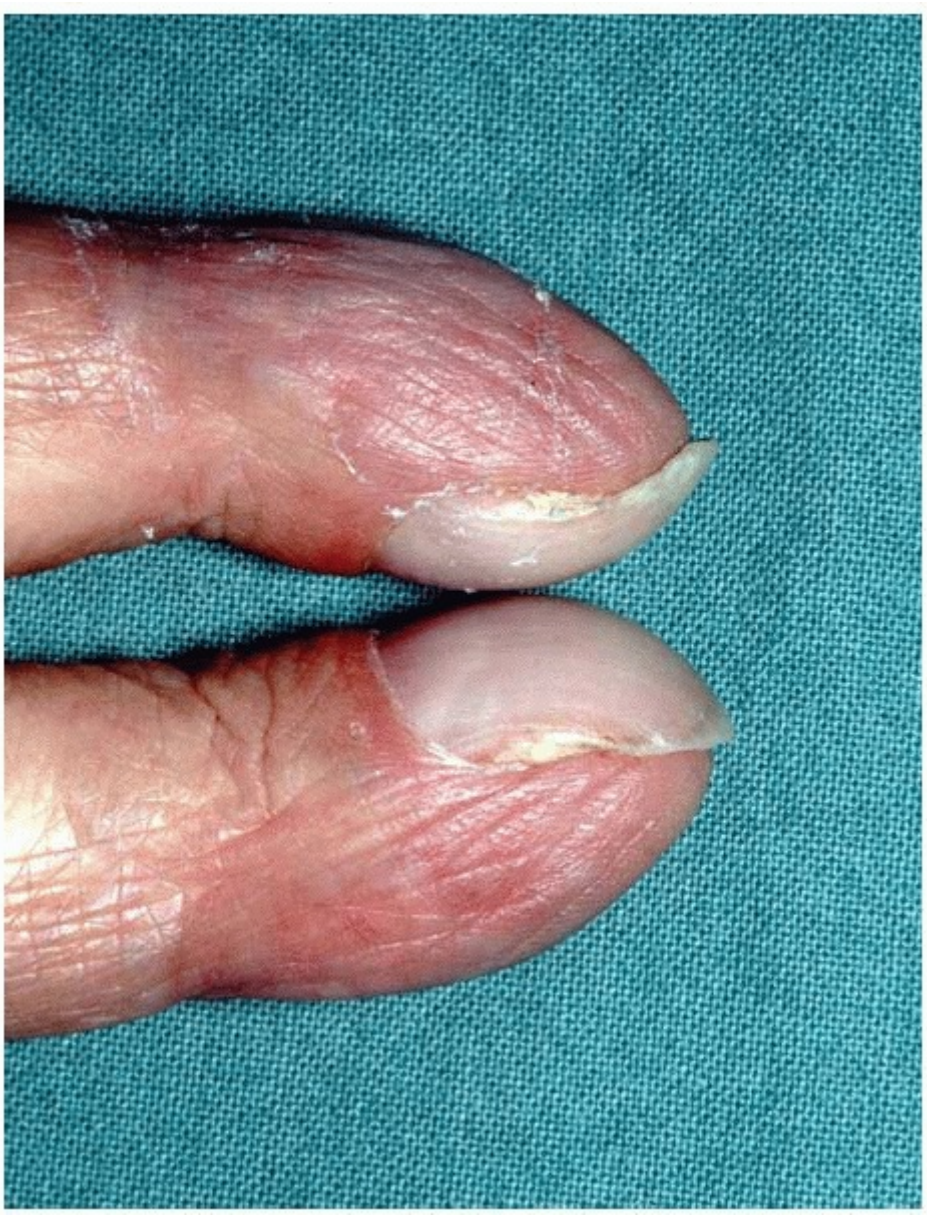


Fig 1. Clubbing: increased curvature of the nail, with loss of angle between the nail and nail-fold.

Deafness

See p456.

Dehydration

See p666.

Diarrhoea

See p238.

Dizziness

is a loose term meaning: *vertigo* (p454), the illusion of rotation ± an unwilled need to cast oneself into any nearby abyss ***or imbalance***, a difficulty in walking straight, from peripheral nerve, posterior column, cerebellar, or other central pathway failure ***or faintness***, ie 'light-headedness', seen in anaemia, ↓BP, postural hypotension, hypoglycaemia, carotid sinus hypersensitivity, and epilepsy. All may co-exist: *'At the place where I stood, the hillside was cut away like a cliff, with the sea groaning at its foot, blue and pure. There was no more than a moment to suffer… how terrible was the dizziness of that thought! Twice I threw myself forward, and I do not know what power flung me back, still alive, on to the grass which I kissed.'*[2]

Dysarthria

See p46.

Dysdiadochokinesis

See p491.

Dyspepsia and indigestion

See 234. These are broad terms, used often to signify epigastric or retrosternal pain (or discomfort), which may be related to meals. Find out exactly what your patient is complaining of. 30% have no abnormality on endoscopy (p248).

Dysphasia

See p46.

Dysphonia

See p46.

Dysphagia

See p232.

Dyspnoea

(p770) is the subjective sensation of shortness of breath, often exacerbated by exertion. Try to quantify exercise tolerance (eg dressing, distance walked, climbing stairs, NYHA classification—p121). May be due to:

- *Cardiac*—eg mitral stenosis, ischaemic heart disease or left ventricular failure (LVF) of any cause. LVF is associated with ***orthopnoea*** (dyspnoea worse on lying; 'how many pillows?') and ***paroxysmal nocturnal dyspnoea*** (PND; dyspnoea waking one up). Other features include ankle oedema, lung crepitations and ↑JVP.
- *Lung*—both airway and interstitial disease. It may be hard to separate from cardiac causes; asthma may also wake the patient, as well as cause early morning dyspnoea and wheeze. Focus on the circumstances in which dyspnoea occurs (eg on exposure to an occupational allergen).
- *Anatomical*—eg diseases of the chest wall, muscles, pleura. Ascites can cause breathlessness by splinting on the diaphragm, restricting its movement.
- *Others* ▸Any patient who is shocked may also be dyspnoeic (p581)—and this may be shock's presenting feature. Other causes: anaemia or metabolic acidosis causing respiratory compensation eg ketoacidosis, aspirin poisoning. Look for other clues—dyspnoea at rest *unassociated with exertion* may be psychogenic: prolonged hyperventilation causes respiratory alkalosis. This causes a fall in ionised calcium leading to an apparent hypocalcaemia. Symptoms and signs include peripheral and perioral paraesthesiae ± carpopedal spasm.

The speed of onset helps diagnosis:

Acute	Subacute	Chronic
Foreign body	Asthma	COPD and chronic

Pneumothorax (p735, fig 1)	Parenchymal disease	parenchymal diseases
Acute asthma	eg alveolitis	Non-respiratory causes
Pulmonary embolus	effusion	eg cardiac failure
Acute pulmonary oedema	pneumonia	anaemia

Dyspraxia

See p46.

Dysuria

is painful micturition from urethral or bladder inflammation, typically from infection (see also urethral syndrome, p282). *Strangury* is pain in the urethra referred from the base of the bladder, associated with the constant distressing desire to urinate even when there is little urine to void. Causes include a stone, an indwelling catheter, cystitis, prostatitis, and bladder cancer.

Facial pain

This can be neurological (eg trigeminal neuralgia, p449) or from any other pain-sensitive structure in the head or neck (see BOX).

Postherpetic neuralgia:

This nasty burning-and-stabbing pain involves dermatomal areas previously affected by shingles (herpes zoster, p388); it may affect cranial nerves V and VII in the face. It all too often becomes chronic and intractable, and the skin affected is exquisitely sensitive. Treatment is difficult. Give strong psychological support whatever else is tried. Transcutaneous nerve stimulation, capsaicin ointment, and infiltration of local anaesthetic may be tried. Amitriptyline eg 10-25mg/24h at night may help, as may carbamazepine (NNT ≈ 4). **NB:** Meta-analyses indicate that famciclovir and valaciclovir given in the acute stage may ↓duration of neuralgia.[3]

Faecal incontinence

This is common in the elderly. Be sure to find out who does the washing: they may be under severe stress (Social Services may help with laundry). The cause may disappear if constipation (p240) is treated (='overflow incontinence'/diarrhoea). Do a PR to check for this.

GI causes:

Rectal prolapse, tumour, sphincter laxity, severe piles, causes of diarrhoea (p238). Others: see BOX.

Faints, Collapse, Blackouts

See p452.

Falls

These are a common cause of admission in the elderly, and can lead to a spiral of loss of confidence and dependence. Causes are often multifactorial and include:

Intrinsic:

CNS disease, visual impairment, cognitive impairment, depression, postural hypotension, peripheral neuropathy, medication (eg antihypertensives, sedatives), pain eg arthritis, Parkinsonism (including medications: prochlorperazine, neuroleptics, metoclopramide), muscle weakness, incontinence, alcohol.

Environment:

Poor lighting, uneven walking surface. Treatment includes addressing injuries, reducing risk factors, and reducing the risk of injury eg treat osteoporosis (p674). A multidisciplinary multifactorial approach alongside occupational therapists and physiotherapists is likely to be beneficial.[4]

Fatigue

This feeling is so common that it is a variant of normality. Only 1 in 400 episodes leads to a consultation with a doctor. ▸Do not miss depression which often presents in this way. Even if the patient is depressed, a screening history and examination is important to rule out chronic disease.

Tests

to consider are FBC, ESR, U&E, plasma glucose, TFT ± CXR. Arrange follow-up to see what develops, and to address any emotional problems that develop.

Fever and night sweats

(see *Sweating*) While some night sweating is common in anxiety, drenching sweats requiring changes of night-clothes are a more ominous symptom associated with infection (eg TB, brucellosis), lymphoproliferative disease, or mesothelioma. Patterns of fever may be relevant (see p376). See Rigors.

Flatulence

400-1300mL of gas are expelled PR per day, and if this, coupled with belching (eructation) and abdominal distension, seems excessive to the patient, he may complain of flatulence. Eructation may occur in those with hiatus hernia—but most patients complaining of flatulence have no GI disease. The most likely cause is air-swallowing (aerophagy).

Frequency (urinary)

means ↑ frequency of micturition. Aim to differentiate ↑ urine production (eg diabetes mellitus, diabetes insipidus, polydipsia, diuretics, alcohol, renal tubular disease, or adrenal insufficiency) from frequent passage of small amounts of urine (eg in cystitis, urethritis, neurogenic bladder), or bladder compression (eg from pregnancy, bladder tumour, or an enlarged prostate).

Gait disorders

See p459.

Guarding

Involuntary reflex contraction of abdominal muscles as you press on the abdomen (gently!), signifying local or general peritoneal inflammation (p580). It is an imperfect sign of peritonism, but is one of the best we have; if you decide not to operate on someone with RIF guarding, the risk of missing appendicitis is about 25%. If you *do* operate, the chance of finding appendicitis is 50%. See Rebound abdominal pain.

Gynaecomastia

p214.

Haematemesis

p244.

Haematuria

p278.

Non-neurological causes of facial pain

Neck	Cervical disc pathology
Sinuses	Sinusitis, neoplasia
Eye	Glaucoma, iritis, eye strain
Temporomandibular joint	Arthritis

Teeth	Caries, abscess, malocclusion
Ear	Otitis media, otitis externa
Vascular	Giant cell arteritis

NB: when all causes are excluded, a group which is mostly young and female remains ('atypical facial pain') who complain of unilateral pain deep in the face or at the angle of cheek and nose, which is constant, severe, and unresponsive to analgesia. Do not dismiss these as psychological: few meet criteria for hysteria or depression. Do not expose these patients to the risks of destructive surgery; while many are prescribed antidepressants, some neurologists advocate no treatment.

Non-gastrointestinal causes of faecal incontinence

Neurological	Spinal cord compression, Parkinson's disease, stroke, MS, spinal trauma (S2-S4), dementia.
Endocrinological	Diabetes mellitus (autonomic neuropathy), hypothyroidism.
Obstetric	Damage to puborectalis (or nerve roots) at childbirth.

Treatment is directed to the cause if possible. Avoid dehydration. Be sure to do a PR to exclude overflow incontinence. If all sensible measures fail, try the brakeand-accelerator approach: enemas to empty the rectum (eg twice weekly) and codeine phosphate eg 15mg/12h PO on non-enema days to constipate. This is not a cure, but makes the incontinence manageable.

Haemoptysis

See BOX. Always think of TB or malignancy; don't confuse with epistaxis or haematemesis. The blood is *coughed up,* eg frothy, alkaline, and bright red, often in a context of known chest disease. **NB:** Melaena may occur if enough blood is swallowed. Haematemesis is acidic and dark. Blood not mixed with sputum suggests lung infarction (pulmonary embolism, PE) or trauma. Haemoptysis rarely needs treating in its own right, but if massive (eg trauma, TB, hydatid cyst, cancer, AV malformation), call a chest physician/surgeon (the danger is drowning; lobe resection, endobronchial tamponade, or arterial embolization may be needed). Set up IVI, do CXR, blood gases, FBC, INR/APTT, crossmatch. If distressing, consider *prompt* IV morphine, eg if inoperable malignancy.[5]

Halitosis

(fetor oris, oral malodour) results from gingivitis (Vincent's angina, p704), metabolic activity of bacteria in plaque, or sulfide-yielding food putrefaction.

Contributory factors:

Smoking, alcohol, drugs (disulfiram; isosorbide); lung disease. Delusional halitosis is quite common.

Treatment:

Try to eliminate anaerobes: • Stand nearer the toothbrush • Dental floss • 0.2% aqueous chlorhexidine gluconate. See *Clinical Evidence* 2006, BMA.

Headache

See p448 & p768.

Heartburn

An intermittent, gripping, retrosternal pain usually worsened by: stooping/lying, large meals and pregnancy. See oesophagitis, p236.

Hemiballismus

This refers to the uncontrolled unilateral flailing movements of proximal limb joints caused by contralateral subthalamic lesions. See p460.

Hepatomegaly

See BOX.

Hoarseness

See p36, and OHCS p568.

Hyperpigmentation

See Skin discolouration (p70).

Hyperventilation

is over-breathing; it may be *fast* (tachypnoea, ie >20breaths/min) or *deep* (hyperpnoea, ie tidal volume ↑). Hyperpnoea is not troublesome to the patient (unlike dyspnoea). It may be enough to cause a respiratory alkalosis, leading to paraesthesiae ± muscle spasm (plasma Ca^{2+}↓). The main cause is anxiety: there is associated dizziness, chest tightness/pain, palpitations, and panic. Rarer causes: response to metabolic acidosis and brainstem lesions.

- *Kussmaul respiration* is deep, sighing breathing that is principally seen in severe metabolic acidosis—eg diabetic ketoacidosis, renal failure.
- *Neurogenic hyperventilation* is produced by pontine lesions.
- The *hyperventilation syndrome* involves panic attacks associated with hyperventilation, palpitations, dizziness, faintness, tinnitus, alarming chest pain/tightness,MLT_6 perioral and peripheral tingling (plasma Ca^{2+}↓). Treatment: relaxation techniques and breathing into a paper bag (↑ inspired CO_2 corrects the alkalosis).

NB: The anxious patient in A&E with hyperventilation and a respiratory alkalosis may actually be presenting with an aspirin overdose (p828).

Insomnia

When we are sleeping well this is a trivial and irritating complaint, but if we suffer a few sleepless nights, sleep becomes the most desirable thing imaginable and the ability to bestow sleep the best thing we can do for a patient, second only to relieving pain. As all *Sons and lovers know*, 'Sleep is most perfect when it is shared with a beloved.'$_7$ Do not resort to drugs without asking: *What is the cause? Can it be treated?* See BOX.

Management:

'Sleep hygiene' • Do not go to bed until you feel sleepy.

- Avoid daytime naps. Establish regular bedtime routines.
- If you can, reserve a room for sleep. Do not eat or study in it.
- Avoid caffeine, nicotine, alcohol—and late-evening hard exercise (sexual activity is the exception: it may produce excellent torpor).
- Consider monitoring with a sleep diary (quantifies sleep pattern and quality), but this could feed insomnia by encouraging obsessions.

Prescribe hypnotics for a few weeks only: they are addictive and cause daytime somnolence ± rebound insomnia on stopping. Warn about driving/machine working. Example: zopiclone 3.75-7.5mg PO.

Obstructive sleep apnoea:

p186 ***parasomnias, sleep paralysis, & hypnopsychic states:*** OHCS p392.

Narcolepsy:

p692.

Causes of haemoptysis

1	*Respiratory causes of haemoptysis*		
		Traumatic	Wounds, post-intubation, foreign body.
		Infective	Bronchiectasis, acute bronchitis, pneumonia, lung abscess, TB, COPD, fungi, paragonimiasis (p433).
		Neoplastic	Primary or secondary.
		Vascular	Lung infarction (PE), vasculitis (pulmonary haemorrhage in Wegener's, RA, SLE, Osler-Weber-Rendu), AV malformation.
		Parenchymal	Diffuse interstitial fibrosis, sarcoidosis, haemosiderosis, Goodpasture's syndrome, cystic fibrosis.
2	*Cardiovascular (pulmonary hypertension)*		Pulmonary oedema, mitral stenosis, aortic aneurysm, Eisenmenger's syndrome (p143).
3	*Bleeding diatheses*		

The science of halitosis

Locally retained bacteria metabolize sulfur-containing amino acids to yield volatile hydrogen sulfide and methylmercaptane. Not only do these stink, but they also damage surrounding tissue, thereby perpetuating bacterial retention and periodontal disease.

At night and between meals conditions are optimal for odour production—so eating regularly may help. To supplement conventional oral hygienic measures, some people advise brushing of the tongue. Oral care products containing metal ions, especially Zn, inhibit odour formation, it is thought, because of affinity of the metal ion to sulfur.

It is possible to measure the level of volatile sulfur-containing compounds in the air in the mouth directly by means of a portable sulfide monitor (a great way to plague your friends).

Causes of hepatomegaly

- *Malignancy:* Metastatic or primary (usually craggy hepatomegaly).
- *Hepatic congestion:* Right heart failure—may be pulsatile in tricuspid incompetence, hepatic vein thrombosis (Budd-Chiari syndrome, p688).
- *Anatomical:* Riedel's lobe (normal variant).
- *Infection:* Infectious mononucleosis (glandular fever), hepatitis viruses, malaria, schistosomiasis, amoebic abscess, hydatid cyst.
- *Haematological:* Leukaemia, lymphoma, myeloproliferative disorders (eg myelofibrosis), sickle-cell disease, haemolytic anaemias.
- *Others:* Fatty liver, early cirrhosis, porphyria, storage disorders (eg amyloidosis, Gaucher's disease).

For causes of hepatosplenomegaly, see p624.

Examples of common causes of insomnia

- *Self-limiting:* Jet lag, depression, stress, shift work, in hospital.
- *Psychological:* Drugs, anxiety, mania, grief.
- *Organic:* Nocturia, alcoholism, pain, itch, tinnitus, asthma, dystonias, obstructive sleep apnoea (p186).

Internuclear ophthalmoplegia

See BOX 1.

Itching (pruritus)

is common and, if chronic, most unpleasant.

Local causes:

Eczema, atopy, urticaria

Scabies

Lichen planus

Dermatitis herpetiformis

Systemic:

(Do FBC, ESR, glucose, LFT, U&E, ferritin, TFT)

Liver disease (bile salts eg PBC)

Chronic renal failure

Malignancy (eg lymphoma)

Polycythaemia rubra vera

Iron deficiency anaemia

Old age; pregnancy

Drugs (eg morphine)

Diabetes mellitus

Thyroid disease

HIV infection

Questions:

Is there itch with weals (urticaria); is itching worse at night and are others affected (scabies); what provokes it? After a bath ≈ polycythaemia rubra vera (p350). Exposure, eg to animals (atopy?) or fibre glass (irritant eczema?) Look for *local causes:* scabies burrows in the finger webs, lice on hair shafts, knee and elbow blisters (dermatitis herpetiformis).

Systemic:

splenomegaly, nodes, jaundice, flushed face or thyroid signs?

Treat

primary diseases; try soothing bland emollients, eg E45®, ± emollient bath oils and sedative antihistamines at night, eg chlorphenamine 4mg PO.

Jaundice

See p242.

Jugular venous pulse and pressure

See p30.

Lid lag

is lagging behind of the upper eyelid as the eye looks down (after first looking upwards).

Lid retraction

is the static state of the upper eyelid traversing the eye *above* the iris, rather than over it, causing a 'staring' appearance.

Cause

(for both): hyperthyroidism (p202).

Lymphadenopathy

may be localised or generalised (see BOX 2). A large left supraclavicular lymph node (Virchow's node) suggests carcinoma of the stomach (Troisier's sign, see p7).

Musculoskeletal symptoms

Chiefly ***pain***, ***deformity***, ***reduced function***.

Pain:

Degenerative arthritis generally produces an aching pain worse with exercise and relieved by rest. Discomfort may worsen with certain motions, and may be associated with 'gelling' of joints, so they get stuck in particular positions. Cervical or lumbar spine degeneration produces a subjective change in sensation not following a dermatomal distribution. Both inflammatory and degenerative joint disease produce *morning stiffness* in affected joints, but in the former this generally improves during the day, while in the latter the pain is worse at the end of the day. The pain of *bone erosion* due to tumour or aneurysm is deep, boring, and constant. The pain of *fracture* or *infection* of the bone is severe and throbbing and is increased by motion of the part. *Acute nerve compression* causes a sharp, severe pain radiating along the distribution of the nerve. Joint pain may be referred, eg from a hip disorder to the anterior and lateral aspect of the thigh or the knee; shoulder to the lateral aspect of the humerus; cervical spine to the interscapular area, medial border of scapulae or shoulder tip + lateral side of arms. (*Back pain*, p528; *GALS locomotor test*, p527.)

Reduced function:

Causes include: pain, bone or joint instability, or ↓ joint movement (due to muscle weakness, contractures, bony fusion or mechanical block by intracapsular bony fragments or cartilage).

Nodules (subcutaneous)

Rheumatoid nodules, PAN, xanthomata, tuberous sclerosis, neurofibromata, sarcoidosis, granuloma annulare, rheumatic fever.

Nystagmus

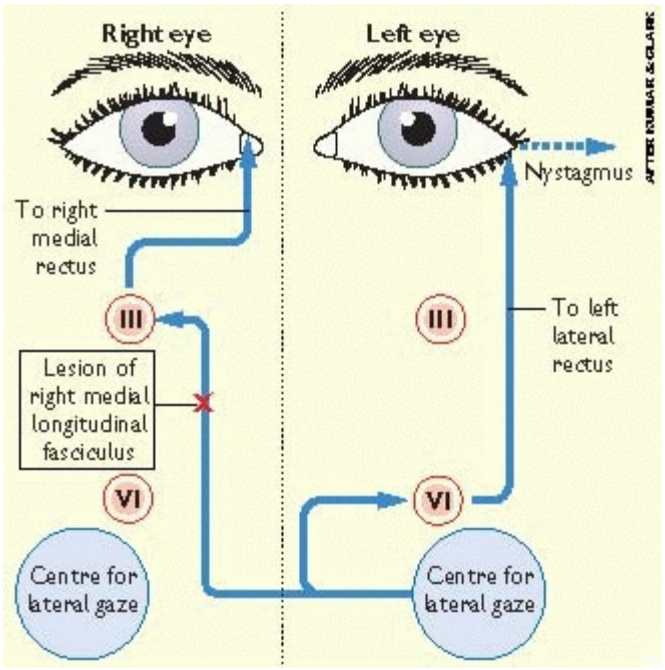
See p44.

Obesity

This is defined by the World Health Organisation as a BMI of over 30kg/m^2. A higher waist to hip ratio, indicating central fat distribution, is commoner in û and is associated with greater health risks, which include Type 2 diabetes mellitus, IHD, dyslipidaemia, ↑BP, osteoarthritis of weight bearing joints, and cancer (breast and bowel). The majority of cases are not due to specific metabolic disorders. Lifestyle change is key to treatment, to increase energy expenditure, and reduce intake (p228). Medication ± surgery may be considered if the patient fulfils strict criteria[1]. Conditions associated with obesity include: genetic (Prader-Willi syndrome, Lawrence-Moon syndrome), hypothyroidism, Cushing's syndrome and hypothalamic damage (eg tumour or trauma → damage to satiety regions).

Internuclear ophthalmoplegia (INO) and its causes

To produce synchronous eye movements, cranial nerves III, IV, and VI communicate through the medial longitudinal fasciculus in the midbrain. In INO, a lesion disrupts this communication, causing weakness in adduction of the ipsilateral eye with nystagmus of the contralateral eye only when it is abducting. There may be incomplete or slow abduction of the ipsilateral eye during lateral gaze. Convergence is preserved. Chief causes: multiple sclerosis or vascular (more rarely: HIV; syphilis; Lyme disease; brainstem tumours; phenothiazine toxicity).[8]



Causes of lymphadenopathy are either reactive or infiltrative

- Reactive
  - Infective

    Bacterial: eg pyogenic, TB, brucella, syphilis.
    Viral: EBV, HIV, CMV, infectious hepatitis.
    Others: Toxoplasmosis, trypanosomiasis).

  - Non-infective Sarcoidosis, amyloidosis, berylliosis, connective tissue disease (eg rheumatoid, SLE), dermatological (eczema, psoriasis), drugs (eg phenytoin).
- Infiltrative
  - Benign Histiocytosis—OHCS p644, lipoidoses.
  - Malignant

    Haematological: Lymphoma or leukaemia: ALL, CLL, AML (p340).
    Metastatic carcinoma: From breast, lung, bowel, prostate, kidney or head and neck cancers.

Oedema

(p564).

Causes:

↑*Local venous pressure* eg DVT or right-heart failure ± *ñintravascular oncotic pressure:* ↓plasma proteins, eg in cirrhosis, nephrotic syndrome, malnutrition, or protein-losing enteropathy: here water moves down the osmotic gradient into the interstitium to dilute the solutes there—Starling's principle. On standing, venous pressure at the ankle rises due to the height of blood from the heart (~100mmHg). This is short-lived if leg movement pumps blood through valved veins, but if venous pressure rises, or valves fail, capillary pressure rises and fluid is forced out causing oedema.

Pitting oedema

(**fig 1** & p564).

Nonpitting oedema:

(ie non-indentible) ≈ poor lymph drainage (lymphoedema), eg primary (Milroy's syndrome, p698) or secondary, due to radiotherapy, malignant infiltration, infection, filariasis. The mechanism is complex.[9]

Oliguria

is defined as a urine output of <400mL/24h. This occurs in renal failure: causes are divided into pre-renal (hypovolaemia, severe dehydration, cardiac failure), intrinsic causes or post-renal (urethral or bilateral ureteric obstruction).

Anuria

means absent urine output. See p284 and p562. ARF: see p292.

Orthopnoea

See Dyspnoea (p58).

Pallor

is a non-specific sign and may be racial or familial. Pathology suggested by pallor includes anaemia, shock, Stokes-Adams attack, vasovagal faint, hypothyroidism, hypopituitarism, and albinism.

Palmar erythema

Causes:

Pregnancy, hyperthyroidism, rheumatoid arthritis, polycythaemia, drugs (eg 5-fluorouracil) or chronic liver disease—via ↓inactivation of vasoactive endotoxins by the liver.

Palpitations

represent to the patient the sensation of feeling his heart beat; to the doctor, the sensation of feeling his heart sink, as the symptom is notoriously elusive. Have the patient tap out the rate and rhythm of the palpitations. • Irregular fast palpitations are likely to be paroxysmal AF, or atrial flutter with variable block • Regular fast palpitations may reflect paroxysmal SVT or VT. • Dropped or missed beats related to rest, recumbency or eating are likely to be atrial or ventricular ectopics. • Regular pounding may be due to anxiety • Slow palpitations are likely to be due to drugs such as Ò-blockers, or due to bigeminus. Ask about associated chest pain, dyspnoea, and faints, suggesting haemodynamic compromise. Ask *when* symptoms occur: anxious people may be aware of their own heartbeat at night. Reassurance is vital and can often be therapeutic. If the diagnosis is not simply heightened awareness, do TSH and a 24h ECG. (Holter monitor, p94) Transtelephonic event recording, if available, is better than 24h ECGs which miss some attacks.

Paraesthesiae

A sensation described as pins and needles, numbness or tingling, which can be intense and painful.

Causes

include: ↓Ca^{2+} (perioral), Raynaud's syndrome or any sensory nerve lesion ie 1 Central—thalamic or parietal lesions, 2 Spinal cord lesions or 3 Peripheral: *mononeuropathies* (p494): Carpal tunnel syndrome, meralgia paraesthetica, lateral popliteal palsy, sciatica; *peripheral neuropathy* (p496)—typically 'glove & stocking' in distribution.

Paraphimosis

occurs when a tight foreskin is retracted and then becomes irreplaceable as the glans swells. It can occur when a doctor/nurse fails to replace the foreskin after catheterization. ▸▸Treat by asking the patient to squeeze the glans for half an hour. Or try soaking a swab in 50% dextrose, and applying it to the oedematous area for an hour before trying to replace the foreskin—the oedema may follow the osmotic gradient.

Percussion pain

Pain on percussing the abdomen is a sign of peritonitis, and is often less painful for the patient than testing Rebound abdominal pain (p70).

Phimosis

The foreskin occludes the meatus, obstructing urine. Time (± trials of gentle retraction) usually obviates the need for circumcision.

Polyuria

is an increase in urine volume eg >3L/24h.

Causes:

Diabetes mellitus, over-enthusiastic IVI treatment, diabetes insipidus (including ↑Ca^{2+}; see p224), psychogenic polydipsia, polyuric phase of renal failure.

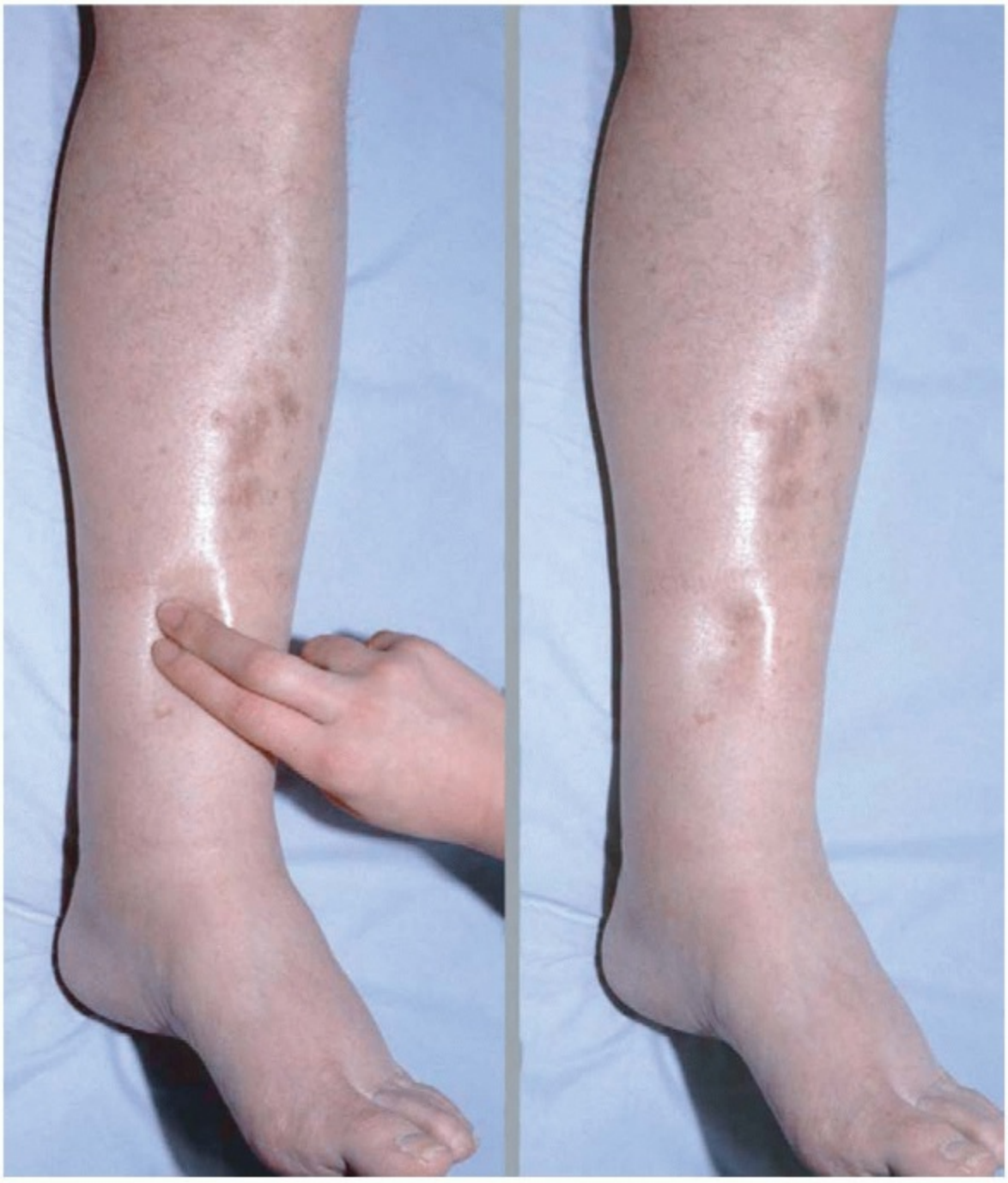


Fig 1. Pitting oedema, detected by applying firm pressure for a few seconds.

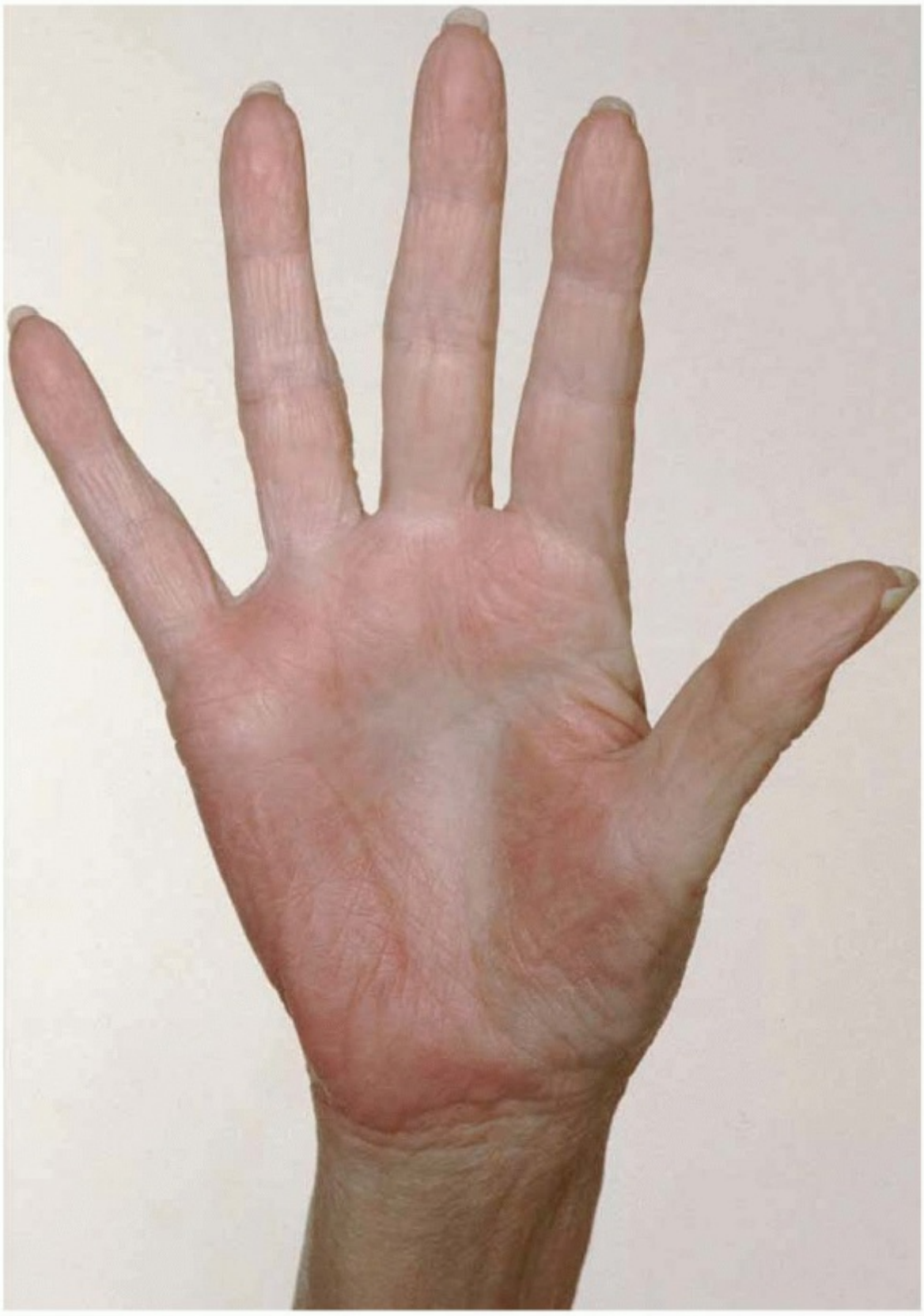


Fig 2. Palmar erythema.

Palpitations, Russian roulette, and hypochondriasis

At night on my pillow the syncopated stagger
Of the pulse in my ear. Russian roulette:
Every heartbeat a fresh throw of the dice …
Hypochondria walked, holding my arm
Like a nurse, her fingers over my pulse …
The sudden lapping at my throat of loose blood …

Ted Hughes, *Birthday Letters*.
Faber & Faber, by kind permission.

Postural hypotension

is defined as a drop in systolic BP >20mmHg or diastolic >10mmHg after standing for 3 minutes, compared with lying down.

Causes:

Hypovolaemia (an early sign), drugs (eg nitrates, diuretics, antihypertensives), Addison's disease (p210), hypopituitarism (↓ACTH), autonomic neuropathy (eg diabetes, multisystem atrophy, p486), idiopathic orthostatic hypotension.

Prostatism

(p40 and p602) Symptoms of prostate enlargement are often termed 'prostatism', but it is better to use the terms *irritative* or *obstructive* bladder symptoms.

1 Irritative bladder symptoms:

Urgency, dysuria, frequency, nocturia (the last two are also associated with causes of Polyuria).

2 Obstructive symptoms:

Reduced size and force of urinary stream, hesitancy and interruption of stream during voiding and terminal dribbling—the usual cause is enlargement of the prostate (prostatic hypertrophy), but other causes include a urethral stricture, tumour, urethral valves, or bladder neck contracture. The maximum flow rate of urine is normally ~18-30mL/s.

Pruritus

See Itching, p64.

Ptosis

is drooping of the upper eyelid. It is best observed with the patient sitting up, his head held by the examiner. The 3rd cranial nerve (oculomotor nerve, CNIII) innervates the main muscle concerned (levator palpebrae), but nerves from the cervical sympathetic chain innervate the superior tarsal muscle, and a lesion of these nerves will cause a mild ptosis which can be overcome on looking up.

Causes:

1 CNIII lesions (p45) cause a unilateral *complete* ptosis. Look for other evidence of a CNIII lesion: ophthalmoplegia with 'down and out' deviation of the eye, pupil dilated and unreactive to light and accommodation. **2** Sympathetic paralysis usually causes a unilateral *partial* ptosis. Look for other evidence of a sympathetic lesion, as in Horner's syndrome (p694): constricted pupil = *miosis*, lack of sweating on same side of the face (= *anhidrosis*). **3** Myopathy eg dystrophia myotonica, myasthenia gravis. These cause a bilateral partial ptosis. **4** Congenital (present since birth). May be unilateral or bilateral, is usually partial and is not associated with other neurological signs.

Pulses

See p30.

Pupillary abnormalities

The key questions are: • Are the pupils equal, central, circular, dilated, or constricted? • Do they react to light, directly and consensually? • Do they constrict normally on convergence/accommodation?

Irregular pupils

are caused by iritis, syphilis, or globe rupture.

Dilated pupils

Causes: 3rd cranial nerve (CNIII) lesions (▸including ↑ICP, p812) and mydriatic drugs. But always ask: is this pupil dilated, or is it the other which is constricted?

Constricted pupils

are associated with old age, sympathetic nerve damage (Horner's syndrome, p694, and see Ptosis above), opiates, miotics (eg pilocarpine eye-drops for glaucoma), and pontine damage.

Unequal pupils (anisocoria)

may be due to a unilateral lesion, eye-drops, eye surgery, syphilis, or be a Holmes-Adie pupil (p70). Some inequality is normal.

Reaction to light:

Test by covering one eye and shining light into the other obliquely. Both pupils should constrict, one by the direct, and the other by the consensual or indirect light reflex. The lesion site may be deduced by knowing the pathway: from the retina the message passes up the optic nerve (cranial nerve II) to the superior colliculus (midbrain) and thence to the CNIII nuclei bilaterally. CNIII causes pupillary constriction. If a light in one eye causes only contralateral constriction, the defect is 'efferent', as the afferent pathways from the retina being stimulated must be intact. Test for a *relative afferent pupillary defect* by moving the torch quickly from pupil to pupil. If there has been incomplete damage to the afferent pathway (eg due to optic neuritis in multiple sclerosis), the affected pupil will paradoxically dilate when the light is moved from the normal eye to the abnormal eye. This is because, in the face of reduced afferent input from the affected eye, the consensual pupillary relaxation response from the normal eye predominates. This phenomenon is also known as the Marcus Gunn sign, and may occur after apparent complete recovery from the initial lesion.

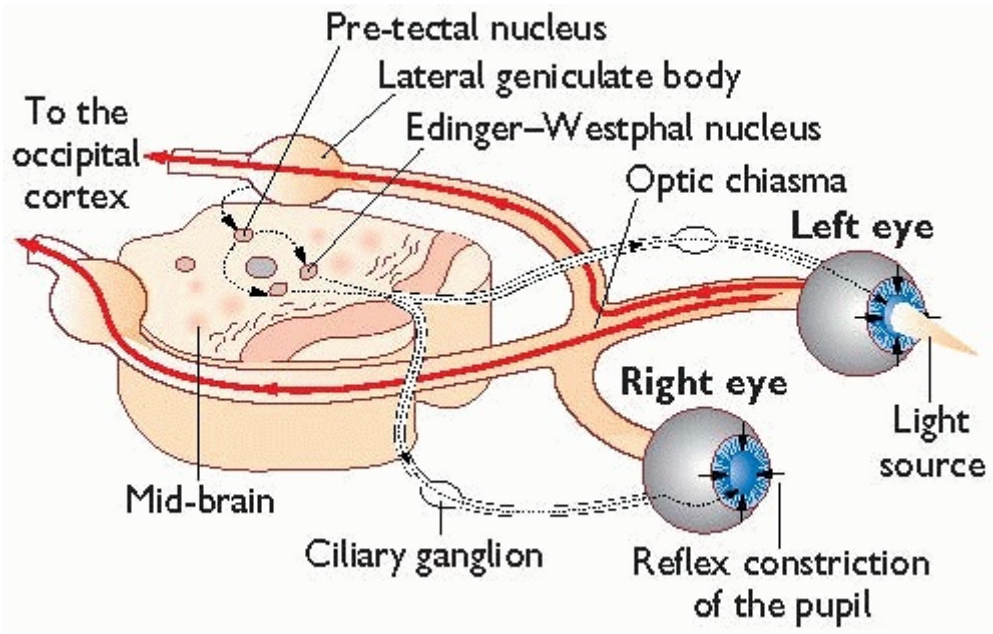


Fig 1. Light reflex. Action potentials are sent down the optic nerve (red arrow) passing through the optic chiasma. These synapse at the pre-tectal nucleus and are sent to the Edinger-Westphal nucleus of cranial nerve III, causing bilateral pupillary constriction.

Reaction to accommodation/convergence:

If the patient first looks at a distant object and then at the examiner's finger held a few inches away, the eyes will converge and the pupils constrict. Afferent fibres in each optic nerve pass to the lateral geniculate bodies. Impulses then pass to the pre-tectal nucleus and then to the parasympathetic nuclei of the 3rd cranial nerves, causing pupillary constriction.

- *Holmes-Adie (myotonic) pupil:* This is a benign condition, which occurs usually in women and is unilateral in about 80% of cases. The affected pupil is normally moderately dilated and is poorly reactive to light, if at all. It is slowly reactive to accommodation; wait and watch carefully: it may eventually constrict more than a normal pupil. It is often associated with diminished or absent ankle and knee reflexes, in which case the Holmes-Adie syndrome is present.
- *Argyll Robertson pupil:* This occurs in neurosyphilis; a similar phenomenon may occur in diabetes mellitus. The pupil is constricted and unreactive to light, but reacts to accommodation. The iris may be patchily atrophied and depigmented. Pseudo-Argyll Robertson pupils occur in Parinaud's syndrome (p700).
- *Hutchinson pupil:* This is the sequence of events resulting from rapidly rising unilateral intracranial pressure (eg in intracerebral haemorrhage). The pupil on the side of the lesion first constricts then widely dilates. The other pupil then goes through the same sequence. ▸See p812.

Radio-femoral and radio-radial delay

See p28.

Rebound abdominal pain

is present if, on the sudden removal of pressure from the examiner's hand, the patient feels a *momentary increase* in pain. It signifies local peritoneal inflammation, manifesting as pain as the peritoneum rebounds after being gently displaced.

Rectal bleeding

Ascertain details about • Pain on defecation? • Any mucus? • Is it fresh or dark blood? • Is blood mixed with stool, or just on surface? • Is blood just on toilet paper, or also in the pan?

Causes & classical features:

Diverticulitis (painless, large volumes of blood in pan); colorectal cancer (blood mixed with stool); haemorrhoids (bright red blood on paper and in pan); fissure-*in-ano* (painful; bright red blood on paper and stool surface); inflammatory bowel disease (blood and mucus mixed with loose stool). Also seen with dysentery (gastroenteritis), trauma, polyps, angiodysplasia, ischaemic colitis, iatrogenic (eg due to radiation proctitis, post-polypectomy bleeding, aorto-enteric fistula after aortic surgery).

Regurgitation

Gastric and oesophageal contents are regurgitated effortlessly into the mouth—without contraction of abdominal muscles and diaphragm (so distinguishing it from true vomiting). It may be worse on lying flat, and can cause cough and nocturnal asthma. Regurgitation is rarely preceded by nausea, and when due to gastro-oesophageal reflux, it is often associated with heartburn. An oesophageal pouch may cause regurgitation. Very high GI obstructions (eg gastric volvulus, p595) cause non-productive retching rather than true regurgitation.

Rigors

are uncontrolled, sometimes violent episodes of shivering, which occur as a patient's temperature rises rapidly. See p376.

Skin discolouration

Generalized hyperpigmentation may be genetic (racial), or due to radiation; ↑ACTH (cross reacts with melanin receptors, eg Addison's disease p210, Nelson's syndrome p700, ectopic ACTH in bronchial carcinoma); chronic renal failure (↑urea, p294); malabsorption; chloasma (seen in pregnancy or with the oral contraceptive pill); biliary cirrhosis; haemochromatosis ('bronzed diabetes'); carotenaemia; or drugs (eg chlorpromazine, busulfan, amiodarone, gold).

Splenomegaly

Abnormally large spleen.

Causes:

See p624. If massive, think of: chronic myeloid leukaemia, myelofibrosis, leishmaniasis or malaria.

Sputum

See p37.

Steatorrhoea

These are pale stools that are difficult to flush, and are caused by malabsorption of fat in the small intestine and hence greater fat content in the stool.

Causes:

Ileal disease (eg Crohn's or ileal resection), pancreatic disease, and obstructive jaundice (due to ↓excretion of bile salts from the gall bladder).

Stridor

is an *inspiratory* sound due to partial obstruction of the upper airways. That obstruction may be due to something within the lumen (eg foreign body, tumour, bilateral vocal cord palsy), within the wall (eg oedema from anaphylaxis, laryngospasm, tumour, croup, acute epiglottitis), or extrinsic (eg goitre, lymphadenopathy). It is a medical (or surgical) emergency (▸▸p760) if the airway is compromised. **NB:** wheeze is an *expiratory* sound.

Surgical (subcutaneous) emphysema

A crackling sensation felt on palpating the skin over the chest or neck. It is caused by air tracking from the lungs, often due to a pneumothorax (or, rarely, a pneumomediastinum, eg after oesophageal rupture).

Sweating excessively (hyperhidrosis)

This may be **primary** (eg hidradenitis suppurativa may be very distressing to the patient who may shun social encounters)—or be **secondary** to fever, pain or anxiety (cold & sweaty) or a systemic condition: the menopause, hyperthyroidism (warm & sweaty), acromegaly, malignancy, phaeochromocytoma, amyloidosis, or neuroleptic malignant syndrome (+hyperthermia). Or it may reflect gabapentin or opiate **withdrawal**, or a **cholinergic** or **parasympathomimetic side-effect** (amitriptyline, bethanechol, distigmine)— also hormonal drugs, eg levothyroxine, gonadorelin or somatostatin analogues, vasopressin, and ephedrine. Also amiodarone, ciprofloxacin, L-dopa, lisinopril, rivastigmine, ritonavir, pioglitazone, venlafaxine. ***At the bedside:*** Ask about *all* drugs, examine *all over* for nodes; any signs of hyperthyroidism? Any splenomegaly? Test the urine; do T°, ESR, TSH, FBC & blood culture.

[prescription take]:

Antiperspirants (aluminium chloride 20%=Driclor®), sympathectomy, or iontophoresis may be tried.

Syncope

See p452.

Tactile vocal fremitus

See p38.

Tenesmus

This is a sensation in the rectum of incomplete emptying *after* defecation. It's common in irritable bowel syndrome (p268), but can be caused by a tumour.

Terminal dribbling

Dribbling at the end of urination, often seen in conjunction with incontinence following incomplete urination, associated with prostatism (p68).

Tinnitus

See p456.

Tiredness

See Fatigue p60.

Tremor

is rhythmic oscillation of limbs, trunk, head, or tongue. 3 types:

1. *Resting tremor*—worst at rest—eg from Parkinsonism (±bradykinesia and rigidity; tremor is more resistant to treatment than other symptoms). It is usually a slow tremor (3-5Hz), typically 'pill-rolling' of the thumb over a finger.
2. *Postural tremor*—worst if arms are outstretched. Typically a rapid tremor (frequency: 8-12Hz). May be exaggerated physiological tremor (eg anxiety, hyperthyroidism, alcohol, drugs), due to brain damage (eg Wilson's disease, syphilis) or *benign essential tremor* (BET). This is usually a familial (autosomal dominant) tremor of arms and head presenting at any age. It is suppressed by large-ish amounts of alcohol. Rarely progressive. Propranolol (40-80mg/8-12h PO) helps in ~30% of patients.
3. *Intention tremor*—worst on movement, seen in cerebellar disease, with pastpointing and dysdiadochokinesia (see p491). No effective drug has been found.

See also chorea (p54), athetosis (p460), and hemiballismus (p460).

Trousseau's sign

Seen in hypocalcaemia (p670). This is elicited by inflating a blood pressure cuff on an arm/leg to above systolic pressure. The hands and feet go into spasm (carpopedal spasm). The metacarpophalangeal joints become flexed and the interphalangeal joints are extended. See also Chvostek's sign.

Urinary changes

Cloudy urine suggests pus (UTI) but is often normal phosphate precipitation in an alkaline urine. ***Pneumaturia*** (bubbles in urine as it is passed) occurs with UTI due to gas-forming organisms or may signal an enterovesical (bowel-bladder) fistula from diverticulitis, Crohn's disease or neoplastic disease of the bowel. ***Nocturia*** occurs with 'prostatism' (p68), diabetes mellitus, UTI, and reversed diurnal rhythm (seen in renal and cardiac failure). ***Haematuria*** (RBC in urine) is due to neoplasia or glomerulonephritis (p288) until proven otherwise.

Urinary frequency

See Frequency p60.

Vaginal discharge

p406.

Vertigo

p454.

Visual loss

▸Get ophthalmic help. See OHCS p434-p455 & BOX. ***If sudden, ask:***

- Is the eye red? (*glaucoma*, *iritis* p544)
- Is there pain?
  - *Giant cell arteritis*: severe temporal headache, jaw claudication, scalp tenderness, ↑ESR: ▸requires urgent steroids (p542).

- *Optic neuritis*: eg as in multiple sclerosis.

- Any flashes/floaters? (TIA, *migraine*, *retinal detachment*?)
- Any past history of trauma, migraine, hypertension, cerebrovascular disease, MS, diabetes or connective tissue disease?

In the examination, consider:

- Is the eye red? See p545 for the *Red Eye*
- Is the cornea cloudy: *corneal ulcer* (OHCS p432), *glaucoma* (OHCS p430)?
- Is there a contact lens problem (*infection*)?
- Is there a visual field problem (*stroke*, *space-occupying lesion*, *glaucoma*)? Formal field testing requires ophthalmic help.
- Are there any focal CNS signs?
- Any valvular heart disease/carotid bruits (*emboli*)?; Hyperlipidaemia (p682)?
- Is there an afferent pupil defect (p68)?
- Any distant signs: eg HIV (causes retinitis), SLE, *sarcoidosis*, *Behçet's disease*?

Perform ophthalmoscopy, examine acuity, pupil reactions, red reflex, field loss.

Voice and disturbance of speech

(p46) may be noted by the patient, relatives or the doctor. Assess if difficulty is with articulation (*dysarthria*, eg from muscle problems), or of word command (*dysphasia*—always central).

Vocal resonance

See p39 and p78.

Vomiting

Causes of nausea/vomiting include (anti-emetic [prescription take]: p233)

Gastrointestinal	CNS	Metabolic/Endocrine
Gastroenteritis	Meningitis/encephalitis	Uraemia
Peptic ulceration	Migraine	Hypercalcaemia
Pyloric stenosis	↑Intracranial pressure	Hyponatraemia
Intestinal obstruction	Brainstem lesions	Pregnancy
Paralytic ileus	Motion sickness	Diabetic ketoacidosis
Acute cholecystitis	Ménière's disease	Addison's disease

Acute pancreatitis	Labyrinthitis		Alcohol and drugs:		
Other	Psychiatric:		•	antibiotics	
Myocardial infarction	•	self-induced	•	cytotoxics	
Autonomic neuropathy	•	psychogenic	•	digoxin	
UTI	•	bulimia nervosa	•	opiates	

The history is vital: ask about timing, relationship to meals, amount, and content (liquid, solid, bile, blood, 'coffee grounds'). Associated symptoms and previous medical history often indicate the cause.

Signs:

Look for signs of dehydration. Examine the abdomen for distension, tenderness, an abdominal mass, a succussion splash (pyloric stenosis), or tinkling bowel sounds (intestinal obstruction).

Walking difficulty ('Off my legs')

In the elderly, this is a common and nonspecific presentation: the reason may not be *local* (typically osteo- or rheumatoid arthritis, but remember fractured neck of femur), and it may not even be *systemic* (eg UTI, pneumonia, anaemia, hypothyroidism, renal failure, drugs, hypothermia)— but it may be a manifestation of depression or bereavement. *It is only rarely a manipulative strategy.* See Falls, and gait disturbance, p459.

If there is ataxia, the cause is not always alcohol: other chemicals may be involved (eg cannabis or prescribed sedatives). There may be a metastatic or non-metastatic manifestation of malignancy, or a cerebellar lesion.

▸Bilateral weak legs may suggest a cord lesion: see p458. If there is associated urinary or faecal incontinence ± saddle anaesthesia or lower limb sensory loss, prompt imaging (MRI) and treatment for cord compression may well be needed.

Causes of vision loss
Sudden

- Acute glaucoma
- Retinal detachment
- Vitreous haemorrhage (eg in diabetic proliferative retinopathy)
- Optic neuritis (eg MS)
- Temporal arteritis
- Central retinal artery or vein occlusion
- Migraine
- CNS: TIA (amaurosis fugax), stroke, space occupying lesion
- Drugs: quinine or methanol toxicity
- Pituitary apoplexy.

Gradual

- Optic atrophy
- Chronic glaucoma
- Cataracts
- Macular degeneration
- Tobacco amblyopia.

Non-gastrointestinal causes of vomiting

▸Try not to forget these serious causes. The following *aide-mémoire* covers the most important non-gastrointestinal causes of vomiting: **ABCDE F GHI.**

- **A**cute renal failure/**A**ddison's disease
- **B**rain (eg ↑ICP, p812)
- **C**ardiac (myocardial infarct)
- **D**iabetic ketoacidosis
- **E**ars (eg labyrinthitis, Ménière's disease)
- **F**oreign substances (alcohol, drugs eg opiates)
- **G**ravidity (eg hyperemesis gravidarum)
- **H**ypercalcaemia/**H**yponatraemia
- **I**nfection (eg UTI, meningitis).

Waterbrash

refers to the excessive secretion of saliva, which suddenly fills the mouth. It typically occurs after meals, and may denote upper GI tract disease. It is suggested that this is an exaggeration of the oesophago-salivary reflex. It should not be confused with regurgitation (p70).

Weight loss

is a feature of chronic disease and depression; also of malnutrition, malignancy, chronic infections (eg TB, HIV/enteropathic AIDS), diabetes mellitus and hyperthyroidism (typically in the presence of increased appetite). Severe generalized muscle wasting is also seen as part of a number of degenerative neurological diseases and in cardiac failure (cardiac cachexia), although in the latter, right heart failure may not make weight loss a major complaint. Do not forget anorexia nervosa (OHCS p348) as an underlying cause of weight loss.

Focus on treatable causes, eg diabetes is easy to diagnose—TB can be very hard. For example, the CXR may look like cancer, so you may forget to send bronchoscopy samples for ZN stain and TB culture (to the detriment not just of the patient, but to the entire ward).

Wheeze

See p38.

Whispering pectoriloquy

This refers to the increased transmission of a patient's whisper heard when auscultating over consolidated lung. It is a manifestation of increased vocal resonance. See p38-p39.

Vocal resonance

is sound vibration of the patient's spoken or whispered voice transmitted to the stethoscope.

Tactile fremitus

is the sound vibration of the spoken or whispered voice transmitted via the lung fields and detected by palpation over the back.

Xanthomata

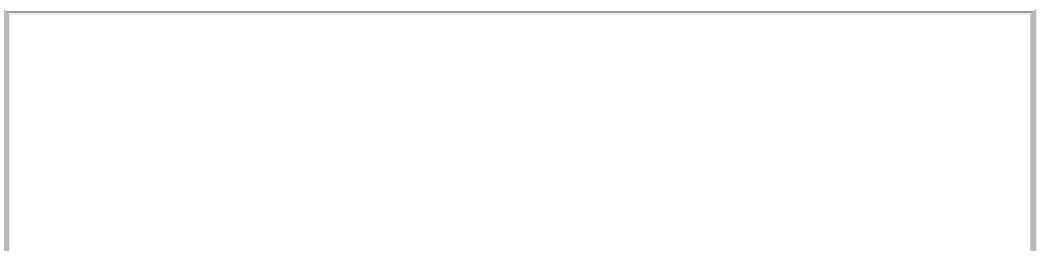
These are localized deposits of fat under the skin, occurring over joints, tendons, hands, and feet. They are a sign of dyslipidaemia (p682).

Xanthelasma

refers to xanthoma on the eyelid (p101, fig 1).

Corneal arcus

is a crescentic shaped opacity at the periphery of the cornea. It is common in the over 60yrs, and can be normal, but may represent hyperlipidaemia, especially in those under this age.



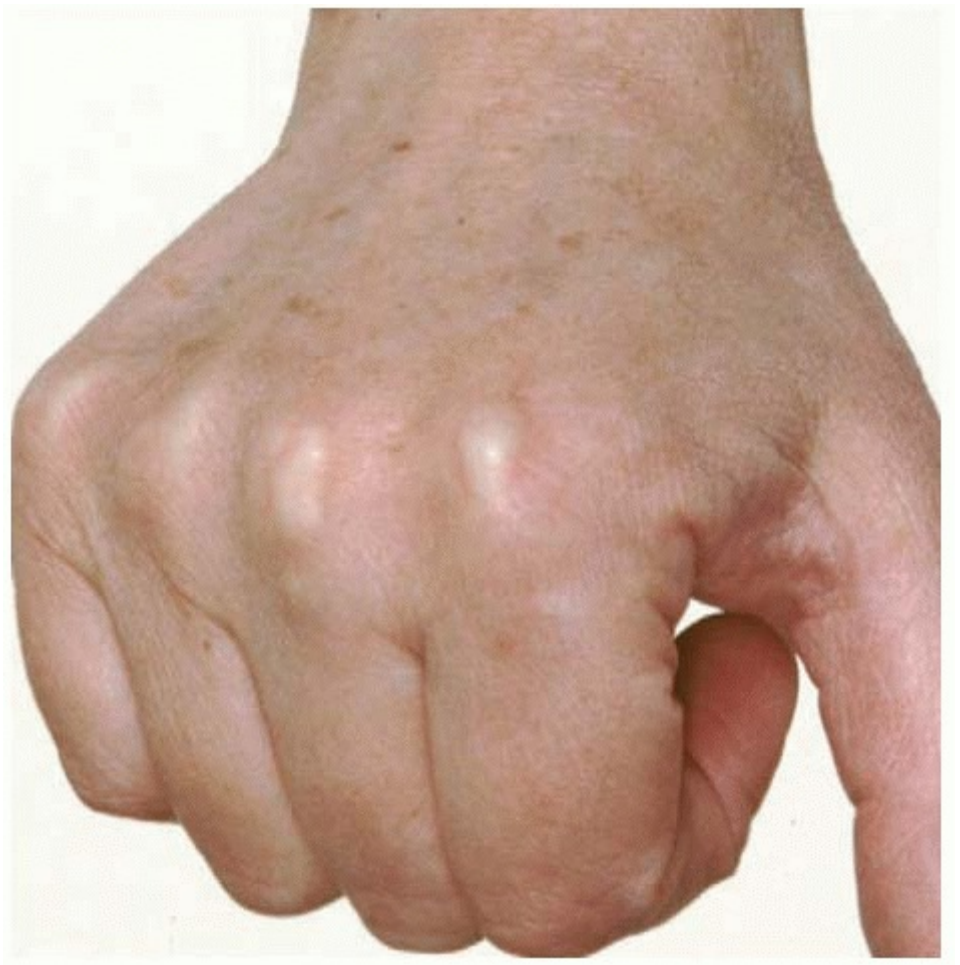


Fig 1. Tendon xanthomata.

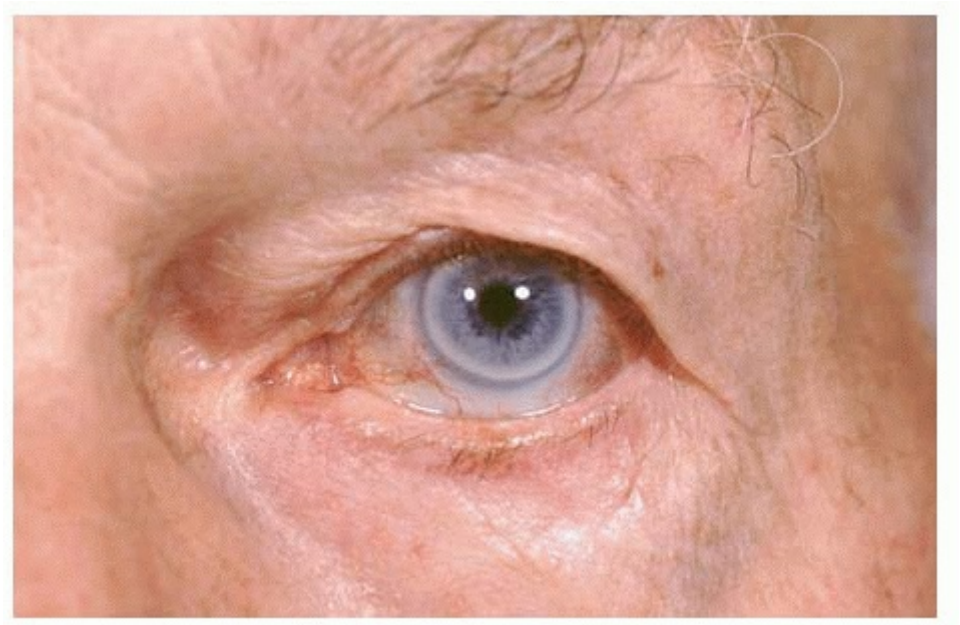


Fig 2. Corneal arcus.

Unexplained signs and symptoms: how to refer a patient for an opinion

▸*When you don't know: ask.*

▸*If you find yourself wondering if you should ask: ask.*

Frequently, the skills needed will lie beyond the firm you are working on, so, during ward rounds, agree who should be asked for an opinion. You will be left with the job of making the arrangements. This can be a daunting task, if you are very junior and have been asked to contact an intimidating registrar or consultant. Don't be intimidated: perhaps this may be an opportunity to learn something new. A few simple points can help the process go smoothly.

- Have the patient's notes, observations, and drug charts to hand.
- Be familiar with the history: you may be interrogated.
- Ask if it is a convenient time to talk.
- At the outset, state if you are just looking for advice or if you are asking if the patient could be seen. Make it clear exactly what the question is that you want addressed, 'We wonder why Mr Smith's legs have become weak today …' This helps the listener to focus their thoughts while you describe the story and will save you wasting time if the switchboard has put you through to the wrong specialist.
- Give the patient's age and occupation to give a snapshot of the person.
- Run through a brief history including relevant past medical history. Do not present the case as if you are in finals—it will take ages to get to the point and the listener will get more and more irritated.
- If you would like the patient to be seen, give warning if they will be going off the ward for a test at a particular time.
- It should not be necessary to write a long letter in the notes if you have given all the salient information available.
- The visiting doctor may be unfamiliar with your ward. When he or she arrives introduce yourself, get the notes and charts, and offer to introduce them to the patient. This will lead to all-round satisfaction and will make it easier to call the same doctor again.

We thank Martin Zeidler for providing the first draft of this page.

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4

Cardiovascular Medicine

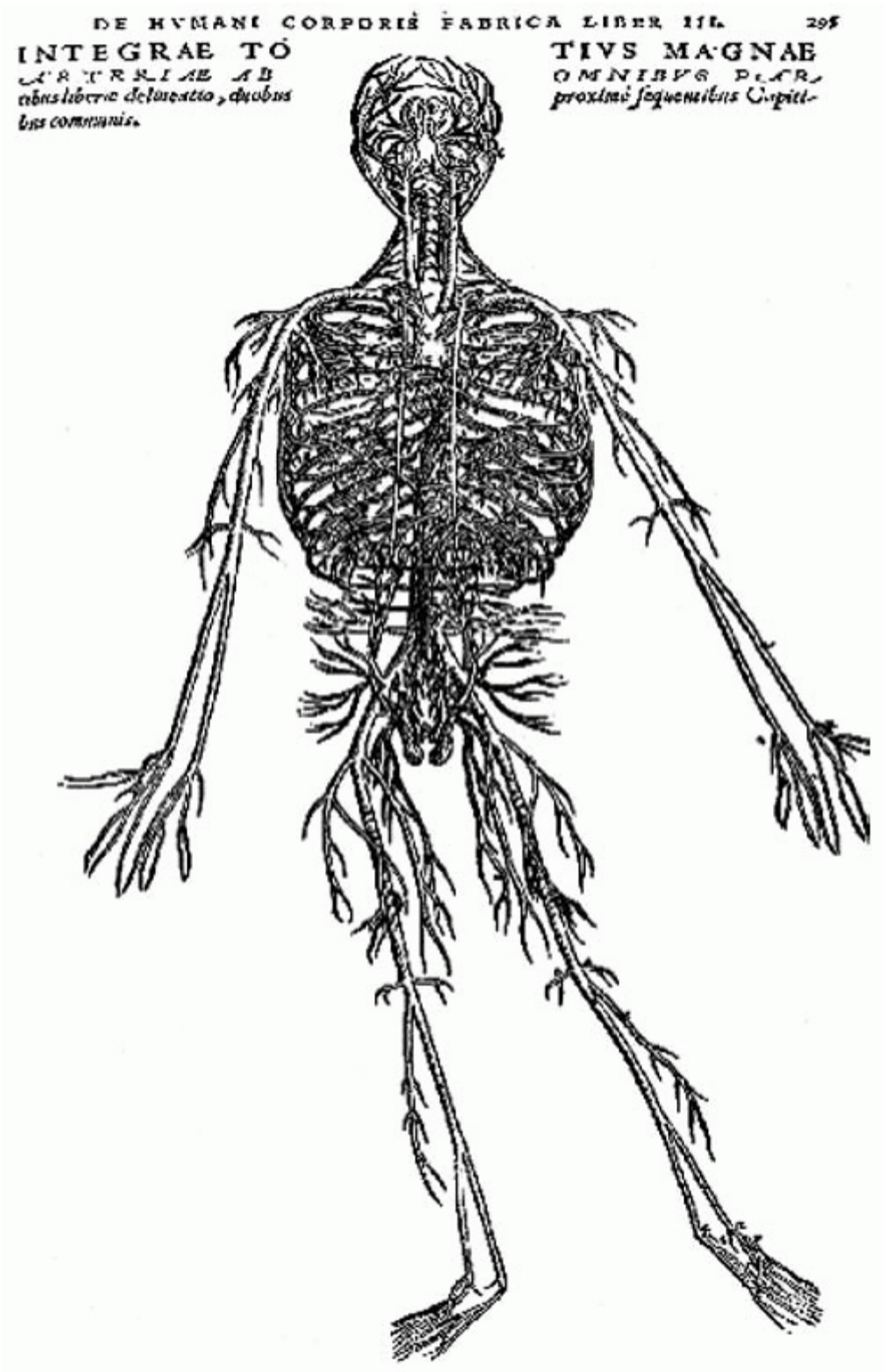


Fig 1. The vasculature, as depicted in Andreas Vesalius's, *De Humani Corporis Fabrica* (On the fabric of the human body). At the age of 23, the day after his finals, he dissected a body with such vivid brilliance that he was at once made Professor of Surgery at Padua. By general acclamation, modern medicine began that day: December 6th, 1537.[1] Galen's infallibility was now and forever trumped by direct observation, experiment, and the painstaking accumulation of data.

Cardiovascular health

Ischaemic heart disease (IHD) is the most common cause of death worldwide. Encouraging cardiovascular health is not *only* about preventing IHD: health entails the ability to *exercise*, and enjoying vigorous activity (within reason!) is one of the best ways of achieving health, not just because the heart likes it (BP↓, 'good' high-density lipoprotein, HDL↑)—it can prevent osteoporosis, improve glucose tolerance, and augment immune function (eg in cancer and if HIV+ve). People who improve *and maintain* their fitness live longer: ▸*age-adjusted mortality from all causes is reduced by >40%.* Avoiding obesity helps too, but weight loss *per se* is only useful in reducing cardiovascular risk and the risk of developing diabetes when combined with regular exercise. Moderate alcohol drinking may also promote cardiovascular health. Alcohol also reduces gastric infection with *Helicobacter pylori*, a known risk marker for cardiovascular disease.[2]

Smoking is the chief risk factor for cardiovascular mortality. You *can* help people give up, and giving up *does* undo much of the harm of smoking. *Simple advice works*. Most smokers want to give up (unlike the eaters of unhealthy diets who are mostly wedded to them by habit, and the pleasures of the palate). Just because smoking advice does *not always* work, do not stop giving it. Ask about smoking in consultations—especially those concerned with smokingrelated diseases.

- Ensure advice is congruent with patient's beliefs about smoking.
- Concentrate on the benefits of giving up.
- Invite the patient to choose a date (when there will be few stresses) on which he or she will become a non-smoker.
- Suggest throwing away all accessories (cigarettes, pipes, ash trays, lighters, matches) in advance; inform friends of the new change; practise saying 'no' to their offers of 'just one little cigarette'.
- *Nicotine gum*, chewed intermittently to limit nicotine release: ≥ ten 2mg sticks may be needed/day. *Transdermal nicotine patches* may be easier. A dose increase at 1wk can help. Written advice offers no added benefit to advice from nurses. Always offer follow-up.
- *Bupropion* (=*amfebutamone*, p443) is said to ↑quit rate to 30% at 1yr *vs* 16% with patches and 15.6% for placebo (patches + bupropion: 35.5%):[3] consider if the above fails. *Dose:* 150mg/24h PO (while still smoking; quit within 2wks); dose may be twice daily from day 7; stop after 7-9wks. ***Warn of* SES*:*** Seizures (risk <1 : 1000), insomnia, headache. **CI*:*** Epilepsy; cirrhosis; pregnancy/lactation; bipolar depression; eating disorders; CNS tumours; on antimalarials etc; alcohol or benzodiazepine withdrawal, sedating antihistamines, systemic corticosteroids.

Lipids and BP (p682 & p124) are the other major modifiable risk factors (few can change their sex or genes).

To calculate how risk factors interact, see **risk equation**, p642.

▸Apply preventive measures such as healthy eating (p228) *early* in life to maximize impact, when there are most years to save, and before bad habits get ingrained.

For an example of implementation of cardiovascular health strategies, see the UK NHS national service framework: www.doh.gov.uk/nsf/coronary.htm

Cardiovascular symptoms

Chest pain

▸Cardiac-sounding chest pain may have no serious cause, but always think '*Could this be a myocardial infarction (*MI*), dissecting aortic aneurysm, pericarditis, or pulmonary embolism?*'

Nature:

Constricting suggests angina, oesophageal spasm, or anxiety; a *sharp* pain may be from the pleura or pericardium. A prolonged (>½h), dull, central crushing pain or pressure suggests MI.

Radiation:

To shoulder, either or both arms, or neck/jaw suggests cardiac ischaemia. The pain of aortic dissection is classically instantaneous, tearing, and interscapular, but may be retrosternal. Epigastric pain may be cardiac.

Precipitants:

Pain associated with cold, exercise, palpitations, or emotion suggest cardiac pain or anxiety; if brought on by food, lying flat, hot drinks, or alcohol, consider oesophageal spasm (but meals *can* cause angina).

Relieving factors:

If pain is relieved *within minutes* by rest or glyceryl trinitrate (GTN), suspect angina (GTN relieves oesophageal spasm more slowly). If antacids help, suspect GI causes. Pericarditic pain improves on leaning forward.

Associations:

Dyspnoea occurs with cardiac pain, pulmonary emboli, pleurisy, or anxiety. MI may cause nausea, vomiting, or sweating. Angina is caused by coronary artery disease—and also by aortic stenosis, hypertrophic obstructive cardiomyopathy (HOCM), paroxysmal supraventricular tachycardia (SVT) and be exacerbated by anaemia. Chest pain with *tenderness* suggests self-limiting Tietze's syndrome.[1]

[1] 25% of non-cardiac chest pain is **musculoskeletal**: look for pain on specific postures or activity. Aim to reproduce the pain by movement and, sometimes, palpation over the structure causing it. Focal injection of local anaesthetic helps diagnostically and is therapeutic. **Tietze's syndrome:** self-limiting costochondritis ± costosternal joint swelling. Causes: idiopathic; microtrauma; infection; psoriatic/rheumatoid arthritis. [prescription take]: NSAIDs or steroid injections. Tenderness is also caused by: fibrositis, lymphoma, chondrosarcoma, myeloma, metastases, rib TB. Imaging: bone scintigraphy; CT.

Pleuritic pain

(ie exacerbated by inspiration) implies inflammation of the pleura from pulmonary infection, inflammation, or infarction. It causes us to 'catch our breath'. ΔΔ: Musculoskeletal pain;[1] fractured rib (pain on respiration, exacerbated by gentle pressure on the sternum); subdiaphragmatic pathology (eg gallstones).

Acutely ill patients:

•Admit to hospital •Check pulse, BP in both arms, JVP, heart sounds; examine legs for DVT •Give O_2 by mask •IV line •Relieve pain (eg morphine 5-10mg IV slowly (2mg/min) + an antiemetic) •Cardiac monitor •12-lead ECG •CXR •Arterial blood gas (ABG).

Famous traps:

Aortic dissection; zoster (p388); ruptured oesophagus; cardiac tamponade (shock with JVP↑); opiate addiction.

Dyspnoea

may be from LVF, pulmonary embolism, any respiratory cause, or anxiety.

Severity:

▸▸Emergency presentations: p770. Ask about shortness of breath at rest or on exertion, exercise tolerance, and in daily tasks.

Associations:

Specific symptoms associated with heart failure are orthopnoea (ask about number of pillows used at night), paroxysmal nocturnal dyspnoea (waking up at night gasping for breath), and peripheral oedema. Pulmonary embolism is associated with acute onset of dyspnoea and pleuritic chest pain; ask about risk factors for DVT.

Palpitation(s)

may be due to ectopics, AF, SVT and ventricular tachycardia (VT), thyrotoxicosis, anxiety, and rarely phaeochromocytoma. See p66.

History:

Ask about previous episodes, precipitating/relieving factors, duration of symptoms, associated chest pain, dyspnoea, or dizziness. *Did the patient check his pulse?*

Syncope

may reflect cardiac or CNS events. Vasovagal 'faints' are common (pulse↓, pupils dilated). The history from an observer is invaluable in diagnosis.

Prodromal symptoms:

Chest pain, palpitations, or dyspnoea point to a cardiac cause, eg arrhythmia. Aura, headache, dysarthria, and limb weakness indicate CNS causes.

During the episode:

Was there a pulse? Limb jerking, tongue biting, or urinary incontinence? **NB:** hypoxia from lack of cerebral perfusion may cause seizures.

Recovery:

Was this rapid (arrhythmia) or prolonged, with drowsiness (seizure)?

How patients communicate ischaemic cardiac sensations

On emergency wards we are always hearing questions such as 'is your pain sharp or dull?', followed by an equivocal answer. The doctor goes on 'Sharp like a knife—or dull and crushing?' The doctor is getting irritated because the patient must know the answer, but is not saying it. A true story paves the way to being less inquisitorial, and having a more creative understanding of the nature of symptoms. A patient came to one of us (JML) saying 'Last night I dreamed I had a pain in my chest. Now I've woken up, and I'm not sure—have I got chest pain, doctor? What do you think?' How odd it is to find oneself examining a patient to exclude a symptom, not a disease. (It turned out that she *did* have serious chest pathology.) Odd, until one realizes that symptoms are often half-formed, and it is our role to give them a local habitation and a name. Dialogue can transform a symptom from 'airy nothingness' to a fact.[1] Patients often avoid using the word 'pain' to describe ischaemia: 'wind', 'tightening', 'pressure', 'burning', or 'a lump in the throat' (angina means to choke) may be used. He may say 'sharp' to communicate severity, and not character. So be as vague in your questioning as your patient is in his answers. 'Tell me some more about what you are feeling (long pause) … as if someone was doing *what* to you?' 'Sitting on me', or 'like a hotness' might be the response (suggesting cardiac ischaemia). Do not ask 'Does it go into your left arm'. Try 'Is there anything else about it?' (pause) … 'Does it go anywhere?' Note down your patient's exact words.

Note also non-verbal clues: the clenched fist placed over the sternum is a telling feature of cardiac pain (Levine sign positive).

A good history, taking account of these features, is the best way to stratify patients likely to have cardiac pain. If the history is non-specific, and there are no risk factors for cardiovascular diseases, and ECG and plasma troponin T (p104) are normal (<0.2μg/L) 6-12h after the onset of pain, discharge will probably be OK.[4] When in doubt, get help. Features making cardiac pain unlikely:

- Stabbing, shooting pain
- Pain lasting <30s, however intense
- Well-localized, left sub-mammary pain ('in my heart, doctor')
- Pains of continually varying location
- Youth.

Do not feel that you must diagnose every pain. ***Chest pain with no cause*** is common, even after extensive tests. Do not reject these patients: explain your findings to them. Some have a 'chronic pain syndrome' which responds to a tricyclic, eg imipramine 50mg at night (this dose does not imply any depression). It is similar to post-herpetic neuralgia.

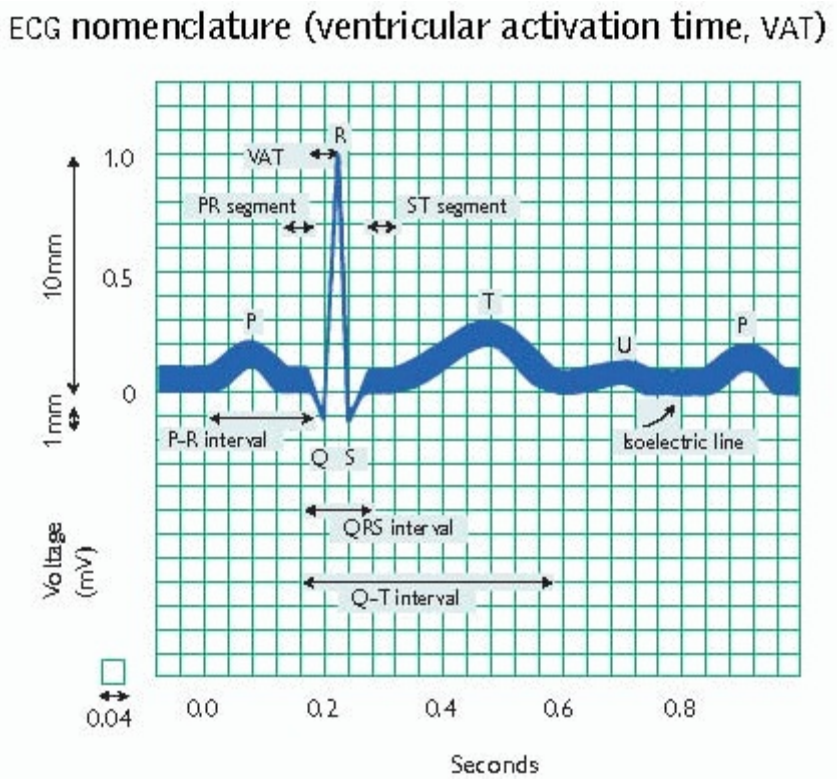
ECG—a methodical approach

▸First confirm the patient's name and age, and the ECG date. Then:

- *Rate:* At usual speed (25mm/s) each 'big square' is 0.2s; each 'small square' is 0.04s. To calculate the rate, divide 300 by the number of big squares per R-R interval (p83).
- *Rhythm:* If the cycles are not clearly regular, use the 'card method': lay a card along ECG, marking positions of 3 successive R waves. Slide the card to and fro to check that all intervals are equal. If not, note if different rates are multiples of each other (ie varying block), or is it 100% irregular (atrial fibrillation (AF) or ventricular fibrillation, VF)? *Sinus rhythm* is characterized by a P wave (upright in II, III, & aVF; inverted in aVR) followed by a QRS complex. AF has no discernible P waves and the QRS complexes are irregularly irregular. *Atrial flutter* (p111) has a 'sawtooth' baseline of atrial depolarization (~300/min) and regular QRS complexes. *Nodal rhythm* has a normal QRS complex but P waves are absent or occur just before or within the QRS complex. *Ventricular rhythm* has QRS complexes >0.12s with P waves following them.
- *Axis:* The mean frontal axis is the sum of all the ventricular forces during ventricular depolarization. The axis lies at 90° to the isoelectric complex (ie the one in which positive and negative deflections are equal). *Normal axis* is between -30° and +90°. As a simple rule of thumb, if the complexes in leads I and II are both 'positive', the axis is normal. *Left axis deviation* (LAD) is -30° to -90°. Causes: left anterior hemiblock, inferior MI, VT from LV focus, Wolff- Parkinson-White (WPW) syndrome (some types). *Right axis deviation* (RAD) is +90° to +180°. Causes: RVH, PE, anterolateral MI, left posterior hemiblock (rare), WPW syndrome (some types).
- *P wave:* Normally precedes each QRS complex. *Absent P wave:* AF, sinoatrial block, junctional (AV nodal) rhythm. Dissociation between P waves and QRS complexes indicates complete heart block. *P mitrale:* bifid P wave, indicates left atrial hypertrophy. *P pulmonale:* peaked P wave, indicates right atrial hypertrophy. Pseudo-P-pulmonale seen if $K^+\downarrow$.
- *P-R interval:* Measure from start of P wave to start of QRS. *Normal range*: 0.12- 0.2s (3-5 small squares). A *prolonged P-R interval* implies delayed AV conduction (1st degree heart block). A *short P-R interval* implies unusually fast AV conduction down an accessory pathway, eg WPW p112 (ECG p117).
- *QRS complex: Normal duration:* <0.12s. If ≥0.12s suggests ventricular conduction defects, eg a bundle branch block (p86 & p111). Large QRS complexes suggest *ventricular hypertrophy* (p86). *Normal Q wave* <0.04s wide and <2mm deep. They are often seen in leads V_5 and V_6, aVL and I, and reflect normal septal depolarization, which usually occurs from left to right. *Pathological Q waves* may occur within a few hours of an acute MI.
- *QT interval:* Measure from start of QRS to *end* of T wave. It varies with rate. Calculate *corrected QT interval (QT^c)* by dividing the measured QT interval by the square root of the cycle length, ie

$$QT^c = QT/\sqrt{RR}$$

. Normal QT^c: 0.38-0.42s. *Prolonged QT interval*: acute myocardial ischaemia, myocarditis, bradycardia (eg AV block), head injury, hypothermia, U&E imbalance ($K^+\downarrow$—ECG p669, $Ca^{2+}\downarrow$, $Mg^{2+}\downarrow$), congenital (Romano-Ward and Jervell-Lange-Nielson syndromes); sotalol, quinidine, antihistamines, macrolides (eg erythromycin), amiodarone, phenothiazines, tricyclics.
- *ST segment:* Usually isoelectric. Planar elevation (>1mm) or depression (>0.5mm) usually implies infarction (p105) or ischaemia (p95), respectively.
- *T wave:* Normally inverted in aVR, V_1 and occasionally V_2. Abnormal if inverted in I, II, and V_4-V_6. Peaked in hyperkalaemia (ECG 13, p669) and flattened in hypokalaemia.



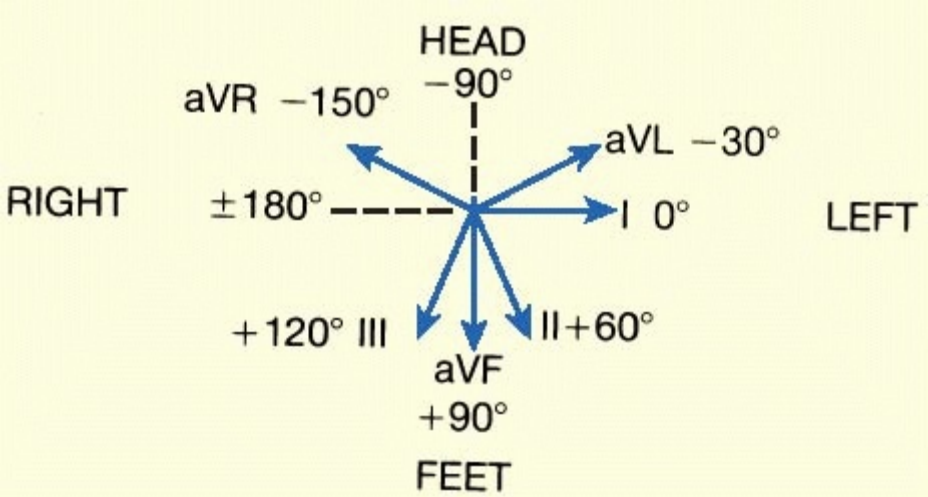
Calculating the R-R interval

To calculate the rate, divide 300 by the number of big squares per R-R interval— if the UK standard ECG speed of 25mm/s is used (elsewhere, 50mm/s may be used: don't be confused!)

R-R duration (s)	Big squares	Rate (per min)
0.2	1	300
0.4	2	150
0.6	3	100
0.8	4	75
1.0	5	60
1.2	6	50
1.4	7	43

Determining the ECG axis

- The axis lies at 90° to the isoelectric complex (the one in which positive and negative deflections are equal in size).
- If the complexes in I and II are both predominantly positive, the axis is normal.



Causes of LAD (left axis deviation)	*Causes of RAD*
Left anterior hemiblock	RVH
Inferior MI	Pulmonary embolism
VT from LV focus	Anterolateral MI
WPW syndrome p112	Left posterior hemiblock (rare)
	WPW syndrome

ECG—abnormalities

Sinus tachycardia:

Rate >100. Causes: Anaemia, anxiety, exercise, pain, ↑T°, sepsis, hypovolaemia, heart failure, pulmonary embolism, pregnancy, thyrotoxicosis, beri beri, CO_2 retention, autonomic neuropathy, sympathomimetics, eg caffeine, adrenaline, and nicotine (may produce abrupt changes in sinus rate, or other

arrhythmia).

Sinus bradycardia:

Rate <60. Causes: Physical fitness, vasovagal attacks, sick sinus syndrome, acute MI (esp. inferior), drugs (ß-blockers, digoxin, amiodarone, verapamil), hypothyroidism, hypothermia, ↑intracranial pressure, cholestasis.

AF:

(ECG p111) *Common causes:* IHD, thyrotoxicosis, hypertension. See p116.

1st and 2nd degree heart block:

Causes: Normal variant, athletes, sick sinus syndrome, IHD, acute carditis, drugs (digoxin, ß-blockers).

3rd degree complete heart block:

Causes: Idiopathic (fibrosis), congenital, IHD, aortic valve calcification, cardiac surgery/trauma, digoxin toxicity, infiltration (abscesses, granulomas, tumours, parasites).

Q waves:

Pathological Q waves are usually >0.04s wide and >2mm deep. Usually as sign of infarction, and may occur within a few hours of an acute MI.

ST elevation:

Normal variant (high take-off), acute MI, Prinzmetal's angina (p701), acute pericarditis (saddle-shaped), left ventricular aneurysm.

ST depression:

Normal variant (upward sloping), digoxin (downward sloping), ischaemic (horizontal): angina, acute posterior MI.

T inversion:

In V_1-V_3: normal (Blacks and children), right bundle branch block (RBBB), pulmonary embolism. In V_2-V_5: subendocardial MI, HOCM, subarachnoid haemorrhage, lithium. In V_4-V_6 and aVL: ischaemia, LVH, associated with left bundle branch block (LBBB).

NB: ST and T wave changes are often non-specific, and must be interpreted in the light of the clinical context.

MI:

(ECG p105.)

- Within hours, the T wave may become peaked and ST segments may begin to rise.
- Within 24h, the T wave inverts, as ST segment elevation begins to resolve. ST elevation rarely persists, unless a left ventricular aneurysm develops. T wave inversion may or may not persist.
- Within a few days, pathological Q waves begin to form. Q waves usually persist, but may resolve in 10%.

The leads affected reflect the site of the infarct: inferior (II, III, aVF), anteroseptal (V_{1-4}), anterolateral (V_{4-6}, I, aVL), posterior (tall R and ST↓ in V_{1-2}).

▸ 'Non-Q wave infarcts' (formerly called subendocardial infarcts) have ST and T changes without Q waves.

Pulmonary embolism:

Sinus tachycardia is commonest. There may be RAD, RBBB (p83), *right ventricular strain pattern* (R-axis deviation. Dominant R wave and T wave inversion/ST depression in V_1 and V_2. Leads II, III and aVF may show similar changes). Rarely, the '$S_IQ_{III}T_{III}$' pattern occurs: deep S waves in I, pathological Q waves in III, inverted T waves in III.

Metabolic abnormalities: Digoxin effect:

ST depression and inverted T wave in V_{5-6} (reversed tick). In *digoxin toxicity,* any arrhythmia may occur (ventricular ectopics and nodal bradycardia are common). *Hyperkalaemia:* Tall, tented T wave, widened QRS, absent P waves, 'sine wave' appearance (ECG 13, p669). *Hypokalaemia:* Small T waves, prominent U waves. *Hypercalcaemia:* Short QT interval. *Hypocalcaemia:* Long QT interval, small T waves.

ECG—additional points

Where to place the chest leads

V_1: right sternal edge, 4th intercostal space

V_2: left sternal edge, 4th intercostal space

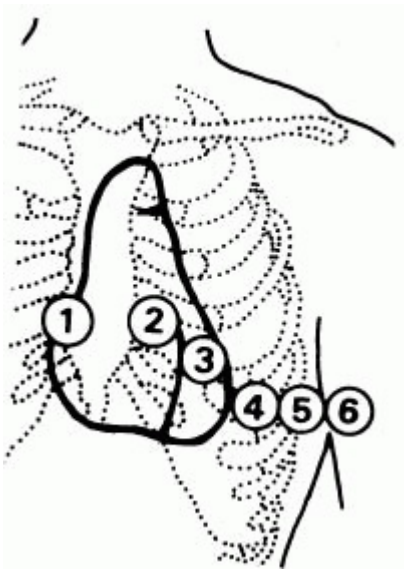
V_3: half-way between V_2 and V_4

V_4: the patient's apex beat (p64); all subsequent leads are in the same horizontal plane as V_4

V_5: anterior axillary line

V_6: mid-axillary line (V_7: posterior axillary line)

Finish 12-lead ECGs with a long rhythm strip in lead II.



Disorders of ventricular conduction

Bundle branch block

(p87-p88, ECGs 1 & 2) Delayed conduction is evidenced by prolongation of QRS >0.12s. Abnormal conduction patterns lasting <0.12s are incomplete blocks. The area that would have been reached by the blocked bundle depolarizes slowly and late. Taking V_1 as an example, right ventricular depolarization is normally +ve and left ventricular depolarization is normally -ve.

In RBBB, the following pattern is seen: QRS >0.12s, 'RSR' pattern in V_1, dominant R in V_1, inverted T waves in V_1-V_3 or V_4, deep wide S wave in V_6. Causes: normal variant (isolated RBBB), pulmonary embolism, cor pulmonale.

In LBBB, the following pattern is seen: QRS >0.12s, 'M' pattern in V_5, no septal Q waves, inverted T waves in I, aVL, V_5-V_6. Causes: IHD, hypertension, cardiomyopathy, idiopathic fibrosis. ▸**NB:** If there is LBBB, no comment can be made on the ST segment or T wave.

Bifascicular block

is the combination of RBBB and left bundle hemiblock, manifest as an axis deviation, eg LAD in the case of left anterior hemiblock.

Trifascicular block

is the combination of bifascicular block and 1st degree heart block.

Ventricular hypertrophy

There is no single marker of ventricular hypertrophy: electrical axis, voltage, and ST wave changes should all be taken into consideration. Relying on a single marker such as voltage may be unreliable as a thin chest wall may result in large voltage whereas a thick chest wall may mask it.

Suspect *left ventricular hypertrophy* (LVH) if the R wave in V_6 >25mm or the sum of the S wave in V_1 and the R wave in V_6 is >35mm (ECG 8 on p127).

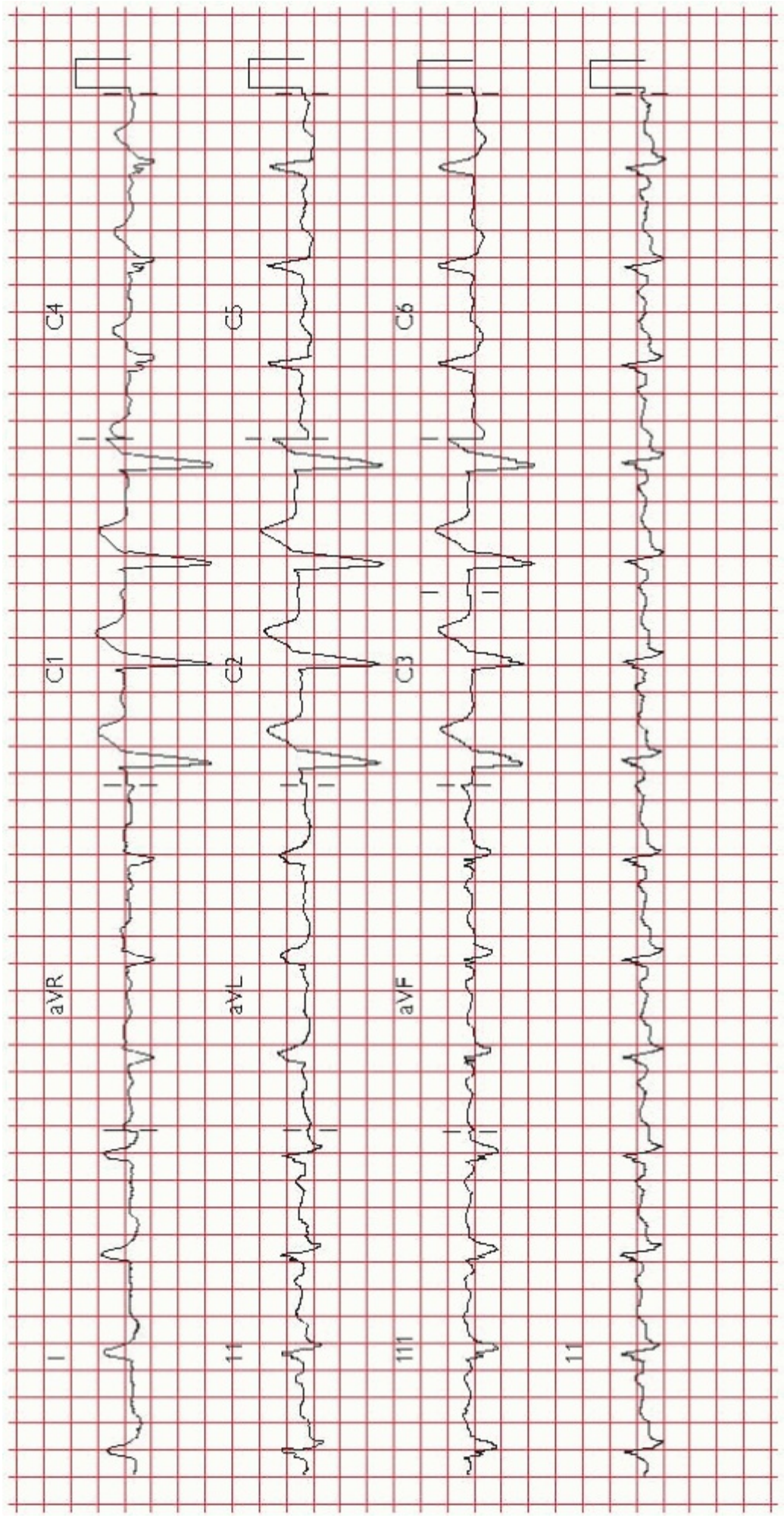
Suspect *right ventricular hypertrophy* (RVH) if dominant R wave in V_1, T wave inversion in V_1-V_3 or V_4, deep S wave in V_6, RAD.

Other causes of ***dominant* R *wave in* V_1**: RBBB, posterior MI, some types of WPW syndrome (p112).

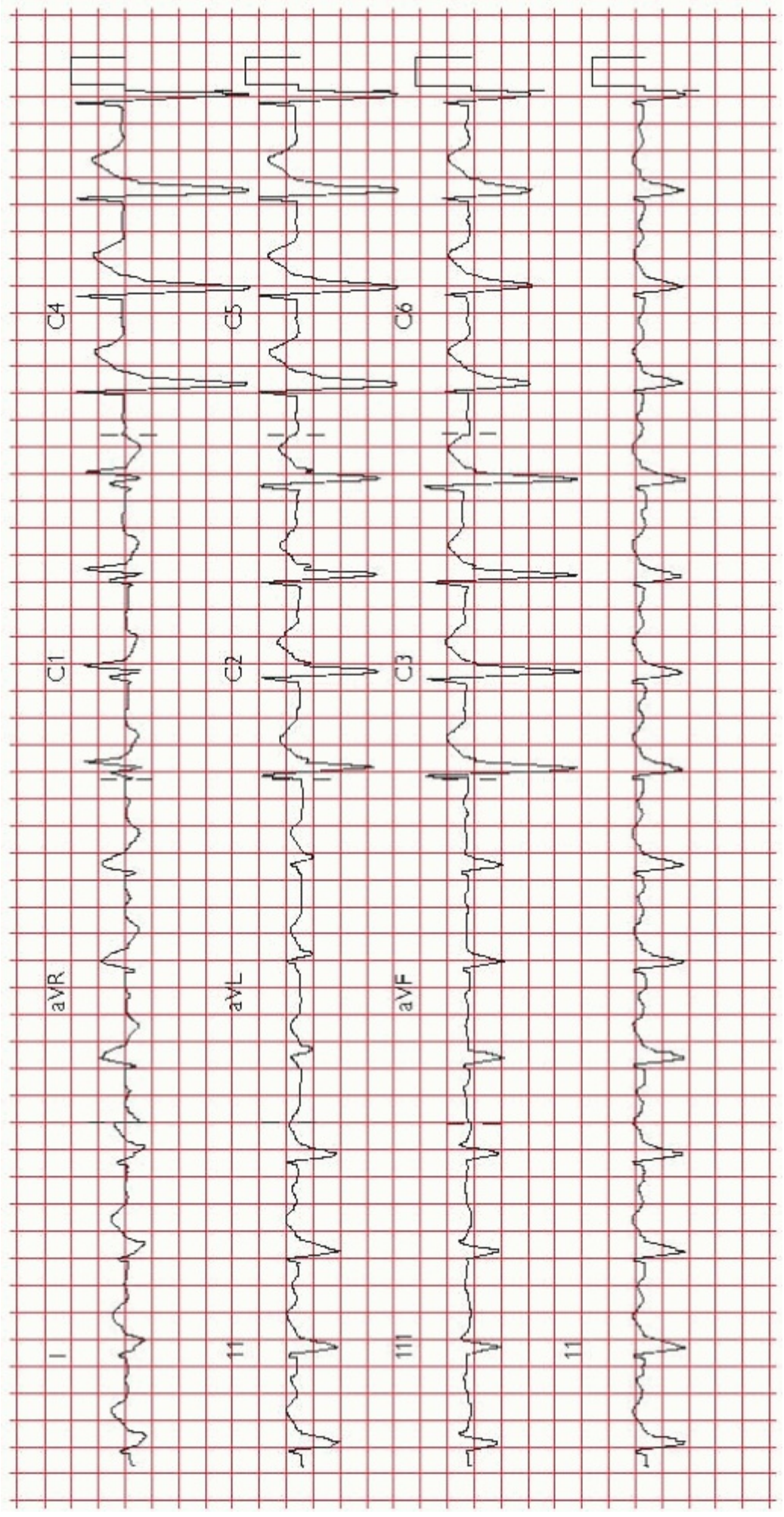
Causes of low voltage QRS complex:

(QRS <5mm in all limb leads) Hypothyroidism, chronic obstructive pulmonary disease (COPD), ↑haematocrit (intra-cardiac blood resistivity is related to haematocrit), changes in chest wall impedance (eg in renal failure, subcutaneous emphysema but *not* obesity), pulmonary embolism, bundle branch block, carcinoid heart disease, myocarditis, cardiac amyloid, adriamycin cardiotoxicity, and other heart muscle diseases, pericardial effusion, pericarditis.[5]

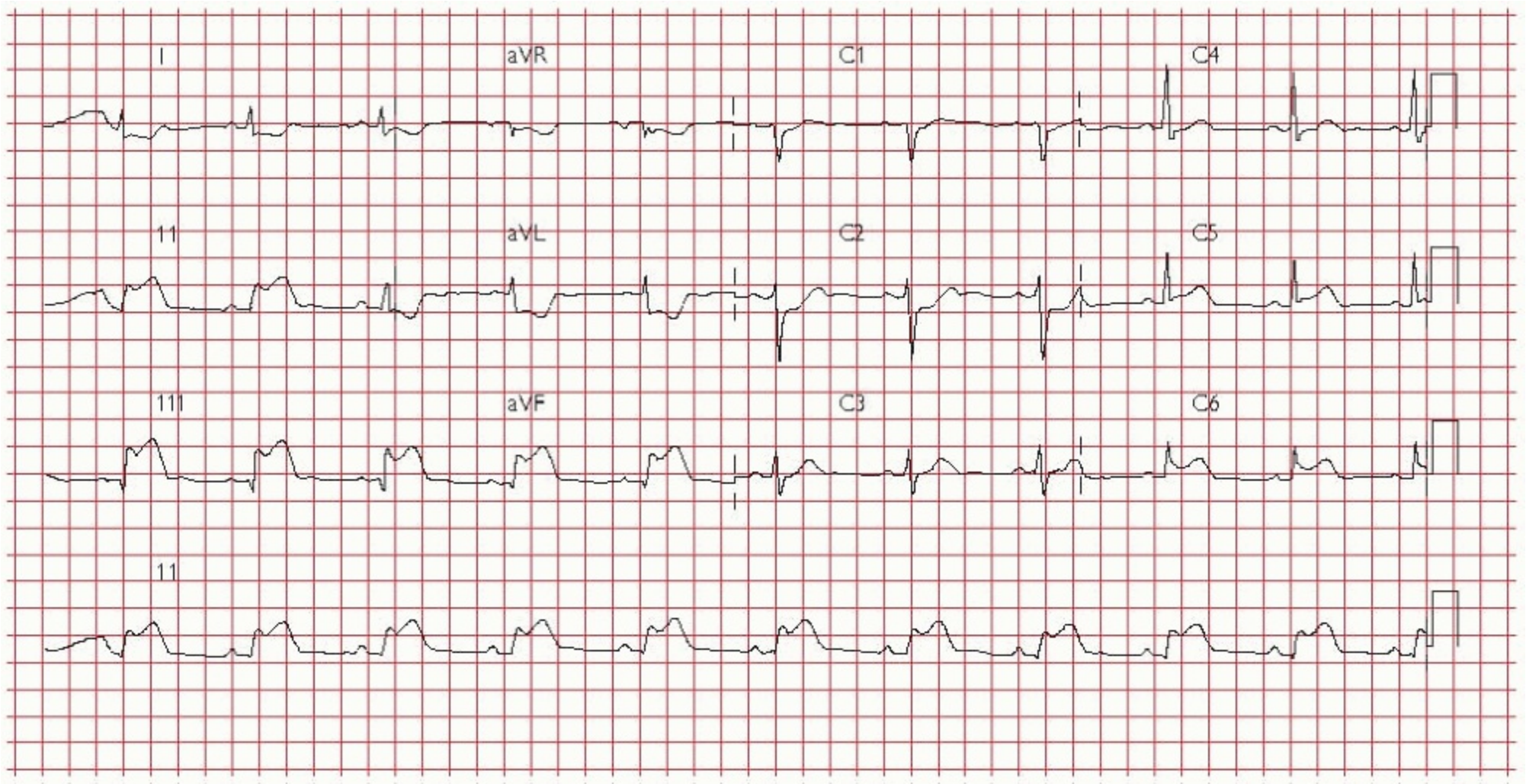
See http://homepages.enterprise.net/djenkins/ecghome.html for MRCP-ish examples of ECGs.



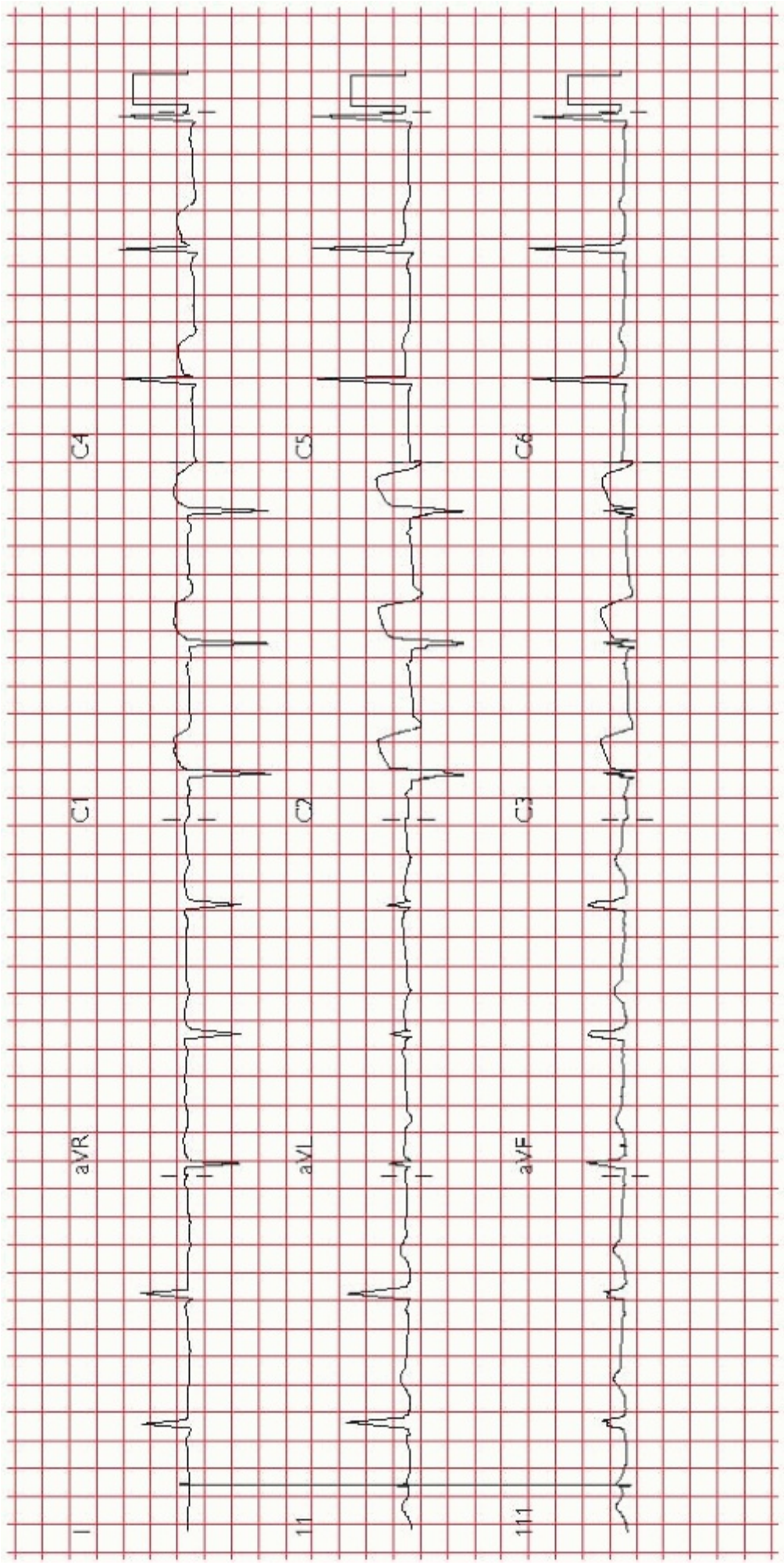
ECG 1—Left bundle branch block: note the W pattern in C1 (=V_1) and the M pattern in C6 (=V_6).



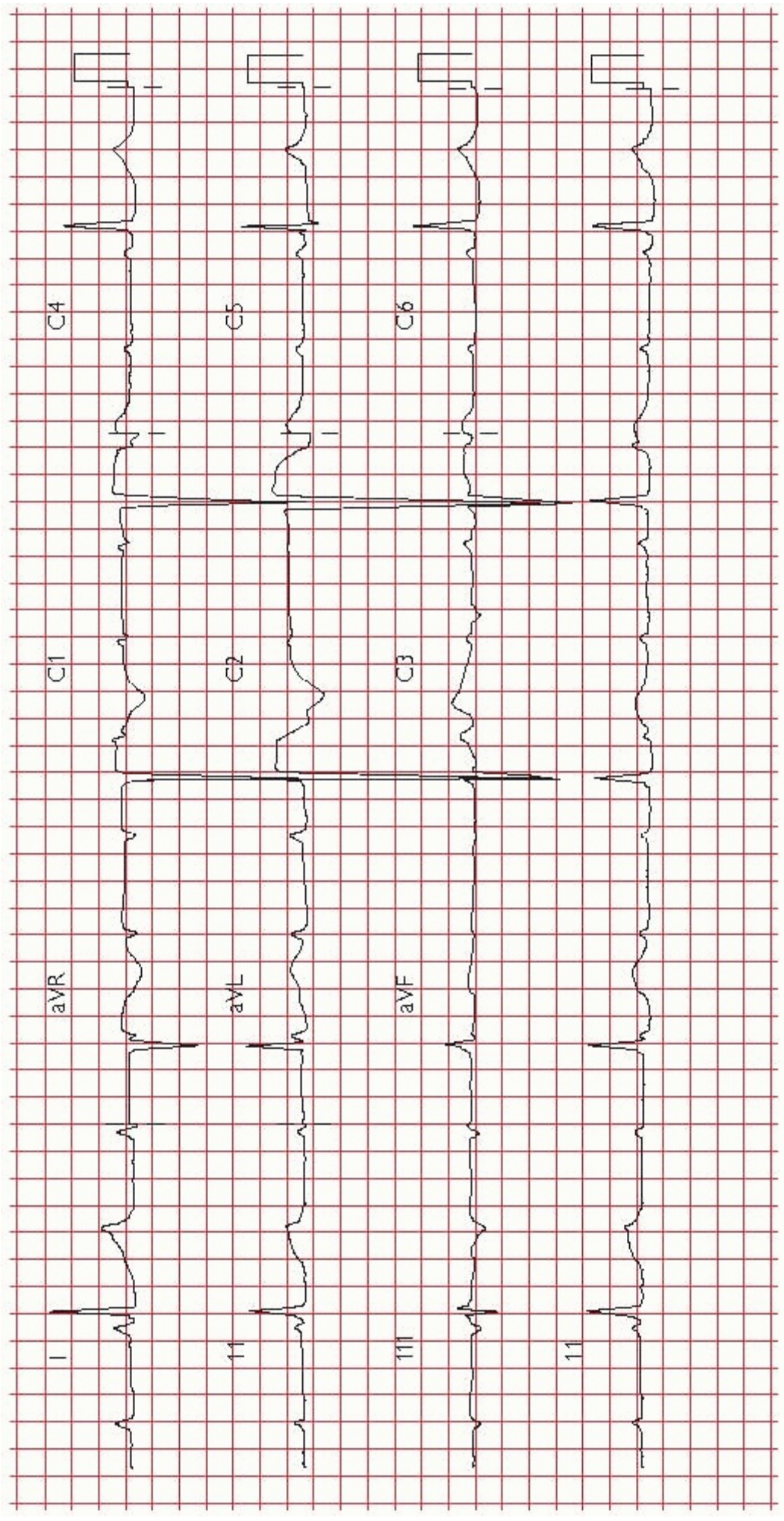
ECG 2—Right bundle branch block—note the M pattern in C1 and the W pattern in C5.


I
aVR
C1
C4
II
aVL
C2
C5
III
aVF
C3
C6
II

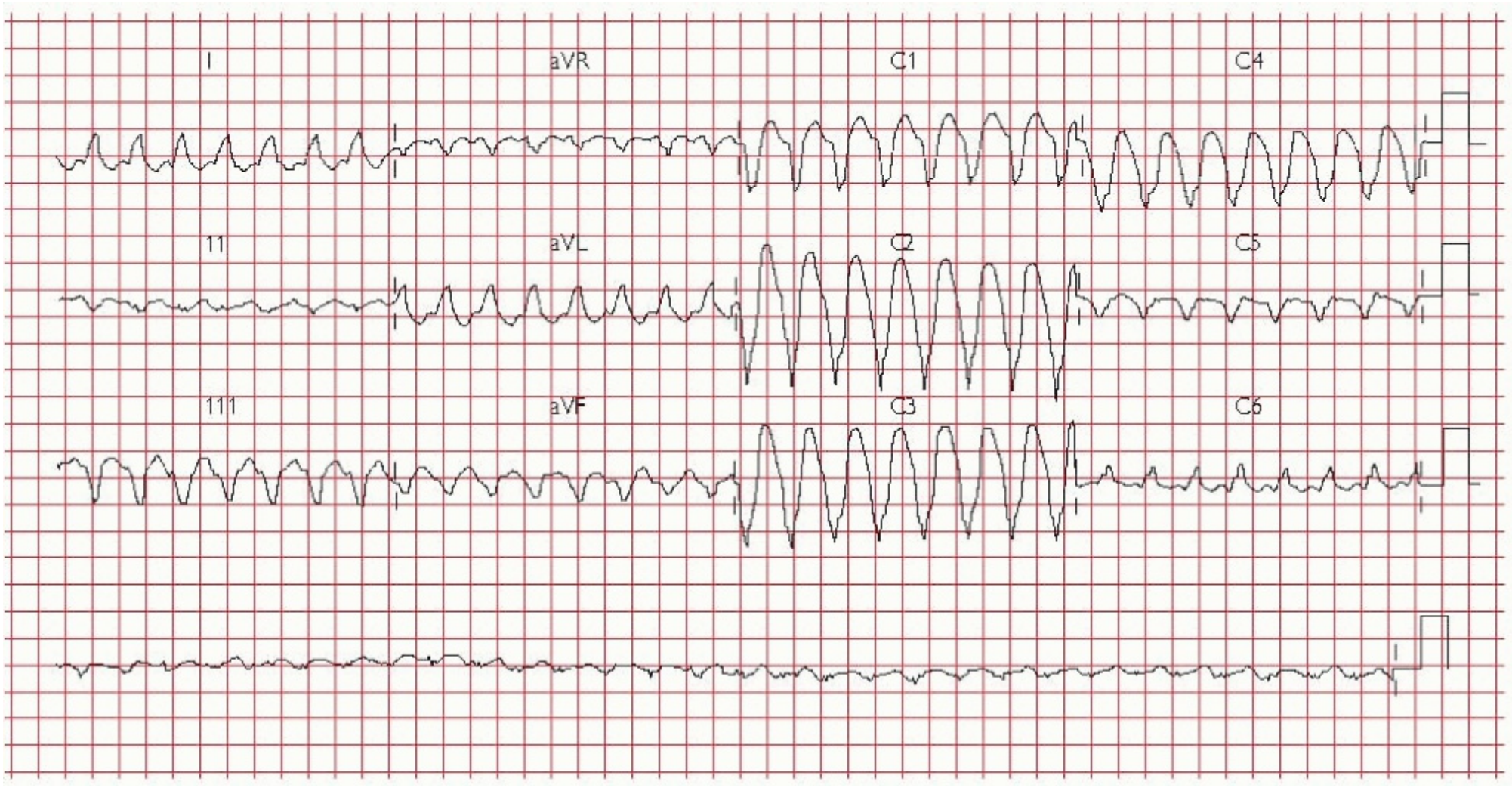
ECG 3—Acute infero-lateral myocardial infarction: note the marked ST elevation in the inferior leads (II, III, aVF), but also in C5 and C6, indicating lateral involvement as well. There is also 'reciprocal change' ie ST-segment depression in leads I and aVL. The latter is often seen with a large myocardial infarction.



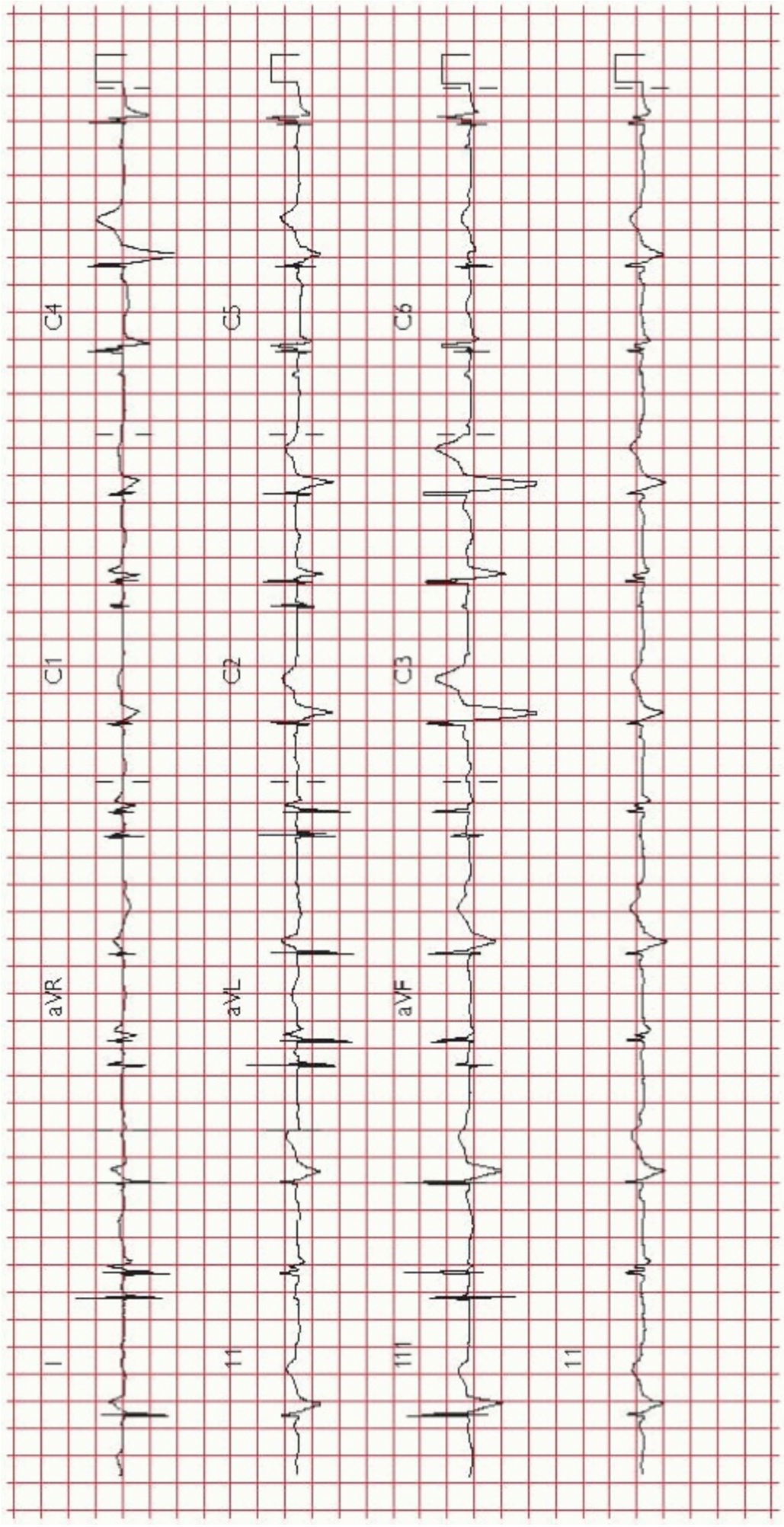
ECG 4—Acute anterior myocardial infarction—note the marked ST segment elevation and evolving Q waves in leads C1-C4.



ECG 5—Complete heart block. Note the dissociation between the P waves and the QRS complexes. QRS complexes are relatively narrow, indicating that there is a ventricular rhythm originating from the conducting pathway.


I
aVR
C1
C4
II
aVL
C2
C5
III
aVF
C3
C6

ECG 6—Ventricular tachycardia—note the broad complexes.



ECG 7—Dual chamber pacemaker. Note the pacing spikes which occur before some of the P waves, and the QRS complexes.

Exercise ECG testing

The patient undergoes a graduated, treadmill exercise test, with continuous 12- lead ECG and blood pressure monitoring. There are numerous treadmill protocols; the 'Bruce protocol' is the most widely used.

Indications:

- To help confirm a suspected diagnosis of IHD.
- Assessment of cardiac function and exercise tolerance.
- Prognosis following MI. Often done pre-discharge (if +ve, worse outcome).
- Evaluation of response to treatment (drugs, angioplasty, coronary artery bypass grafting, CABG).
- Assessment of exercise-induced arrhythmias.

Contraindications:

- Unstable angina
- Recent Q wave MI (<5 days ago)
- Severe AS
- Uncontrolled arrhythmia, hypertension, or heart failure.

Be cautious about arranging tests that will be hard to perform or interpret:

- Complete heart block, LBBB
- Pacemaker patients
- Osteoarthritis, COPD, stroke, or other limitations to exercise.

Stop the test if:

- Chest pain or dyspnoea occurs.
- The patient feels faint, exhausted, or is in danger of falling.
- ST segment elevation/depression >2mm (with or without chest pain).
- Atrial or ventricular arrhythmia (not just ectopics).
- Fall in blood pressure, failure of heart rate or blood pressure to rise with effort, or excessive rise in blood pressure (systolic >230mmHg).
- Development of AV block or LBBB.
- Maximal or 90% maximal heart rate for age is achieved.

Interpreting the test:

A positive test only allows one to assess the *probability* that the patient has IHD. 75% with significant coronary artery disease have a positive test, but so do 5% of people with normal arteries (the false positive rate is even higher in middle-aged women, eg 20%). The more positive the result, the higher the predictive accuracy. Down-sloping ST depression is much more significant than up-sloping, eg 1mm J-point depression with down-sloping ST segment is 99% predictive of 2-3 vessel disease.

Morbidity:

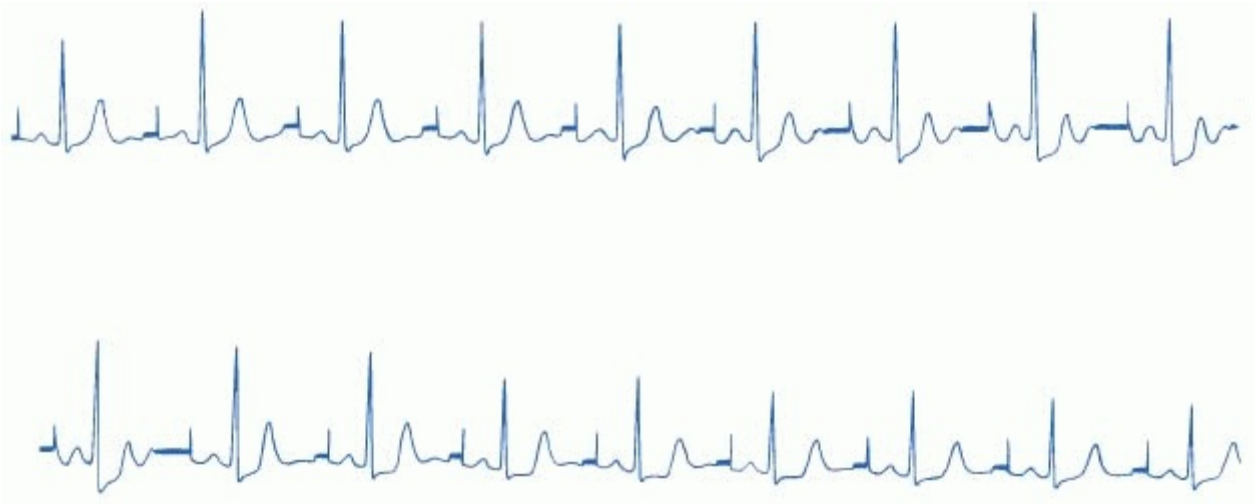
24 in 100,000.

Mortality:

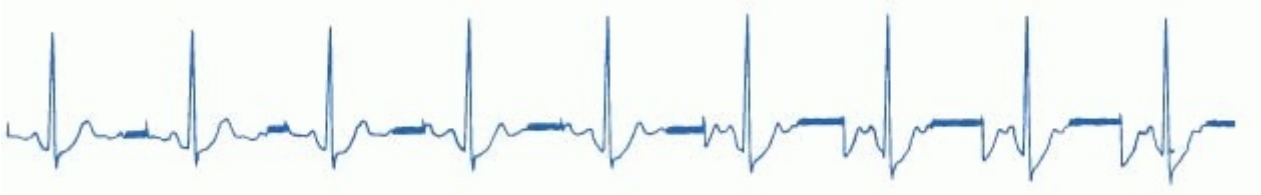
10 in 100,000.

Ambulatory ECG monitoring (Holter monitor)

Continuous ECG monitoring for 24h may be used to try and pick up paroxysmal arrhythmias. However, >70% of patients will not have symptoms during the period of monitoring. ~20% will have a normal ECG during symptoms and only up to 10% will have an arrhythmia coinciding with symptoms. Give these patients a recorder they can activate themselves during an episode. Recorders may be programmed to detect ST segment depression, either symptomatic (to prove angina), or to reveal 'silent' ischaemia (predictive of re-infarction or death soon after MI).



Each complex is taken from sample ECGs (lead C5) recorded at 1-min intervals during exercise (top line) and recovery (bottom line). At maximum ST depression, the ST segment is almost horizontal. This is a positive exercise test.



This is an exercise ECG in the same format. It is negative because although the J point is depressed, the ensuing ST segment is steeply up-sloping.

Cardiac catheterization

This involves the insertion of a catheter into the heart via the femoral (or radial/brachial) artery or vein. The catheter is manipulated within the heart and great vessels to measure pressures. Catheterization can also be used to:

- Sample blood to assess oxygen saturation.
- Inject radiopaque contrast medium to image the anatomy of the heart and flow in blood vessels.
- Perform angioplasty (± stenting), valvuloplasty, and cardiac biopsies.
- Perform intravascular ultrasound to quantify arterial narrowing.

During the procedure, ECG and arterial pressures are monitored continuously. In the UK, 40% of cardiac catheters are performed as day-case procedures (provided the patient can rest lying down for 4h).

Indications:

- *Coronary artery disease:* diagnostic (assessment of coronary vessels and graft patency); therapeutic (angioplasty, stent insertion).
- *Valvular disease:* diagnostic (to assess severity); therapeutic valvuloplasty (if the patient is too ill or declines valve surgery).
- *Congenital heart disease:* diagnostic (assessment of severity of lesions); therapeutic (balloon dilatation or septostomy).
- *Other:* cardiomyopathy; pericardial disease; endomyocardial biopsy.

Pre-procedure checks:

- Brief history/examination; **NB:** peripheral pulses, bruits, aneurysms.
- Investigations: FBC, U&E, LFT, clotting screen, group & save, CXR, ECG.
- Consent for angiogram ± angioplasty ± stent ± CABG. Explain reason for procedure and possible complications (below).
- IV access, ideally in the left hand.
- Patient should be nil by mouth (NBM) from 6h before the procedure.
- Patients should take all their morning drugs (and pre-medication if needed). Withhold oral hypoglycaemics.

Post-procedure checks:

- Pulse, blood pressure, arterial puncture site (for bruising or swelling? false aneurysm), peripheral pulses.
- Investigations: FBC and clotting (if suspected blood loss), ECG.

Complications:

- *Haemorrhage:* Apply firm pressure over puncture site. If you suspect a false aneurysm, ultrasound the swelling and consider surgical repair.
- *Contrast reaction:* This is usually mild with modern contrast agents.
- *Loss of peripheral pulse:* May be due to dissection, thrombosis, or arterial spasm. Occurs in <1% of brachial catheterizations. Rare with femoral catheterization.
- *Angina:* May occur during or after cardiac catheterization. Usually responds to sublingual GTN; if not give analgesia and IV nitrates.
- *Arrhythmias:* Usually transient. Manage along standard lines.
- *Pericardial tamponade:* Rare, but should be suspected if the patient becomes hypotensive and anuric.
- *Infection:* Post-catheter pyrexia is usually due to a contrast reaction. If it persists for >24h, take blood cultures before giving antibiotics.

Mortality:

<1 in 1000 patients, in most centres.

Intra-cardiac electrophysiology

This catheter technique can determine types and origins of arrhythmias, and locate (and ablate) aberrant pathways (eg causing atrial flutter or ventricular tachycardia). Arrhythmias may be induced, and the effectiveness of control by drugs assessed.

Normal values for intracardiac pressures and saturations

Location		Pressure (mmHg)		Saturation (%)
		Mean	Range	
Inferior vena cava				76
Superior vena cava				70
Right atrium		4	0-8	74
Right ventricle				74
	Systolic	25	15-30	

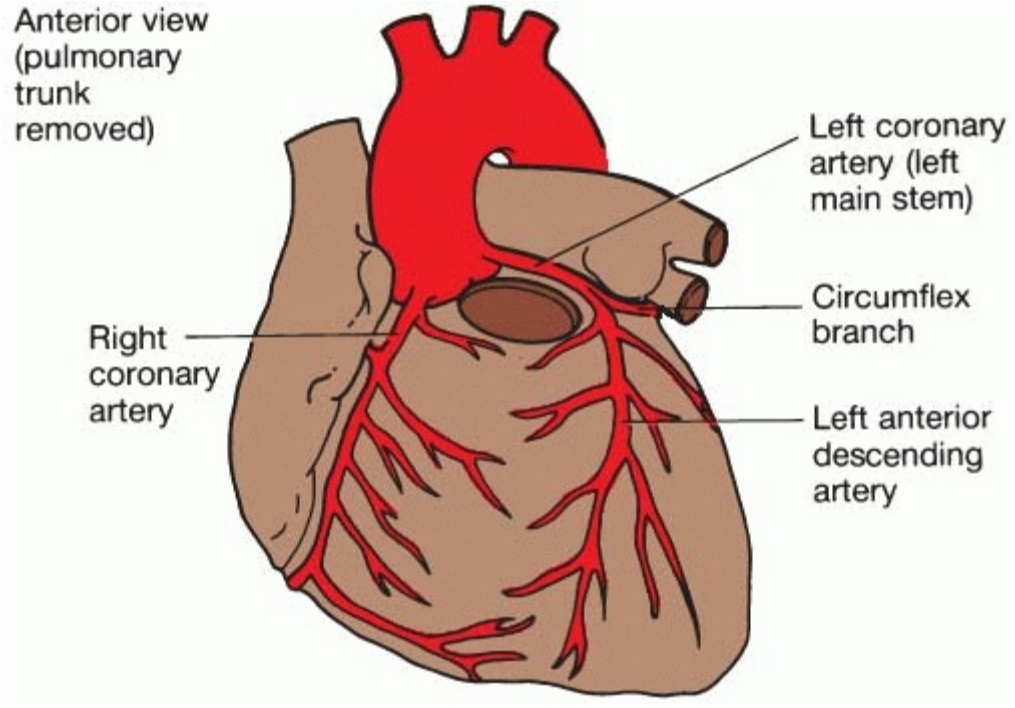
	End-diastolic	4	0-8	
Pulmonary artery				74
	Systolic	25	15-30	
	Diastolic	10	5-15	
	Mean	15	10-20	
Pulmonary artery		a	3-12	74
	Wedge pressure	v	3-15	
Left ventricle				
	Systolic	110	80-140	98
	End-diastolic	70	60-90	
Aorta				
	Systolic	110	80-140	98
	Diastolic	70	60-90	
	Mean	85	70-105	

Brachial				
	Systolic	120	90-140	98
	Diastolic	72	60-90	
	Mean	83	70-105	

Gradients across stenotic valves

Valve	Normal gradient	Stenotic gradient (mmHg)		
	(mmHg)	Mild	Moderate	Severe
Aortic	0	<30	30-50	>50
Mitral	0	<5	5-15	>15
Prosthetic	5-10			

Coronary artery anatomy



Understanding Angina © American Heart Association; by kind permission

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Echocardiography

This non-invasive technique uses the differing ability of various structures within the heart to reflect ultrasound waves. It not only demonstrates anatomy but provides a continuous display of the functioning heart throughout its cycle. There are various types of scan:

M-mode (motion mode):

Scans are displayed on light-sensitive paper moving at constant speed to produce a permanent single dimension (time) image.

2-dimensional (real time):

A 2-D, fan-shaped image of a segment of the heart is produced on the screen, which may be 'frozen' and hard-copied. Several views are possible and the 4 commonest are: long axis, short axis, 4-chamber, and subcostal. 2-D echocardiography is good for visualizing conditions such as: congenital heart disease, LV aneurysm, mural thrombus, LA myxoma, septal defects.

Doppler and colour-flow echocardiography:

Different coloured jets illustrate flow and gradients across valves and septal defects (p142). (Doppler effect, p722)

Trans-oesophageal echocardiography (TOE)

is more sensitive than transthoracic echocardiography (TTE) as the transducer is nearer to the heart. Indications: diagnosing aortic dissections; assessing prosthetic valves; finding cardiac source of emboli, and IE/SBE. Don't do if oesophageal disease or cervical spine instability.

Stress echocardiography is used to evaluate ventricular function, ejection fraction, myocardial thickening, and regional wall motion pre- and post-exercise. Dobutamine or dipyridamole may be used if the patient cannot exercise. Inexpensive and as sensitive/specific as a thallium scan (p726).

Uses of echocardiography

Quantification of global LV function:

Heart failure may be due to systolic or diastolic ventricular impairment (or both). Echo helps by measuring end-diastolic volume. If this is large, systolic dysfunction is the likely cause. If small, diastolic. Pure forms of diastolic dysfunction are rare. Differentiation is important, as vasodilators are less useful in diastolic dysfunction as a high ventricular filling pressure is required.

Echo is also useful for detecting focal and global hypokinesia, LV aneurysm, mural thrombus, and LVH (echo is 5-10 times more sensitive than ECG in detecting this).

Estimating right heart haemodynamics:

Doppler studies of pulmonary artery flow allow evaluation of RV function and pressures.

Valve disease:

Measurement of pressure gradients and valve orifice areas in stenotic lesions. Detecting valvular regurgitation and estimating its significance is less accurate. Evaluating function of prosthetic valves is another role.

Congenital heart disease:

Establishing the presence of lesions and determining their functional significance.

Endocarditis:

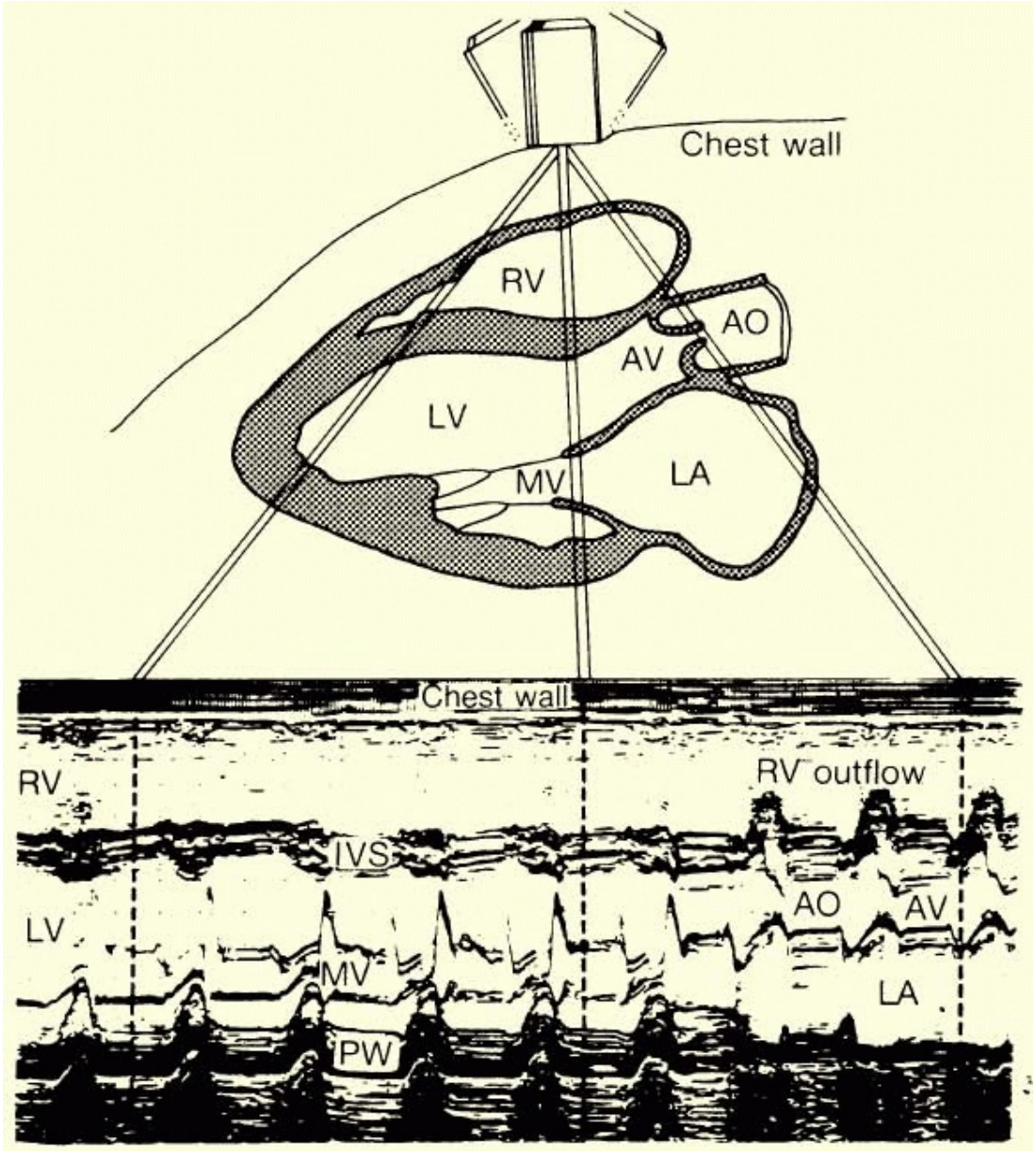
Vegetations may not be seen if <2mm in size. TTE with colour doppler is best for aortic regurgitation (AR). TOE is useful for visualizing mitral valve vegetations, leaflet perforation, or looking for an aortic root abscess.

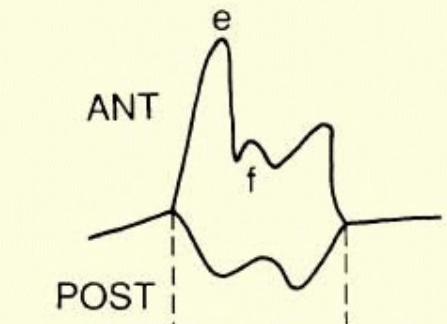
Pericardial effusion

is best diagnosed by echo. Fluid may first accumulate between the posterior pericardium and the left ventricle, then anterior to both ventricles and anterior and lateral to the right atrium. There may be paradoxical septal motion.

HOCM

(p138): Echo features include asymmetrical septal hypertrophy, small LV cavity, dilated left atrium, and systolic anterior motion of the mitral valve.



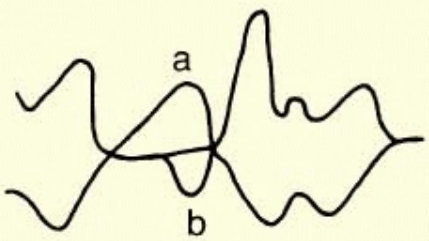


1. Normal mitral valve

CLOSED | OPEN | CLOSED

2. Mitral stenosis
   - reduced e–f slope

3. Aortic regurgitation
   - fluttering of ant. leaflet



4. (a) Systolic anterior leaflet movement (SAM) in HOCM
   (b) Mitral valve prolapse (late systole)

Normal M-mode echocardiogram (RV=right ventricle; LV=left ventricle; AO= aorta; AV=aortic valve; LA=left atrium; MV=mitral valve; PW=posterior wall of LV; IVS=interventricular septum).

After R Hall *Med International* **17** 774.

Cardiovascular drugs

Antiplatelet drugs

Aspirin irreversibly acetylates cyclo-oxygenase, preventing production of thromboxane A_2, thereby inhibiting platelet aggregation. Used in low dose (eg 75mg/24h PO) for secondary prevention following MI, TIA/stroke, and for patients with angina or peripheral vascular disease. May have a role in primary prevention.[6] ADP receptor antagonists (eg clopidogrel) also block platelet aggregation, but may cause less gastric irritation. They have a role if truly intolerant of aspirin, and post-coronary stent insertion.

ß-blockers

Block ß-adrenoceptors, thus antagonizing the sympathetic nervous system. Blocking $ß_1$-receptors is negatively inotropic and chronotropic (pulse↓ by ↓firing of sinoatrial node), and $ß_2$-receptors induce peripheral vasoconstriction and bronchoconstriction. Drugs vary in their $ß_1/ß_2$ selectivity (eg propranolol is non-selective, and bisoprolol relatively $ß_1$ selective), but this does not seem to alter their clinical efficacy. *Uses:* Angina, hypertension (2nd line), antidysrhythmic, post MI (↓mortality), heart failure (with caution).

CI:

Asthma/COPD, heart block.

Caution:

Peripheral vascular disease, heart failure/(but see carvedilol, p122).

SE:

Lethargy, erectile dysfunction, *joie de vivre*↓, nightmares, headache.

Diuretics

Loop diuretics (eg *furosemide=frusemide*) are used in heart failure, and inhibit the Na/2Cl/K co-transporter. Thiazides are used in hypertension and inhibit Na/Cl co-transporter.

SE:

Loop: dehydration, $\downarrow K^+$, $\downarrow Ca^{2+}$, ototoxic; *thiazides:* $\downarrow K^+$, $\uparrow Ca^{2+}$, $\downarrow Mg^{2+}$, ↑urate (±gout), impotence (**NB:** small doses, eg bendroflumethiazide 2.5mg/24h rarely cause significant SEs); *Amiloride:* $\uparrow K^+$, GI upset.

Vasodilators used in heart failure, IHD, and hypertension. Nitrates preferentially dilate veins and the large arteries, ñ filling pressure (pre-load), while hydralazine (often used with nitrates) primarily dilates the resistance vessels thus ↓ BP (afterload). Prazosin (an ×-blocker) dilates arteries and veins.

Calcium antagonists

These ↓cell entry of Ca^{2+} via voltage-sensitive channels on smooth muscle cells, thereby promoting coronary and peripheral vasodilatation and reducing myocardial oxygen consumption.

Pharmacology:

All current drugs block L-type Ca^{2+} channels. However, their effects differ because of differential binding properties. The *dihydropyridines* eg nifedipine; amlodipine, are mainly peripheral vasodilators (also dilate coronary arteries) and cause a reflex tachycardia, so are often used with a ß-blocker. They are used mainly in hypertension and angina. The *non*-dihydropyridines—verapamil and diltiazem— also slow conduction at the atrioventricular and sinoatrial nodes and may be used to treat hypertension, angina, and dysrhythmias. Don't give verapamil with ßblockers (risk of bradycardia ± LVF).

SE:

Flushes, headache, oedema (diuretic unresponsive), LV function↓, gingival hypertrophy.

CI:

heart block.

Digoxin[7] [8]

Blocks the Na^+/K^+ pump. It is used to slow the pulse in fast AF (p116; aim for <100). As it is a weak +ve inotrope, its role in heart failure in sinus rhythm may

be best reserved if symptomatic despite optimal ACE-i therapy (p123);[9] here there is little benefit *vis-à-vis* mortality (but admissions for worsening CCF are ↓by ~25%).[10] Old people are at ↑risk of toxicity: use lower doses. Do plasma levels >6h post-dose (p739). Typical dose: 500µg stat PO, repeated after 12h, then 125µg (if elderly) to 375µg/d PO (62.5µg/d is almost never enough). IV dose: 0.75-1mg in 0.9% NaCl over 2h.[11] Toxicity risk↑ if: K^+↓, Mg^{2+}↓, or Ca^{2+}↑. t½ ≈ 36h. If on digoxin, use less energy in cardioversion (start at 5J). ▸If on amiodarone , halve the dose of digoxin.

SE:

Any arrhythmia (supraventricular tachycardia with AV block is suggestive), nausea, appetite↓, yellow vision, confusion, gynaecomastia. In toxicity, stop digoxin; check K^+; treat arrhythmias; consider Digibind® by IVI (p826).

CI:

HOCM; WPW syndrome (p112 & p792).

ACE-inhibitors

p123;

Nitrates

p102;

Antihypertensives

p142.

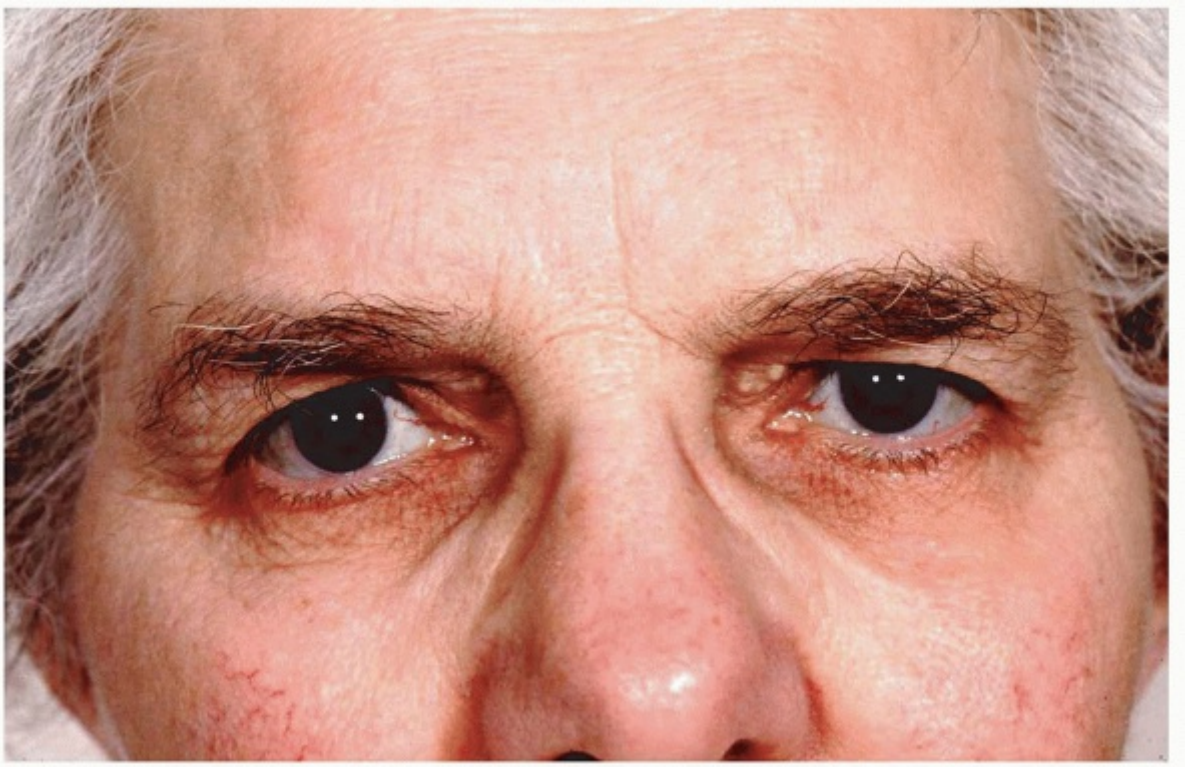


Fig 1. Xanthelasma. *Xanthos* is Greek for yellow, and *elasma* means plate. Xanthelasma are lipid-laden yellow plaques congregating around the lids. They are typically a few mm wide, and signify hyperlipidaemia, p682

Statins

Statins (eg simvastatin, pravastatin, p682) inhibit the enzyme HMG-COA reductase, which is responsible for the *de novo* synthesis of cholesterol in the liver. This leads to an increase in LDL receptor expression by hepatocytes and ultimately reduced circulating LDL cholesterol. More effective if given at night, but optimum dose, and target cholesterol are unknown. SE: muscle aches, abdominal discomfort, ↑transaminases (eg ALT), ↑CK, myositis, rarely rhabdomyolysis (more common when used in combination with fibrates). Besides lowering LDL cholesterol, statins have other favourable or 'pleiotropic' effects:

- Anti-thrombotic.
- Anti-inflammatory (CRP↓).
- Plaque stabilization; high doses *may* even reverse plaque growth (note that recent trials have not shown that when this occurs there is ↓morbidity —and high doses of some statins may cause renal impairment and myopathy). [12]
- Restoration of normal endothelial function.
- Reduction in cholesterol synthesis by within-vessel macrophages.
- Reduction of within-vessel macrophage proliferation and migration.

Angina pectoris

This is due to myocardial ischaemia and presents as a central chest tightness or heaviness, which is brought on by exertion and relieved by rest. It may radiate to one or both arms, the neck, jaw or teeth.

Other precipitants:

Emotion, cold weather, and heavy meals.

Associated symptoms:

Dyspnoea, nausea, sweatiness, faintness.

Causes

Mostly atheroma. Rarely: anaemia, AS; tachyarrhythmias; HOCM; arteritis/small vessel disease (microvascular angina/cardiac syndrome X).

Types of angina

Stable angina: induced by effort, relieved by rest. *Unstable (crescendo) angina:* angina of increasing frequency or severity; occurs on minimal exertion or at rest; associated with ↑↑risk of MI. *Decubitus angina:* precipitated by lying flat. *Variant (Prinzmetal's) angina:* caused by coronary artery spasm (rare; may co-exist with fixed stenoses).

Tests

ECG: usually normal, but may show ST depression; flat or inverted T waves; signs of past MI. If resting ECG normal, consider exercise ECG (p94), thallium scan (p726), or coronary angiography. Exclude precipitating factors: anaemia, diabetes, hyperlipidaemia, thyrotoxicosis, giant cell arteritis.

Management

Alteration of lifestyle: Stop smoking, encourage exercise, weight loss. *Modify risk factors:* Hypertension, diabetes, etc., p79.

- *Aspirin* (75-150mg/24h) reduces mortality by 34%.
- *β-blockers:* eg atenolol 50-100mg/24h PO, reduce symptoms unless contraindications (asthma, COPD, LVF, bradycardia, coronary artery spasm).
- *Nitrates:* for symptoms, give GTN spray or sublingual tabs, up to every 1/2h. Prophylaxis: give regular oral nitrate, eg isosorbide mononitrate 10-30mg PO (eg bd; an 8h nitrate-free period to prevent tolerance) or slow-release nitrate (eg Imdur® 60mg/24h). Alternatives: adhesive nitrate skin patches or buccal pills. SE: headaches, BP↓.
- *Calcium antagonists:* amlodipine 10mg/24h; diltiazem-MR 90-180mg/12h PO.
- If total cholesterol >4mmol/L give a statin—see p682.
- Consider adding a K^+ *channel activator*, eg nicorandil 10-30mg/12h PO.

▸Unstable angina requires admission and urgent treatment: *emergencies*, p784.

Indications for referral

Diagnostic uncertainty; new angina of sudden onset; recurrent angina if past MI or CABG; angina uncontrolled by drugs; unstable angina. Some units routinely do exercise tolerance tests on those <70yrs old, but age alone is a poor way to stratify patients.

Percutaneous transluminal coronary angioplasty (PTCA)

involves balloon dilatation of the stenotic vessel(s). *Indications:* poor response or intolerance to medical therapy; refractory angina in patients not suitable for CABG; previous CABG; post-thrombolysis in patients with severe stenoses, symptoms, or positive stress tests. Comparisons of PTCA vs drugs alone show that PTCA may control symptoms better but with more frequent early cardiac events (eg MI and need for CABG[13]) and little effect on overall mortality. However, early intervention may benefit high risk patients presenting with non-ST-segment elevation ACS (p104).[14] *Complications:* Restenosis (20-30% within 6 months); emergency CABG (<3%); MI (<2%); death (<0.5%). Stenting reduces restenosis rates and the need for bail out CABG. NICE recommends that >70% of angioplasties should be accompanied by stenting. Drug-coated stents reduce restenosis. Antiplatelet agents, eg clopidogrel reduce the risk of stent thrombosis. IV platelet glycoprotein IIb/IIIa-inhibitors (eg eptifibatide) can reduce procedure-related ischaemic events.[15]

CABG:

Indications: Left main stem disease, multi-vessel disease; multiple severe stenoses; distal vessel disease; patient unsuitable for angioplasty; failed angioplasty; refractory angina; MI; pre-operatively (valve or vascular surgery). Comparisons of CABG *vs* PTCA have found that CABG results in better symptom control and lower reintervention rate, but longer recovery time and length of inpatient stay.

Acute coronary syndromes (ACS)

Definitions

ACS includes unstable angina and evolving MI, which share a common underlying pathology—plaque rupture, thrombosis, and inflammation. However, ACS may rarely be due to emboli or coronary spasm in normal coronary arteries, or vasculitis (p542). Usually divided into ***ACS with ST-segment elevation*** or new onset LBBB—what most of us mean by acute MI; and ***ACS without ST-segment elevation***— the ECG may show ST-depression, T-wave inversion, non-specific changes, or be normal (includes non-Q wave or subendocardial MI). The degree of irreversible myocyte death varies, and significant necrosis can occur without ST-elevation. Cardiac troponins (T and I) are the most sensitive and specific markers of myocardial necrosis, and are the test of choice in patients with ACS (see below).

Risk factors

Non-modifiable: age, ♂ gender, family history of IHD (MI in first degree relative <55yrs). *Modifiable:* smoking, hypertension, DM, hyperlipidaemia, obesity, sedentary lifestyle. *Controversial* risk factors include: stress, type A personality, LVH, apoprotein A↑, fibrinogen↑, hyperinsulinaemia, homocysteine levels↑ (p79), ACE genotype, and cocaine use.

Incidence

5/1000 per annum (UK) for ST-segment elevation.

Diagnosis is based on the presence of at least 2 out of 3 of: typical history, ECG changes, and cardiac enzyme rise (WHO criteria).

Symptoms

Acute central chest pain, lasting >20min, often associated with nausea, sweatiness, dyspnoea, palpitations. May present without chest pain ('silent' infarct) eg in elderly or diabetics. In such patients, presentations may include: syncope, pulmonary oedema, epigastric pain and vomiting, post-operative hypotension or oliguria, acute confusional state, stroke, diabetic hyperglycaemic states.

Signs

Distress, anxiety, pallor, sweatiness, pulse↑ or ↓, BP↑ or ↓, 4th heart sound. There may be signs of heart failure (↑ JVP, 3rd heart sound and basal crepitations) or a pansystolic murmur (papillary muscle dysfunction/rupture, VSD). A low-grade pyrexia may be present. Later, a pericardial friction rub or peripheral oedema may develop.

Tests ECG:

Classically, hyperacute (tall) T waves, ST elevation or new LBBB occur within hours of acute Q wave (transmural infarction). T wave inversion and the development of pathological Q waves follow over hours to days (p84). In other ACS: ST-depression, T-wave inversion, non-specific changes, or normal. ▸*In 20% of* MI*s, the* ECG *may be normal initially.*

CXR:

Look for cardiomegaly, pulmonary oedema, or a widened mediastinum (?aortic dissection). Don't routinely delay [prescription take] whilst waiting for a CXR.

Blood:

FBC, U&E, glucose↑, lipids↓, cardiac enzymes (CK, AST, LDH, troponin)↑, CK is found in myocardial and skeletal muscle. It is raised in: MI; after trauma (falls, seizures); prolonged exercise; myositis; Afro-Caribbeans; hypothermia; hypothyroidism. Check CK-MB isoenzyme levels if there is doubt as to the source (normal CK-MB/CK ratio <5%). Troponin T better reflects myocardial damage (peaks at 12- 24h; elevated for >1wk). If normal ≥6h after onset of pain, and ECG normal, risk of missing MI is tiny (0.3%).[16] Peak post-MI levels also help risk stratification.[17]

Differential diagnosis

(p80) Angina, pericarditis, myocarditis, aortic dissection (p586), pulmonary embolism, and oesophageal reflux/spasm.

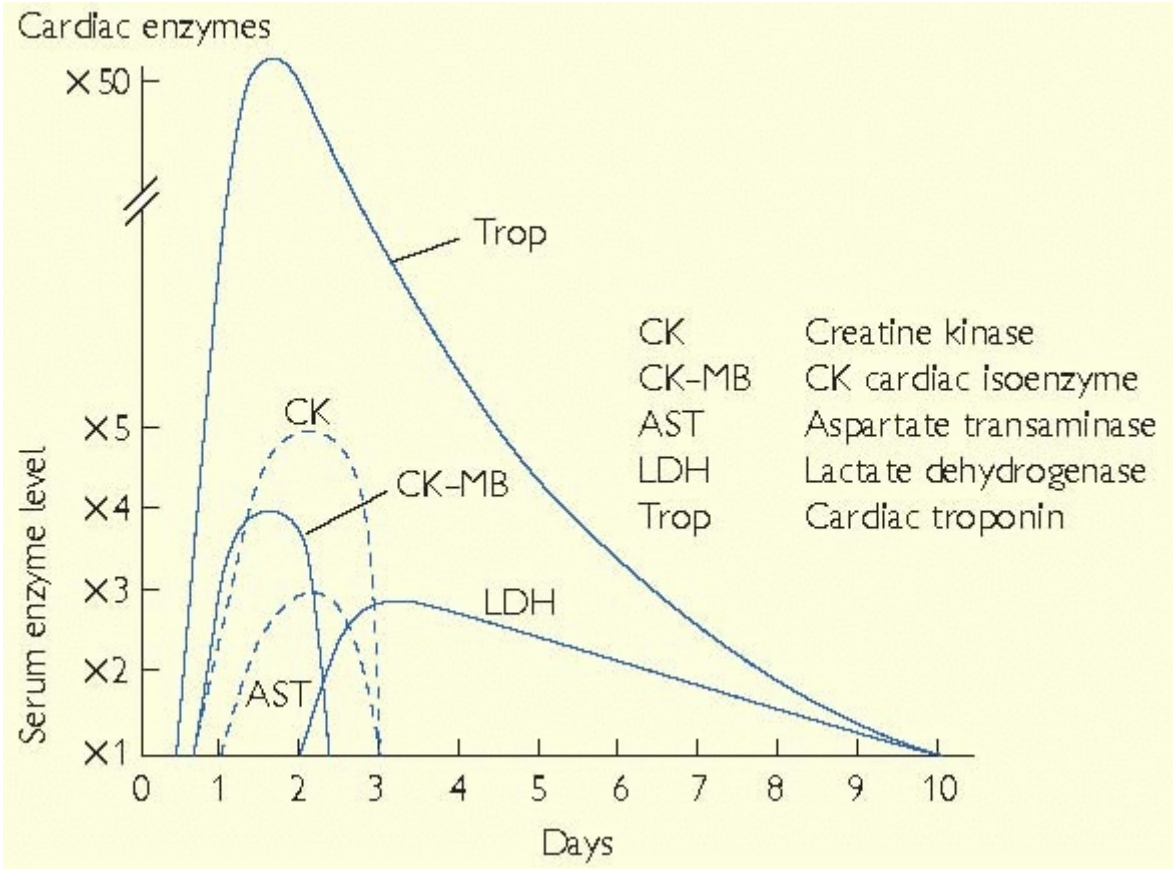
Management

See *emergencies*, p782. The management of ACS with and without ST-segment elevation varies. Likewise, if there is no ST-elevation, and symptoms settle without a rise in cardiac troponin, then no myocardial damage has occurred, the prognosis is good, and patients can be discharged. Therefore, the two key questions are: is there ST-segment elevation; and is there a rise in troponin?

Mortality

50% of deaths occur within 2h of onset of symptom.

Enzyme changes following acute MI



Sequential ECG changes following acute MI

Management of acute coronary syndrome (ACS)

Pre-hospital

Arrange emergency ambulance. Aspirin 300mg chewed$_{18}$ (if no *absolute* CI) and GTN sublingual. Analgesia, eg morphine 5-10mg IV + metoclopramide 10mg IV (not IM because of risk of bleeding with thrombolysis).

In hospital—

O_2, IVI, morphine, aspirin ▸▸p782

Then the key question for subsequent management of ACS is whether there is ST-segment elevation (includes new onset LBBB or a true posterior MI).

ST-segment elevation

- *Thrombolysis*, if no contraindication, or primary angioplasty ▸▸ p782.
- *ß-blocker*, eg atenolol 5mg IV unless contraindicated, eg asthma.
- ACE-inhibitor: Consider starting ACE-i (eg lisinopril 2.5mg) in all normotensive patients (systolic ≥120mm/Hg) within 24h of acute MI, especially if there is clinical evidence of heart failure or echo evidence of LV dysfunction.

ACS without ST-segment elevation[19]

- *ß-blocker*, eg atenolol 5mg IV unless contraindicated.
- *Low molecular weight heparin* (eg enoxaparin 1mg/kg/12h SC for 2-8d).
- *Nitrates*, unless contraindication (usually given intravenously).
- High-risk patients (persistent or recurrent ischaemia, ST-depression, diabetes, ↑ troponin) require infusion of a *GPIIb/IIIa antagonist* (eg tirofiban)[20], and, ideally, urgent angiography. *Clopidogrel*, in addition to aspirin, should be considered for up to 12 months.[21]
- Low-risk patients (no further pain, flat or inverted T waves, or normal ECG, **and** negative troponin) can be discharged if a repeat troponin is negative. Treat medically and arrange further investigation eg stress test, angiogram.

Subsequent management

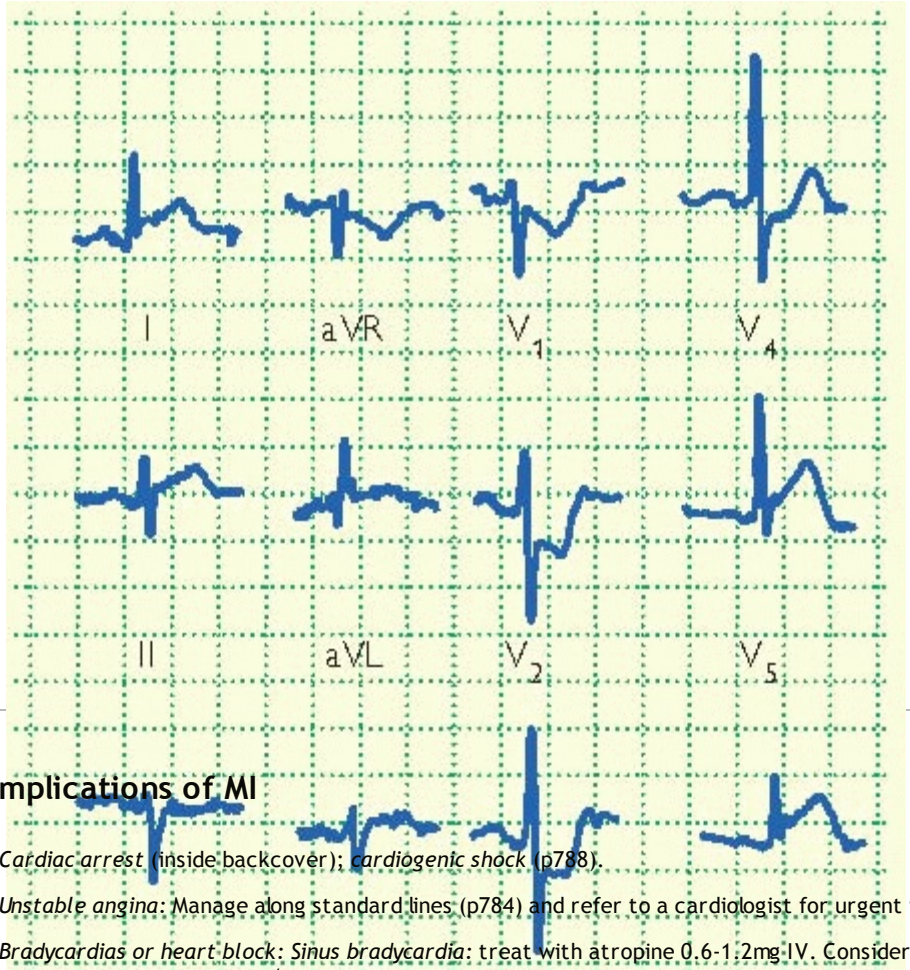
*Bed rest for 48*h; continuous ECG monitoring.

- Daily examination of heart, lungs, and legs for complications (p108).
- Daily 12-lead ECG, U&E, cardiac enzymes for 2-3d.
- *Prophylaxis against thromboembolism:* eg heparin 5000U/12h SC until fully mobile. If large anterior MI, consider warfarin anticoagulation for 3 months as prophylaxis against systemic embolism from LV mural thrombus. Continue daily *low-dose aspirin* (eg 75-150mg) indefinitely. Aspirin reduces vascular events (MI, stroke, or vascular death) by 29%.
- Start oral ß-*blocker* (eg metoprolol ~50mg/6h, enough to decrease the pulse to ≤60; continue for at least 1yr). Long-term ß-blockade reduces mortality from all causes by ~25% in patients who have had a previous MI. If contraindicated, consider verapamil or diltiazem as an alternative.
- *Continue* ACE-i in all patients. ACE-i in those with evidence of heart failure ↓2yr mortality by 25-30%.
- *Start a* statin.[22] Cholesterol reduction post-MI has been shown to be of benefit in patients with both elevated and normal cholesterol levels. Some treat all patients, others only if total cholesterol >4.0mmol/L (p682).
- *Address modifiable risk factors:* Discourage smoking (p79). Encourage exercise. Identify and treat diabetes mellitus, hypertension, and hyperlipidaemia.
- *Exercise* ECG. May be useful in risk stratification post-MI after 3-4wks, and in subjects without ST-segment elevation or a troponin rise.
- *General advice*. If uncomplicated, discharge after 5-7d. *Work:* He may return to work after 2 months. A few occupations should not be restarted post-MI: airline pilots; air traffic controllers; divers. Drivers of public service or heavy goods vehicles may be permitted to return to work if they meet certain criteria.[23] Patients undertaking heavy manual labour should be advised to seek a lighter job. *Diet:* A diet high in oily fish, fruit, vegetables, and fibre, and low in saturated fats should be encouraged. *Exercise:* Encourage regular daily exercise. *Sex:* Intercourse is best avoided for 1 month. *Travel:* Avoid air travel for 2 months.

*Review at 5*wks *post*-MI *to review symptoms:* Angina? dyspnoea? palpitations? If angina recurs, treat conventionally, and consider coronary angiography.

Review at 3 months Check fasting lipids. Is there a need for a statin (p682)?

Acute postero-lateral MI



Complications of MI

- *Cardiac arrest* (inside backcover); *cardiogenic shock* (p788).
- *Unstable angina*: Manage along standard lines (p784) and refer to a cardiologist for urgent investigation.
- *Bradycardias or heart block*: *Sinus bradycardia:* treat with atropine 0.6-1.2mg IV. Consider temporary cardiac pacing if no response, or poorly tolerated by the patient. *1st degree AV block:* Observe closely as approximately 40% develop higher degrees of AV block. *Wenckebach (Mobitz type I) block:* Does not require pacing unless poorly tolerated. *Mobitz type II block:* Carries a high risk of developing complete AV block; should be paced. *Complete* AV *block:* insert pacemaker; may not be necessary after inferior MI if narrow QRS and reasonably stable and pulse ≥40-50. *Bundle branch block:* MI complicated by trifascicular block or non-adjacent bifascicular disease should be paced.
- *Tachyarrhythmias:* **NB:** K^+↓, hypoxia and acidosis all predispose to arrhythmias and should be corrected. Regular broad complex tachycardia after MI is almost always VT. If haemodynamically stable, treat with antidysrhythmic. Early VT (<24h): give lidocaine by infusion for 12-24h or amiodarone. Late VT (>24h) amiodarone and start oral therapy (amiodarone or sotalol): if compromised give DC shock. *SVT:* p112. AF *or flutter:* If compromised, DC cardioversion. Otherwise, control rate with digoxin (load with 0.5mg/12h PO for 3 doses; maintenance: 0.125-0.25mg/24h) ± ß-blocker. In atrial flutter or intermittent AF, try amiodarone or sotalol (details p130).
- *Left ventricular failure (*LVF*):* p786.
- *Right ventricular failure (*RVF*)/infarction:* Presents with low cardiac output and JVP↑. Consider a Swan-Ganz catheter to measure right-sided pressures and guide fluid replacement. If BP remains low, give inotropes.
- *Pericarditis:* Central chest pain, relieved by sitting forwards. ECG: saddle-shaped ST elevation. Treatment: NSAIDs. Echo to check for effusion.
- DVT & PE: Patients are at risk of developing DVT & PE and should be prophylactically heparinized (enoxaparin, p106) until fully mobile.
- *Systemic embolism:* May arise from a LV mural thrombus. After large anterior MIs, consider anticoagulation with warfarin for 3 months.
- *Cardiac tamponade:* (p788) Presents with low cardiac output, pulsus paradoxus, JVP↑, muffled heart sounds. Diagnosis: Echo. Treatment: Pericardial aspiration (provides temporary relief ▸▸see p761 for technique), surgery.
- *Mitral regurgitation:* May be mild (minor papillary muscle dysfunction) or severe (chordal or papillary muscle rupture or ischaemia). Presentation: Pulmonary oedema. Treat LVF (p786) and consider valve replacement.
- *Ventricular septal defect:* Presents with pansystolic murmur, JVP↑, cardiac failure. Diagnosis: Echo. Treatment: Surgery. 50% mortality in first week.
- *Late malignant ventricular arrhythmias:* Occur 1-3wks post-MI and are the cardiologist's nightmare. Avoid hypokalaemia, the most easily avoidable cause. Consider 24h ECG monitoring prior to discharge if large MI.
- *Dressler's syndrome:* (p690) Recurrent pericarditis, pleural effusions, fever, anaemia and ESR↑ 1-3wks post-MI. Treatment: NSAIDs; steroids if severe.
- *Left ventricular aneurysm:* This occurs late (4-6wks post-MI), and presents with LVF, angina, recurrent VT, or systemic embolism. ECG: Persistent ST segment elevation. Treatment: anticoagulate, consider excision.

Arrhythmias (Emergency management: ▸▸p790 & p792)

Disturbances of cardiac rhythm or arrhythmias are:

- Common
- Often benign (but may reflect underlying heart disease)

- Often intermittent, causing diagnostic difficulty
- Occasionally severe, causing cardiac compromise.

Causes

Cardiac: MI, coronary artery disease, LV aneurysm, mitral valve disease, cardiomyopathy, pericarditis, myocarditis, aberrant conduction pathways. *Noncardiac:* Caffeine, smoking, alcohol, pneumonia, drugs (β_2-agonists, digoxin, L-dopa, tricyclics, adriamycin, doxorubicin), metabolic imbalance (K^+, Ca^{2+}, Mg^{2+}, hypoxia, hypercapnia, metabolic acidosis, thyroid disease), & phaeochromocytoma.

Presentation

is with palpitation, chest pain, presyncope/syncope, hypotension, or pulmonary oedema. Some arrhythmias may be asymptomatic and incidental, eg AF.

History

Take a detailed history of palpitations (p66). Ask about precipitating factors, onset, nature (fast or slow, regular or irregular) duration, associated symptoms (chest pain, dyspnoea, collapse). Review drug history. Ask about past medical history or family history of cardiac disease.

Tests

FBC, U&E, glucose, Ca^{2+}, Mg^{2+}, TSH. ECG: Look for signs of IHD, AF, short P-R interval (WPW syndrome), long QT interval (metabolic imbalance, drugs, congenital), U waves (hypokalaemia). 24h ECG monitoring; several recordings may be needed. Echo: Any structural heart disease, eg mitral stenosis, HOCM? Provocation tests: Exercise ECG, cardiac catheterization ± electrophysiological studies may be needed.

Treatment

If the ECG is normal during palpitations, reassure the patient. Otherwise, treatment depends on the type of arrhythmia.

Bradycardia:

(p111) If asymptomatic and rate >40bpm, no treatment is required. Look for a cause (drugs, sick sinus syndrome, hypothyroidism) and stop any drugs that may be contributing (ß-blocker, digoxin). If rate <40bpm or patient is symptomatic, give atropine 0.6-1.2mg IV (up to maximum of 3mg). If no response, insert a temporary pacing wire (p764). If necessary, start an isoprenaline infusion or use external cardiac pacing.

Sick sinus syndrome:

Sinus node dysfunction causes bradycardia ± arrest, sinoatrial block or SVT alternating with bradycardia/asystole (tachy-brady syndrome). AF and thromboembolism may occur. Pace if symptomatic.

SVT:

(p112) Narrow complex tachycardia (rate >100bpm, QRS width <120ms). Acute management: Vagotonic manoeuvres followed by IV adenosine or verapamil (if not on ß-blocker); DC shock if compromised. Maintenance therapy: ß-blockers or verapamil.

AF/flutter:

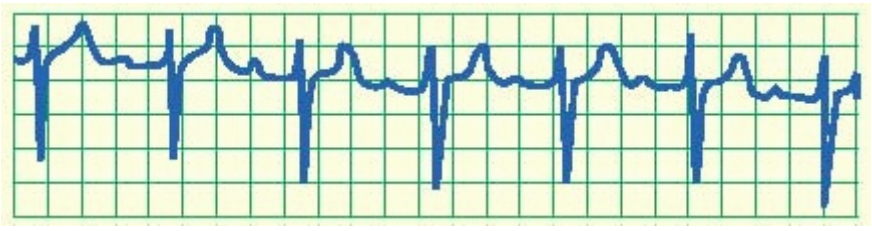
(p130) May be incidental finding. Control ventricular rate with digoxin: loading dose (~500µg/12h × 2) followed by maintenance dose (0.125-0.25mg/24h). Alternatives: Verapamil, ß-blocker, or amiodarone. Flecainide for pre-excited AF. DC shock if compromised (p758).

VT:

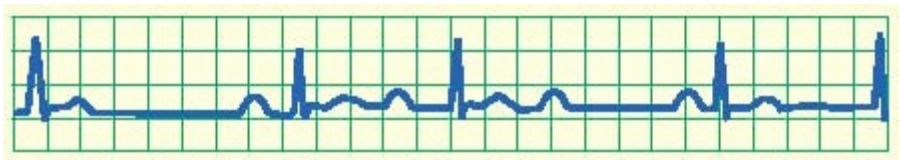
(p114) Broad complex tachycardia (rate >100bpm, QRS duration >120ms). Acute management: IV lidocaine (=lignocaine), or amiodarone IV, if no response or if compromised DC shock. Oral therapy: amiodarone loading dose (200mg/8h PO for 7d, then 200mg/12h for 7d) followed by maintenance therapy (200mg/24h). SE: Corneal deposits, photosensitivity, hepatitis, pneumonitis, lung fibrosis, nightmares, INR↑ (warfarin potentiation), T4↑, T3↓. Monitor LFT and TFT.

▸Finally, permanent pacing may be used to overdrive tachyarrhythmias, to treat bradyarrhythmias, or prophylactically in conduction disturbances (p118). Implanted automatic defibrillators can save lives.

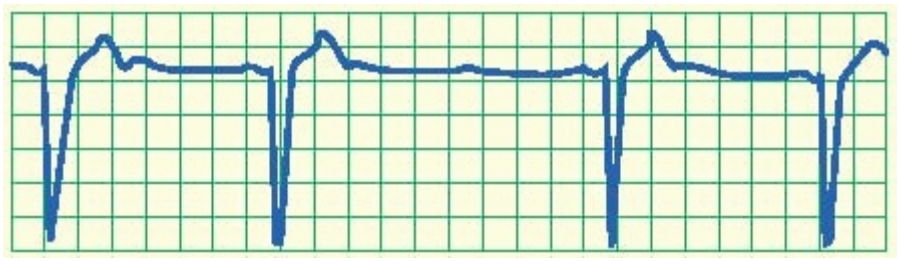
Diagnosis of bradycardias and AV block



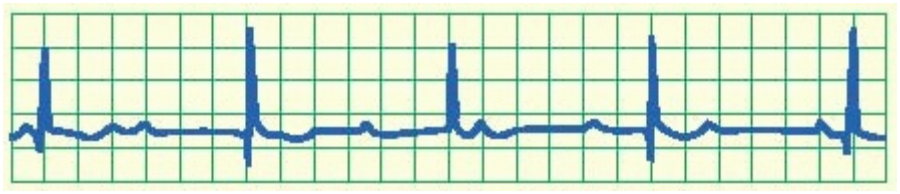
First degree AV block. P-R interval=0.28s



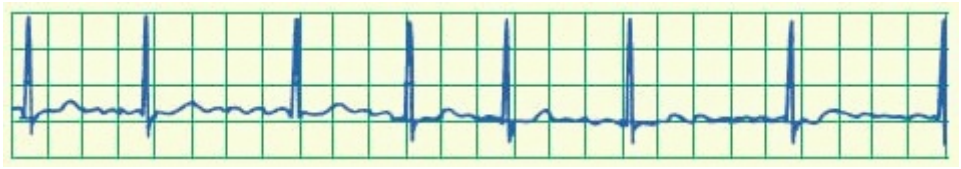
Mobitz type I (Wenckebach) AV block. With each succesive QRS, the P-R interval increases—until there is a non-conducted P wave.



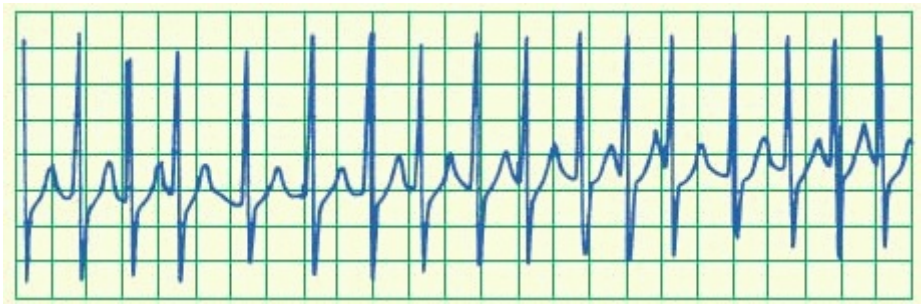
Mobitz type II AV block. Ratio of AV conduction varies from 2:1 to 3:1



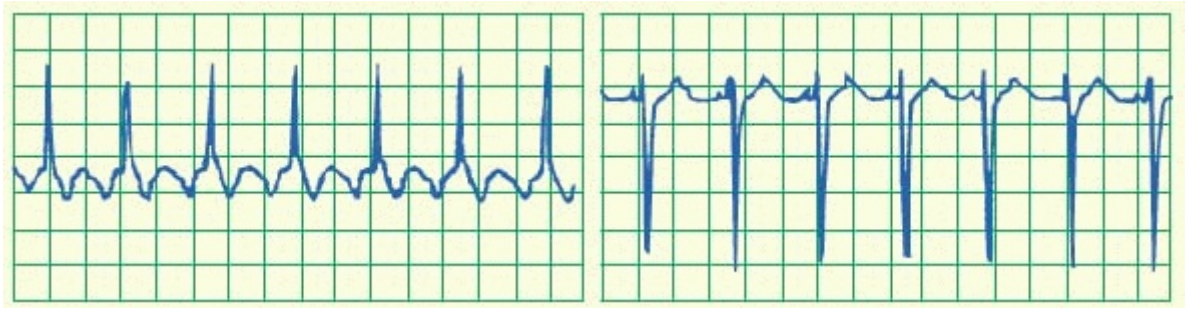
Complete AV block with narrow ventricular complexes.
There is no relation between atrial and the slower ventricular activity.



Atrial fibrillation



Atrial fibrillation with a rapid ventricular response. Diagnosis is based on the totally irregular ventricular rhythm.



Atrial flutter with 2:1 AV block. Lead aVF (on left) shows the characteristic saw-tooth baseline whereas lead V1 (on right) shows discrete atrial activity, alternate ‘F’ waves being superimposed on ventricular T waves.

Narrow complex tachycardia

ECG shows rate of >100bpm and QRS complex duration of <120ms.

Differential diagnosis

- Sinus tachycardia: normal P wave followed by normal QRS.

- Supraventricular tachycardia (SVT): P wave absent or inverted after QRS.
- AF: absent P wave, irregular QRS complexes.
- Atrial flutter: atrial rate usually 300bpm giving 'flutter waves' or 'sawtooth' baseline (p111), ventricular rate often 150bpm (2:1 block).
- Atrial tachycardia: abnormally shaped P waves, may outnumber QRS.
- Multifocal atrial tachycardia: 3 or more P wave morphologies, irregular QRS complexes.
- Junctional tachycardia: rate 150-250bpm, P wave either buried in QRS complex or occurring after QRS complex.

Principles of management

See p792.

- If the patient is compromised, use DC cardioversion (p758).
- Otherwise, identify the underlying rhythm and treat accordingly.
- Vagal manoeuvres (carotid sinus massage, Valsalva manoeuvre) transiently increase AV block, and may unmask an underlying atrial rhythm.
- If unsuccessful, give adenosine which causes transient AV block. It has a short t1/2 (10-15s) and works in 2 ways: by transiently slowing ventricles to show underlying atrial rhythm; by cardioverting a junctional tachycardia to sinus rhythm.

Adenosine dose: Give 6mg IV bolus into a big vein; follow by saline flush, while recording a rhythm strip; if unsuccessful, after 1-2min, give 12mg, then 12mg again, unless on dipyridamole or post cardiac transplantation (see BNF). Warn of SE: transient chest tightness, dyspnoea, headache, flushing. CI: asthma, $2^{nd}/3^{rd}$ degree AV block, or sinoatrial disease (unless pacemaker). Drug interactions: potentiated by dipyridamole, antagonized by theophylline. Transplanted hearts are very sensitive; use a smaller dose.

Specific management

Sinus tachycardia

Identify and treat the cause (p84).

SVT:

If adenosine fails, use verapamil 2.5-5mg IV over 2min, or over 3min if elderly (▸not if already on ß-blocker). If no response, give further dose of 5mg IV after 5-10min. Alternatives: atenolol 2.5mg IV at 1mg/min repeated at 5min intervals to a maximum of 10mg or sotalol 20-60mg IV. If no good, use DC cardioversion.

AF/flutter:

Manage along standard lines (p116).

Atrial tachycardia:

Rare. If due to digoxin toxicity, stop digoxin; consider digoxin-specific antibody fragments (p826). Maintain K^+ at 4-5mmol/L.

Multifocal atrial tachycardia:

Most commonly occurs in COPD. Correct hypoxia and hypercapnia. Consider verapamil if rate remains >110bpm.

Junctional tachycardia:

There are 3 types of junctional tachycardia: AV nodal re-entry tachycardia (AVNRT), AV re-entry tachycardia (AVRT), and His bundle tachycardia. Where anterograde conduction through the AV node occurs, vagal manoeuvres are worth trying. Adenosine will usually cardiovert a junctional rhythm to sinus rhythm. If it recurs, treat with a ß-blocker or amiodarone. Radiofrequency ablation is increasingly being used in AVRT and in some patients with AVNRT.[24]

WPW syndrome

(Wolff-Parkinson-White ECG p117) Caused by congenital accessory conduction pathway between atria and ventricles. Resting ECG shows short P-R interval and wide QRS complex due to slurred upstroke or 'delta wave'. 2 types: WPW type A (+ve σ wave in V_1), WPW type B (-ve § wave in V_1). Patients present with SVT which may be due to an AVRT, pre-excited AF, or pre-excited atrial flutter. Refer to cardiologist for electrophysiology and ablation of accessory pathway.

Broad complex tachycardia

ECG shows rate of >100 and QRS complexes >120ms (>3 small squares, p82). If no clear QRS complexes, it is VF or asystole, p766.

Principles of management

- Identify the underlying rhythm and treat accordingly.
- If in doubt, treat as ventricular tachycardia (VT)—the commonest cause.

Differential diagnosis

- VT; includes Torsade de pointes, below
- Supraventricular tachycardia (SVT) with aberrant conduction, eg AF, atrial flutter.

(**NB:** Ventricular ectopics should not cause confusion when occurring singly; but if >3 together at rate of >120, this constitutes VT.)

Identification of the underlying rhythm

(see OPPOSITE) may be difficult, seek expert help. Diagnosis is based on the history (IHD increases the likelihood of a ventricular arrhythmia), a 12-lead ECG, and the lack of response to IV adenosine (p112). ECG findings in favour of VT:

- Positive QRS concordance in chest leads
- Marked left axis deviation
- AV dissociation (occurs in 25%) or 2:1 or 3:1 AV block
- Fusion beats or capture beats; see OPPOSITE
- RSR complex in V_1 (with positive QRS in V_1)
- QS complex in V_6 (with negative QRS in V_1).

Concordance

means QRS complexes are all +ve or -ve. ***A fusion beat*** is when an 'normal beat' fuses with a VT complex to create an unusual complex, and a ***capture beat*** is a normal QRS between abnormal beats (see OPPOSITE).

Management

Connect to a cardiac monitor; have a defibrillator to hand.

- Give high-flow oxygen by face mask
- Obtain IV access and take blood for U&E, cardiac enzymes, Ca^{2+}, Mg^{2+}
- Obtain 12-lead ECG
- ABG (if evidence of pulmonary oedema, reduced conscious level, sepsis).

VT :

Haemodynamically stable

- Correct hypokalaemia and hypomagnesaemia.
- Amiodarone 300mg IV over 20-60min, then 900mg over 24hr.
- OR lidocaine 50mg over 2min repeated every 5min to 200mg max.
- If this fails, or if cardiac arrest, use DC shock (p758 & inside backcover).
- After correction of VT, establish the cause from history/investigations.
- Maintenance antiarrhythmic therapy may be required. If VT occurs <24h after MI, give IV amiodarone or IVI lidocaine for 12-24h. If VT occurs >24h after MI, give IV lidocaine infusion and start oral antiarrhythmic: eg amiodarone.
- Prevention of recurrent VT: Surgical isolation of the arrhythmogenic area or implantation of tiny automatic defibrillators may help.

Ventricular fibrillation (VF) :

(ECG, see OPPOSITE) ▸▸Use asynchronized DC shock (p758): see also the *European Resuscitation Guidelines* (see inside backcover).

Ventricular extrasystoles (ectopics)

are the commonest post-MI arrhythmia but they are also seen in healthy people (≥10/h). Post-MI they suggest electrical instability, and there is a risk of VF if the 'R on T' pattern (ie no gap before the T wave) is seen. If frequent (>10/min), consider amiodarone IV as above. Otherwise, just observe patient.

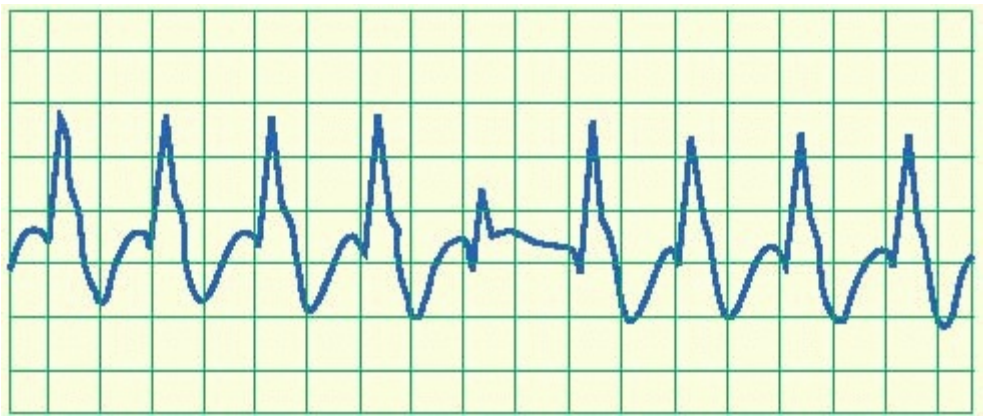
Torsade de pointes:

Looks like VF but is VT with varying axis (ECG, see OPPOSITE). It is due ↑QT interval (a SE of anti-arrhythmics, so consider stopping).

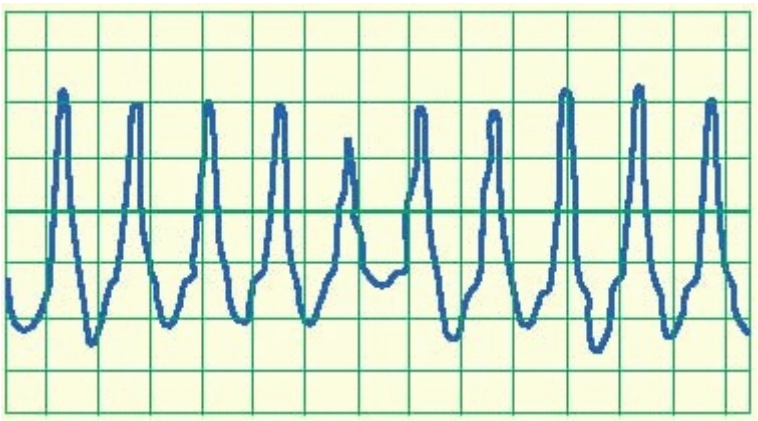
[prescription take]:

Mg sulfate, 2g IV over 10 min ± overdrive pacing.

Fusion and capture beats

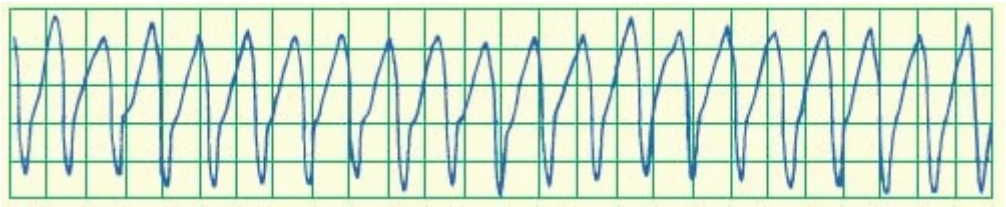


(a) A capture beat

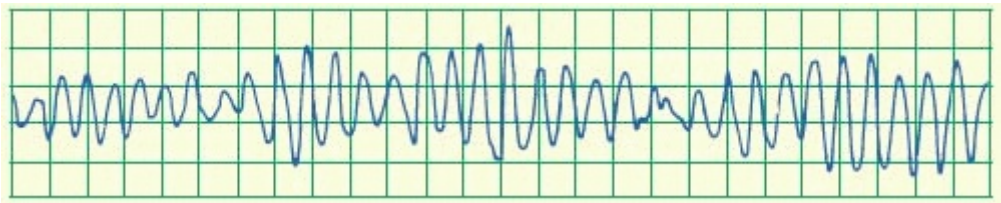


(b) A fusion beat

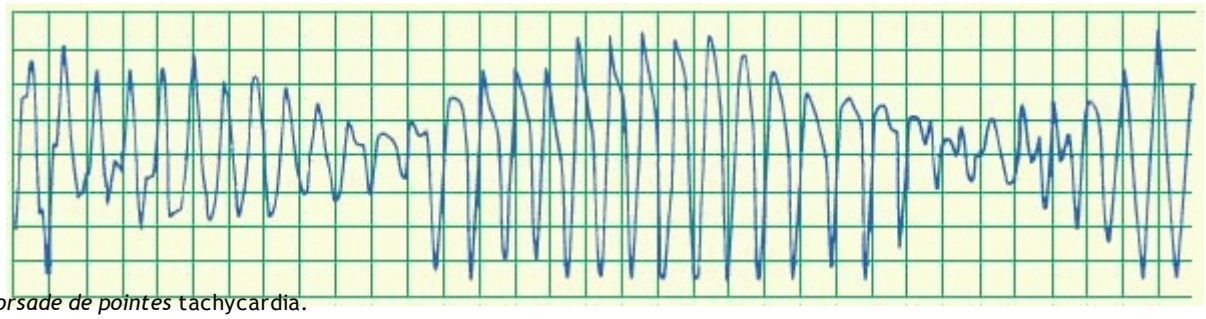
Specimen rhythm strips



VT with a rate of 235/min.



VF (p767).



Torsade de pointes tachycardia.

Atrial fibrillation (AF) and flutter NICE 2006

AF is a chaotic, irregular atrial rhythm at 300-600bpm; the AV node responds intermittently, hence an irregular ventricular rate. If the ventricles aren't primed reliably by the atria, cardiac output drops by 10-20%. AF is common in the elderly (≤9%). The main risk is embolic stroke. Warfarin reduces this to 1%/yr from 4%. So, *do an* ECG *on everyone with an irregular pulse* (±24h ECG if dizzy, faints, palpitations etc).

Causes

Heart failure/ischaemia; hypertension; MI (seen in 22%);[25] PE; mitral valve disease; pneumonia; hyperthyroidism; alcohol; post-op; K^+↓; Mg^{2+}↓.[26]

Rare causes:

Cardiomyopathy; constrictive pericarditis; sick sinus syndrome; lung cancer; atrial myxoma; endocarditis; haemochromatosis; sarcoid. 'Lone' AF means no cause found.

Symptoms

May be asymptomatic or cause chest pain, palpitations, dyspnoea, or faintness.

Signs:

Irregularly irregular pulse, the apical pulse rate is greater than the radial rate and the 1st heart sound is of variable intensity; signs of LVF (p786).

▸Examine the whole patient: AF is *often* associated with non-cardiac disease.

Tests

ECG shows absent P waves, irregular QRS complexes. *Blood tests:* U&E, cardiac enzymes, thyroid function tests. Consider echo to look for left atrial enlargement, mitral valve disease, poor LV function, and other structural abnormalities.

Acute AF (≲48h)

Treat associated illnesses (eg MI, pneumonia). Control ventricular rate (as *below*) and start full anticoagulation with **heparin** 5000-10000U IV (p334), to keep options open for cardioversion even if the 48h time limit is running out (thrombi are now prevented).[27] If the 48h period has elapsed, cardioversion without anticoagulation is OK if trans-oesophageal echo shows no intracardiac thrombus. *Cardioversion regimen:* ▸▸O_2 ▸▸ITU/CCU ▸▸GA or IV sedation ▸▸200J ▸▸360J ▸▸360J (monophasic; if 100J is tried 1st, it only works in <20%). Relapses back into AF are common, and *drug cardioversion* is often preferred: **amiodarone** IVI (5mg/kg over 1h then ~900mg over 24h via a central line max 1.2g in 24h) or PO (200mg/8h for 1wk, 200mg/12h for 1wk, 100-200mg/24h maintenance). Alternative (if stable and no known IHD or WPW): **flecainide** 2mg/kg IV over >25min, max 150mg (or 300mg PO stat); monitor ECG. Unfortunately, flecainide is a strong negative inotrope.

Chronic AF

• **Control rate**, as below. Rate-control is as good as rhythm-control in decreasing morbidity & mortality in most people with chronic AF.[28][29] • Consider rhythm control if 1st episode or younger patient, as below. • Anticoagulate with **warfarin** (INR 2-3).[30] Less good alternative: **aspirin** ~300mg/d PO—eg if warfarin contraindicated or at very low risk of emboli (<65yrs, and no hypertension, diabetes, LV dysfunction, ↑LA size, rheumatic valve disease, MI, or past TIA).

CI to warfarin in AF:[31]

Bleeding diathesis; platelets $<50\times10^9$/L; BP>160/90 (consistently); compliance issues around dosing or INR monitoring; patient choice, after risks discussed. Factors such as age ≳75-80yrs old, frequent falls, on NSAIDs, past intracranial bleeds, Hb↓, and polypharmacy are CI according to some authorities,[32] but are less evidence-based.

Paroxysmal AF

Pill-in-the-pocket may be appropriate (see box); if not, try a regular ß-blocker (below). If fails and no LV dysfunction, **sotalol** 40mg/12h PO; after >48h, gradually ↑dose to 80mg/12h, then 160mg/12h if needed; SE: ↑QT interval, so monitor QT on ECG.[33] Alternative if LV dysfunction: **amiodarone** PO. Anticoagulate.

Controlling the ventricular rate

In *acute* or *paroxysmal* AF, a good 1st choice is: **diltiazem** (60-120mg/8h PO) *or* **verapamil** (40-120mg/8h PO) *or* **metoprolol (**50mg/12h PO, or just 10mg/8h to start with if LV function poor). 2nd-line: **digoxin** and **amiodarone**. For *chronic* AF, a ß-blocker or rate limiting Ca^{2+} blocker are 1st choice. If this fails, add **digoxin (**p100), then consider **amiodarone**. **Digoxin** as monotherapy in chronic AF is only OK in sedentary patients. ▸*Don't give ß-blockers with diltiazem or verapamil without expert advice (bradycardia risk).* NB: bad effects of rapid rates: greater irregularity of ventricular response, variable changes in autonomic output,[34] and tachycardia-mediated cardiomyopathy.[35][36] Don't get fixated on a single figure to aim at: dialogue with patients tells what works best, and allows desired exercise levels, eg <90 at rest and on exertion 200-age (yrs) if ambulatory.

Managing various AF scenarios (NICE 2006) When in doubt…get help.

1. If acute onset AF and very ill or haemodynamically unstable: ▸▸O_2 ▸▸U&E ▸▸Emergency cardioversion; if unavailable try IV amiodarone. Do not delay emergency treatment in order to start anticoagulation. In other patients…
2. Try rate control 1st if: • >65yrs • Coronary artery disease • Contraindications to antiarrhythmics • Unsuitable for cardioversion, ie anticoagulants contraindicated; left atrium >5cm across or mitral stenosis (maintaining *longterm* sinus rhythm is unlikely); AF has lasted >1yr; past attempts have failed (despite concurrent antiarrhythmics); an on-going *reversible* cause, eg thyrotoxicosis.
3. Try rhythm control 1st if: • Symptomatic or CCF • Younger • Presenting for 1st time with lone AF • AF is secondary to a corrected precipitant (eg U&E↑↓). If cardioversion is chosen, do pre-cardioversion echo; pre-treat for ≥4wks with **sotalol** or **amiodarone** if there is ↑risk of cardioversion failure (past failure, or past AF recurrence). In pharmacological cardioversion, **flecainide** is 1st-choice if no structural heart disease (IV **amiodarone** if structural heart disease).
4. In paroxysmal AF 'pill in the pocket' (eg flecainide PRN) may be tried if: infrequent AF, BP >100mmHg systolic, no past LV dysfunction. Anticoagulate (below).
5. If despite, the above, AF continues to cause big problems, AV node ablation, pacing, and pulmonary vein ablation are options to ask about.[37]
6. Use heparin in acute AF until a full risk assessment for emboli (see below) is made—eg AF started <48h ago and elective cardioversion is being planned (if >48h, ensure ≥3wks of therapeutic anticoagulation before elective cardioversion; NB trans-oesophageal-guided cardioversion is also an option here).
7. Use warfarin (target INR: 2.5; range 2-3) if risk of emboli **high** (past ischaemic stroke, TIA or emboli; ≳75yrs with BP↑, DM; coronary or peripheral arterial disease; evidence of valve disease or ↓LV function/CCF (only do echo if unsure).
8. Use aspirin if warfarin contraindicated or <65 + no risk factors (?also if risk **moderate**, ie ≳65 + no high-risk factors or <75 + BP↑, DM or vascular disease. If 'warfarin or aspirin?' is equivocal, consider an echo (warfarin if abnormal).
9. Use no anti-coagulation if *stable* sinus rhythm has been restored **and** no risk factors for emboli, **and** AF recurrence unlikely (ie no failed cardioversions, no structural heart disease, no previous recurrences, no sustained AF for >1yr).

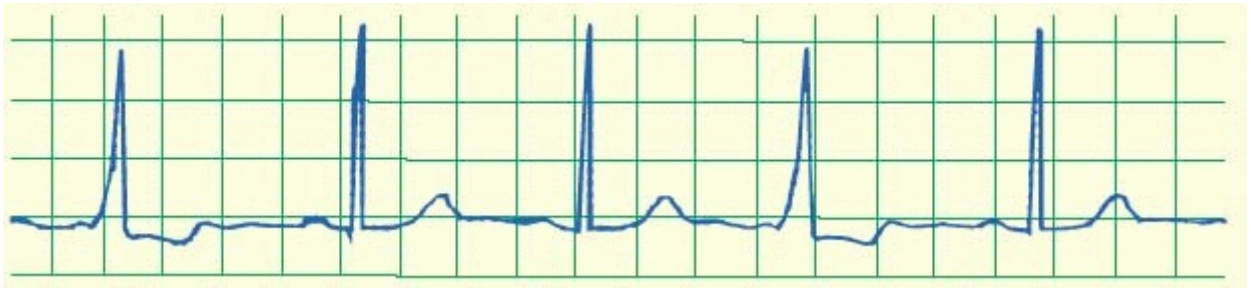
Note on atrial flutter See p111 for ECGs.

ECG: continuous atrial depolarization (eg ~300/min, but very variable) produces a sawtooth baseline ± 2 : 1 AV block (as if SVT at, eg 150bpm). **Carotid sinus massage** and IV **adenosine** transiently block the AV node and may unmask flutter waves.

Treatment

Cardioversion may be indicated (anticoagulate before, see opposite). Anti-AF drugs may not work—but consider amiodarone to restore sinus rhythm, and amiodarone or sotalol to maintain it. Cavotricuspid isthmus ablation (this 'flutter isthmus' is low in the right atrium) may be tried.[38]

Wolff-Parkinson-White (WPW) syndrome



ECG of WPW syndrome (p112) in 1st & 4th beats; compared with the other beats, it can be seen how the delta wave both broadens the ventricular complex, and shortens the PR interval. ▸If WPW is the underlying cause of AF, avoid AV node blockers such as diltiazem, verapamil and digoxin—but flecainide may be used.

Pacemakers

Pacemakers supply electrical initiation to myocardial contraction. The pacemaker lies subcutaneously where it may be programmed through the skin as necessary. Pacemakers usually last 7-15yrs.

Indications for temporary cardiac pacing

- Symptomatic bradycardia, unresponsive to atropine.
- After acute *anterior* MI, prophylactic pacing is required in:
  - Complete AV block
  - Mobitz type I AV block (Wenckebach)
  - Mobitz type II AV block
  - Non-adjacent bifascicular or trifascicular block (p86).
- After *inferior* MI, pacing may not be needed in complete AV block if reasonably stable, and rate is >40-50, and QRS complexes are narrow.
- Suppression of drug-resistant tachyarrhythmias, eg SVT, VT.
- Special situations: During general anaesthesia; during cardiac surgery; during electrophysiological studies; drug overdose (eg digoxin, β-blockers, verapamil).

▸See p764 for further details and insertion technique.

Indications for a permanent pacemaker

- Complete AV block (Stokes-Adams attacks, asymptomatic, congenital)
- Mobitz type II AV block (p111)
- Persistent AV block after anterior MI
- Symptomatic bradycardias (eg sick sinus syndrome, p110)
- Drug-resistant tachyarrhythmias.

Some say persistent bifascicular block after MI requires a permanent system: this remains controversial.

Pre-operative assessment:

FBC, clotting screen, hepatitis B status. Insert IV cannula. Consent for procedure under local anaesthetic. Consider pre-medication. Give antibiotic cover (eg flucloxacillin 500mg IM and benzylpenicillin 600mg IM) 20min before, and 1 and 6h after.

Post-op assessment:

Prior to discharge, check wound for bleeding or haematoma; check position on CXR; check pacemaker function. During 1st week, inspect for wound haematoma or dehiscence. Count apical rate (p64): if this is ≥6 bpm below the rate quoted for the pacemaker, suspect malfunction. Other problems: lead fracture; pacemaker interference (eg from patient's muscles). Driving rules: p144.

3-letter codes

These enable pacemaker identification: the 1st letter indicates the chamber paced (**A**=atria, **v**=ventricles, **D**=dual chamber); the 2nd letter identifies the chamber sensed (**A**=atria, **V**=ventricles, **D**=dual chamber, **O**=none), and the 3rd letter indicates the pacemaker response (**T**=triggered, **I**=inhibited, **D**=dual, **R**=reverse). **VVI** pacemakers are the most frequently used in the UK. **DDD** pacemakers are the only pacemakers that sense and pace both chambers.

5-letter codes

In the 4th letter, **P**=programmable; **M**=multiprogrammable. In the 5th letter, **P** means that in tachycardia, the pacemaker will pace the patient. **S** means that in tachycardia the pacemaker shocks the patient. **D**=dual ability to pace and shock. **O**=neither of these.

ECG of paced rhythm:

(ECG 7 p105, and OPPOSITE for rhythm strip) If the system is on 'demand' of 60bpm, a pacing spike will be seen only if the intrinsic heart rate is <60bpm. If it is cutting in at a higher rate, its sensing mode is malfunctioning. If it is failing to cut in at slower rates, its pacing mode is malfunctioning, ie the lead may be dislodged, the pacing threshold is too high, or the lead (or insulation) is faulty. If you see spikes but no capture (ie no systole), suspect dislodgment.

Some confusing pacemaker terms

Fusion beat:

Union of native depolarization and pacemaker impulse.

Pseudofusion:

The pacemaker impulse occurs just after cardiac depolarization, so it is ineffective, but it distorts the QRS morphology.

Pseudopseudofusion beat:

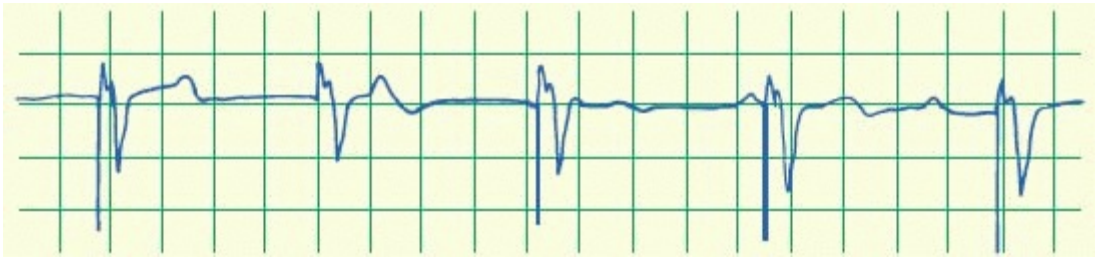
If a DVI pacemaker gives an atrial spike within a native QRS complex, the atrial output is non-contributory.

Pacemaker syndrome:

In single-chamber pacing, retrograde conduction to the atria, which then contract during ventricular systole. This leads to retrograde flow in pulmonary veins, and ↓cardiac output.

Pacemaker tachycardia:

In dual-chamber pacing, a short-circuit loop goes between the electrodes, causing an artificial wpw-like syndrome. Solution: Single-chamber pacing. For ecg images, see www.monroecc.edu./depts/pstc/backup/paracar6.htm



ECG of paced rhythm.

Heart failure—basic concepts[39]

Definition

Cardiac output and BP are inadequate for the body's requirements. Prognosis is poor with 82% of patients dying within 6yrs of diagnosis.

Classification

LVF and RVF may occur independently, or together as ***congestive cardiac failure (*CCF*)***. ***Low-output cardiac failure:*** The heart's output is inadequate (eg ejection fraction <35%), or is only adequate with high filling pressures. Causes: Usually ischaemia, hypertension, valve disorders, or ↑alcohol use.

- *Pump failure due to:*

  Heart muscle disease: IHD; cardiomyopathy (p138).

  Restricted filling: Constrictive pericarditis, tamponade, restrictive cardiomyopathy. This may be the mechanism of action of fluid overload: an expanding right heart impinges on the LV, so filling is restricted by the ungiving pericardium (the mechanism invoking a 'hump in the Starling curve' is now said to be an error based on an artefact).

  Inadequate heart rate: ß-blockers, heart block, post MI.

  Negatively inotropic drugs: eg most antiarrhythmic agents.

- ***Excessive preload:*** eg mitral regurgitation or fluid overload (eg NSAID causing fluid retention). Fluid overload may cause LVF in a normal heart if renal excretion is impaired or big volumes are involved (eg IVI running too fast). More common if there is simultaneous compromise of cardiac function, and in the elderly.

- ***Chronic excessive afterload:*** eg aortic stenosis, hypertension.

NB: High-output failure is rare. Here, output is normal or increased in the face of much increased needs. Failure occurs when cardiac output fails to meet these needs. It will occur with a normal heart, but even earlier if there is heart disease.

Causes:

Heart disease with anaemia or pregnancy, hyperthyroidism, Paget's disease, arteriovenous malformation, beri beri.

Consequences:

Initially features of RVF; later LVF becomes evident.

Symptoms

Depend on which ventricle is more affected. LVF: Dyspnoea, poor exercise tolerance, fatigue, orthopnoea, paroxysmal nocturnal dyspnoea (PND), nocturnal cough (±pink frothy sputum), wheeze (cardiac 'asthma'), nocturia, cold peripheries, weight loss, muscle wasting. RVF: Peripheral oedema (up to thighs, sacrum, abdominal wall), abdominal distension (ascites), nausea, anorexia, facial engorgement, pulsation in neck and face (tricuspid regurgitation), epistaxis. In addition, patients may be depressed or complain of drug-related side effects.

Signs

Looks ill and exhausted, cool peripheries, peripheral cyanosis. Pulse: resting tachycardia, pulsus alternans. Systolic BP↓, narrow pulse pressure, raised JVP. Praecordium: displaced apex (LV dilatation), RV heave (pulmonary hypertension), Auscultation: S_3 gallop (p32), murmurs of mitral or aortic valve disease. Chest: tachypnoea, bibasal end-inspiratory crackles, wheeze ('cardiac asthma'), pleural effusions. Abdomen: hepatomegaly (pulsatile in tricuspid regurgitation), ascites, peripheral oedema.

Investigations

According to NICE,[40] if ECG and BNP (b-type natriuretic peptide (BNP), p665) are normal, heart failure is unlikely, and an alternative diagnosis should be considered; if either abnormal, then echocardiography (p98) is required.

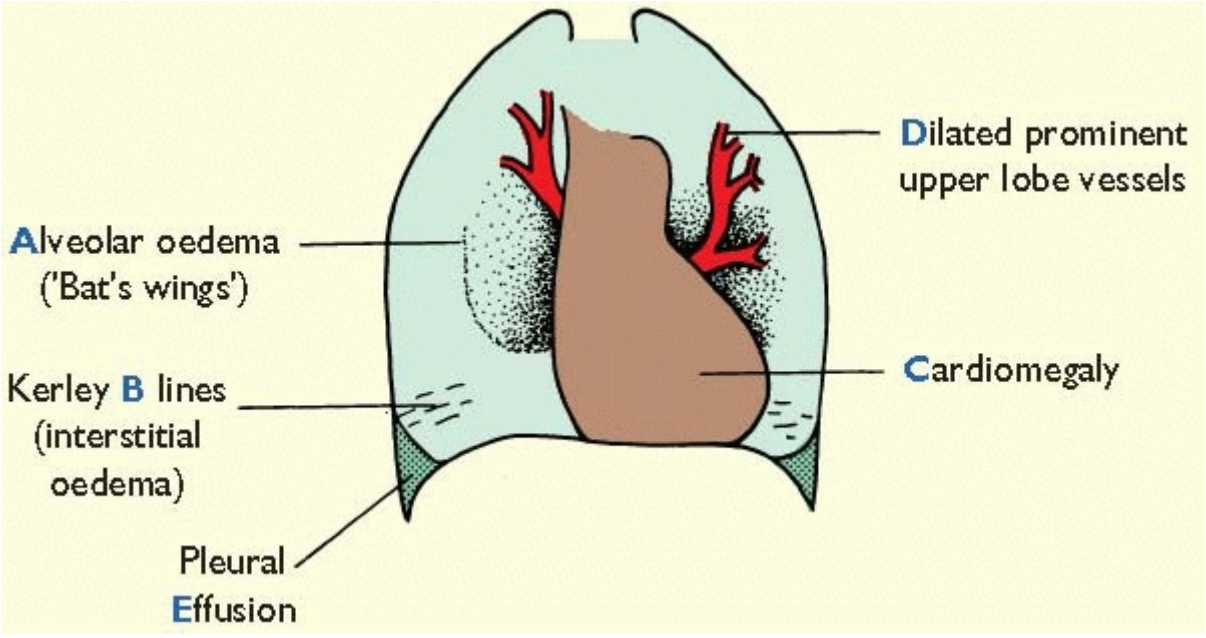
Blood tests:

FBC; U&E; BNP; **CXR**: Cardiomegaly (cardiothoracic ratio >50%), prominent upper lobe veins (upper lobe diversion), peribronchial cuffing, diffuse interstitial or alveolar shadowing, classical perihilar 'bat's wing' shadowing, fluid in the fissures, pleural effusions, Kerley B lines (variously attributed to interstitial oedema[41] and engorged peripheral lymphatics[42]). **ECG** may indicate cause (look for evidence of ischaemia, MI, or ventricular hypertrophy). It is rare to get a completely normal **ECG** in chronic heart failure. ***Echocardiography*** is the key investigation.[43] It may indicate the cause (MI, valvular heart disease) and can confirm the presence or absence of LV dysfunction. ***Endomyocardial biopsy*** is rarely needed.

New York classification of heart failure: summary

I	Heart disease present, but no undue dyspnoea from ordinary activity.
II	Comfortable at rest; dyspnoea on ordinary activities.
III	Less than ordinary activity causes dyspnoea, which is limiting.
IV	Dyspnoea present at rest; all activity causes discomfort.

The CXR in left ventricular failure (see also fig 2 p714)



These features can be remembered as A B C D E.

Heart failure—management[44]

Acute heart failure

▸▸This is a medical emergency (p786).

Chronic heart failure

Treat the cause (eg if dysrhythmias; valve disease).

- Treat exacerbating factors (anaemia, thyroid disease, infection, ↑BP).
- Avoid exacerbating factors, eg NSAIDs (cause fluid retention), and verapamil (negative inotrope).
- Stop smoking. Eat less salt. Maintain optimal weight and nutrition.
- Drugs: the following are used:

1. ***Diuretics:*** Loop diuretics routinely used to relieve symptoms eg **furosemide** 40mg/24h PO; increase dose as necessary. SE: K^+↓, renal impairment. Monitor U&E and add K^+ sparing diuretic (eg **spironolactone**) if K^+ <3.2mmol/L, predisposition to arrhythmias, concurrent digoxin therapy (K^+↓ increases risk of digoxin toxicity), or pre-existing K^+-losing conditions. If refractory oedema, consider adding a thiazide eg **metolazone** 5-20mg/24h PO.
2. **ACE-inhibitor***:* Consider in all patients with left ventricular systolic dysfunction; improves symptoms and prolongs life (see OPPOSITE). If cough is a problem an angiotensin receptor antagonist may be substituted (eg candesartan 4mg/d; max 32mg PO). These are occasionally used in combination by specialists, SE ↑K^+.
3. ***ß-blockers*** (eg **carvedilol**) Recent randomized trials show that ß-blockers ↓mortality in heart failure.[45] These benefits appear to be additional to those of ACE-i in patients with heart failure due to LV dysfunction.[46] Should be initiated after diuretic and ACE-i. Use with caution: 'start low and go slow'; if in doubt seek specialist advice first (eg carvedilol 3.125mg/bd → 25-50mg/bd); wait ≥2wks between each dose increment.
4. ***Spironolactone:*** The RALES trial showed that spironolactone (25mg/24h PO) ↓mortality by 30% when added to conventional therapy. It should be initiated in patients who remain symptomatic despite optimal therapy as listed above. It improves endothelial dysfunction (↑nitric oxide bio-availability) and prevents remodelling. Spironolactone is K^+-sparing, but there is little risk of significant hyperkalaemia, even when given with ACE-i.
5. ***Digoxin*** improves symptoms even in those with sinus rhythm (data from the RADIANCE and other trials). Use it if diuretics, ACE-i, and ß-blocker do not control symptoms, or in patients with AF. Dose: 0.125-0.25mg/24h PO. Monitor U&E and maintain K^+ at 4-5mmol/L. Other inotropes are unhelpful in terms of outcome.
6. ***Vasodilators:*** The combination of **hydralazine** (SE: drug-induced lupus) and **isosorbide dinitrate** should be used in combination in people intolerant of an ACE-i or angiotensin receptor antagonist as it reduces mortality. It also reduces mortality when given in addition to standard therapy (including ACE-i) in Black subjects with heart failure[47].

Intractable heart failure

Reassess the cause. Are they taking the drugs?—at maximum dose? Admit to hospital for:

- Strict bed rest.
- Metolazone and IV frusemide (p786).
- IV opiates and nitrates may relieve symptoms (p786).
- Daily weight and frequent U&E (beware K^+↓).
- DVT prophylaxis: eg heparin 5000U/8h SC and TED (thromboembolic deferrent) stockings.
- *In extremis*, IV inotropes (p788) may be needed (it may be difficult to wean patients off them).
- Finally, consider a heart transplant. **NB**: reports of the Jarvik thumb-sized titanium axial-flow impeller pump seem promising.[48] It is implanted in to the LV. A graft takes the blood to the descending aorta—making surgery hazardous.

How to start ACE-inhibitors

Check that there are no contraindications/cautions:

- Renal failure (serum creatinine >200µol/L; but not an absolute CI)
- Hyperkalaemia: K^+ >5.5mmol/L
- Hyponatraemia: caution if <130mmol/L (relates to a poorer prognosis)
- Hypovolaemia
- Hypotension (systolic BP <90mmHg)

- Aortic stenosis or LV outflow tract obstruction
- Pregnancy or lactation
- Severe COPD or cor pulmonale (not an absolute CI)
- Renal artery stenosis[1] (Suspect if arteriopathic, eg cerebrovascular disease, IHD, peripheral vascular disease. ACE-inhibitors reduce GFR and may precipitate acute renal failure).

Warn the patient about possible side effects:

- Hypotension, especially with 1st dose (so lie down after swallowing)
- Dry cough (1:10)
- Taste disturbance
- Hyperkalaemia
- Renal impairment
- Urticaria and angioneurotic oedema (<1:1,000)
- Rarely: proteinuria, leucopenia, fatigue

Starting ACE-inhibitors:

Hypertensive patients can be safely started on ACE-inhibitors as outpatients. Warn them about SE (*note: postural hypotension is rare in pure hypertension*) and advise them to take the 1st dose on going to bed. Use a long-acting ACE-inhibitor, eg lisinopril 10mg PO per day, 2.5mg per day in the elderly.

Patients with CCF are best started on ACE-inhibitors under close medical supervision. Start with small dose and increase every 2wks until at target dose (equivalent of 30-40mg lisinopril a day) or side effects supervene (↓BP, ↑creatinine). Review in ~1wk for assessment; monitor U&E regularly. Patients on high doses of diuretics (>80mg furosemide a day) may need a reduction in their diuretic dose first—seek expert help.

Hypertension

▸Hypertension is a major risk factor for stroke and MI. It is usually asymptomatic, so screening is vital.

Defining hypertension

Blood pressure has a skewed normal distribution (p737) within the population, and risk is continuously related to blood pressure.[49] Therefore, it is impossible to define 'hypertension'. We choose to select a value above which risk is significantly increased, and the benefit of treatment is clear cut, see below. BP should be assessed over a period of time (don't rely on a single reading). The 'observation' period depends on the BP and the presence of other risk factors or end-organ damage.

Whom to treat

All patients with malignant hypertension or a sustained pressure ≥160/100mmHg should be treated (see p125). For those ≥140/90, the decision depends on the risk of coronary events, presence of diabetes or end-organ damage; see the *Joint British Guidelines*, p125.

Systolic SBP or diastolic DBP pressure?

For many years diastolic pressure was considered to be more important than systolic pressure. However, evidence from the Framingham and the MrFIT studies indicates that systolic pressure is the most important determinant of cardiovascular risk in the over 50s.

Isolated systolic hypertension (ISH):

The most common form of hypertension in the UK—affects >50% of the over 60s, and results from stiffening of the large arteries (arteriosclerosis). It is not benign: doubles risk of MI, triples risk of CVA. Treatment reduces this is excess risk, and is as, if not more effective than treating moderate hypertension in middle-aged patients.

'Malignant' hypertension:

This refers to severe hypertension (eg systolic >200, diastolic>130mmHg) in conjunction with bilateral retinal haemorrhages and exudates; papilloedema may or may not be present. Symptoms are common, eg headache ± visual disturbance. Alone it requires urgent treatment. However, it may precipitate acute renal failure, heart failure, or encephalopathy, which are hypertensive emergencies. Untreated, 90% die in 1yr; treated, 70% survive 5yrs. Pathological hallmark is fibrinoid necrosis. It is more common in younger patients and in Blacks. Look hard for any underlying cause.

Essential hypertension

(primary, cause unknown). ~95% of cases.

Secondary hypertension

~5% of cases. Causes include:

- ***Renal disease:*** The most common secondary cause. 75% are from *intrinsic renal disease:* glomerulonephritis, polyarteritis nodosa (PAN), systemic sclerosis, chronic pyelonephritis, or polycystic kidneys. 25% are due to *renovascular disease,* most frequently atheromatous (elderly ♂ cigarette smokers, eg with peripheral vascular disease) or rarely fibromuscular dysplasia (young ♀), p300.

- ***Endocrine disease:*** Cushing's (p208) and Conn's syndromes (p212), phaeochromocytoma (p212), acromegaly, hyperparathyroidism.
- ***Others:*** Coarctation, pregnancy (OHCS p48), steroids, MAOI, 'the Pill'.

Signs & symptoms

Usually asymptomatic (except malignant hypertension, above). Headache is no more common than in the general population. Always examine the CVS system fully and check for retinopathy. Are there features of an underlying cause (phaeochromocytoma, p212 etc.), signs of renal disease, radio-femoral delay, or weak femoral pulses (coarctation), renal bruits, palpable kidneys, or Cushing's syndrome? Look for end-organ damage: LVH, retinopathy and proteinuria—indicates severity and duration of hypertension and associated with a poorer prognosis.

Investigations

Basic: U&E, creatinine, cholesterol, glucose, ECG, urine analysis (for protein, blood). *Specific* (exclude a secondary cause): renal ultrasound, renal arteriography, 24h urinary VMA × 3 (p212), urinary free cortisol (p209), renin, and aldosterone. ECHO and 24h ambulatory BP monitoring may be helpful in some cases eg white coat or borderline hypertension. Ambulatory readings are always lower; add-on 12/7mmHg to 'convert' to clinic pressures for decision making).

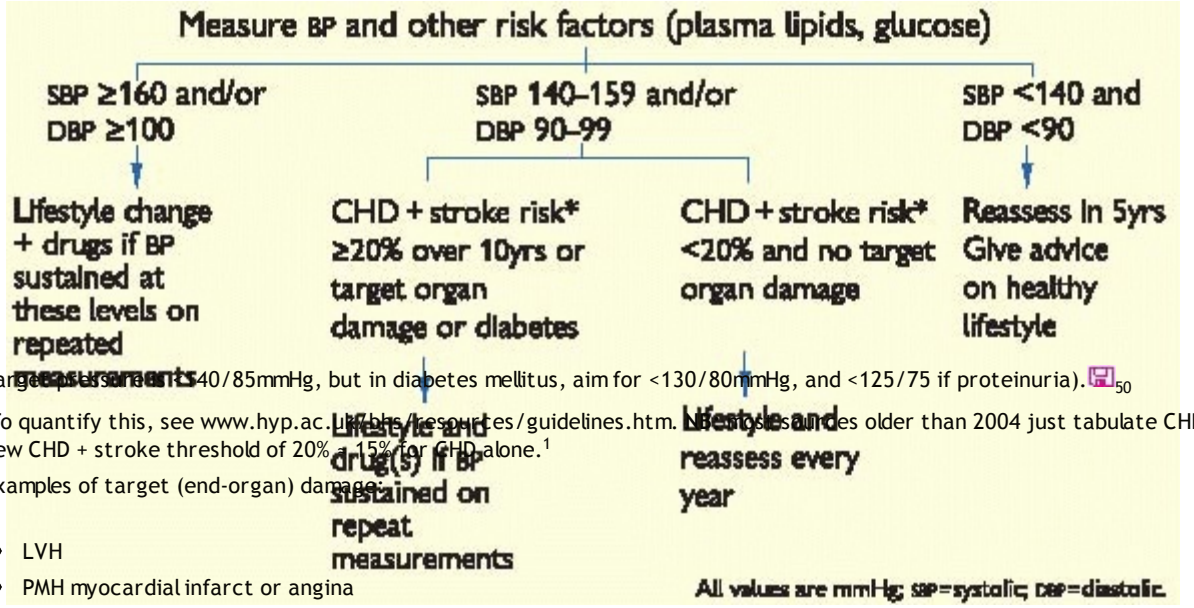
Hypertensive retinopathy
Grade

I	Tortuous arteries with thick shiny walls (silver or copper wiring, p544, **fig 2**)
II	A-V nipping (narrowing where arteries cross veins, p544, **fig 1**)
III	Flame haemorrhages and cotton wool spots
IV	Papilloedema, p544, **fig 3**.

Measuring blood pressure (see also p29)

- Use the correct size cuff. The cuff width should be >40% of the arm circumference. The bladder should be centred over the brachial artery, and the cuff applied snugly. Support the arm in a horizontal position at mid-sternal level.
- Inflate the cuff while palpating the brachial artery, until the pulse disappears. This provides an estimate of systolic pressure.
- Inflate the cuff until 30mmHg above systolic pressure, then place stethoscope over the brachial artery. Deflate the cuff at 2mmHg/s.
- *Systolic pressure:* The appearance of sustained repetitive tapping sounds (Korotkoff I).
- *Diastolic pressure:* Usually the disappearance of sounds (Korotkoff V). However, in some individuals (eg pregnant women) sounds are present until the zero-point. In this case, the muffling of sounds, Korotkoff IV, should be used. State which is used for a given reading. For children, see OHCS p156.

Joint British recommendation on preventing coronary heart disease[1] www.bhsoc.org/latest_BHS_management_guidelines.htm



Target BP is <140/85mmHg, but in diabetes mellitus, aim for <130/80mmHg, and <125/75 if proteinuria).[50]

*To quantify this, see www.hyp.ac.uk/bhs/resources/guidelines.htm. Lifestyle guidelines older than 2004 just tabulate CHD risk, not CHD + stroke. The new CHD + stroke threshold of 20% ≈ 15% for CHD alone.[1]

Examples of target (end-organ) damage:

- LVH
- PMH myocardial infarct or angina
- PMH stroke/TIA
- Peripheral vascular disease
- Renal failure.

Hypertension—management NICE/BHS 2006

Look for and treat underlying causes (eg renal disease, alcohol↑: see p124). Drug therapy reduces the risk of cardiovascular disease and death. Almost any adult over 50 would benefit from the antihypertensives below, *whatever their starting* BP.[51] Treatment is especially important if: BP is persistently ≥160/100mmHg **or** cardiovascular risk ↑ (10yr risk of vascular disease ≳20%) **or** existing vascular disease **or** target organ damage (eg brain, kidney, heart, retina) with BP >140/90mmHg.

Treatment goal

<140/85mmHg (<130/80 in diabetes). Reduce blood pressure *slowly*; rapid reduction can be fatal, especially in the context of an acute stroke.

Lifestyle changes

↓Concomitant risk factors: stop smoking; low-fat diet. Reduce alcohol and salt intake; increase exercise; reduce weight if obese.

Drugs

Explain that long-term treatment is needed. Essential hypertension is not 'curable'. The ALLHAT study suggests that adequate BP reduction is more important than the specific drug used;[52] but ALLHAT did not include ß-blockers, and new data cast doubt on their value,[53] particularly atenolol, and especially if combined with a thiazide.[54] Conversely, ACE-i may provide added ***renal*** benefit in diabetics or if GFR↓.

- If ≥55yrs, and in Black patients of any age, 1st choice is a Ca^{2+} channel blocker or thiazide. If <55, 1st choice is ACE-i (or ARB if ACE-i intolerant, eg from cough).
- If initial [prescription take] was with a Ca^{2+} channel blocker or a thiazide, and a 2nd drug is needed, add an ACE-i. If initial [prescription take] was with ACE-i, add a Ca^{2+} channel blocker or a thiazide.
- If treatment with 3 drugs is needed, try ACE-i, Ca^{2+} channel blocker and thiazide.
- If BP still uncontrolled on adequate doses of 3 drugs, add a 4th and get help.
- If a 4th drug is needed, consider: higher dose thiazide (unlikely to help) or a new diuretic, eg spironolactone (monitor U&E), or ß-blockers, or selective α-blockers.
- ß-blockers are not 1st-line for hypertension, but consider in younger people, particularly: if intolerance or contra-indication to ACE-i/ARB (angiotensin receptor blockers) exists, or she is a women of child-bearing potential, or there is ↑sympathetic drive. Here, if therapy is initiated with a ß-blocker and a 2nd drug is needed, add a Ca^{2+} blocker not a thiazide to reduce risk of developing diabetes.

Dose examples

Thiazides:

eg chlortalidone 25-50mg/24h PO mane. SEs: K^+↓, Na^+↓, postural hypotension, impotence. CI: gout.

Ca^{2+} channel blockers:

eg nifedipine MR 30-60mg/24h PO. SE: flushes, fatigue, gum hyperplasia, ankle oedema. Avoid short-acting drugs.

ACE-i:

eg lisinopril 2.5-20mg/24h PO (max 40mg/d). ACE-i may be 1st choice if co-existing LVF, or in diabetics (esp. if microalbuminuria, p301) or proteinuria. SE: cough, K^+↑, renal failure, angio-oedema. CI bilateral renal artery or aortic valve stenosis; p123.

ARB:

losartan (50mg/d); caution if valve disease or cardiomyopathy; monitor K^+. SE: diarrhoea, vertigo, urticaria, pruritus.

B-blockers:

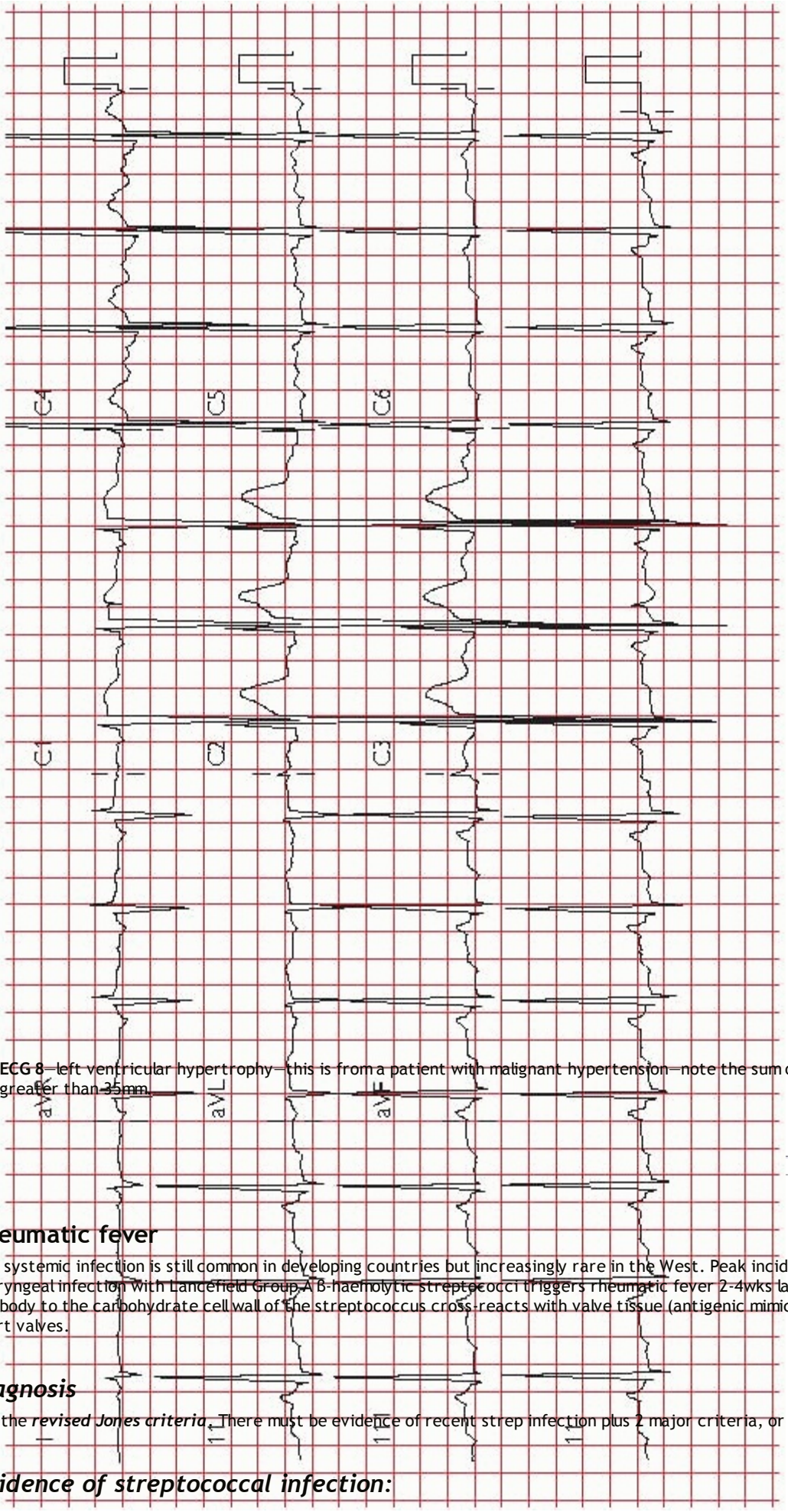
eg bisoprolol 2.5-5mg/24h PO. SE: bronchospasm, heart failure, cold peripheries, lethargy, impotence. CI: asthma; caution in heart failure. Consider *aspirin* when BP controlled, if aged >55yrs. Add a *statin* (p682, esp. if other risk factors). ▸Most drugs take 4-8wks to gain maximum effect: don't assess efficacy with just one BP measurement.

Malignant hypertension

In general, use oral therapy, unless there is encephalopathy or CCF. The aim is for a controlled reduction in blood pressure over days, not hours. Avoid sudden drops in BP as cerebral autoregulation is poor (so stroke risk↑).

- Bed rest; there is no ideal hypotensive, but atenolol, or long-acting Ca^{2+} blockers may be used PO.
- Encephalopathy (headache, focal CNS signs, seizures, coma): aim to reduce BP to ~110mmHg diastolic over 4h. Admit to monitored area. Insert intra-arterial line for pressure monitoring. Furosemide 40-80mg IV; then either IV labetalol (eg 50mg IV over 1min, repeated every 5min, max 200mg), or sodium nitroprusside infusion (0.5µg/kg/min IVI titrated up to 8µg/kg/min, eg 50mg in 1L dextrose 5%; expect to give 100-200mL/h for a few hours only, to avoid cyanide risk).

▸Never use sublingual nifedipine to reduce BP (∵ big drop in BP and stroke risk).[55]



ECG 8—left ventricular hypertrophy—this is from a patient with malignant hypertension—note the sum of the S-wave in C2 and R-wave in C6 is greater than 35mm.

Rheumatic fever

This systemic infection is still common in developing countries but increasingly rare in the West. Peak incidence: 5-15yrs. Tends to recur unless prevented. Pharyngeal infection with Lancefield Group A β-haemolytic streptococci triggers rheumatic fever 2-4wks later, in the susceptible 2% of the population. An antibody to the carbohydrate cell wall of the streptococcus cross-reacts with valve tissue (antigenic mimicry) and may cause permanent damage to the heart valves.

Diagnosis

Use the ***revised Jones criteria***. There must be evidence of recent strep infection plus 2 major criteria, or 1 major + 2 minor.

Evidence of streptococcal infection:

- Recent streptococcal infection
- History of scarlet fever
- Positive throat swab
- Increase in ASOT >200U/mL
- Increase in DNase B titre.

Major criteria:

- *Carditis:* Tachycardia, murmurs (mitral or aortic regurgitation, Carey Coombs' murmur, p34), pericardial rub, CCF, cardiomegaly, conduction defects (45-70%). An apical systolic murmur may be the only sign.[56]
- *Arthritis:* A migratory, 'flitting' polyarthritis; usually affects larger joints (75%).
- *Subcutaneous nodules:* Small, mobile painless nodules on extensor surfaces of joints and spine (2-20%).
- *Erythema marginatum:* Geographical-type rash with red, raised edges and clear centre; occurs mainly on trunk, thighs, arms in 2-10% (p546).
- *Sydenham's chorea* (St Vitus' dance): Occurs late in 10%. Unilateral or bilateral involuntary semi-purposeful movements. May be preceded by emotional lability and uncharacteristic behaviour.[57]

Minor criteria:

- Fever
- Raised ESR or CRP
- Arthralgia (but not if arthritis is one of the major criteria)
- Prolonged P-R interval (but not if carditis is major criterion)
- Previous rheumatic fever.

Management

- Bed rest until CRP normal for 2wks (may be 3 months).
- Benzylpenicillin 0.6-1.2g IM stat then penicillin V 250mg/6h PO.
- Analgesia for carditis/arthritis: Aspirin 100mg/kg/d PO in divided doses (max 8g/d) for 2d, then 70mg/kg/d for 6wks. Monitor salicylate level. Toxicity causes tinnitus, hyperventilation, metabolic acidosis. Alternative: NSAIDs (p532).
- Steroids are thought not to have a major impact on sequelae, but they may improve symptoms.[58][59]
- Immobilize joints in severe arthritis.
- Haloperidol (0.5mg/8h PO) or diazepam for the chorea.

Prognosis

60% with carditis develop chronic rheumatic heart disease. This correlates with the severity of the carditis.[60] Acute attacks last an average of 3 months. Recurrence may be precipitated by further streptococcal infections, pregnancy, or use of the Pill. Cardiac sequelae affect mitral (70%), aortic (40%), tricuspid (10%), and pulmonary (2%) valves. Incompetent lesions develop during the attack, stenoses years later.

Secondary prophylaxis

Penicillin V 250mg/12h PO until no longer at risk (>30yrs). Alternative: sulfadiazine 1g daily (0.5g if <30kg). Thereafter, give antibiotic prophylaxis for dental or other surgery (p136).

Mitral valve disease

Mitral stenosis

Causes:

Rheumatic; congenital, mucopolysaccharidoses, endocardial fibroelastosis, malignant carcinoid (p270), prosthetic valve.

Presentation:

Dyspnoea; fatigue; palpitations; chest pain; systemic emboli; haemoptysis; chronic bronchitis-like picture ± complications (below).

Signs:

Malar (ie cheek) flush; low-volume pulse; AF common; tapping, non-displaced, apex beat (palpable S_1). On auscultation: loud S_1; opening snap (pliable valve); rumbling mid-diastolic murmur (heard best in expiration, with patient on left side). Graham Steell murmur (p34) may occur. *Severity:* The more severe the

stenosis, the longer the diastolic murmur, and the closer the opening snap is to S_2.

Tests:

ECG: AF; P-mitrale if in sinus rhythm; RVH; progressive RAD. CXR: left atrial enlargement; pulmonary oedema; mitral valve calcification. *Echocardiography* is diagnostic. Significant stenosis exists if the valve orifice is $<1cm^2/m^2$ body surface area. Indications for *cardiac catheterization:* previous valvotomy; signs of other valve disease; angina; severe pulmonary hypertension; calcified mitral valve.

Management:

If in AF, *rate control (*p116*) is crucial*; anticoagulate with warfarin (p334). Diuretics ↓preload and pulmonary venous congestion. If this fails to control symptoms, balloon valvuloplasty (if pliable, non-calcified valve), open mitral valvotomy or valve replacement. SBE/IE prophylaxis for dental or surgical procedures (p136). Oral penicillin as prophylaxis against recurrent rheumatic fever if <30yrs old (p128).

Complications:

Pulmonary hypertension; emboli, pressure from large LA on local structures, eg hoarseness (recurrent laryngeal nerve), dysphagia (oesophagus), bronchial obstruction; infective endocarditis (rare).

Mitral regurgitation

Causes:

Functional (LV dilatation); annular calcification (elderly); rheumatic fever, infective endocarditis, mitral valve prolapse, ruptured chordae tendinae; papillary muscle dysfunction/rupture; connective tissue disorders (Ehlers-Danlos, Marfan's); cardiomyopathy; congenital (may be associated with other defects, eg ASD, AV canal); appetite suppressants (eg fenfluramine, phentermine).

Symptoms:

Dyspnoea; fatigue; palpitations; infective endocarditis.

Signs:

AF; displaced, hyperdynamic apex; RV heave; soft S_1; split S_2; loud P_2 (pulmonary hypertension) pansystolic murmur at apex radiating to axilla. *Severity:* The more severe, the larger the left ventricle.

Tests:

ECG: AF ± P-mitrale if in sinus rhythm (may mean left atrial size↑); LVH. CXR: big LA & LV; mitral valve calcification; pulmonary oedema.

Echocardiogram

to assess LV function (trans-oesophageal to assess severity and suitability for repair rather than replacement). *Doppler echo* to assess size and site of regurgitant jet. *Cardiac catheterization* to confirm diagnosis, exclude other valve disease, assess coronary artery disease.

Management:

Control rate if fast AF. Anticoagulate if: AF; history of embolism; prosthetic valve; additional mitral stenosis. Diuretics improve symptoms. Surgery for deteriorating symptoms; aim to repair or replace the valve before LV irreversibly impaired. Antibiotics to prevent endocarditis.

Mitral valve prolapse

Prevalence: ~5%. Occurs alone or with: ASD, patent ductus arteriosus, cardiomyopathy, Turner's syndrome, Marfan's syndrome, osteogenesis imperfecta, pseudoxanthoma elasticum, WPW (p112).

Symptoms:

Asymptomatic— or atypical chest pain and palpitations.

Signs:

Mid-systolic click and/or a late systolic murmur.

Complications:

Mitral regurgitation, cerebral emboli, arrhythmias, sudden death.

Tests:

Echocardiography is diagnostic. ECG may show inferior T wave inversion.

[prescription take]:

ß-blockers may help palpitations and chest pain. Give endocarditis prophylaxis (p136), if co-existing mitral regurgitation.

Aortic valve disease

Aortic stenosis (AS)

Causes:

Senile calcification is the commonest.[61] Others: congenital (bicuspid valve, William's syndrome, p139).

Presentation:

Angina; dyspnoea; dizziness; faints; systemic emboli if infective endocarditis; CCF; sudden death.

Signs:

Slow rising pulse with narrow pulse pressure (feel for diminished and delayed carotid upstroke—'*parvus et tardus*'); heaving, non-displaced apex beat; LV heave; aortic thrill; ejection systolic murmur (heard at the base, left sternal edge and the aortic area, radiates to the carotids). As stenosis worsens, A_2 is increasingly delayed, giving first a single S_2 and then reversed splitting. But this sign is rare. More common is a quiet A_2. In severe AS, A_2 may be inaudible (calcified valve). There may be an ejection click (pliable valve) or an S_4 (said to occur more often with bicuspid valves, but not in all populations).[62]

Tests:

ECG: P-mitrale, LVH with strain pattern; LAD (left anterior hemiblock); poor R wave progression; LBBB or complete AV block (calcified ring). CXR: LVH; calcified aortic valve; post-stenotic dilatation of ascending aorta. Echo: diagnostic (p98). *Doppler echo* can estimate the gradient across valves: severe stenosis if gradient $\gtrsim$50mmHg and valve area <0.5cm^2. If the aortic jet velocity is >4m/s (or is increasing by >0.3m/s per yr) risk of complications is increased.[63] *Cardiac catheter* can assess: valve gradient; LV function; coronary artery disease; the aortic root.

Differential diagnosis:

Hypertrophic obstructive cardiomyopathy (HOCM, p138).

Management:

If symptomatic, prognosis is poor: 2-3yr survival if angina/syncope; 1-2yr if cardiac failure. Prompt valve replacement (p134) is recommended. In asymptomatic patients with severe AS and a deteriorating ECG, valve replacement is also recommended. If the patient is not medically fit for surgery, percutaneous valvuloplasty may be attempted. Endocarditis prophylaxis (p136).

Aortic sclerosis

is senile degeneration of the valve. There is an ejection systolic murmur, no carotid radiation, and a normal pulse and S_2.

Aortic regurgitation (AR)

Causes:

Congenital valve disease: rheumatic fever; infective endocarditis, rheumatoid arthritis; SLE; pseudoxanthoma elasticum; appetite suppressants (eg fenfluramine, phentermine). *Aortic root disease:* hypertension; trauma; aortic dissection; seronegative arthritides (ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy); Marfan's syndrome; osteogenesis imperfecta; syphilitic aortitis.

Symptoms:

Dyspnoea; palpitations; cardiac failure.

Signs:

Collapsing (waterhammer) pulse—see p31; wide pulse pressure; displaced, hyperdynamic apex beat; high pitched early diastolic murmur (heard best in expiration, with patient sitting forward). Eponyms: **Corrigan's sign** (carotid pulsation); **de Musset's sign** (head nodding); **Quincke's sign** (capillary pulsations in nail beds); **Duroziez's sign** (femoral diastolic murmur as blood flows *backwards* in diastole); **Traube's sign** ('pistol shot' sound over femoral arteries). In severe AR, an **Austin Flint** murmur may be heard (p34).

Tests:

ECG: LVH. CXR: cardiomegaly; dilated ascending aorta; pulmonary oedema. *Echocardiography* is diagnostic. *Cardiac catheterization* to assess: severity of lesion; anatomy of aortic root; LV function; coronary artery disease; other valve disease.

Management:

Indications for surgery: increasing symptoms; enlarging heart on CXR/echo; ECG deterioration (T wave inversion in lateral leads); infective endocarditis refractory to medical therapy. Aim to replace the valve before significant LV dysfunction occurs. Endocarditis prophylaxis (p136).

Right heart valve disease

Tricuspid regurgitation

Causes:

Functional (pulmonary hypertension); rheumatic fever; infective endocarditis (IV drug abusers); carcinoid syndrome; congenital (eg ASD, AV canal, Ebstein's anomaly ie downward displacement of the tricuspid valve— see OHCS p642).

Symptoms:

Fatigue; hepatic pain on exertion; ascites; oedema.

Signs:

Giant *v* waves and prominent *y* descent in JVP (p30); RV heave; pansystolic murmur, heard best at lower sternal edge in inspiration; pulsatile hepatomegaly; jaundice; ascites.

Management:

Treat underlying cause. Drugs: diuretics, digoxin, ACE-inhibitors. Valve replacement (20% operative mortality).

Tricuspid stenosis

Cause:

Rheumatic fever; almost always occurs with mitral or aortic valve disease.

Symptoms:

Fatigue, ascites, oedema.

Signs:

Giant *a* wave and slow *y* descent in JVP (p30); opening snap, early diastolic murmur heard at the left sternal edge in inspiration.

Diagnosis:

Doppler echo.

Treatment:

Diuretics; surgical repair.

Pulmonary stenosis

Causes:

Usually congenital (Turner's syndrome, Noonan's syndrome, William's syndrome, Fallot's tetralogy, rubella). Acquired causes: rheumatic fever, carcinoid syndrome.

Symptoms:

Dyspnoea; fatigue; oedema; ascites.

Signs:

Dysmorphic facies (congenital causes); prominent *a* wave in JVP; RV heave. In mild stenosis, there is an ejection click, ejection systolic murmur (which radiates to the left shoulder); widely split S_2. In severe stenosis, the murmur becomes longer and obscures A_2. P_2 becomes softer and may be inaudible.

Tests:

ECG: RAD, P-pulmonale, RVH, RBBB. CXR: post-stenotic dilatation of pulmonary artery; oligaemic lung fields; RV hypertrophy; right atrial hypertrophy.

Cardiac catheterization is diagnostic.

Treatment:

Pulmonary valvuloplasty or valvotomy.

Pulmonary regurgitation

is caused by any cause of pulmonary hypertension (p186). A decrescendo murmur is heard in early diastole at the left sternal edge (the Graham Steell murmur).

Cardiac surgery

Valvuloplasty

can be used in mitral or pulmonary stenosis (pliable, non-calcified valve, no regurgitation). A balloon catheter is inserted across the valve and inflated.

Valvotomy

Closed valvotomy is rarely performed now. Open valvotomy is performed under cardiopulmonary bypass through a median sternotomy.

Valve replacements

Mechanical valves may be of the ball-cage (Starr-Edwards), tilting disc (Bjork-Shiley), or double tilting disc (St Jude) type. These valves are very durable but the risk of thromboembolism is high; patients require lifelong anticoagulation. *Xenografts* are made from porcine valves or pericardium. These valves are less durable and may require replacement at 8-10yrs. Anticoagulation is not required unless there is AF. *Homografts* are cadaveric valves. They are particularly useful in young patients and in the replacement of infected valves. *Complications of prosthetic valves:* systemic embolism, infective endocarditis, haemolysis, structural valve failure, arrhythmias.

CABG

See OPPOSITE.

Cardiac transplantation

Consider this when cardiac disease is *severely* curtailing quality of life, and survival is not expected beyond 6-12 months. Refer to a specialist centre.

Coronary artery bypass grafts (CABG)

Indications for CABG: to improve survival

- Left mainstem disease
- Triple vessel disease involving proximal part of the left anterior descending

To relieve symptoms

- Angina unresponsive to drugs
- Unstable angina (sometimes)
- If angioplasty is unsuccessful

NB: When CABG and percutaneous coronary intervention (PCI, eg angioplasty) are both clinically valid options, NICE recommends that the availability of new stent technology should push the decision towards PCI.

Procedure:

Surgery is planned in the light of angiograms. Not all stenoses are bypassable. The heart is stopped and blood pumped artificially by a machine outside the body (cardiac bypass). (Minimally invasive thoracotomies not requiring this are well-described,[64] but have not yet been validated in randomized trials.) The patient's own saphenous vein or internal mammary artery is used as the graft. Several grafts may be placed. >50% of vein grafts close in 10yrs (low-dose aspirin helps prevent this). Internal mammary artery grafts last longer (but may cause chest-wall numbness).

After CABG:

If angina persists or recurs (from poor run-off from the graft, distal disease, new atheroma, or graft occlusion) restart anti-anginal drugs, and consider angioplasty (repeat surgery is dangerous). Mood, sex, and intellectual problems[65] are common early. Rehabilitation helps:

- Exercise: walk→cycle→swim→jog
- Drive at 1 month: no need to tell DVLA if non-HGV licences, p144
- Get back to work eg at 3 months
- Attend to: smoking; BP; lipids
- Aspirin 75mg/24h PO forever; consider clopidogrel if aspirin CI.

Infective endocarditis (IE)

▸*Fever + new murmur = endocarditis until proven otherwise.*

Classification

- 50% of all endocarditis occurs on *normal valves*. It follows an *acute course*, and presents with acute heart failure.
- Endocarditis on *abnormal valves* tends to run a *subacute course*. Predisposing cardiac lesions: aortic or mitral valve disease; tricuspid valves in IV drug users; coarctation; patent ductus arteriosus; VSD; prosthetic valves. Endocarditis on prosthetic valves may be 'early' (acquired at the time of surgery, poor prognosis) or 'late' (acquired haematogenously).

Causes

Bacteria:

Any cause of bacteraemia exposes valves to the risk of bacterial colonization (dentistry; UTI; urinary catheterization; cystoscopy; respiratory infection; endoscopy ( ); colon cancer; gall bladder disease; skin disease; IV cannulation; surgery; abortion; fractures). Quite often, no cause is found. *Strep viridans* is the commonest (35-50%). Others: enterococci; *Staph aureus* or *epidermidis;* diphtheroids and icroaerophilic streptococci. Rarely: **HACEK** group of Gram -ve bacteria (***H**aemophilus-**A**ctinobacillus-**C**ardiobacterium-**E**ikenella-**K**ingella*); *Coxiella burnetii*; *Chlamydia*.

Fungi:

These include *Candida, Aspergillus,* and *Histoplasma*.

Other causes:

SLE (Libman-Sacks endocarditis); malignancy.

Clinical features

The patient may present with any of the following:

Septic signs:

Fever, rigors, night sweats, malaise, weight loss, anaemia, splenomegaly, and clubbing.

Cardiac lesions:

Any new murmur, or a change in the nature of a pre-existing murmur, should raise the suspicion of endocarditis. Vegetations may cause valve destruction, and severe regurgitation, or valve obstruction. An aortic root abscess causes prolongation of the P-R interval, and may lead to complete AV block. LVF is a common cause of death.

Immune complex deposition:

Vasculitis (p542) may affect any vessel. Microscopic haematuria is common; glomerulonephritis and acute renal failure may occur. Roth spots (boat-shaped retinal haemorrhage with pale centre; **fig 1**, p376); splinter haemorrhages (on finger or toe nails); Osler's nodes (painful pulp infarcts in fingers or toes) and Janeway lesions (painless palmar or plantar macules) are pathognomonic.

Embolic phenomena:

Emboli may cause abscesses in the relevant organ, eg brain, heart, kidney, spleen, GI tract. In right-sided endocarditis, pulmonary abscesses may occur.

Diagnosis

The *Duke* criteria 66 for definitive diagnosis of endocarditis are given OPPOSITE.

Blood cultures:

Take 3 sets at different times and from different sites at peak fever. 85-90% are diagnosed from the first two sets; 10% are culture-negative.

Blood tests:

Normochromic, normocytic anaemia, neutrophil leucocytosis, high ESR/CRP. Also check U&E, Mg^{2+}, LFT.

Urinalysis for microscopic haematuria. CXR (cardiomegaly) and ECG (prolonged P-R interval) at regular intervals.

Echocardiography

TTE (p98) may show vegetations, but only if >2mm. TOE (p98) is more sensitive, and better for visualizing mitral lesions and possible development of aortic root abscess.

Management

Liaise early with a microbiologist and a cardiologist.

- Antibiotics: see BOX.
- Consider surgery if: heart failure, valvular obstruction; repeated emboli; fungal endocarditis; persistent bacteraemia; myocardial abscess; unstable infected prosthetic valve.[67]

Prognosis

30% mortality with staphylococci; 14% with bowel organisms; 6% with sensitive streptococci.

Prevention

▸See BNF 5.1. Example: amoxicillin 3g PO 1h before dentistry. This is suitable for those who have not received penicillin in the last month, including those with prosthetic valves. (If penicillin allergic, clindamycin 600mg PO 1h pre-op). If past endocarditis, IV gentamicin and amoxicillin (see BNF).

Duke criteria for infective endocarditis

Major criteria:

- Positive blood culture:
  - typical organism in 2 separate cultures or
  - persistently +ve blood cultures, eg 3, >12h apart (or majority if ≥4)
- Endocardium involved:
  - positive echocardiogram (vegetation, abscess, dehiscence of prosthetic valve) or
  - new valvular regurgitation (change in murmur not sufficient).

Minor criteria:

- Predisposition (cardiac lesion; IV drug abuse)
- Fever >38°C
- Vascular/immunological signs
- Positive blood culture that do not meet major criteria
- Positive echocardiogram that does not meet major criteria.

How to diagnose:

Definite infective endocarditis: 2 major **or** 1 major and 3 minor **or** all 5 minor criteria (if no major criterion is met).

Antibiotic therapy for infective endocarditis

- Consult a microbiologist early. The following are guidelines only:
- *Empirical therapy:* **benzylpenicillin**[1] 1.2g/4h IV + **gentamicin**, eg 1mg/kg/8h IV for 4wks. Do gentamicin levels (p738; in IE/SBE, the BNF recommends a serum peak of 3-5mg/L & a pre-dose trough of <1mg/L; see p738). If acute, add **flucloxacillin** 2g/6h IV to cover staphylococci.
- *Enterococci:* **amoxicillin**[1] 1g/6h IV + gentamicin as above.
- *Streptococci:* **benzylpenicillin**[1] 1.2g/4h IV for 2-4wks; then **amoxicillin** 1g/8h PO for 2wks. Monitor minimum inhibitory concentration (MIC). Add gentamicin.
- *Staphylococci*: **flucloxacillin**[1] 2g/6h IV + **gentamicin** as above IV. Treat for 6-8wks; stop gentamicin after 1wk. If prosthetic valve or MRSA suspected, substitute flucloxacillin with vancomycin plus rifampicin.
- *Coxiella:* **doxycycline** 100mg/12h PO indefinitely + **co-trimoxazole**, **rifampicin**, or **ciprofloxacin**.
- *Fungi:* **flucytosine** 50mg/kg/6h IVI over 30 minutes followed by **fluconazole** 50mg/24h PO (higher doses may be needed). **Amphotericin** (p160) if flucytosine resistance or *Aspergillus*. **Miconazole** if renal function is poor.

Diseases of heart muscle

Acute myocarditis

Causes:

Inflamed myocardium from viruses (coxsackie, polio, HIV, Lassa fever); bacteria (Clostridia, diphtheria, Meningococcus, Mycoplasma, psittacosis); spirochaetes (Leptospirosis, syphilis, Lyme disease); protozoa (Chagas' disease p426); drugs; toxins; vasculitis, p542.

Signs & symptoms:

Fatigue, dyspnoea, chest pain, palpitations, tachycardia, soft S_1, S_4 gallop (p32).

Tests:

ECG: ST segment elevation/depression, T wave inversion, atrial arrhythmias, transient AV block. Serology may be helpful.

Management:

Treat the underlying cause. Supportive measures. Patients may recover or get intractable heart failure (p122).

Dilated cardiomyopathy

A dilated, flabby heart of unknown cause. Associations: alcohol, ↑BP, haemochromatosis, viral infection, autoimmune, peri- or postpartum, thyrotoxicosis, congenital (X-linked).

Prevalence:

0.2%.

Presentation:

Fatigue, dyspnoea, pulmonary oedema, RVF, emboli, AF, VT.

Signs:

↑Pulse, ↓BP, ↑JVP, displaced, diffuse apex, S_3 gallop, mitral or tricuspid regurgitation (MR/TR), pleural effusion, oedema, jaundice, hepatomegaly, ascites.

Tests:

CXR: cardiomegaly, pulmonary oedema. ECG: tachycardia, non-specific T wave changes, poor R wave progression. Echo: globally dilated hypokinetic heart and low ejection fraction. Look for MR, TR, LV mural thrombus.

Management:

Bed rest, diuretics, digoxin, ACE-inhibitor, anticoagulation. Consider cardiac transplantation.

Mortality:

Variable, eg 40% in 2yrs.

Hypertrophic cardiomyopathy

HOCM≈LV outflow tract (LVOT) obstruction from asymmetric septal hypertrophy.

Prevalence:

0.2%. Autosomal dominant inheritance, but 50% are sporadic. 70% have mutations in genes encoding ß-myosin, ×-tropomyosin, and troponin T. May present at any age. Ask about family history or sudden death.

Symptoms & signs:

Angina; dyspnoea; palpitation; syncope; sudden death (VF is amenable to implantable defibrillators). Jerky pulse; *a* wave in JVP; double apex beat; systolic thrill at lower left sternal edge; harsh ejection systolic murmur.

Tests:

ECG: LVH; progressive T wave inversion; deep Q waves (inferior + lateral leads); AF; WPW syndrome (p112); ventricular ectopics; VT. Echo: asymmetrical septal hypertrophy; small LV cavity with hypercontractile posterior wall; midsystolic closure of aortic valve; systolic anterior movement of mitral valve. *Cardiac catheterization* may provoke VT. It helps assess: severity of gradient; coronary artery disease or mitral regurgitation. Electrophysiological studies may be needed (eg if WPW, p112). Exercise test (p94) ± Holter monitor (p66) to risk stratify.

Management:

ß-blockers or verapamil for symptoms (p100). Amiodarone (p116) for arrhythmias (AF, VT). Anticoagulate for paroxysmal AF or systemic emboli. Dual-chamber pacing (p118) is used if symptomatic despite drugs. Septal myomectomy (surgical, or chemical, with alcohol, to ↓LV outflow tract gradient) is reserved for those with severe symptoms. Consider implantable defibrillator.

Mortality:

5.9%/yr if <14yrs; 2.5%/yr if >14yrs. *Poor prognostic factors:* age <14yrs or syncope at presentation; family history of HOCM/sudden death.

Restrictive cardiomyopathy

Causes:

Amyloidosis; haemochromatosis; sarcoidosis; scleroderma; Löffler's eosinophilic endocarditis, endomyocardial fibrosis.

Presentation

is like constrictive pericarditis (p140). Features of RVF predominate: ↑JVP, with prominent *x* and *y* descents; hepatomegaly; oedema; ascites.

Diagnosis:

Cardiac catheterization.

Cardiac myxoma

Rare benign cardiac tumour. Prevalence ≤5/10,000, ♀:♂≈2:1. Usually sporadic, may be familial (autosomal-dominant). It may mimic infective endocarditis (fever, weight loss, clubbing, ↑ESR), or mitral stenosis (left atrial obstruction, systemic emboli, AF). A 'tumour plop' may be heard, and signs may vary according to posture.

Tests:

Echocardiography.

Treatment:

Excision.

The heart in various, mostly rare, systemic diseases

This list reminds us to look at the heart *and* the whole patient, not just in exams (where those with odd syndromes congregate), but always.

Acromegaly:

(p222) BP↑; LVH; hypertrophic cardiomyopathy; high output cardiac failure; coronary artery disease.

Amyloidosis:

(p354) Restrictive cardiomyopathy.

Ankylosing spondylitis:

Conduction defects; AV block; AR.

Behçet's disease:

(p686) Aortic regurgitation; arterial ± venous thrombi.

Cushing's syndrome:

(p208) Hypertension.

Down's syndrome:

(OHCS p152) ASD; VSD; mitral regurgitation.

Ehlers-Danlos syndrome:

(OHCS p642) Mitral valve prolapse + hyperelastic skin ± aneurysms and GI bleeds. Joints are loose and hypermobile; mutations exist, eg in genes for procollagen (COL3A1); there are 6 types.

Friedreich's ataxia:

(p690) Hypertrophic cardiomyopathy.

Haemochromatosis:

(p254) AF; cardiomyopathy.

Holt-Oram syndrome:

ASD or VSD with upper limb defects.[68]

Human immunodeficiency virus:

(p396) Myocarditis; dilated cardiomyopathy; effusion; ventricular arrhythmias; SBE/IE; non-infective thrombotic (marantic) endocarditis; RVF (pulmonary hypertension); metastatic Kaposi's sarcoma.

Hypothyroidism:

(p204) Sinus bradycardia; low pulse pressure; pericardial effusion; coronary artery disease; low voltage ECG.

Kawasaki disease:

(OHCS p646) Coronary arteritis similar to PAN; commoner than *rheumatic fever* (p128) as a cause of acquired heart disease.

Klinefelter's syndrome:♂

(OHCS p646) ASD. Psychopathy; learning difficulties; libido↓; gynaecomastia; sparse facial hair and small firm testes. XXY.

Marfan's syndrome:

(p698) Mitral valve prolapse; AR; aortic dissection. Look for long fingers and a high-arched palate.

Noonan's syndrome:

(OHCS p650) ASD; pulmonary stenosis ± low-set ears.

PAN:

(p543) Small and medium vessel vasculitis + angina; MI; arrhythmias; CCF; pericarditis and conduction defects.

Rheumatoid nodules:

Conduction defects; pericarditis; LV dysfunction; aortic regurgitation; coronary arteritis. Look for arthritis signs, p532.

Sarcoidosis:

(p178) Infiltrating granulomas may cause complete AV block; ventricular or supraventricular tachycardia; myocarditis; CCF; restrictive cardiomyopathy. ECG may show Q waves.

Syphilis:

(p419) Myocarditis; ascending aortic aneurysm.

Systemic lupus erythematosus:

(p540) Pericarditis/effusion; myocarditis; Libman-Sacks endocarditis; mitral valve prolapse; coronary arteritis.

Systemic sclerosis:

(p538) Pericarditis; pericardial effusion; myocardial fibrosis; myocardial ischaemia; conduction defects; cardiomyopathy.

Thyrotoxicosis:

(p202) Pulse↑; AF ± emboli; wide pulse pressure; hyperdynamic apex; loud heart sounds; ejection systolic murmur; pleuropericardial rub; angina; high output cardiac failure.

Turner's syndrome:♀

Coarctation of aorta. Look for webbed neck. XO.

William's syndrome:

Supravalvular aortic stenosis (visuo-spatial IQ↓).

Pericardial diseases

Acute pericarditis

Inflammation of the pericardium which may be primary or secondary to systemic disease.

Causes:

- Viruses (coxsackie, 'flu, Epstein-Barr, mumps, varicella, HIV)
- Bacteria (pneumonia, rheumatic fever, TB)
- Fungi
- Myocardial infarction, Dressler's (p690)
- Others: uraemia, Rheumatoid arthritis, SLE, myxoedema, trauma, surgery, malignancy, radiotherapy, procainamide, hydralazine.

Clinical features:

Central chest pain worse on inspiration or lying flat ± relief by sitting forward. A pericardial friction rub may be heard. Look for evidence of a pericardial effusion or cardiac tamponade (see below). Fever may occur.

Tests:

ECG classically shows concave (saddle-shaped) ST segment elevation, but may be normal or non-specific (10%). *Blood tests:* FBC, ESR, U&E, cardiac enzymes (*NB: troponin may be raised*), viral serology, blood cultures, and, if indicated, autoantibodies (p539), fungal precipitins, thyroid function tests. Cardiomegaly on CXR may indicate a pericardial effusion. Echo (if suspected pericardial effusion).

Treatment:

Analgesia, eg ibuprofen 400mg/8h PO with food. Treat the cause. Consider colchicine before steroids/immunosuppressants if relapse or continuing symptoms occur. 15-40% *do* recur.[69]

Pericardial effusion

Accumulation of fluid in the pericardial sac.

Causes:

Any cause of pericarditis (see above).

Clinical features:

Dyspnoea, raised JVP (with prominent x descent, p31), bronchial breathing at left base (Ewart's sign: large effusion compressing left lower lobe). Look for signs of cardiac tamponade (see below).

Diagnosis:

CXR shows an enlarged, globular heart. ECG shows low voltage QRS complexes and alternating QRS morphologies (electrical alternans). *Echocardiography* shows an echo-free zone surrounding the heart.

Management:

Treat the cause. Pericardiocentesis may be *diagnostic* (suspected bacterial pericarditis) or *therapeutic* (cardiac tamponade). See p761. Send pericardial fluid for culture, ZN stain/TB culture, and cytology.

Constrictive pericarditis

The heart is encased in a rigid pericardium.

Causes:

Often unknown (UK); elsewhere TB, or after *any* pericarditis.

Clinical features:

These are mainly of right heart failure with ↑JVP (with prominent x and y descents, p30); Kussmaul's sign (JVP rising paradoxically with inspiration); soft, diffuse apex beat; quiet heart sounds; S_3 ; diastolic pericardial knock, hepatosplenomegaly, ascites, and oedema.

Tests:

CXR: small heart ± pericardial calcification (if none, CT/MRI helps distinguish from other cardiomyopathies). Echo; cardiac catheterization.

Management:

Surgical excision.

Cardiac tamponade

Accumulation of pericardial fluid raises intra-pericardial pressure, hence poor ventricular filling and fall in cardiac output.

Causes:

Any pericarditis (above); aortic dissection; haemodialysis; warfarin; transseptal puncture at cardiac catheterization; post cardiac biopsy.

Signs:

Pulse↑, BP↓, pulsus paradoxus, JVP↑, Kussmaul's sign, muffled S_1 & S_2.

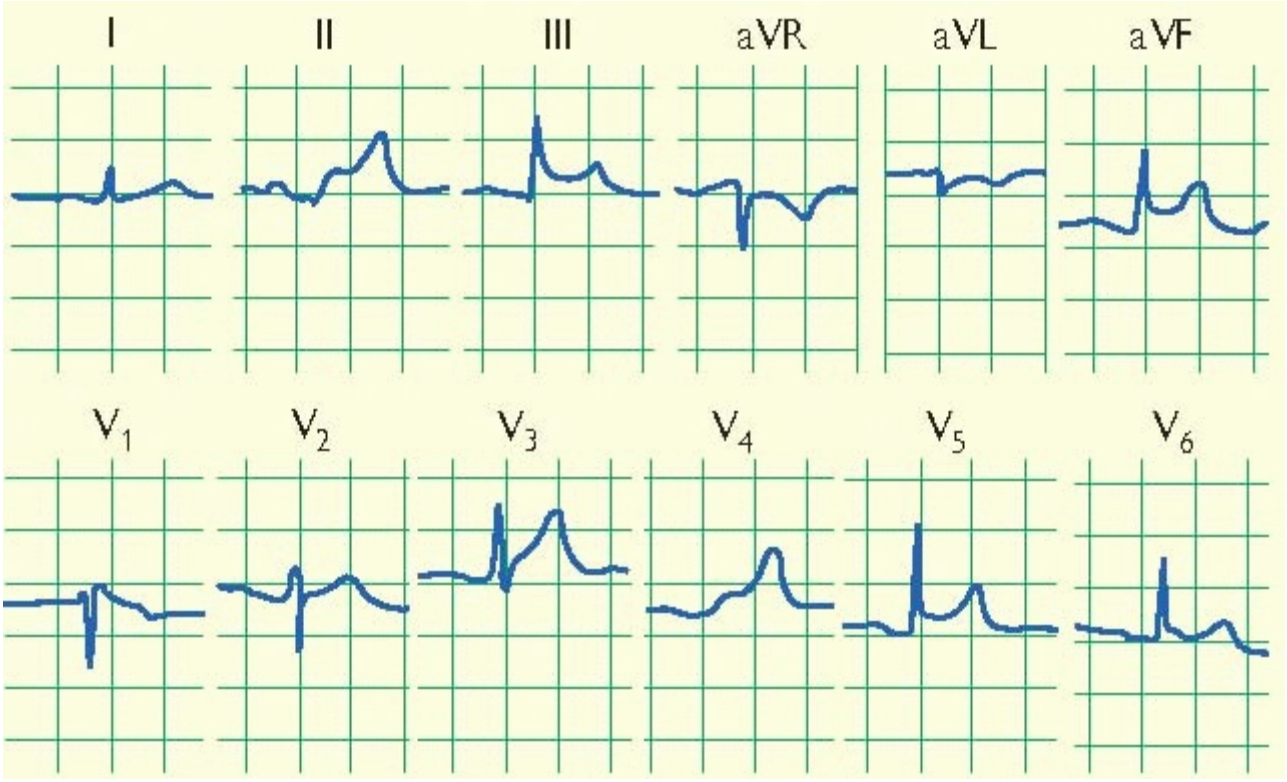
Diagnosis:

Beck's triad: falling BP; rising JVP; small, quiet heart. CXR: big globular heart (if >250mL fluid). ECG: low voltage QRS ± electrical alternans. Echo is diagnostic: echo-free zone (>2cm, or >1cm if acute) around the heart ± diastolic collapse of right atrium and right ventricle.

Management:

Seek expert help. The pericardial effusion needs urgent drainage (p761). Send fluid for culture, ZN stain/TB culture and cytology.

Pericarditis



Congenital heart disease

The spectrum of congenital heart disease in adults is considerably different from that in infants and children; adults are unlikely to have complex lesions. The commonest lesions, in descending order of frequency, are:

Bicuspid aortic valve

These function well at birth and go undetected. Most eventually develop AS (requiring valve replacement) and/or AR (predisposing to IE/SBE). See p132.

Atrial septal defect (ASD)

A hole connects the atria. *Ostium secundum* defects (high in the septum) are commonest; *ostium primum* defects (opposing the endocardial cushions) are associated with AV valve anomalies. Primum ASDs present early. Secundum ASDs are often asymptomatic until adulthood, as the L→R shunt depends on compliance of the right and left ventricles. The latter decreases with age (esp. if BP↑). This augments L→R shunting causing dyspnoea and heart failure, eg at age 40-60. There may be pulmonary hypertension, cyanosis, arrhythmia, haemoptysis, and chest pain.

Signs:

AF; ↑JVP; wide, fixed split S_2; pulmonary ejection systolic murmur. Pulmonary hypertension may cause pulmonary or tricuspid regurgitation.

Complications:

Reversal of left to right shunt (Eisenmenger's complex, see OPPOSITE), paradoxical embolism (rare).

Tests:

ECG: RBBB with LAD and prolonged P-R interval (primum defect) or RAD (secundum defect). CXR: small aortic knuckle, pulmonary plethora, progressive atrial enlargement. Echocardiography is diagnostic. Cardiac catheterization shows step up in O_2 saturation in the right atrium.

Treatment:

In children, surgical closure is recommended before age 10yrs. In adults, closure is recommended if symptomatic, or if asymptomatic but having pulmonary to systemic blood flow ratios of ≥1.5:1.

Ventricular septal defect (VSD)

A hole connecting the two ventricles.

Causes:

congenital (prevalence 2:1000 births); acquired (post-MI).

Symptoms:

May present with severe heart failure in infancy, or remain asymptomatic and be detected incidentally in later life.

Signs:

These depend upon the VSD'S size and site: smaller holes, which are haemodynamically less significant, give louder murmurs. Classically, a harsh pansystolic murmur is heard at the left sternal edge, with a systolic thrill, ± left parasternal heave. Larger holes are associated with signs of pulmonary hypertension.

Complications:

AR, infundibular stenosis, infective endocarditis, pulmonary hypertension, Eisenmenger's complex (OPPOSITE).

Tests:

ECG: normal (small VSD), LAD + LVH (moderate VSD) or LVH + RVH (large VSD). CXR: normal heart size ± mild pulmonary plethora (small VSD) or cardiomegaly, large pulmonary arteries and marked pulmonary plethora (large VSD). Cardiac catheter: step up in O_2 saturation in right ventricle.

Treatment:

This is medical, at first, as many VSDs close spontaneously. Indications for surgical closure: failed medical therapy, symptomatic VSD, shunt >3 : 1, SBE/IE. Give SBE/IE prophylaxis for untreated defects (p136).

Coarctation of the aorta

Congenital narrowing of the descending aorta; usually occurs just distal to the origin of the left subclavian artery. More common in boys.

Associations:

Bicuspid aortic valve, Turner's syndrome.

Signs:

Radio-femoral delay, weak femoral pulse, BP↑, scapular bruit, systolic murmur (best heard over the left scapula).

Complications:

Heart failure, infective endocarditis.

Tests:

CXR shows rib notching.

Treatment:

Surgery.

Pulmonary stenosis

may occur alone or with other lesions (p134).

Eisenmenger's syndrome

A congenital heart defect which is at first associated with a left to right shunt may lead to pulmonary hypertension and shunt reversal. If so, cyanosis develops (± heart failure and respiratory infections), and Eisenmenger's syndrome is present.

Driving and the heart[1] (Ordinary UK licences only)

UK licences are inscribed 'You are required by law to inform Drivers Medical Branch, DVLA, Swansea SA99 1AT at once if you have any disability (physical or medical), which is, or may become likely to affect your fitness as a driver, unless you do not expect it to last more than 3 months'. It is the responsibility of drivers to inform the DVLA, and that of their doctors to advise patients that medical conditions (and drugs) may affect their ability to drive and for which conditions patients should inform the DVLA. Drivers should also inform their insurance company of any condition disclosed to the DVLA. If in doubt, ask your defence union. The following are examples of the guidance for holders of standard licences. **Different rules apply for group 2 vehicle licence-holders (eg lorries, buses).**

Angina

Driving must cease when symptoms occur at rest or at the wheel. Driving may recommence when satisfactory symptom control is achieved. DVLA need not be notified.

Angioplasty

Driving must cease for 1wk, and may recommence thereafter provided no other disqualifying condition. DVLA need not be notified.

MI/CABG

Driving must cease for >4wks. Driving may recommence thereafter provided there is no other disqualifying condition. DVLA need not be notified.

Arrhythmias

Sinoatrial:

Driving may recommence 4 weeks after successful control provided there is no other disqualifying condition.

Significant atrioventricular conduction defects:

Driving may be permitted when underlying cause has been identified and controlled for >4wks.

AF/flutter:

DVLA need not be notified unless there are distracting/disabling symptoms.

Pacemaker implant

Stop driving for 1wk.

Implanted cardioverter/defibrillator

The licence is subject to annual review.

Driving may occur when these criteria can be met:

- The 1st device has been implanted for at least 6 months.
- The device has not administered therapy (shock and/or symptomatic antitachycardia pacing) within the last 6 months (except during testing).
- Any previous therapy has not been accompanied by *incapacity* (whether caused by the device or arrhythmia).
- A period of 1 month off driving must occur following any revision of the device (generator and/or electrode) or alteration of antiarrhythmics.
- The device is subject to regular review with interrogation.
- There is no other disqualifying condition.

Syncope

Simple faint:

no restriction. ***Unexplained syncope*** with low risk of recurrence 4wks off driving, high risk of recurrence 4wks off driving if cause identified and treated otherwise, 6 months off. See driving and epilepsy, OPPOSITE. Patients who have had a single episode of loss of consciousness (no cause found) still need to have at least 1yr off driving.

Hypertension

Driving may continue unless treatment causes unacceptable side effects. DVLA need not be notified.

Other conditions: UK DVLA[1] state they must be informed if:

- An epileptic event. A person who has suffered an epileptic attack while awake must not drive for 1yr from the date of the attack. A person who has suffered an attack while asleep must also refrain from driving for 1yr from the date of the attack, unless they have had an attack while asleep >3yrs ago and have not had any awake attacks since that asleep attack. In any event, they should not drive if they are likely to cause danger to the public or themselves.
- Patients with TIA or stroke should not drive for at least 1 month. There is no need to inform the DVLA unless there is residual neurological defect after 1 month eg visual field defect. If TIAs have been recurrent and frequent, a 3-month period free of attacks may be required.
- Sudden attacks or disabling giddiness, fainting, or blackouts. Multiple sclerosis, Parkinson's (any ‘freezing’ or on-off effects), motor neurone diseases are relevant here.
- Severe mental handicap. Those with dementia should only drive if the condition is mild (do not rely on armchair judgements: on-the-road trials are better). Encourage relatives to contact DVLA if a dementing relative should not be driving. GPs may desire to breach confidentiality (the GMC approves) and inform DVLA of demented or psychotic patients (tel. 01792 783686). Many elderly drivers (~1 in 3) who die in accidents are found to have Alzheimer's.
- A pacemaker, defibrillator, or anti-ventricular tachycardia device fitted.
- Diabetes controlled by insulin or tablets.

- Angina while driving.
- Parkinson's disease.
- Any other chronic neurological condition.
- A serious problem with memory.
- A major or minor stroke with deficit continuing for >1 month.
- Any type of brain surgery, brain tumour. Severe head injury involving inpatient treatment at hospital.
- Any severe psychiatric illness or mental disorder.
- Continuing/permanent difficulty in the use of arms or legs which affects ability to control a vehicle.
- Dependence on or misuse of alcohol, illicit drugs, or chemical substances in the past 3yrs (do not include drink/driving offences).
- Any visual disability which affects *both* eyes (do not declare short/long sight or colour blindness).

Vision (new drivers) should be 6/9 on Snellen's scale in the better eye and 6/12 on the Snellen scale in the other eye and (wearing glasses or contact lenses if needed) and 3/60 in each eye without glasses or contact lenses.

Acknowledgements

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Editors: Longmore, Murray; Wilkinson, Ian B; Turmezei, Tom; Cheung, Chee Kay
Title: *Oxford Handbook of Clinical Medicine, 7th Edition*

5

Chest Medicine

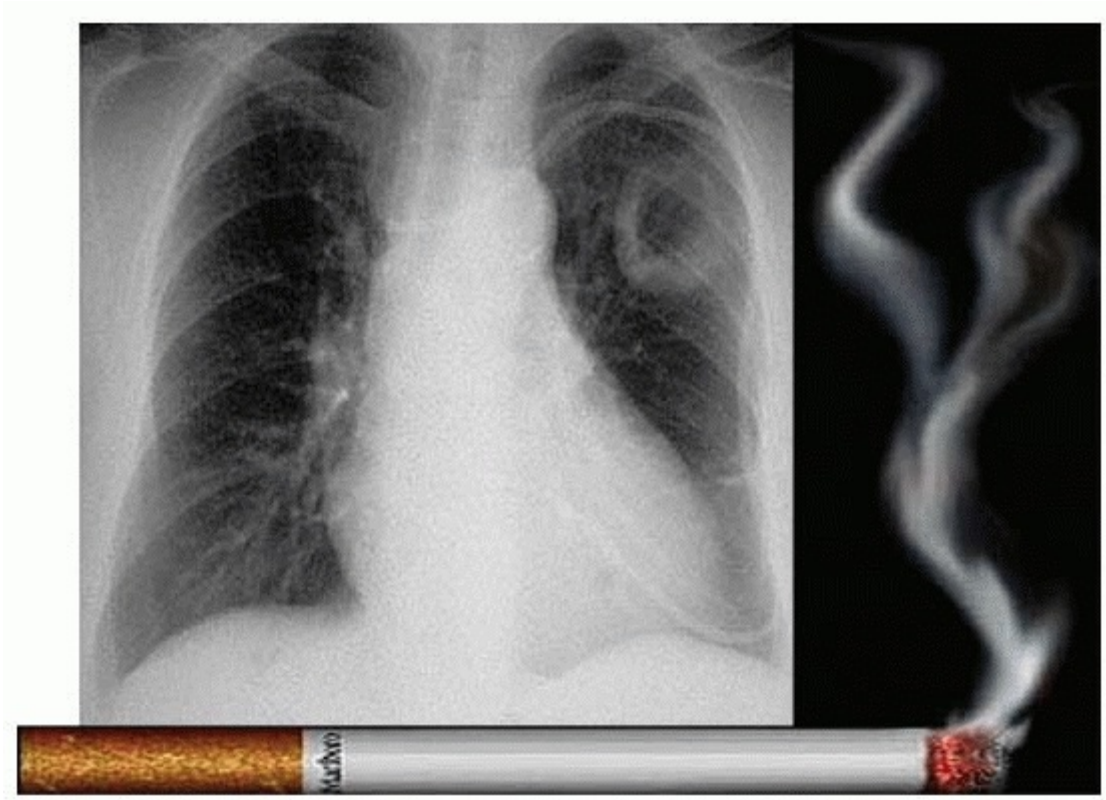


Fig 1. Smoke ring sign: cavitating lung carcinoma 🖫1 (OTM)

Bedside tests in chest medicine

Sputum examination

Collect a good sample; if necessary ask a physiotherapist to help. Note the appearance: clear and colourless (chronic bronchitis), yellow-green (pulmonary infection), red (haemoptysis), black (smoke, coal dust), or frothy whitepink (pulmonary oedema). Send the sample to the laboratory for microscopy (Gram stain and auramine/ZN stain, if indicated), culture, and cytology.

Peak expiratory flow (PEF)

is measured by a maximal forced expiration through a peak flow meter. It correlates well with the forced expiratory volume in 1 second (FEV_1) and is used as an estimate of airway calibre. Peak flow rates should be measured regularly in asthmatics to monitor response to therapy and disease control.

Pulse oximetry

allows non-invasive assessment of peripheral O_2 saturation (SpO_2). It provides a useful tool for monitoring those who are acutely ill or at risk of deterioration. On most pulse oximeters, the alarm is set at 90%. An oxygen saturation of ≤80% is clearly abnormal and action is required (unless this is normal for the patient, eg in COPD). Here, check arterial blood gases (ABG) as P_aCO_2 may be rising despite a normal P_aO_2). Erroneous readings may be caused by: poor perfusion, motion, excess light, skin pigmentation, nail varnish, dyshaemoglobinaemias, and carbon monoxide poisoning. As with any bedside test, be sceptical, and check ABG, whenever indicated (p173).

Arterial blood gas (ABG) analysis

Heparinized blood is taken from the radial, brachial, or femoral artery (see p759), and pH, P_aO_2, and P_aCO_2 are measured using an automated analyser.

Remember to note the FiO_2 (fraction or percent of inspired O_2).

- ***Acid-base balance:*** Normal pH is 7.35-7.45. A pH <7.35 indicates *acidosis* and a pH >7.45 indicates *alkalosis*. For interpretation of abnormalities, see p658.
- ***Oxygenation:*** Normal P_aO_2 is 10.5-13.5kPa. Hypoxia is caused by one or more of the following reasons: ventilation/perfusion ([V with dot above]/[Q with dot above]) mismatch, hypoventilation, abnormal diffusion, right to left cardiac shunts. Of these, [V with dot above]/[Q with dot above] mismatch is the commonest cause. Severe hypoxia is defined as a P_aO_2 <8kPa (see p172).
- ***Ventilatory efficiency:*** Normal P_aCO_2 is 4.5-6.0kPa. P_aCO_2 is directly related to alveolar ventilation. A P_aCO_2 <4.5kPa indicates *hyperventilation* and a P_aCO_2 >6.0kPa indicates *hypoventilation*. Type 1 respiratory failure is defined as P_aO_2 <8kPa and P_aCO_2 <6.0kPa, whereas type II respiratory failure is defined as P_aO_2 <8kPa and P_aCO_2 >6.0kPa.

Alveolar-arterial O_2 concentration gradient

may be calculated from the FiO_2, P_aO_2, and P_aCO_2: see OPPOSITE.

Spirometry

measures functional lung volumes. Forced expiratory volume in 1s (FEV_1) and forced vital capacity (FVC) are measured from a full forced expiration into spirometer (Vitalograph®); exhalation continues until no more breath can be exhaled. FEV_1 is less effort-dependent than PEF. The FEV_1/FVC ratio gives a good estimate of the severity of airflow obstruction; normal ratio is 75-80%.

- ***Obstructive defect*** (eg asthma, COPD) FEV_1 is reduced more than the FVC and the FEV_1/FVC ratio is <75%.
- ***Restrictive defect*** (eg lung fibrosis) FVC is ↓ and the FEV_1/FVC ratio is ↔ or ↑. Other causes: sarcoidosis; pneumoconiosis, interstitial pneumonias; connective tissue diseases; pleural effusion; obesity; kyphoscoliosis; neuromuscular problems.

(Aa)PO_2: the Alveolar-arterial (Aa) oxygen gradient

This is the difference in the O_2 partial pressures between the alveolar and arterial sides. In type II respiratory failure it helps tell if hypoventilation is from lung disease or poor respiratory effort. (Aa)PO_2 = P_AO_2 - P_aO_2. How do we find P_AO_2, the partial pressure of oxygen in the alveoli? Respiratory physiology teaches that this depends on **R**, the respiratory quotient (≈0.8, nearer to 1 if eating all carbohydrates); barometric pressure (P_B ≈ 101kPa at sea level), and P^{H_2O}, the water saturation of airway gas (P^{H_2O} ≈ 6.2kPa as inspired air is usually fully saturated by the time it gets to the carina). P_AO_2 clearly depends on F_iO_2, the fractional concentration of O_2 in inspired air (eg F_iO_2 is 0.5 if breathing 50% O_2, and 0.21 if breathing room air). So...

$P_AO_2 = (P_B - P^{H_2O}) \times F_iO_2 - (P_aCO_2/R) = (101 - 6.2) \times F_iO_2 - (P_aCO_2/0.8)$ (at sea level) $= (94.8 \times F_iO_2) - (1.25 \times P_aCO_2)$

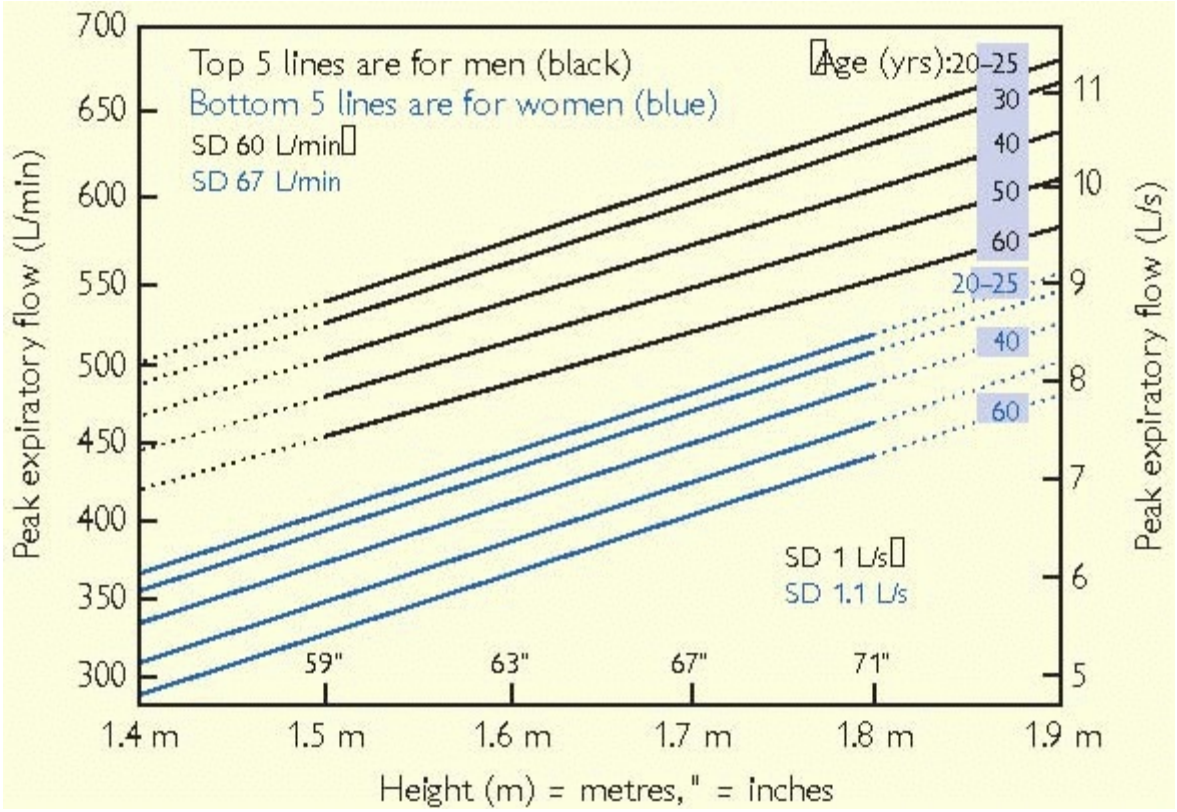
See A Williams BMJ 1998 **317** 1213

Breathing air and having a P_aCO_2 of 8kPa.

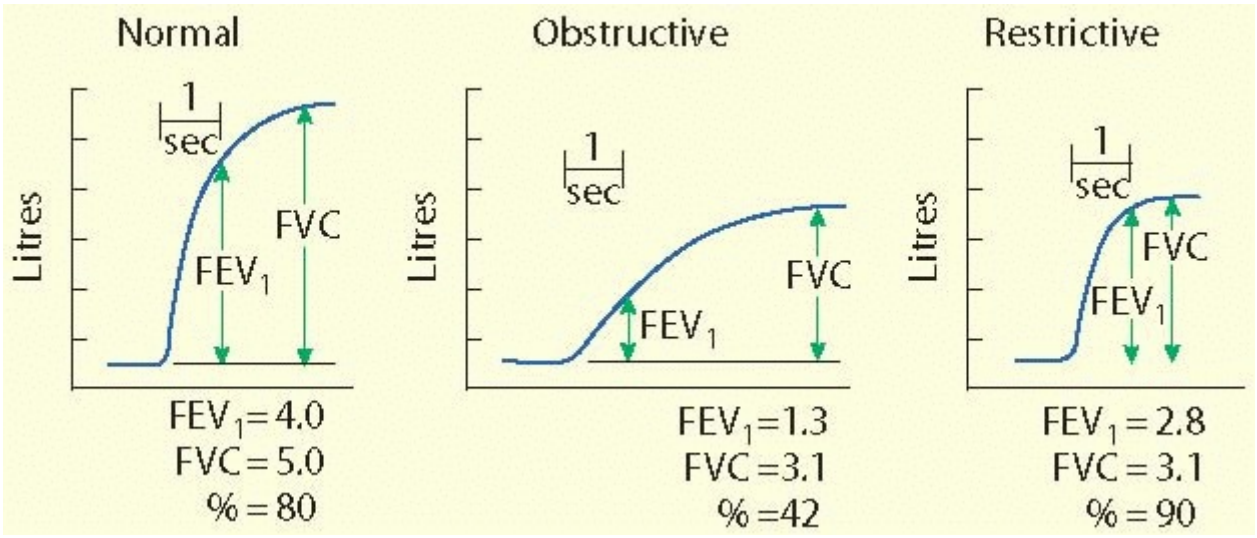
In this case, $P_AO_2 = 94.8 \times 0.21 - (1.25 \times 8) = 10$kPa. *Aa normal ranges breathing air*: 0.2-1.5kPa at 25yrs old; increasing with age to 1.5-3.0 at 75yrs.

Examples of expected Aa gradients: 6.65 at an F_iO_2 of 0.5 ($P_AO_2 - P_aO_2 = 44.6 - 37.95 = 6.65$) and 16 for an F_iO_2 of 1.0 ($P_AO_2 - P_aO_2 = 89 - 73 = 16$).

Normal peak expiratory flow (PEF)



Examples of spirograms



Further investigations in chest medicine

Lung function tests

PEF, FEV_1, FVC (see p148). ***Total lung capacity*** (TLC) and ***residual volume*** (RV) are useful in distinguishing obstructive and restrictive diseases. TLC and RV are increased in obstructive airways disease and reduced in restrictive lung diseases and musculoskeletal abnormalities. The ***gas transfer*** coefficient (KCO) across alveoli is calculated by measuring carbon monoxide uptake from a single inspiration in a standard time (usually 10s). Low in emphysema and interstitial lung disease, high in alveolar haemorrhage. KCO represents the carbon monoxide diffusing capacity (DLCO) corrected for alveolar volume.[3] *Flow volume loop* measures flow at various lung volumes. Characteristic patterns are seen with intra-thoracic airways obstruction (asthma, emphysema) and extra-thoracic airways obstruction (tracheal stenosis).

Radiology

Chest x-ray

see p714.

Ultrasound

is used in the diagnosis and drainage of pleural effusions (particularly loculated effusions) and empyema.

Radionuclide scans

Ventilation/perfusion ([V with dot above]/[Q with dot above], p724*) scans* are used to diagnose pulmonary embolism (PE) (unmatched perfusion defects are seen). *Bone scans* are used to diagnose bone metastases.

Computed tomography

(CT, p718) of the thorax is used for diagnosing and staging lung cancer, imaging the hila, mediastinum and pleura, and guiding biopsies. Thin (1-1.5mm) section high resolution CT (HRCT) is used in the diagnosis of interstitial lung disease and bronchiectasis. Spiral CT pulmonary angiography (CTPA, p725) is used increasingly in the diagnosis of PE.

Pulmonary angiography

is also used for diagnosing PE and pulmonary hypertension.

Fibreoptic bronchoscopy

is performed under local anaesthetic via the nose or mouth. *Diagnostic indications:* suspected lung carcinoma, slowly resolving pneumonia, pneumonia in the immunosuppressed, interstitial lung disease. Bronchial lavage fluid may be sent to the lab for microscopy, culture, and cytology. Mucosal abnormalities may be brushed (cytology) and biopsied (histopathology). *Therapeutic indications:* aspiration of mucus plugs causing lobar collapse or removal of foreign bodies. *Pre-procedure investigations:* FBC, CXR, spirometry, pulse oximetry and arterial blood gases (if indicated). Check clotting if recent anticoagulation and a biopsy may be performed. *Complications:* respiratory depression, bleeding, pneumothorax (**fig 1**, p785).

Bronchoalveolar lavage

(BAL) is performed at the time of bronchoscopy by instilling and aspirating a known volume of warmed, buffered 0.9% saline into the distal airway. *Diagnostic indications:* suspected malignancy, pneumonia in the immunosuppressed (especially HIV), suspected TB (if sputum negative), interstitial lung diseases (eg sarcoidosis, extrinsic allergic alveolitis, histiocytosis X). *Therapeutic indications:* alveolar proteinosis. *Complications:* hypoxia (give supplemental O_2), transient fever, transient CXR shadow, infection (rare).

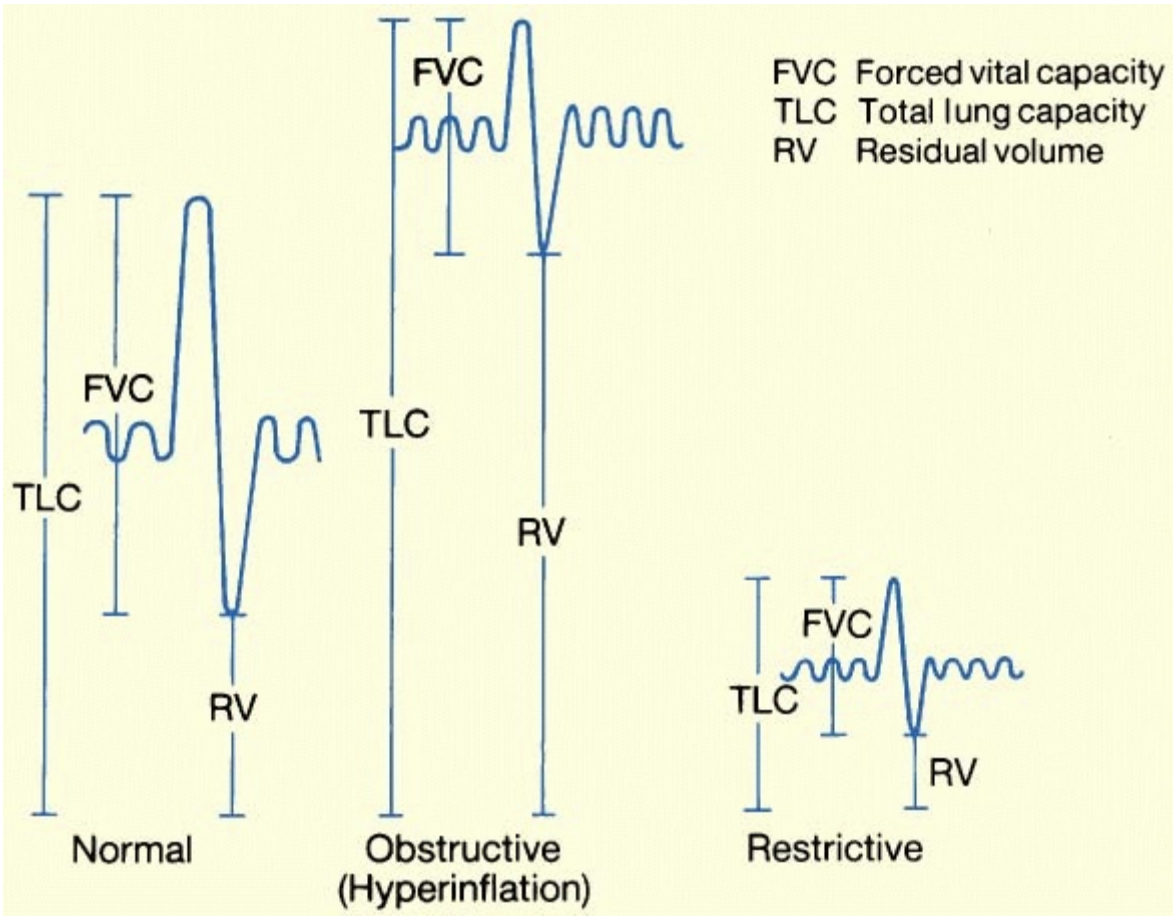
Lung biopsy

may be performed in several ways. ***Percutaneous needle biopsy*** is performed under radiological guidance and is useful for peripheral lung and pleural lesions. ***Transbronchial biopsy*** performed at bronchoscopy may help in diagnosing diffuse lung diseases, eg sarcoidosis. If these are unsuccessful, an ***open lung biopsy*** may be performed under general anaesthetic.

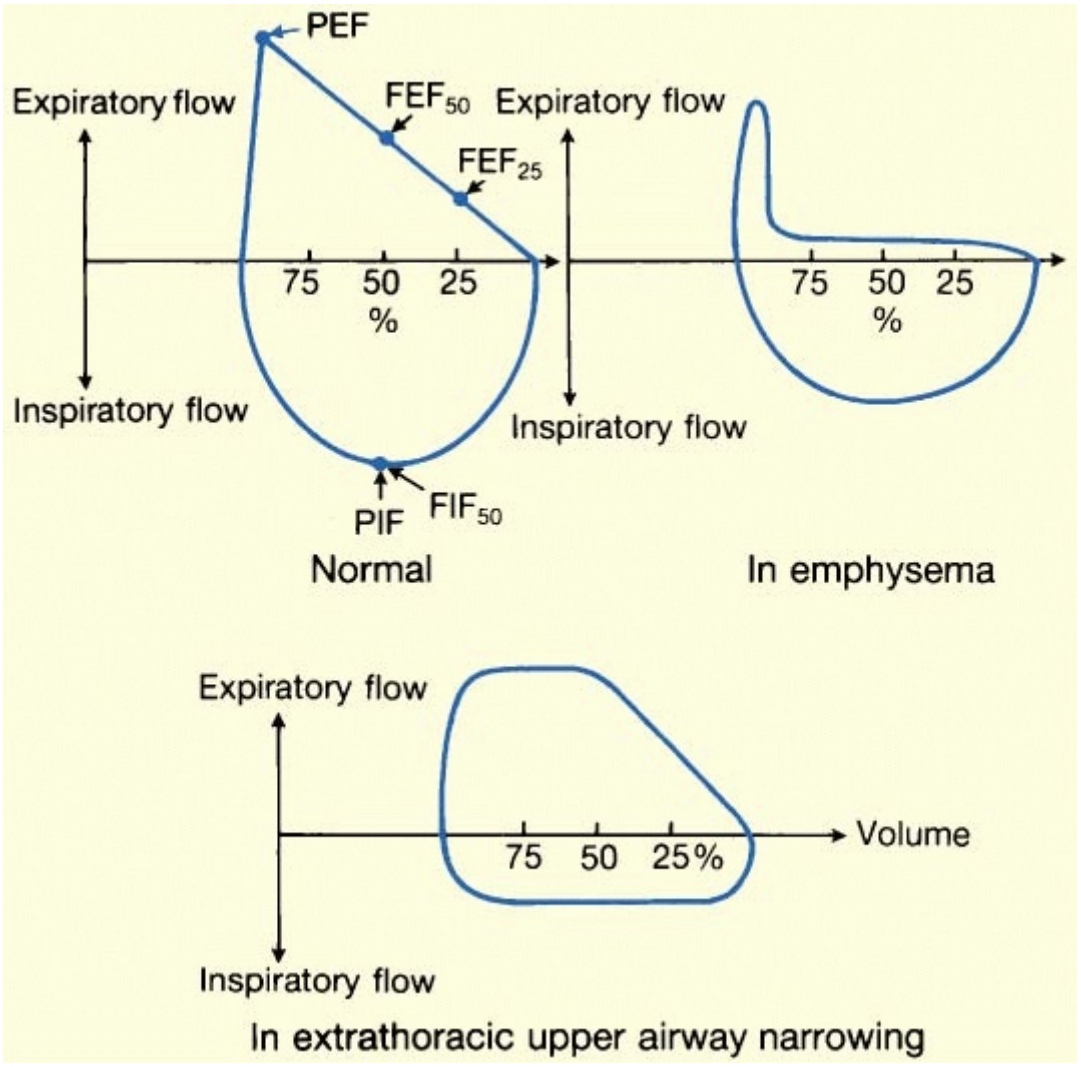
Surgical procedures

are performed under general anaesthetic. ***Rigid bronchoscopy*** provides a wide lumen, enables larger mucosal biopsies, controlling bleeding, and removal of foreign bodies. ***Mediastinoscopy*** and ***mediastinotomy*** enable examination and biopsy of the mediastinal lymph nodes/lesions. ***Thoracoscopy*** allows examination and biopsy of pleural lesions, drainage of pleural effusions, and talc pleurodesis.

Lung volumes: physiological and pathological $_4$



Flow volume loops[5]



Pneumonia [6] [7] ▸▸Emergency treatment: p800

An acute lower respiratory tract illness associated with fever, symptoms and signs in the chest, and abnormalities on the chest x-ray—**fig 1**, p714. Incidence: 1-3/1000 population. Mortality: 10% (patients admitted to hospital).

Classification and causes

Community-acquired pneumonia (CAP) may be primary or secondary to underlying disease. *Streptococcus pneumoniae* is the commonest cause, followed by *Haemophilus influenzae* and *Mycoplasma pneumoniae*. *Staphylococcus aureus*, *Legionella* species, *Moraxella catarrhalis*, and *Chlamydia* account for most of the remainder. Gram negative bacilli, *Coxiella burnetii* and anaerobes are rare. Viruses account for up to 15%.

Hospital acquired (nosocomial) (>48h after hospital admission). Most commonly Gram negative enterobacteria or *Staph. aureus*. Also *Pseudomonas*, *Klebsiella, Bacteroides*, and *Clostridia*.

Aspiration Those with stroke, myasthenia, bulbar palsies, ↓consciousness (eg postictal or drunk), oesophageal disease (achalasia, reflux), or with poor dental hygiene, risk aspirating oropharyngeal anaerobes.

Immunocompromised patient *Strep. pneumoniae*, *H. influenzae*, *Staph. aureus*, *M. catarrhalis, M. pneumoniae*, Gram -ve bacilli and *Pneumocystis jiroveci (formerly named P. carinii*, p398-9). Other fungi, viruses (CMV, HSV), and mycobacteria.

Clinical features

Symptoms: Fever, rigors, malaise, anorexia, dyspnoea, cough, purulent sputum, haemoptysis, and pleuritic pain. ***Signs:*** Fever, cyanosis, confusion (may be the only sign in the elderly), tachypnoea, tachycardia, hypotension, signs of consolidation (diminished expansion, dull percussion note, ↑tactile vocal fremitus/vocal resonance, bronchial breathing), and a pleural rub.

Tests

aim to establish diagnosis, identify pathogen, and assess severity (see below). **CXR** (**fig 1**, p714): lobar or multilobar infiltrates, cavitation or pleural effusion. ***Assess oxygenation:*** oxygen saturation, p148 (ABGs if S_aO_2 <92% or severe pneumonia). ***Blood tests:*** FBC, U&E, LFT, CRP, blood cultures. ***Sputum*** for microscopy and culture. In severe cases, check for *Legionella* (sputum culture, urine antigen), atypical organism/viral serology (complement fixation tests acutely and paired serology) and check for pneumococcal antigen in urine. ***Pleural fluid*** may be aspirated for culture. Consider ***bronchoscopy*** and bronchoalveolar lavage if patient is immunocompromized or on ITU.

Severity

Core adverse features: **'CURB-65'** score: **C**onfusion (abbreviated mental test ≤8); **U**rea >7mmol/L; **R**espiratory rate ≥30/min; **B**P <90 systolic and/or 60mmHg diastolic); age ≥**65**. Score: 0-1 home treatment possible; 2 hospital therapy; ≥3 indicates severe pneumonia. Other features increasing the risk of death are: co-existing disease; bilateral/ multilobar involvement; P_aO_2 <8kPa/S_aO_2 <92%.

Management

▸▸p800. ***Antibiotics*** (p153), orally if not severe and not vomiting; severe give by IV. ***Oxygen*** keep P_aO_2 >8.0 and/or saturation ≥92%. ***IV fluids*** (anorexia, dehydration, shock). ***Analgesia*** if pleurisy—eg paracetamol 1g/6h. Consider ITU if shock, hypercapnia, or uncorrected hypoxia. If failure to improve, or CRP remains high, repeat CXR and look for progression/complications. All patients need 6week follow-up with repeat CXR.

Complications

(p156) Pleural effusion, empyema, lung abscess, respiratory failure, septicaemia, brain abscess, pericarditis, myocarditis, cholestatic jaundice. Repeat CRP and CXR in patients not progressing satisfactorily.

Pneumococcal vaccine

(eg 23-valent Pneumovax II®, 0.5mL SC) Offer to at-risk groups: • ≥65yrs old •Chronic heart, liver (eg cirrhosis), renal (eg renal failure, nephrosis*, post-transplant*) or lung conditions •Diabetes mellitus •Immunosuppression, eg spleen function↓ (eg splenectomy, asplenia*, sickle cell* or coeliac disease), AIDS, or on chemotherapy or prednisolone >20mg/d). CI: pregnancy, lactation, fever. If at ↑ risk of fatal pneumococcal infection (* above), re-vaccinate after 6yrs (3-5yrs in children >2yrs old), unless past severe vaccine reaction.

Empirical treatment of pneumonia [8] [9]

Clinical setting	Organisms	Antibiotic (further dosage details: p368 & p369)
Community acquired		

Mild not previously [prescription take]	*Streptococcus pneumoniae Haemophilus influenzae*	Amoxicillin 500mg-1.0g/8h or erythromycin[1] 500mg/6h PO
Mild	*Streptococcus pneumoniae Haemophilus influenzae Mycoplasma pneumoniae*	Amoxicillin 500mg-1.0g/8h PO + erythromycin[1] 500mg/6h PO or fluoroquinolone; if IV required: ampicillin 500mg/6h + erythromycin[1] 500mg/6h IVI
Severe	As above	Co-amoxiclav IV or cephalosporin IV (eg cefuroxime 1.5g/8h IV) AND erythromycin[1] 1g/6h IVI
Atypical	*Legionella pneumophilia*	Clarithromycin 500mg/12h PO/IVI ± rifampicin
	Chlamydia species	Tetracycline
	Pneumocystis jiroveci	High-dose co-trimoxazole (p398-9)
Hospital acquired		
	Gram negative bacilli Pseudomonas Anaerobes	Aminoglycoside IV + antipseudomonal penicillin IV or 3rd gen. cephalosporin IV (p369)
Aspiration		
	Streptococcus pneumoniae Anaerobes	Cefuroxime 1.5g/8h IV + metronidazole 500mg/8h IV
Neutropenic patients		
	Gram positive cocci Gram negative bacilli Fungi (p160)	Aminoglycoside IV + antipseudomonal penicillin IV or 3rd gen. cephalosporin IV Consider antifungals after 48h

3rd gen=3rd generation, eg cefotaxime, p369; gentamicin is an example of an aminoglycoside (p371).

[1] Clarithromycin 500mg/12h PO/IVI may be used in place of erythromycin throughout the above.

Specific pneumonias

For antibiotic doses, see p368 & p370. TB: ▸see p386.

Pneumococcal

pneumonia is the commonest bacterial pneumonia. It affects all ages, but is commoner in the elderly, alcoholics, post-splenectomy, immunosuppressed, and patients with chronic heart failure or pre-existing lung disease. Clinical features: fever, pleurisy, herpes labialis. CXR shows lobar consolidation. Treatment: amoxicillin, benzylpenicillin, or cephalosporin.

Staphylococcal

pneumonia may complicate influenza infection or occur in the young, elderly, intravenous drug users, or patients with underlying disease (eg leukaemia, lymphoma, cystic fibrosis, (CF). It causes a bilateral cavitating bronchopneumonia. Treatment: flucloxacillin. MRSA: contact lab; consider vancomycin.

Klebsiella

pneumonia is rare. Occurs in elderly, diabetics and alcoholics. Causes a cavitating pneumonia, particularly of the upper lobes. Treatment: cefuroxime.

Pseudomonas

is a common pathogen in bronchiectasis and CF. It also causes hospital acquired infections, particularly on ITU or after surgery. Treatment: antipseudomonal penicillin, ceftazidime, meropenem, or ciprofloxacin.

Mycoplasma pneumoniae

occurs in epidemics about every 4yrs. It presents insidiously with 'flu-like symptoms (headache, myalgia, arthralgia) followed by a dry cough. CXR shows bilateral patchy consolidation. Diagnosis: mycoplasma serology. Cold agglutinins may cause an autoimmune haemolytic anaemia. Complications: skin rash (erythema multiforme, **fig 3**, p546), Stevens-Johnson syndrome), meningoencephalitis or myelitis; Guillain-Barré syndrome. Treatment: erythromycin/clarithromycin or tetracycline.

Legionella pneumophilia

colonizes water tanks kept at <60°C (eg hotel air-conditioning and hot water systems) causing outbreaks of Legionnaire's disease. 'Flu-like symptoms (fever, malaise, myalgia) precede a dry cough and dyspnoea. Extra-pulmonary features include anorexia, D&V, hepatitis, renal failure, confusion, and coma. CXR shows bi-basal consolidation. Blood tests may show lymphopenia, hyponatraemia, and deranged LFTs. Urinalysis may show haematuria. Diagnosis: *Legionella* serology/urine antigen. Treatment: clarithromycin ± rifampicin or fluoroquinolone. 10% mortality.

Chlamydia pneumoniae

is the commonest chlamydial infection.[10] Person-to-person spread occurs causing a biphasic illness: pharyngitis, hoarseness, otitis, followed by pneumonia. Diagnosis: *Chlamydia* serology (non-specific).[11] Treatment: tetracycline.

Chlamydia psittaci

causes psittacosis, an ornithosis acquired from infected birds (typically parrots). Symptoms include headache, fever, dry cough, lethargy, arthralgia, anorexia, and D&V. Extra-pulmonary features are legion but rare, eg meningoencephalitis, infective endocarditis, hepatitis, nephritis, rash, splenomegaly. CXR shows patchy consolidation. Diagnosis: *Chlamydia* serology. Treatment: tetracycline.

Viral pneumonia

The commonest cause is influenza (p390 and BOX). Other viruses that can affect the lung are: measles, CMV, and varicella zoster.

Pneumocystis pneumonia

(PCP) causes pneumonia in the immunosuppressed (eg HIV). The organism responsible was previously called *pneumocystis carinii*, and now called *pneumocystis jiroveci*.[12] It presents with a dry cough, exertional dyspnoea, fever, bilateral crepitations. CXR may be normal or show bilateral perihilar interstitial shadowing. Diagnosis: visualization of the organism in induced sputum, bronchoalveolar lavage, or in a lung biopsy specimen. Drugs: high-dose co-trimoxazole (p398-9), or pentamidine by slow IVI for 2-3 weeks (p399). Steroids are beneficial if severe hypoxaemia. Prophylaxis is indicated if the CD4 count is $<200\times10^6$/L or after the 1st attack.[13]

Avian influenza

Avian-to-human transmission of the H5N1 strain of influenza A causes serious infection in humans with a ≥50% mortality. Human-to-human transmission is reported but is unusual. Oseltamivir (Tamiflu®) can reduce morbidity from influenza A by 1-2 days (see p390; note that oseltamivir-resistant H5N1 has been reported).[14] A vaccine is under development, but the most likely cause of a pandemic of 'flu is a new mutant developing between human and avian influenza virus (genetic reassortment, p390) which may require a different vaccine.

▸Suspect avian 'flu if undiagnosed fever and dyspnoea/pneumonia rapidly progresses to acute respiratory distress syndrome, especially if there is lymphopenia or thrombocytopenia.[15] There may also be a history of close contact with poultry. **NB**: D&V, abdominal pain, pleuritic pain, and bleeding from the nose and gums are reported to be an early feature in some patients.[16]

Diagnosis:

Viral culture ± reverse transcriptase-PCR with H5 & N1 specific primers.[17]

Management:

Get help. O_2; ventilatory support; antivirals. Contain the outbreak (p390). Nebulizers and high-air flow O_2 masks are implicated in nosocomial spread (so use only with meticulous precautions).[18]

SARS[19]

Severe acute respiratory syndrome (SARS) is caused by SARS-COV virus—a coronavirus. Major features are persistent fever >38°centigrade, chills, rigors, myalgia, dry cough, headache, diarrhoea, and dyspnoea—with an abnormal CXR and WCC↓. Respiratory failure is the big complication; >50% need supplemental O_2; ~20% progress to acute respiratory distress syndrome requiring invasive ventilation.[20]

Mortality is 1-50%, depending on age. Close contact with an index case, or travel to an area with known cases should raise suspicion. The mechanism of transmission of SARS-COV is only by close contact with other patients.

Management is supportive. No drugs have convincing efficacy (experts may advise on antivirals). Rapid diagnosis, early isolation, and good infection control measures are vital. Communicate with your consultant in infectious diseases.[21]

Complications of pneumonia

Respiratory failure

(See p172.) Type 1 respiratory failure (P_aO_2 <8kPa) is relatively common. Treatment is with high-flow (60%) oxygen. *Transfer the patient to* ITU *if hypoxia does not improve with O_2 therapy or P_aCO_2 rises to* >6kPa. Be careful with O_2 in COPD patients; check ABGS frequently, and consider elective ventilation if rising P_aCO_2 or worsening acidosis. Aim to keep SaO_2 at 90-94%.

Hypotension

may be due to a combination of dehydration and vasodilatation due to sepsis. If systolic BP is <90mmHg, give an intravenous fluid challenge of 250mL colloid/crystalloid over 15min. If BP does not rise, insert a central line and give intravenous fluids to maintain the systolic BP >90mmHg. If systolic BP remains <90mmHg despite fluid therapy, request ITU assessment for inotropic support (adrenaline, noradrenaline).

Atrial fibrillation

(p116) is quite common, particularly in the elderly. It usually resolves with treatment of the pneumonia. Digoxin may be required to slow the ventricular response rate in the short term.

Pleural effusion

Inflammation of the pleura by adjacent pneumonia may cause fluid exudation into the pleural space. If this accumulates in the pleural space faster than it is reabsorbed, a pleural effusion develops (**fig 1**, p714). If this is small it may be of no consequence. If it becomes large and symptomatic, or infected (empyema), drainage is required (p176 & p754).

Empyema

is pus in the pleural space. It should be suspected if a patient with a resolving pneumonia develops a recurrent fever. Clinical features and the CXR indicate a pleural effusion. The aspirated pleural fluid is typically yellow and turbid with a pH <7.2, glucose↓, and LDH↑. The empyema should be drained using a chest drain, preferably inserted under radiological guidance. Although intra-pleural streptokinase has been used to break down the adhesions (p176) the latest data indicate no benefit, and its routine use is not recommended.

Lung abscess

is a cavitating area of localized, suppurative infection within the lung.

Causes:

•Inadequately treated pneumonia •Aspiration (eg alcoholism, oesophageal obstruction, bulbar palsy) •Bronchial obstruction (tumour, foreign body) •Pulmonary infarction •Septic emboli (septicaemia, right heart endocarditis, IV drug use) •Subphrenic or hepatic abscess.

Clinical features:

Swinging fever; cough; purulent, foul-smelling sputum; pleuritic chest pain; haemoptysis; malaise; weight loss. Look for: finger clubbing; anaemia; crepitations. Empyema develops in 20-30%.

Tests:

Blood: FBC (anaemia, neutrophilia), ESR, CRP, blood cultures. *Sputum* microscopy, culture, and cytology. CXR: walled cavity, often with a fluid level. Consider CT scan to exclude obstruction, and bronchoscopy to obtain diagnostic specimens.

Treatment:

Antibiotics as indicated by sensitivities; continue until healed (4-6 wks). Postural drainage. Repeated aspiration, antibiotic instillation, or surgical excision may be required.

Septicaemia

may occur as a result of bacterial spread from the lung parenchyma into the bloodstream. This may cause metastatic infection, eg infective endocarditis, meningitis. Treatment with IV antibiotic according to sensitivities.

Pericarditis and myocarditis

may also complicate pneumonia.

Jaundice

This is usually cholestatic, and may be due to sepsis or secondary to antibiotic therapy (particularly flucloxacillin and co-amoxiclav).

Bronchiectasis

Pathology

Chronic infection of the bronchi and bronchioles leading to permanent dilatation of these airways. Main organisms: *H. influenzae*; *Strep. pneumoniae; Staph. aureus; Pseudomonas aeruginosa*.

Causes

Congenital: CF; Young's syndrome; primary ciliary dyskinesia; Kartagener's syndrome. ***Post-infection:*** measles; pertussis; bronchiolitis; pneumonia; TB; HIV. ***Other:*** Bronchial obstruction (tumour, foreign body); allergic bronchopulmonary aspergillosis (ABPA p160); hypogammaglobulinaemia; rheumatoid arthritis; ulcerative colitis; idiopathic.

Clinical features

Symptoms: persistent cough; copious purulent sputum; intermittent haemoptysis. ***Signs:*** finger clubbing; coarse inspiratory crepitations, wheeze (asthma, COPD, ABPA). ***Complications:*** pneumonia, pleural effusion; pneumothorax; haemoptysis; cerebral abscess; amyloidosis.

Tests

Sputum culture. CXR: cystic shadows, thickened bronchial walls (tramline and ring shadows). *HRCT chest:* (p150) to assess extent and distribution of disease. *Spirometry* often shows an obstructive pattern; reversibility should be assessed. *Bronchoscopy* to locate site of haemoptysis or exclude obstruction. *Other tests:* serum immunoglobulins; CF sweat test; *Aspergillus* precipitins or skin-prick test.

Management

•***Postural drainage*** should be performed twice daily. Chest physiotherapy may aid sputum expectoration and mucous drainage. •***Antibiotics*** should be prescribed according to bacterial sensitivities. Patients known to culture *Pseudomonas* will require either oral ciprofloxacin or IV antibiotics. •***Bronchodilators*** (eg nebulized salbutamol) may be useful in patients with asthma, COPD, CF, ABPA (p160). •***Corticosteroids*** (eg prednisolone) for ABPA. •***Surgery*** may be indicated in localized disease or to control severe haemoptysis.

Cystic fibrosis (CF) See *OHCS* (*Paediatrics*, p162)

One of the commonest life-threatening autosomal recessive conditions (1 : 2000 live births) affecting Caucasians. Caused by mutations in the CF transmembrane conductance regulator (CFTR) gene on chromosome 7 (>800 mutations have now been identified). This leads to a combination of defective chloride secretion and increased sodium absorption across airway epithelium. The changes in the composition of airway surface liquid predisposes the lung to chronic pulmonary infections and bronchiectasis.

Clinical features

Neonate:

Failure to thrive; meconium ileus; rectal prolapse.

Children and young adults:

Respiratory: cough; wheeze; recurrent infections; bronchiectasis; pneumothorax; haemoptysis; respiratory failure; cor pulmonale. *Gastrointestinal:* pancreatic insufficiency (diabetes mellitus, steatorrhoea); distal intestinal obstruction syndrome (meconium ileus equivalent); gallstones; cirrhosis. *Other:* male infertility; osteoporosis; arthritis; vasculitis (p542); nasal polyps; sinusitis; and hypertrophic pulmonary osteoarthropathy (HPOA). ***Signs:*** Cyanosis; finger clubbing; bilateral coarse crackles.

Diagnosis

Sweat test: sweat sodium and chloride >60mmol/L; chloride usually > sodium. *Genetics:* screening for known common CF mutations should be considered. *Faecal elastase* is a simple and useful screening test for exocrine pancreatic dysfunction.

Tests

Blood: FBC, U&E, LFTs; clotting; vitamin A, D, E levels; annual glucose tolerance test (p190). *Bacteriology:* cough swab, sputum culture. *Radiology:* CXR; hyperinflation; bronchiectasis. *Abdominal ultrasound:* fatty liver; cirrhosis; chronic pancreatitis; *Spirometry:* obstructive defect. *Aspergillus serology/skin test* (20% develop ABPA, p160). *Biochemistry:* faecal fat analysis.

Management of cystic fibrosis

Patients with cystic fibrosis are best managed by a multidisciplinary team, eg physician, physiotherapist, specialist nurse, and dietician with attention to psychosocial as well as physical well-being. Gene therapy (transfer of CFTR gene using liposome or adenovirus vectors) is not yet possible.

Chest:

Physiotherapy regularly (postural drainage, active cycle techniques or forced expiratory techniques). Antibiotics are given for acute infective exacerbations (PO for *Staph. aureus*, IV for *P. aeruginosa*) and prophylactically PO (flucloxacillin) or nebulized (colomycin or tobramycin). Mucolytics may be useful (eg DNase, ie Dornase alfa, 2.5mg daily nebulized, OHCS p163). Bronchodilators.

Gastrointestinal:

Pancreatic enzyme replacement; fat soluble vitamin supplements (A, D, E, K); ursodeoxycholic acid for impaired liver function; cirrhosis may require liver transplantation.

Other:

Treatment of CF-related diabetes; screening for and treatment of osteoporosis; treatment of arthritis, sinusitis, and vasculitis; fertility and genetic counselling.

Advanced lung disease:

Oxygen, diuretics (cor pulmonale); non-invasive ventilation; lung or heart/lung transplantation.

Prognosis:

Median survival is now over 30yrs.

Fungi and the lung

Aspergillus

This group of fungi affects the lung in 5 ways:

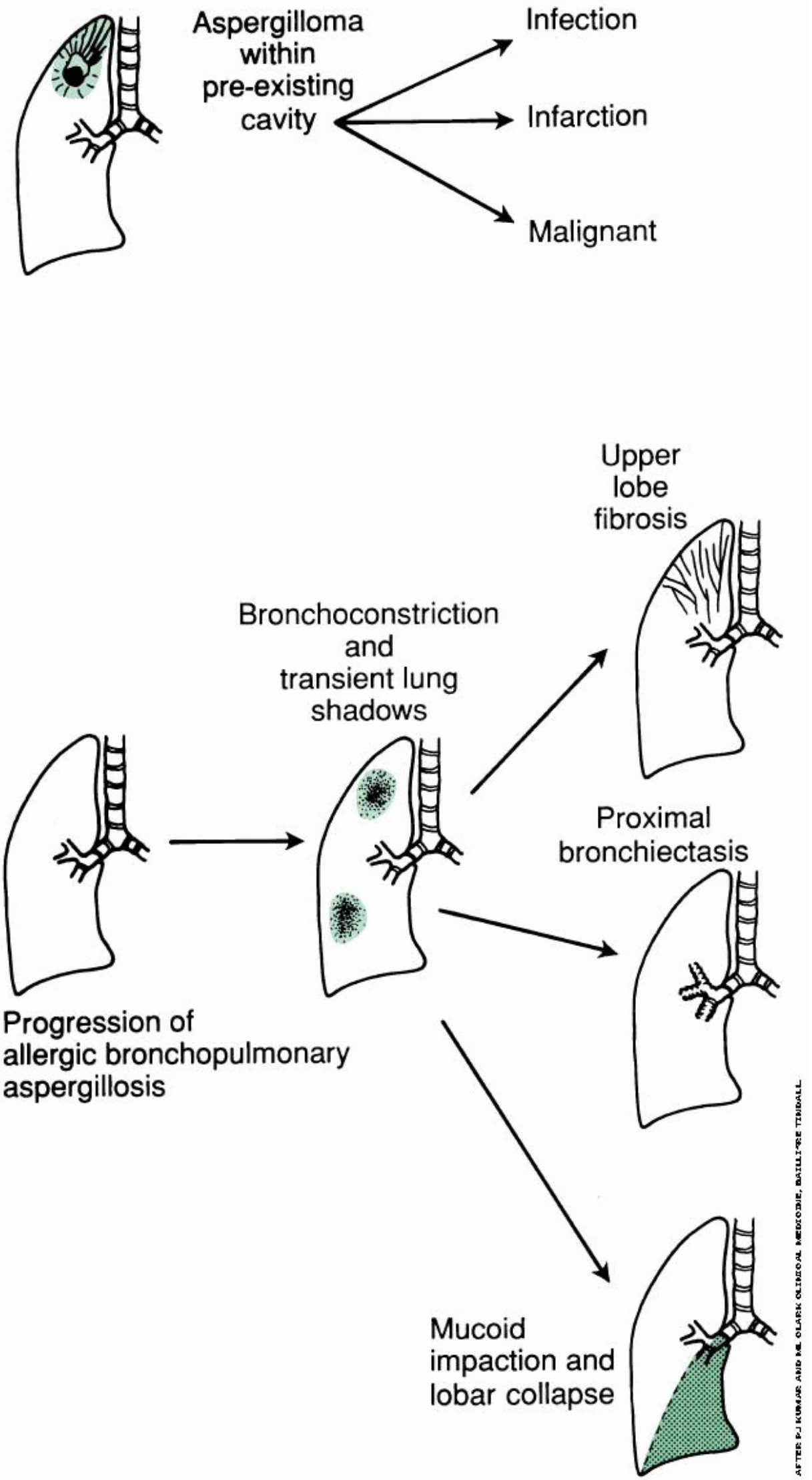
1. ***Asthma:*** Type I hypersensitivity (atopic) reaction to fungal spores, p164.
2. ***Allergic bronchopulmonary aspergillosis (*ABPA*):*** This results from a Type I and III hypersensitivity reaction to *Aspergillus fumigatus*. Early on, the allergic response causes bronchoconstriction, but as the inflammation persists, permanent damage occurs, causing bronchiectasis. *Symptoms:* wheeze, cough, sputum (plugs of mucus containing fungal hyphae), dyspnoea, and 'recurrent pneumonia'. *Investigations:* CXR (transient segmental collapse or consolidation, bronchiectasis); *Aspergillus* in sputum; positive aspergillus skin test and/or aspergillus-specific IgE RAST (radioallergosorbent test); positive serum precipitins; eosinophilia; raised serum IgE. *Treatment:* Prednisolone 30-40mg/24h PO for acute attacks; maintenance dose 5-10mg/d. Sometimes itraconazole is used in combination with corticosteroids. Bronchodilators for asthma. Sometimes bronchoscopic aspiration of mucous plugs is needed.
3. ***Aspergilloma (mycetoma):*** A fungus ball within a pre-existing cavity (often caused by TB, sarcoidosis). It is usually asymptomatic but may cause cough, haemoptysis (may be torrential), lethargy ± weight loss. *Investigations:* CXR (round opacity within a cavity, usually apical); sputum culture; strongly positive serum precipitins; *Aspergillus* skin test (30% +ve). *Treatment* (only if symptomatic). Consider surgical excision for solitary symptomatic lesions or severe haemoptysis. Oral itraconazole and other antifungals have been tried with limited success. Local instillation of amphotericin paste under CT-guidance yields partial success in carefully selected patients, eg in massive haemoptysis.
4. ***Invasive aspergillosis: Risk factors:*** [22] immunocompromise, eg HIV, leukaemia, burns, Wegener's (p707), and SLE, or after broad-spectrum antibiotic therapy. *Investigations:* sputum culture; serum precipitins; CXR (consolidation, abscess). Early chest CT and serial serum measurements of galactomannan (an *Aspergillus* antigen) can be very helpful. Diagnosis may only be made at lung biopsy or autopsy. *Treatment:* IV amphotericin B (see below). Alternatives: IV miconazole or ketoconazole (less effective). *Prognosis:* very poor. [23]
5. ***Extrinsic allergic alveolitis (EAA)*** is caused by sensitivity to *Aspergillus clavatus* ('malt worker's lung'). Clinical features and treatment are as for other causes of EAA (p180). Diagnosis is based on a history of exposure and presence of serum precipitins to *A. clavatus*. Pulmonary fibrosis may occur if untreated.

Using amphotericin B

Test dose: 1mg in 20mL 5% dextrose IV over 20-30min. Observe closely for the next ½h for signs of anaphylaxis (shock, swelling, wheeze etc). There are various formulations. Consult BNF. *Do not give any other drug in the same* IVI. SE: anaphylaxis; serious nephrotoxicity; fever; rash; anorexia; nausea; D&V; headache; myalgia; arthralgia; anaemia; $\downarrow K^+$; $\downarrow Mg^{2+}$; hepatotoxicity; arrhythmias; hearing loss; diplopia; seizures; neuropathy; phlebitis. *Monitor* U&E *daily*. ***AmBisome***® (liposomal amphotericin) has fewer SEs, but is expensive; it is indicated in systemic or deep mycoses where nephrotoxicity precludes conventional amphotericin; IV initial test dose: 1mg over 10min, then 1mg/kg/d, as a single IVI dose; gradually↑ if needed to 3mg/kg/d (max 5mg/kg/d).[24] Alternatives: ***Abelcet***® and ***Amphocil***®.

Other fungal infections

Candida and ***Cryptococcus*** may cause pneumonia in the immunosuppressed (see p428).


Aspergilloma within pre-existing cavity
Infection
Infarction
Malignant
Upper lobe fibrosis
Bronchoconstriction and transient lung shadows
Proximal bronchiectasis
Progression of allergic bronchopulmonary aspergillosis
Mucoid impaction and lobar collapse
AFTER P.J. KUMAR AND M.L. CLARK: CLINICAL MEDICINE, BAILLIÈRE TINDALL

Lung tumours[25]

Carcinoma of the bronchus

Accounts for ≈ 19% of all cancers and 27% of cancer deaths (40,000 cases/yr in UK). Incidence is increasing in women.

Risk factors:

Cigarette smoking is the major risk factor.[26] Others: asbestos, chromium, arsenic, iron oxides, and radiation (radon gas).

Histology:

Squamous (30%); adenocarcinoma (30%); small (oat) cell (25%); large cell (15%); alveolar cell carcinoma (rare, <1%). Clinically the most important division is between small cell and non-small cell (NSCLC).

Symptoms:

Cough (80%); haemoptysis (70%); dyspnoea (60%); chest pain (40%); recurrent or slowly resolving pneumonia; anorexia; weight loss.

Signs:

Cachexia; anaemia; clubbing; HPOA (hypertrophic pulmonary osteoarthropathy, causing wrist pain); supraclavicular or axillary nodes. *Chest signs:* none, or: consolidation; collapse; pleural effusion. *Metastases:* bone tenderness; hepatomegaly; confusion; fits; focal CNS signs; cerebellar syndrome; proximal myopathy; peripheral neuropathy.

Complications:

Local: recurrent laryngeal nerve palsy; phrenic nerve palsy; SVC obstruction; Horner's syndrome (Pancoast's tumour); rib erosion; pericarditis; AF. *Metastatic:* brain; bone (bone pain, anaemia, $\uparrow Ca^{2+}$); liver; adrenals (Addison's). *Endocrine:* ectopic hormone secretion, eg SIADH ($\downarrow Na^{+}$ and ↑ADH, p666) and ACTH (Cushing's) by small cell tumours; PTH ($\uparrow Ca^{2+}$) by squamous cell tumours. *Non-metastatic neurological:* confusion; fits; cerebellar syndrome; proximal myopathy; neuropathy; polymyositis; Eaton-Lambert syndrome (p504). *Other:* clubbing, HPOA, dermatomyositis; acanthosis nigricans (p546); thrombophlebitis migrans (p268).

Tests:

Cytology: sputum & pleural fluid (send at least 20mL). CXR: peripheral circular opacity; hilar enlargement; consolidation; lung collapse; pleural effusion; bony secondaries. Peripheral lesions and superficial lymph nodes may be amenable to *percutaneous fine needle aspiration* or *biopsy*. *Bronchoscopy:* to give histology and assess operability. CT to stage the tumour (BOX). *^{18}Fdeoxyglucose PET scan* to help in staging (PET= positron emission tomography). *Radionuclide bone scan:* if suspected metastases. *Lung function tests*.

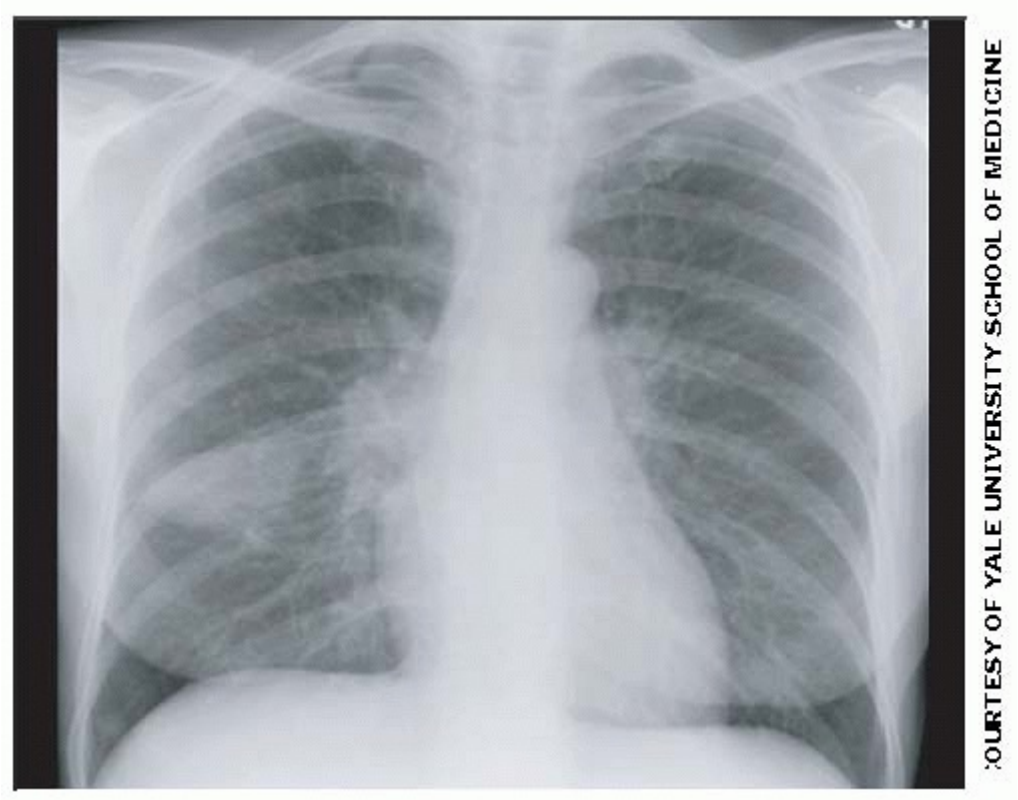


Fig 1. Name 3 abnormalities.[1]

[1] A wedge-shaped density in the right middle lobe (a secondary). Also note a coin lesion at the right costophrenic angle. The sharp upper boundary of the right middle lobe triangular mass is the right middle lobe fissure. The right hilar structures are enlarged from metastases within the hilar lymph nodes.

Treatment:

Non-small cell tumours: *Excision* is the treatment of choice for peripheral tumours, with no metastatic spread: stage I/II (~25%). *Curative radiotherapy* is an alternative if respiratory reserve is poor. *Chemotherapy ± radiotherapy* for more advanced disease. ***Small cell tumours*** are nearly always disseminated at presentation. They may respond to *chemotherapy* (cyclophosphamide+doxorubicin+vincristine+ etoposide; **or** cisplatin±*radiotherapy* if limited disease). ***Palliation:*** *Radiotherapy* is used for bronchial obstruction, SVC obstruction, haemoptysis, bone pain, and cerebral metastases. SVC *stent* + radiotherapy and dexamethasone for SVC obstruction. *Endobronchial therapy:* tracheal stenting, cryotherapy, laser, brachytherapy (a radioactive source is placed close to the tumour). *Pleural drainage/pleurodesis* for symptomatic pleural effusions. *Drugs:* analgesia; steroids; antiemetics; cough linctus (codeine); bronchodilators; anti-depressants.

Prognosis:

Non-small cell: 50% 2yr survival without spread; 10% with spread. *Small cell:* median survival is 3 months if untreated; 1-1½yrs if treated.

Prevention:

Quit smoking, p79. Prevent occupational exposure to carcinogens.

Other lung tumours

Bronchial adenoma: Rare, slow-growing. 90% are carcinoid tumours; 10% cylindromas. Â: surgery. ***Hamartoma:*** Rare, benign; CT: lobulated mass ±flecks of calcification; ?excise to exclude malignancy. ***Mesothelioma*** (p184).

Coin lesions of the lung on a CXR

- Malignancy (1° or 2°)
- Abscesses (p156)
- Granuloma
- Carcinoid tumour
- Pulmonary hamartoma
- Arterio-venous malformation
- Encysted effusion (fluid, blood, pus)
- Cyst
- Foreign body
- Skin tumour (eg seborrhoeic wart)

TNM staging for non-small cell lung cancer

Primary tumour (T)	TX	Malignant cells in bronchial secretions, no other evidence of tumour

	Tis	Carcinoma *in situ*	
	T0	None evident	
	T1	≤3cm, in lobar or more distal airway	
	T2	>3cm and >2cm distal to carina *or* any size if pleural involvement *or* obstructive pneumonitis extending to hilum, but not all the lung	
	T3	Involves the chest wall, diaphragm, mediastinal pleura, pericardium, or <2cm from, but not at, carina	
	T4	Involves the mediastinum, heart, great vessels, trachea, oesophagus, vertebral body, carina, *or* a malignant effusion is present	
Regional nodes (N)	N0	None involved (after mediastinoscopy)	
	N1	Peribronchial and/or ipsilateral hilum	
	N2	Ipsilateral mediastinum or subcarinal	
	N3	Contralateral mediastinum or hilum, scalene, or supraclavicular	
Distant metastasis (M)	M0	None	
	M1	Distant metastases present	
Stage	**Tumour**	**Lymph nodes**	**Metastasis**

Occult	TX	N0	M0
I	Tis, T1, or T2	N0	M0
II	T1 or T2	N1	M0
	T3	N0	M0
IIIa	T3	N1	M0
	T1-T3	N2	M0
IIIb	T1-T4	N3	M0
	T4	N0-N2	M0
IV	T1-T4	N0-N3	M1

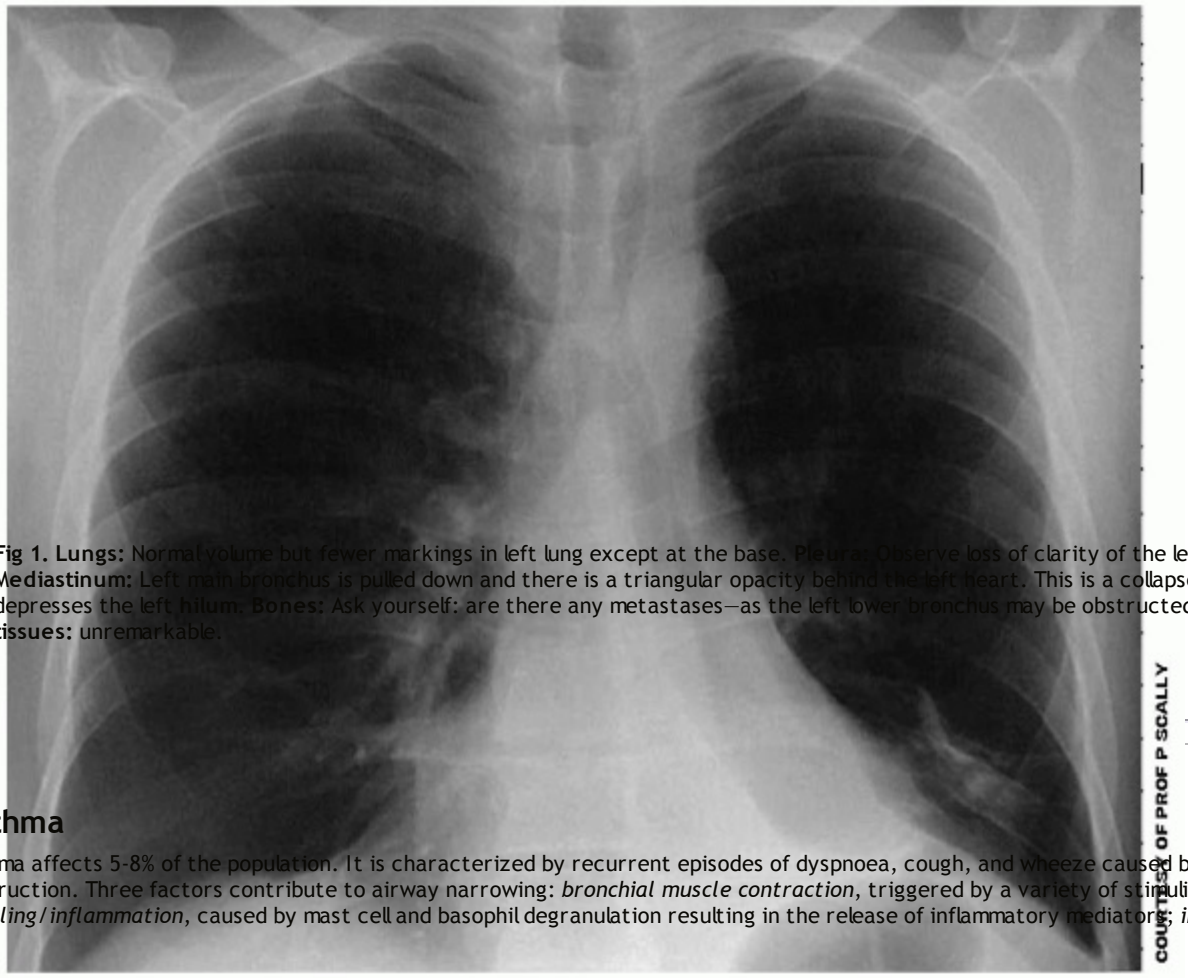


Fig 1. Lungs: Normal volume but fewer markings in left lung except at the base. **Pleura:** Observe loss of clarity of the left hemidiaphragm. **Mediastinum:** Left main bronchus is pulled down and there is a triangular opacity behind the left heart. This is a collapsed left lower lobe. It depresses the left hilum. **Bones:** Ask yourself: are there any metastases—as the left lower bronchus may be obstructed by a neoplasm. **Soft tissues:** unremarkable.

Asthma

Asthma affects 5-8% of the population. It is characterized by recurrent episodes of dyspnoea, cough, and wheeze caused by reversible airways obstruction. Three factors contribute to airway narrowing: *bronchial muscle contraction*, triggered by a variety of stimuli; *mucosal swelling/inflammation*, caused by mast cell and basophil degranulation resulting in the release of inflammatory mediators; *increased mucus production*.

Symptoms

Intermittent dyspnoea, wheeze, cough (often nocturnal) and sputum. Ask specifically about:

- ***Precipitants:*** Cold air, exercise, emotion, allergens (house dust mite, pollen, animal fur), infection, drugs (eg aspirin, NSAIDs, ß-blockers).
- ***Diurnal variation*** in symptoms or peak flow. Marked morning dipping of peak flow is common and can tip the balance into a serious attack, despite having normal peak flow at other times.
- ***Exercise:*** Quantify the exercise tolerance.
- ***Disturbed sleep:*** Quantify as nights per week (a sign of severe asthma).
- ***Acid reflux:*** This has a known association with asthma.
- ***Other atopic disease:*** Eczema, hay fever, allergy, or family history?
- ***The home (especially the bedroom):*** Pets? Carpet? Feather pillows or duvet? Floor cushions and other 'soft furnishings'?
- ***Occupation:*** If symptoms remit at weekends or holidays, something at work may be a trigger. Ask the patient to measure his peak flow at intervals at work and at home (at the same time of day) to confirm this.
- ***Days per week off work or school.***

Signs

Tachypnoea; audible wheeze; hyperinflated chest; hyperresonant percussion note; diminished air entry; widespread, polyphonic wheeze. ***Severe attack:*** inability to complete sentences; pulse >110bpm; respiratory rate >25/min; PEF 33-50% of predicted. ***Life-threatening attack:*** silent chest; cyanosis; bradycardia; exhaustion; PEF <33% of predicted; confusion; feeble respiratory effort.

Tests

Acute attack: PEF, sputum culture, FBC, U&E, CRP, blood cultures. ABG analysis usually shows a normal or slightly reduced P_aO_2 and low P_aCO_2 (hyperventilation). If P_aO_2 normal but the patient is hyperventilating, watch carefully and repeat the ABG a little later. ▸*If* P_aCO_2 *is raised, transfer to high dependency unit or* ITU *for ventilation*, as this signifies failing respiratory effort. CXR (to exclude infection or pneumothorax). ***Chronic asthma:*** PEF monitoring (p148): a diurnal variation of >20% on ≥3d a wk for 2wks. Spirometry: obstructive defect (↓FEV_1/FVC, ↑RV p148); usually ≥15% improvement in FEV_1 following ß2 agonists or steroid trial. CXR: hyperinflation. Skin-prick tests may help to identify allergens. Histamine or methacholine challenge. *Aspergillus* serology.

Treatment

Chronic asthma (p166). Emergency treatment (p794).

Differential diagnosis

Pulmonary oedema ('cardiac asthma'); COPD (often coexists); large airway obstruction (eg foreign body, tumour); SVC obstruction (wheeze/dyspnoea not episodic); pneumothorax; PE; bronchiectasis; obliterative bronchiolitis (suspect in elderly).

Associated diseases

Acid reflux; polyarteritis nodosa (PAN, p543); Churg-Strauss syndrome (p688); ABPA (p160).

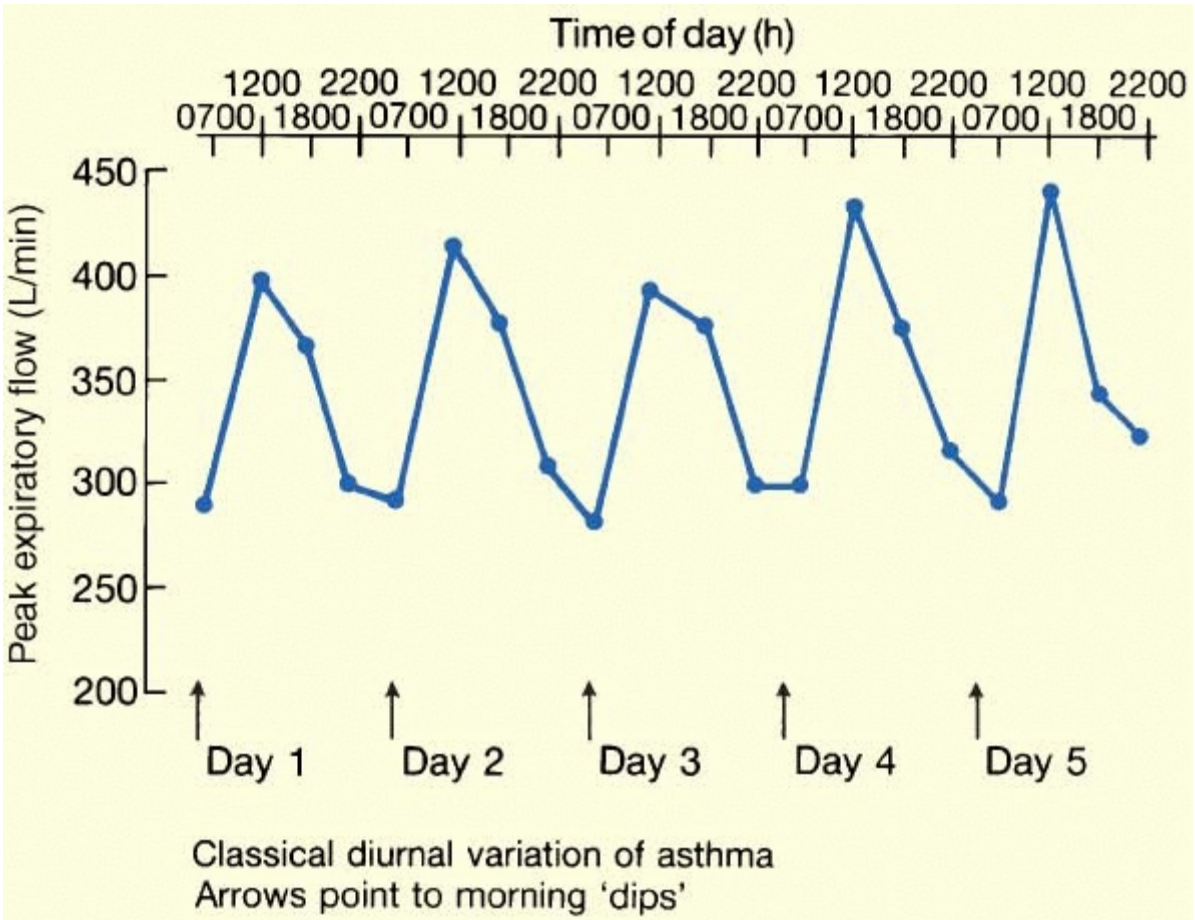
Natural history

Most childhood asthmatics (see OHCS p164) either grow out of asthma in adolescence, or suffer much less as adults. A significant number of people develop chronic asthma late in life.

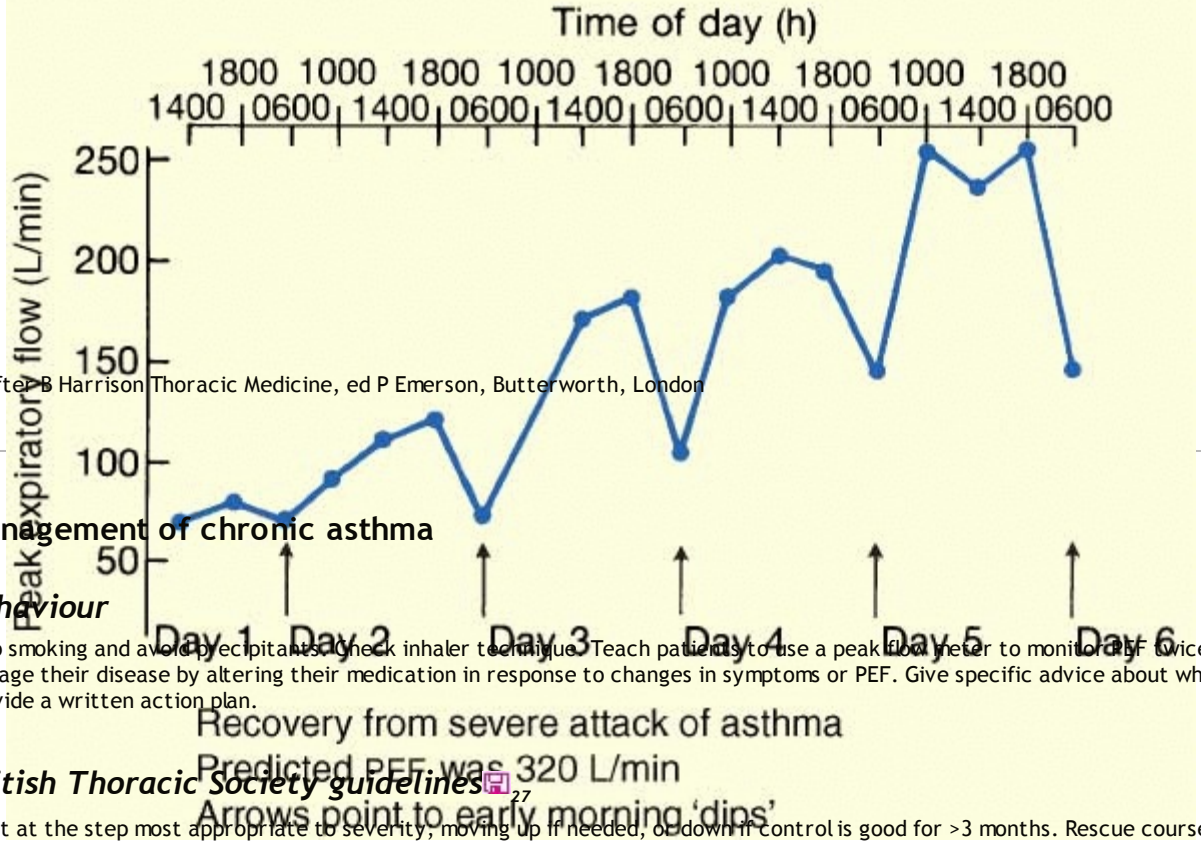
Mortality

Death certificates give a figure of 2000/yr (UK): more careful surveys more than halve this figure. 50% are >65yrs old.

Examples of serial peak flow charts



Classical diurnal variation of asthma
Arrows point to morning 'dips'



Recovery from severe attack of asthma
Predicted PEF was 320 L/min
Arrows point to early morning 'dips'

After B Harrison Thoracic Medicine, ed P Emerson, Butterworth, London

Management of chronic asthma

Behaviour

Stop smoking and avoid precipitants. Check inhaler technique. Teach patients to use a peak flow meter to monitor PEF twice a day. Educate patients to manage their disease by altering their medication in response to changes in symptoms or PEF. Give specific advice about what to do in an emergency; provide a written action plan.

British Thoracic Society guidelines[27]

Start at the step most appropriate to severity, moving up if needed, or down if control is good for >3 months. Rescue courses of prednisolone may be used at any time.

Step 1

Occasional short-acting inhaled **β2-agonist** as required for symptom relief. If used more than once daily, or night-time symptoms, go to Step 2.

Step 2

Add standard-dose inhaled steroid: eg **beclometasone** 200µg/12h or **fluticasone** 50-250µg/12h. Titrate to lowest dose needed for effective control.

Step 3

Add long-acting β_2-agonist (eg **salmeterol** 50µg/12h or formoterol 12µg/12h). If benefit—but still inadequate control—continue and ↑dose of **beclometasone** to 400µg/12h. If no effect of long acting β_2-agonist stop it.

Step 4

Consider trials of: **beclometasone** up to 1000µg/12h; modified-release oral **theophylline**; modified-release oral **β_2-agonist**; or oral leukotriene receptor antagonist (see below), in conjunction with previous therapy.

Step 5

Add regular oral prednisolone (1 dose daily, at the lowest possible dose). Refer to asthma clinic.

Drugs

β_2-adrenoceptor agonists relax bronchial smooth muscle (↑cAMP), acting within minutes. Salbutamol is best given by inhalation (aerosol, powder, nebulizer), but may also be given PO or IV. SE: tachyarrhythmias, $\downarrow K^+$, tremor, anxiety. Long-acting inhaled β_2-agonist (eg salmeterol, formoterol) can help nocturnal symptoms and reduce morning dips. They may be an alternative to ↑steroid dose when symptoms are uncontrolled. SE: as salbutamol, paradoxical bronchospasm (salmeterol). 🖫$_{28}$ Also: tolerance and arrhythmias may be a problem.

Corticosteroids

are best inhaled to minimize systemic effects, eg beclometasone via spacer (or powder), but may be given PO or IV. They act over days to ↓bronchial mucosal inflammation. Rinse mouth after inhaled steroids to prevent oral candidiasis. Oral steroids are used acutely (high-dose, short courses, eg prednisolone 40mg/24h PO for 7d) and longer term in lower dose (eg 5-10mg/24h) if control is not optimal on inhalers. Warn about SEs: p361.

Aminophylline

(metabolized to theophylline) may act by inhibiting phosphodiesterase, thus ↓bronchoconstriction by ↑cAMP levels. Try as prophylaxis, at night, PO, to prevent morning dipping. Stick with one brand name (bioavailability variable). It is also useful as an adjunct if inhaled therapy is inadequate. In acute severe asthma, it may be given IVI. It has a narrow therapeutic ratio, causing arrhythmias, GI upset, and fits in the toxic range. Check theophylline levels (p739), and do ECG monitoring and check plasma levels after 24h if IV therapy is used.

Anticholinergics

(eg ipratropium, tiotropium) may ↓muscle spasm synergistically with β_2-agonists but are not recommended in current guidelines for asthma. They may be of more benefit in COPD.

Cromoglicate

May be used as prophylaxis in mild and exercise-induced asthma (always inhaled), especially in children. It may precipitate asthma.

Leukotriene receptor antagonists

(eg montelukast, zafirlukast) block the effects of cysteinyl leukotrienes in the airways.

Anti-IgE monoclonal antibody

Omalizumab be of use in highly selected patients with persistent allergic asthma.

Doses of some inhaled drugs used in bronchoconstriction

	Inhaled aerosol	Inhaled powder	Nebulized *(supervised)*
Salbutamol			
Dose example: Airomir® is a CFC-free example of a breath-actuated inhaler	100-200µg/6h	200-400µg/6h	2.5-5mg/6h

Terbutaline			
Single dose		500µg[1]	2.5mg/mL
Recommended regimen		500µg/6h	5-10mg/6-12h
Salmeterol			
Dose/puff	25µg	50µg	—
Recommended regimen	50-100µg/12h	50-100µg/12h	—
Ipratropium bromide (COPD)			
Dose/puff	20µg	40µg	250µg/mL
Recommended regimen	20-40µg/6h	40-80µg/6h	250-500µg/6h
Steroids			
(Becotide®=beclometasone; Pulmicort®=budesonide;[1] Flixotide®=fluticasone)			
Fluticasone (Flixotide®)			
	50, 100µg & 250µg &	As for	

Doses available/puff	500µg	aerosol	250µg/mL
Recommended regimen	100-250µg/12h	100-250µg/12h max 1mg/12h	½-2mg/12h
Becotide 50 & 100®			
Doses available/puff	50 & 100µg	—	—
	Becloforte®=250µg		
Recommended regimen	100µg/12h ↓ 200µg/12h ↓ 250µg/12h ↓ 500-1000µg/12h		

▸Prescribe beclometasone by brand name, and state that a CFC-free inhaler should be dispensed. This is because, dose for dose, Qvar® is twice as potent as the other available CFC-free brand (Clenil Modulite®) and older CFC-containing inhalers such as Becotide®.

Any dose [2]250µg ≈ significant steroid absorption: carry a steroid card; this recommendation is being widened, and lower doses (beclomethasone) are now said to merit a steroid card (manufacturer's information).

[1] Available as a Turbohaler®; Autohalers® are an alternative (breath-actuated) and don't need breathing coordination eg Airomir (salbutamol) & Aerobec® & Qvar® (both beclometasone). Accuhalers deliver dry powders (eg Flixotide®, Serevent®).
Systemic absorption (via the throat) is less if inhalation is through a **large-volume device**, eg Volumatic® or AeroChamber Plus® (for Airomir & Qvar) devices. The latter is more compact. Static charge on some devices reduces dose delivery, so wash in water before dose; leave to dry (don't rub). It is pointless to squirt many puffs into a device: it is best to repeat single doses, and be sure to inhale *as soon as the drug is in the spacer*. SE: local (oral) candidiasis (p230); ↑ rate of cataract if lifetime dose ≥2g beclometasone.

Chronic obstructive pulmonary disease (COPD) [29]

Definitions

COPD is a common progressive disorder of airway obstruction (FEV_1 <80% predicted; FEV_1/FVC <0.7) with little or no reversibility. COPD includes chronic bronchitis and emphysema. Usually patients have *either* COPD *or* asthma, not both: COPD is favoured by: •Age of onset >35yrs •Smoking related •Chronic dyspnoea •Sputum production •No marked diurnal or day-to-day FEV_1 variation. ***Chronic bronchitis*** is defined *clinically* as cough, sputum production on most days for 3 months of 2 successive years. There is no excess mortality if lung function is normal. Symptoms improve in 90% if they stop smoking. ***Emphysema*** is defined *histologically* as enlarged air spaces distal to the terminal bronchioles, with destruction of the alveolar walls.

Prevalence

~1 million. **COPD *mortality:*** 23,000 deaths/yr in England & Wales.[30]

Pink puffers and blue bloaters

(Ends of a spectrum) ***Pink puffers*** have ↑alveolar ventilation, a near normal P_aO_2 and a normal or low P_aCO_2. They are breathless but are not cyanosed. They may progress to type 1 respiratory failure (p172). *Blue bloaters* have ↓alveolar ventilation, with a low P_aO_2 and a high P_aCO_2. They are cyanosed but not breathless and may go on to develop cor pulmonale. Their respiratory centres are relatively insensitive to CO_2 and they rely on hypoxic drive to maintain respiratory effort (p172)—▸*supplemental oxygen should be given with care*.

Clinical features

Symptoms: Cough, sputum, dyspnoea, and wheeze. ***Signs:*** Tachypnoea; use of accessory muscles of respiration; hyperinflation; ↓cricosternal distance (<3cm); ↓expansion; resonant or hyperresonant percussion note; quiet breath sounds (eg over bullae); wheeze; cyanosis; cor pulmonale. ***Complications:*** Acute exacerbations ± infection; polycythaemia; respiratory failure; cor pulmonale (oedema; JVP↑); pneumothorax (ruptured bullae); lung carcinoma.

Tests

FBC*:* PCV↑. CXR*:* Hyperinflation (>6 anterior ribs seen above diaphragm in mid-clavicular line); flat hemidiaphragms; large central pulmonary arteries; ↓peripheral vascular markings; bullae. **ECG*:*** Right atrial and ventricular hypertrophy (cor pulmonale). **ABG*:*** P_aO_2 ↓ ± hypercapnia. ***Lung function*** (p148-151): obstructive + air trapping (FEV_1 <80% of predicted—see p148, FEV_1:FVC ratio <70%, TLC↑, RV↑, DLCO↓ in emphysema). Learn how to do spirometry from an experienced person: ensure *maximal* expiration of the full breath (it takes ²4sec; it's *not* a quick puff out). ***Trial of steroids:*** See BOX.

Treatment

Chronic stable: see BOX; ▸▸***Emergency Â:*** p796. Offer ***smoking cessation advice*** with cordial vigour (p79). BMI is often low: ***diet advice*** ± ***supplements*** [31] *may* help, p572. ***Mucolytics*** (BNF 3.7) may help chronic productive cough (NICE).[32] Disabilities may cause serious, treatable ***depression;*** screen for this (p13). ***Respiratory failure:*** p172. ***'Flu and pneumococcal vaccinations:*** p390.

Long-term O_2 therapy (LTOT):

An MRC trial showed that if P_aO_2 was maintained ≥8.0kPa for 15h a day, 3yr survival improved by 50%. UK DoH guidelines suggest LTOT should be given for: **1** clinically stable non-smokers with P_aO_2 <7.3kPa— despite maximal Â. These values should be stable on two occasions >3 wks apart. **2** If P_aO_2 7.3-8.0 ***and*** pulmonary hypertension (eg RVH; loud S_2) + cor pulmonale. **3** O_2 can also be prescribed for terminally ill patients.

Predicted FEV_1 (Caucasian males; litres, ↓level in other races)[1] ♀

Height cm	**150**	**155**	**160**	**165**	**170**	**175**	**180**	**185**	**190**	**195**	**145**
♂ ***Age(yr)*** **10**	**2.5**	**2.8**	**3.0**	**3.2**	**3.5**	**3.7**	**3.9**	**4.1**	**4.4**	**4.6**	**2.1**
25	**2.9**	**3.2**	**3.4**	**3.7**	**4.0**	**4.2**	**4.3**	**4.7**	**5.0**	**5.3**	**2.6**

30	2.8	3.1	3.3	3.6	3.8	4.1	4.3	4.6	4.9	5.1	2.5
40	2.5	2.8	3.0	3.3	3.6	3.8	4.1	4.3	4.6	4.9	2.3
50	2.2	2.5	2.8	3.0	3.3	3.5	3.8	4.0	4.3	4.6	2.1
60	2.0	2.2	2.5	2.8	3.0	3.3	3.5	3.8	4.0	4.3	1.7
70	1.7	2.0	2.2	2.5	2.7	3.0	3.3	3.5	3.8	4.0	1.6
80	1.4	1.7	2.0	2.2	2.5	2.7	3.0	3.3	3.5	3.8	1.4

[1] African FEV_1 is 10-15% lower; Chinese: 20% lower; Indian: 10% lower; NB: PEF varies little between groups.

British Thoracic Society (BTS)/NICE COPD guidelines[33]

Assessment of COPD	Spirometry Bronchodilator response Trial of oral steroids;[1] look for >15% ↑ in FEV_1 CXR: ?bullae ?other pathology ABG: ?hypoxia ?hypercapnia	
Severity of COPD	Mild	FEV_1 50-80% predicted
	Moderate	FEV_1 30-49% predicted
	Severe	FEV_1 <30% predicted

Treating stable COPD	**NB:** air travel is risky if FEV_1 <50% or P_aO_2 <6.7kPa
Non-pharmacological	Stop smoking, encourage exercise, treat poor nutrition or obesity, influenza and pneumococcal vaccination, pulmonary rehabilitation/palliative care.[2] NIPPV p797

Pharmacological: For inhaler regimens, see p167

Mild	Antimuscarinic eg ipratropium or $ß_2$ agonist inhaled PRN.
Moderate	Regular ipratropium[3] or long-acting inhaled $ß_2$ agonist (salmeterol) ± inhaled steroid (fluticasone) if FEV_1<50% and ≥2 exacerbations/yr. Seretide® combines these. Symbicort® is budesonide + formoterol; there is conflicting evidence on whether this ↑quality of life and symptom scores; but it *may* ↑time to 1st exacerbation.[34] Oral theophylline.
Severe	Combination therapy with regular short-acting $ß_2$-agonist and anticholinergic. Refer to specialist. Consider steroid trial;[1] assess for home nebulizers.
Pulmonary hypertension	Assess the need for LTOT (see opposite) Treat oedema with diuretics.

[1] Steroid trial: 30mg prednisolone/24h PO for 2wks. If FEV_1 rises by >15%, the COPD is 'steroid responsive' and benefit may be had by using longterm inhaled corticosteroids (p167). If this doesn't achieve the post-prednisolone FEV_1, do not simply give longterm oral prednisolone (side-effects may be lethal, p361); instead, request expert help. (BTS advice). **NB:** NICE says that 'reversibility testing is not necessary as a part of the diagnostic process or to plan initial therapy with bronchodilators or corticosteroids. It may be unhelpful or misleading because: (1) repeated FEV_1 measurements can show small spontaneous fluctuations; (2) results of a reversibility tests on different occasions can be inconsistent and not reproducible; (3) Over-reliance on a single reversibility test may be misleading unless the change in FEV_1 is >400 mL. (4) Definition of a significant change is arbitrary; (5) Response to long-term therapy is not predicted by acute reversibility testing.'

[2] Palliative care involves referral to a multidisciplinary team ± use of benzodiazepines, antidepressants, opiates, major tranquillizers, and O_2 with a view to diminish symptoms in end-stage COPD.

[3] Tiotroprium is like ipratropium, but longer acting: better in some trials.

More advanced COPD

- Consider pulmonary rehabilitation[2] ± theophylline (monitor blood levels).
- Consider LTOT if P_aO_2 <7.3kPa (see OPPOSITE).
- Indications for surgery: recurrent pneumothoraces; isolated bullous disease; lung volume reduction surgery (selected patients).
- Assess home set-up and support needed. Treat depression (p13).

Indications for specialist referral

- Uncertain diagnosis.
- Suspected severe COPD or a rapid decline in FEV_1.
- Onset of cor pulmonale.
- Assessment for oral corticosteroids, nebulizer therapy, or LTOT.
- Bullous lung disease (to assess for surgery).
- <10 pack-years smoking (=PYS=the number of packs/day × number of years of smoking). Smokers have an excess loss of FEV_1 of 7.4-12.6mL/PYS for men and 4.4-7.2mL per pack year for women.[35]
- Symptoms disproportionate to lung function tests.
- Frequent infections (to exclude bronchiectasis).
- COPD in patient <40yrs (eg is the cause α_1-antitrypsin deficiency? p256).

Acute respiratory distress syndrome (ARDS)

ARDS, or acute lung injury, may be caused by direct lung injury or occur secondary to severe systemic illness. Lung damage and release of inflammatory mediators cause increased capillary permeability and non-cardiogenic pulmonary oedema, often accompanied by multiorgan failure.

Causes

Pulmonary: Pneumonia; gastric aspiration; inhalation; injury; vasculitis (p542); contusion. ***Other:*** Shock; septicaemia; haemorrhage; multiple transfusions; DIC (p336); pancreatitis; acute liver failure; trauma; head injury; malaria; fat embolism; burns; obstetric events (eclampsia; amniotic fluid embolus); drugs/toxins (aspirin, heroin, paraquat).

Clinical features

Cyanosis; tachypnoea; tachycardia; peripheral vasodilatation; bilateral fine inspiratory crackles.

Investigations

FBC, U&E, LFT, amylase, clotting, CRP, blood cultures, ABG. CXR shows bilateral pulmonary infiltrates. Pulmonary artery catheter to measure pulmonary capillary wedge pressure (PCWP).

Diagnostic criteria

One consensus requires these 4 to exist: **(1)** Acute onset. **(2)** CXR: bilateral infiltrates. **(3)** PCWP <19mmHg or a lack of clinical congestive heart failure. **(4)** Refractory hypoxaemia with P_aO_2 : FiO_2 <200 for ARDS. Others include total thoracic compliance <30mL/cm H_2O.

Management

Admit to ITU; give supportive therapy; treat the underlying cause.

- ***Respiratory support*** In early ARDS, continuous positive airway pressure (CPAP) with 40-60% oxygen may be adequate to maintain oxygenation. But most patients need mechanical ventilation. Indications for ventilation: P_aO_2: <8.3kPa despite 60% O_2; P_aCO_2: >6kPa. The large tidal volumes (10-15mL/kg) produced by conventional ventilation plus reduced lung compliance in ARDS may lead to high peak airway pressures ± pneumothorax. A low-tidal-volume, pressurelimited approach, with either low or moderate high positive end-expiratory pressure (PEEP) improves outcome.
- ***Circulatory support*** Invasive haemodynamic monitoring with an arterial line and Swan-Ganz catheter aids the diagnosis and may be helpful in monitoring PCWP and cardiac output. A conservative fluid management approach improves outcome. Maintain cardiac output and O_2 delivery with inotropes (eg dobutamine 2.5-10µg/kg/min IVI), vasodilators, and blood transfusion. Consider treating pulmonary hypertension with low-dose (20-120 parts per million) nitric oxide, a pulmonary vasodilator. Haemofiltration may be needed in renal failure and to achieve a negative fluid balance.[36]
- ***Sepsis*** Identify organism(s) and treat accordingly. If clinically septic, but no organisms cultured, use empirical broad-spectrum antibiotics (p153). Avoid nephrotoxic antibiotics.
- ***Other:*** Nutritional support: enteral is best: p572 & p574, with high fat, antioxidant formulations. Steroids protect those at risk of fat embolization and

with pneumocystosis and may improve outcome in subacute ARDS.

Prognosis

Overall mortality is 50%-75%. Prognosis varies with age of patient, cause of ARDS (pneumonia 86%, trauma 38%), and number of organs involved (3 organs involved for >1wk is 'invariably' fatal).

Risk factors for ARDS

- Sepsis
- Hypovolaemic shock
- Trauma
- Pneumonia
- Diabetic ketoacidosis
- Gastric aspiration
- Pregnancy
- Eclampsia
- Amniotic fluid embolus
- Drugs/toxins
- Paraquat, heroin, aspirin
- Pulmonary contusion
- Massive transfusion
- Burns (p830)
- Smoke inhalation (p831)
- Near drowning
- Acute pancreatitis
- DIC (p336)
- Head injury
- ICP↑
- Fat embolus
- Heart/lung bypass
- Tumour lysis syndrome (p514)
- Malaria

Respiratory failure

Respiratory failure occurs when gas exchange is inadequate, resulting in hypoxia. It is defined as a P_aO_2 <8kPa and subdivided into 2 types according to P_aCO_2 level.

Type I respiratory failure

is defined as hypoxia (P_aO_2 <8kPa) with a normal or low P_aCO_2. It is caused primarily by ventilation/perfusion ([V with dot above]/[Q with dot above]) mismatch. Causes include:

- Pneumonia
- Pulmonary oedema
- PE
- Asthma
- Emphysema
- Fibrosing alveolitis
- ARDS (p170).

Type II respiratory failure

is defined as hypoxia (P_aO_2 <8kPa) with hypercapnia (P_aCO_2 is >6.0kPa). This is caused by alveolar hypoventilation, with or without [V with dot above]/[Q with dot above] mismatch. Causes include:

- *Pulmonary disease:* asthma, COPD, pneumonia, pulmonary fibrosis, obstructive sleep apnoea (OSA, p186).

- *Reduced respiratory drive:* sedative drugs, CNS tumour, or trauma.
- *Neuromuscular disease:* cervical cord lesion, diaphragmatic paralysis, poliomyelitis, myasthenia gravis, Guillain-Barré syndrome.
- *Thoracic wall disease:* flail chest, kyphoscoliosis.

Clinical features

are those of the underlying cause together with symptoms and signs of hypoxia, with or without hypercapnia.

Hypoxia:

Dyspnoea; restlessness; agitation; confusion; central cyanosis. If longstanding hypoxia: polycythaemia; pulmonary hypertension; cor pulmonale.

Hypercapnia:

Headache; peripheral vasodilatation; tachycardia; bounding pulse; tremor/flap; papilloedema; confusion; drowsiness; coma.

Investigations

are aimed at determining the underlying cause:

- Blood tests: FBC, U&E, CRP, ABG
- Radiology: CXR
- Microbiology: sputum and blood cultures (if febrile)
- Spirometry (COPD, neuromuscular disease, Guillain-Barré syndrome).

Management

depends on the cause:

Type I respiratory failure

- Treat underlying cause.
- Give oxygen (35-60%) by face mask to correct hypoxia.
- Assisted ventilation if P_aO_2 <8kPa despite 60% O_2.

Type II respiratory failure

the respiratory centre may be relatively insensitive to CO_2 and respiration could be driven by hypoxia. ▸*Oxygen therapy should be given with care*. Nevertheless, don't leave the hypoxia untreated.

- Treat underlying cause.
- Controlled oxygen therapy: start at 24% O_2.
- Recheck ABG after 20min. If P_aCO_2 is steady or lower, increase O_2 concentration to 28%. If P_aCO_2 has risen >1.5kPa and the patient is still hypoxic, consider a respiratory stimulant (eg doxapram 1.5-4mg/min IVI) or assisted ventilation (eg NIPPV, p797, ie non-invasive positive pressure ventilation).
- If this fails, consider intubation and ventilation, if appropriate.

When to consider ABG (arterial blood gas) measurement

In these clinical scenarios:

Any unexpected deterioration in an ill patient.

Anyone with an acute exacerbation of a chronic chest condition.

Anyone with impaired consciousness.

Anyone with impaired respiratory effort.

Or if any of these signs or symptoms are present:

Bounding pulse, drowsy, tremor (flapping), headache, pink palms, papilloedema (signs of CO_2 retention).

Cyanosis, confusion, visual hallucinations (signs of hypoxia).

Or to monitor the progress of a critically ill patient:

Monitoring the treatment of known respiratory failure.

Anyone ventilated on ITU.

After major surgery.

After major trauma.

To validate measurements from transcutaneous pulse oximetry:

Pulse oximetry (p148) *sometimes* suffices when it is not critical to know P_aCO_2. Even so, it is wise to do periodic blood gas checks.

Learn arterial puncture from an expert (local anaesthesia *does* ↓pain) see p759.

Pulmonary embolism (PE)

Causes

PEs usually arise from a venous thrombosis in the pelvis or legs. Clots break off and pass through the venous system and the right side of the heart before lodging in the pulmonary circulation. Rare causes include: right ventricular thrombus (post-MI); septic emboli (right-sided endocarditis); fat, air, or amniotic fluid embolism; neoplastic cells; parasites. ***Risk factors:*** Any cause of immobility or hyper-coagulability:

- Recent surgery
- Recent stroke or MI
- Disseminated malignancy
- Thrombophilia/antiphospholipid syn. (p358)
- Prolonged bed rest
- Pregnancy; postpartum; the Pill/HRT

Clinical features

These depend on the number, size, and distribution of the emboli; small emboli may be asymptomatic, whereas large emboli are often fatal.

Symptoms:

Acute breathlessness, pleuritic chest pain, haemoptysis; dizziness; syncope. Ask about risk factors (above), past history or family history of thromboembolism.

Signs:

Pyrexia; cyanosis; tachypnoea; tachycardia; hypotension; raised JVP, pleural rub; pleural effusion. Look for signs of a cause, eg deep vein thrombosis; scar from recent surgery.

Tests

- FBC, U&E, baseline clotting, D-dimers (BOX).
- **ABG** may show a low P_aO_2 and a low P_aCO_2.
- **CXR** may be normal, or may show oligaemia of affected segment, dilated pulmonary artery, linear atelectasis, small pleural effusion, wedge-shaped opacities or cavitation (rare).
- **ECG** may be normal, or show tachycardia, right bundle branch block, right ventricular strain (inverted T in V_1 to V_4). The classical $S_I\,Q_{III}T_{III}$ pattern (p84) is rare.

▸Further investigations are shown on p802; see also BOX, p725.

Treatment

▸▸See p802. Anticoagulate with low molecular weight heparin (eg dalteparin 200U/kg/24h SC, max dose 18,000U/24h) and start oral warfarin 10mg (p334). Stop heparin when INR is >2 and continue warfarin for a minimum of 3 months (see p335); aim for an INR of 2-3. Consider placement of a ***vena caval filter*** in patients who develop emboli despite adequate anticoagulation (NB increased risk if placed without concomitant anticoagulation).

Prevention

Give heparin (eg dalteparin 2500U/24h SC) to all immobile patients. Prescribe compression stockings and encourage early mobilization. Stop HRT and the Pill pre-op (if reliable with another form of contraception). If past or family history of thromboembolism, consider investigation for thrombophilia (p358).

Pneumothorax *Management* ▸▸p798.

Causes

Often spontaneous (especially in young thin men) due to rupture of a subpleural bulla. Other causes: asthma; COPD; TB; pneumonia; lung abscess;

carcinoma; cystic fibrosis; lung fibrosis; sarcoidosis; connective tissue disorders (Marfan's syndrome, Ehlers-Danlos syndrome), trauma; iatrogenic (subclavian CVP line insertion, pleural aspiration or biopsy, transbronchial biopsy, percutaneous liver biopsy, positive pressure ventilation).

Clinical features

Symptoms: There may be no symptoms (especially if fit, young and small pneumothorax) or there may be sudden onset of dyspnoea and/or pleuritic chest pain. Patients with asthma or COPD may present with a sudden deterioration. Mechanically ventilated patients may present with hypoxia or an increase in ventilation pressures. ***Signs:*** Reduced expansion, hyper-resonance to percussion and diminished breath sounds on the affected side. *With a tension pneumothorax, the trachea will be deviated away from the affected side.* See x-ray p735.

▸▸*Managing a tension pneumothorax*

See p798. Placing a chest drain, ▸▸p754.

Investigating suspected PE[37]

Diagnosis of PE is improved by adopting a stepwise approach, combining an objective probability score, with subsequent investigations, as follows.

- ***Assess the clinical probability of a* PE*:*** many systems exist and are usually based around elements drawn from the history and clinical examination

Scoring system for investigation of suspected DVT*

Feature	Score
Active cancer, or treatment within 6 months	1
Paralysis, paresis, or recent plaster immobilization of lower limbs	1
Recently bed-ridden (>3 days) or major surgery (< 4weeks)	1
Localized tenderness along venous system	1
Entire leg swollen	1
Calf circumference >3cm more than other side, 10cm below tibial tuberosity	1
Pitting oedema > than in asymptomatic leg	1
Collateral superficial veins	1

Alternative diagnosis as, or more, likely than DVT	-2
Total score: 0=low probability; 1-2 moderate probability; ≥3 high probability	

- ***D-dimers:*** only perform in those patients **without** a high probability of a PE. A negative D-dimer test excludes a PE in those with a low or intermediate clinical probability, and imaging is NOT required. However, a positive test does not prove a diagnosis of a PE, and imaging is required.
- ***Imaging:*** The conventional 1st-line, if the CXR is normal, is a **[V with dot above]/[Q with dot above]** ***scan*** (p150, p724 & p802; look for perfusion defects with no corresponding ventilation defects). If 'normal', a PE is reliably excluded. If non-diagnostic, further imaging is required, but may give some false positives. The recommended 1st-line imaging modality is now CT pulmonary angiography (**CTPA**), which can show clots down to 5th-order pulmonary arteries (after the 4th branching). This may also be useful for subjects with indeterminant isotope scans. Bilateral leg ultrasound (or rarely venograms) may also be sufficient to **confirm**, but not exclude, a PE in patients with a co-existing clinical DVT.

Major risk factors for PE

- Surgery:
  Major abdominal/pelvic
  Hip/knee replacement
- Obstetrics:
  Late pregnancy; post-partum
  Caesarean section
- Lower limb problems:
  Fracture
  Varicose veins
- Malignancy
- Reduced mobility
- Previous PE

Pleural effusion

Definitions

A pleural effusion is fluid in the pleural space. Effusions can be divided by their protein concentration into *transudates* (<25g/L) and *exudates* (>35g/L), see OPPOSITE. Blood in the pleural space is a *haemothorax*; pus in the pleural space is an *empyema*, and chyle (lymph with fat) is a *chylothorax*. Both blood and air in the pleural space is called a *haemopneumothorax*.

Causes

Transudates may be due to ↑venous pressure (cardiac failure, constrictive pericarditis, fluid overload), or hypoproteinaemia (cirrhosis, nephrotic syndrome, malabsorption). Also occur in hypothyroidism and Meigs' syndrome (right pleural effusion and ovarian fibroma). ***Exudates*** are mostly due to increased leakiness of pleural capillaries secondary to infection, inflammation, or malignancy. Causes: pneumonia; TB; pulmonary infarction; rheumatoid arthritis; SLE; bronchogenic carcinoma; malignant metastases; lymphoma; mesothelioma; lymphangitis carcinomatosis.

Symptoms

Asymptomatic—or dyspnoea, pleuritic chest pain.

Signs

Decreased expansion; stony dull percussion note; diminished breath sounds occur on the affected side. Tactile vocal fremitus and vocal resonance are ↓ (inconstant and unreliable). Above the effusion, where lung is compressed, there may be *bronchial breathing* and *aegophony* (bleating vocal resonance). With large effusions there may be *tracheal deviation* away from the effusion. Look for aspiration marks and signs of associated disease: malignancy (cachexia, clubbing, lymphadenopathy, radiation marks, mastectomy scar); stigmata of chronic liver disease; cardiac failure; hypothyroidism; rheumatoid arthritis; butterfly rash of SLE.

Tests

CXR:

Small effusions blunt the costophrenic angles, larger ones are seen as water-dense shadows with concave upper borders. A completely horizontal upper

border implies that there is also a pneumothorax. (See **figs 1&2**, p714)

Ultrasound

is useful in identifying the presence of pleural fluid and in guiding diagnostic or therapeutic aspiration.

Diagnostic aspiration:

Percuss the upper border of the pleural effusion and choose a site 1 or 2 intercostal spaces below it (don't go too low or you'll be in the abdomen!). Infiltrate down to the pleura with 5-10mL of 1% lidocaine. Attach a 21G needle to a syringe and insert it just above the upper border of an appropriate rib (avoids neurovascular bundle). Draw off 10-30mL of pleural fluid and send it to the lab for *clinical chemistry* (protein, glucose, pH, LDH, amylase); *bacteriology* (microscopy and culture, auramine stain, TB culture); *cytology* and, if indicated, *immunology* (rheumatoid factor, ANA, complement).

Pleural biopsy:

If pleural fluid analysis is inconclusive, consider parietal pleural biopsy with an Abrams' needle. See p752 for details. Thoracoscopic or CT-guided pleural biopsy increases diagnostic yield (by enabling direct visualization of the pleural cavity and biopsy of suspicious areas).

Management

is of the underlying cause.

- ***Drainage*** If the effusion is symptomatic, drain it, repeatedly if necessary. Fluid is best removed slowly (≤2L/24h). It may be aspirated in the same way as a diagnostic tap, or using an intercostal drain (see p754).
- ***Pleurodesis*** with tetracycline, bleomycin, or talc may be helpful for recurrent effusions. Thorascopic talc pleurodesis is most effective for malignant effusions. Empyemas (p156) are best drained using a chest drain, inserted under ultrasound or CT guidance.
- ***Intra-pleural streptokinase*** Of no benefit.
- ***Surgery:*** Persistent collections and increasing pleural thickness (on ultrasound) requires surgery.[38]

Pleural fluid analysis

Gross appearance	*Cause*
Clear, straw-coloured	Transudate, exudate
Turbid, yellow	Empyema, parapneumonic effusion[1]
Haemorrhagic	Trauma, malignancy, pulmonary infarction
Cytology	
Neutrophils ++	Parapneumonic effusion, PE
Lymphocytes ++	Malignancy, TB, RA, SLE, sarcoidosis

Mesothelial cells ++		Pulmonary infarction
Abnormal mesothelial cells		Mesothelioma
Multinucleated giant cells		RA
Lupus erythematosus cells		SLE
Clinical chemistry		
Protein	<25g/L	Transudate
	>35g/L	Exudate
	25-35g/L	If pleural fluid protein/serum protein>0.5, effusion is an exudate
Glucose <3.3mmol/L		Empyema, malignancy, TB, RA, SLE
pH <7.2		Empyema, malignancy, TB, RA, SLE
LDH↑ (pleural:serum >0.6)		Empyema, malignancy, TB, RA, SLE
Amylase↑		Pancreatitis, carcinoma, bacterial pneumonia, oesophageal rupture
Immunology		
Rheumatoid factor		RA

Antinuclear antibody	SLE
Complement levels↓	RA, SLE, malignancy, infection

[1] Inflammation of the pleura caused by pneumonia may lead to infected pleural fluid (empyema); if it is not infected, the term parapneumonic effusion is used.

Sarcoidosis

A multisystem granulomatous disorder of unknown cause. Prevalence in UK: 10-20/10^5 population. Commonly affects adults aged 20-40yrs. Afro-Caribbeans are affected more frequently and more severely than Caucasians, particularly by extrathoracic disease.

Clinical features

Asymptomatic In 20-40%, the disease is discovered incidentally, after a routine CXR. ***Acute sarcoidosis*** often presents with erythema nodosum (**fig 1**, p547)[1] ± polyarthralgia. It usually resolves spontaneously.

Pulmonary disease

90% have abnormal CXRs with bilateral hilar lymphadenopathy (**BHL**) ± pulmonary infiltrates or fibrosis; see below for staging. *Symptoms:* Dry cough, progressive dyspnoea, ↓exercise tolerance and chest pain. In 10-20% symptoms progress, with concurrent deterioration in lung function.

Non-pulmonary manifestations

are legion: lymphadenopathy; hepatomegaly; splenomegaly; uveitis; conjunctivitis; keratoconjunctivitis sicca; glaucoma; terminal phalangeal bone cysts; enlargement of lacrimal and parotid glands (**fig 4** on p339); Bell's palsy; neuropathy; meningitis; brainstem and spinal syndromes; space-occupying lesion; erythema nodosum (**fig 1**, p547); lupus pernio; subcutaneous nodules; cardiomyopathy; arrhythmias; hypercalcaemia; hypercalciuria; renal stones; pituitary dysfunction.

Tests

Blood: ↑ESR, lymphopenia, LFT↑, ↑serum ACE, ↑Ca^{2+}, ↑immunoglobulins. ***24h urine:*** Ca^{2+}↑. ***Tuberculin skin test*** is -ve in two-thirds; **CXR** is abnormal in 90%: *Stage 0:* normal. *Stage 1:* BHL. *Stage 2:* BHL + peripheral pulmonary infiltrates. *Stage 3:* peripheral pulmonary infiltrates alone. *Stage 4:* progressive pulmonary fibrosis; bulla formation (honeycombing); pleural involvement. **ECG** may show arrhythmias or bundle branch block. ***Lung function tests*** may be normal or show reduced lung volumes, impaired gas transfer, and a restrictive ventilatory defect. ***Tissue biopsy*** (lung, liver, lymph nodes, skin nodules, or lacrimal glands) is diagnostic and shows non-caseating granulomata.

Bronchoalveolar lavage (BAL)

shows ↑lymphocytes in active disease; ↑neutrophils with pulmonary fibrosis.

Ultrasound

may show nephrocalcinosis or hepatosplenomegaly.

Bone x-rays

show 'punched out' lesions in terminal phalanges.

CT/MRI

may be useful in assessing severity of pulmonary disease or diagnosing neurosarcoidosis. ***Ophthalmology assessment*** (slit lamp examination, fluorescein angiography) is indicated in ocular disease. ***Kveim tests*** are obsolete.

Management

▸*Patients with BHL alone do not require treatment since the majority recover spontaneously.* ***Acute sarcoidosis:*** Bed rest, NSAIDs.

Indications for corticosteroid therapy:

- Parenchymal lung disease (symptomatic, static, or progressive)
- Uveitis
- Hypercalcaemia
- Neurological or cardiac involvement.

Prednisolone (40mg/24h) PO for 4-6 wks, then ↓dose over 1yr according to clinical status. A few patients relapse and may need a further course or long-term therapy. In severe illness, IV methylprednisolone or immunosuppressants (methotrexate, ciclosporin, cyclophosphamide) may be needed.

Prognosis

60% of patients with thoracic sarcoidosis show spontaneous resolution within 2yrs. 20% of patients respond to steroid therapy. In the remainder, improvement is unlikely despite therapy.

Causes of BHL (bilateral hilar lymphadenopathy)

Sarcoidosis	
Infection	TB Mycoplasma
Malignancy	Lymphoma Carcinoma Mediastinal tumours
Organic dust disease	Silicosis Berylliosis
Extrinsic allergic alveolitis	

Differential diagnosis of granulomatous diseases

Infections	Bacteria	TB Leprosy Syphilis Cat scratch fever
	Fungi	*Cryptococcus neoformans Coccidioides immitis*
	Protozoa	Schistosomiasis

Autoimmune	Primary biliary cirrhosis Granulomatous orchitis
Vasculitis (p542)	Giant cell arteritis Polyarteritis nodosa Takayasu's arteritis Wegener's granulomatosis
Organic dust disease	Silicosis Berylliosis
Idiopathic	Crohn's disease de Quervain's thyroiditis Sarcoidosis
Extrinsic allergic alveolitis	
Histiocytosis X	

Interstitial lung disease (ILD)

This is the generic term used to describe a number of conditions that primarily affect the lung parenchyma in a diffuse manner. They are characterized by chronic inflammation and/or progressive interstitial fibrosis, and share a number of clinical and pathological features.

Clinical features

Dyspnoea on exertion; non-productive paroxysmal cough; abnormal breath sounds; abnormal CXR or high resolution CT; restrictive pulmonary spirometry with a reduced DLCO (p150).

Pathological features

Fibrosis and remodelling of the interstitium; chronic inflammation; hyperplasia of type II epithelial cells or type II pneumocytes.

Classification

The ILDS can be broadly grouped into three categories:

- *Those with known aetiology eg*
  - Occupational/environmental eg asbestosis, berylliosis, silicosis
  - Drugs eg nitrofurantoin, bleomycin, amiodarone, sulfasalazine, busulfan
  - Hypersensitivity reactions eg extrinsic allergic alveolitis
  - Infections eg TB, fungi, viral
- *Those associated with systemic disorders eg*
  - Sarcoidosis
  - Rheumatoid arthritis
  - SLE, systemic sclerosis, mixed connective tissue disease, Sjögren's syndrome
  - Ulcerative colitis, renal tubular acidosis, autoimmune thyroid disease

- *Idiopathic eg*
  - Idiopathic pulmonary fibrosis (IPF)/cryptogenic fibrosing alveolitis (p182)
  - Cryptogenic organizing pneumonia
  - Lymphocytic interstitial pneumonia

Extrinsic allergic alveolitis (EAA)

In sensitized individuals, inhalation of allergens (fungal spores or avian proteins) provokes a hypersensitivity reaction. In the acute phase, the alveoli are infiltrated with acute inflammatory cells. With chronic exposure, granuloma formation and obliterative bronchiolitis occur.

Causes

- Bird fancier's and pigeon fancier's lung (proteins in bird droppings).
- Farmer's and mushroom worker's lung (*Micropolyspora faeni, Thermoactinomyces vulgaris*).
- Malt worker's lung (*Aspergillus clavatus*).
- Bagassosis (*Thermoactinomyces sacchari*).

Clinical features

4-6h post-exposure: Fever, rigors, myalgia, dry cough, dyspnoea, crackles (no wheeze). ***Chronic:*** Increasing dyspnoea, weight↓, exertional dyspnoea, Type I respiratory failure, cor pulmonale.

Tests

Acute:

Blood: FBC (neutrophilia); ESR↑; ABGs; positive serum precipitins (indicate exposure only). CXR: mid-zone mottling/consolidation; hilar lymphadenopathy (rare). *Lung function tests:* reversible restrictive defect; reduced gas transfer during acute attacks.

Chronic:

Blood tests: positive serum precipitins. CXR: upper-zone fibrosis; honeycomb lung. *Lung function tests:* persistent changes (see above). Bronchoalveolar lavage (BAL) fluid shows ↑ lymphocytes and mast cells.

Management

Acute attack:

Remove allergen and give O_2 (35-60%), then:

- Oral prednisolone (40mg/24h PO), followed by reducing dose.

Chronic:

Avoid exposure to allergens, or wear a face mask or +ve pressure helmet. Long-term steroids often achieve CXR and physiological improvement. Compensation (UK Industrial Injuries Act) may be payable.

Idiopathic pulmonary fibrosis

Inflammatory cell infiltrate and pulmonary fibrosis of unknown cause (also known as cryptogenic fibrosing alveolitis). The commonest cause of interstitial lung disease.

Symptoms

Dry cough; exertional dyspnoea; malaise; weight↓; arthralgia.

Signs

Cyanosis; finger clubbing; fine end-inspiratory crepitations.

Complications

Type 1 respiratory failure; increased risk of lung cancer.

Tests

Blood: ABG (P_aO_2↓; P_aCO_2↑); CRP↑; immunoglobulins↑; ANA (30% +ve), rheumatoid factor (10% +ve). **CXR:** (**fig 1**) Lung volume↓; bilateral lower zone reticulo-nodular shadows; honeycomb lung (advanced disease). Magnetic resonance scan/CT show similar changes to the CXR but is more sensitive and is an essential tool for diagnosis. ***Spirometry:*** Restrictive (p148); ↓transfer factor. **BAL** (bronchoalveolar lavage) may indicate activity of alveolitis: lymphocytes↑ (good response/prognosis) or neutrophils and eosinophils↑ (poor response/prognosis). ***$^{99}TC^m$-DTPA scan*:** (diethylene-triamine-penta-acetic acid) may reflect disease activity. ***Lung biopsy*** may be needed for diagnosis.[39]

Management

A large proportion of patients have chronic irreversible disease unresponsive to treatment. Prednisolone 0.5mg/kg/24h PO for 4 wks, then 0.25mg/kg/24h PO for 48 wks, then taper (≈20% respond). Alternative: cyclophosphamide 100-120mg/24h PO + prednisolone 20mg PO on alternate days. Monitor response with symptom enquiry, CXR, and lung function tests. The patient may be suitable for lung transplantation.[40] **Prognosis** 50% 5yr survival rate (range 1-20yrs).

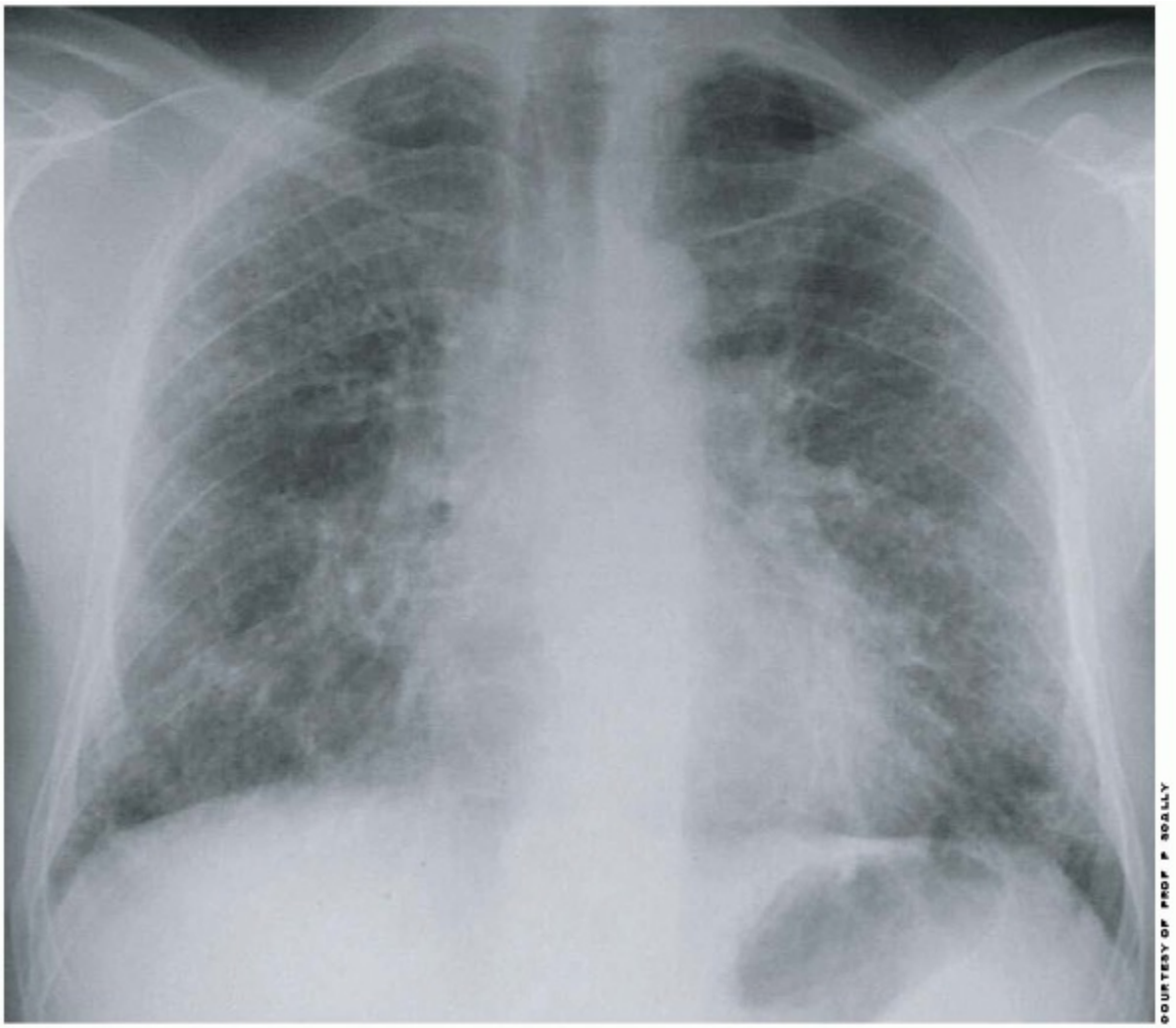


Fig 1. Systematic approach: **Lungs:** Lung volumes are normal, but the parenchyma shows increased markings extending to the chest wall. Normally arteries and veins are only seen for 80% of the distance from hilum to pleura. Bronchi should barely be visible.

Pleura: Following the pleura demonstrates that the heart borders are poorly defined, reflecting interstitial disease in the lung, adjacent to the heart.

Mediastinum: The mediastinal structures are normal.

Hila: The hila are difficult to interpret. So what? It is not unusual to be missing a piece of information when making a clinical decision. No need for wringing of hands. Either go ahead without it, or, if it is essential, find it (look at old films; do CT).

Bones and soft tissue: These appear normal.

Comment: This is interstitial lung disease (a similar appearance to the interstitial oedema of moderate left heart failure, but without a big heart). Check the previous films to see if it is acute. It is not. The diagnosis here is fibrosing alveolitis.

Industrial dust diseases

Coal worker's pneumoconiosis (CWP)

is the commonest dust disease in the UK. It results from inhalation of coal dust particles (1-3μm in diameter) over 15-20yrs. These are ingested by macrophages which die, releasing their enzymes and causing fibrosis.

Clinical features:

Asymptomatic, but co-existing chronic bronchitis is common. CXR: many round opacities (1-10mm), especially upper zone.

Management:

Avoid exposure to coal dust; treat co-existing chronic bronchitis; claim compensation (in the UK, *via* the Industrial Injuries Act).

Progressive massive fibrosis (PMF)

is due to progression of CWP, which causes progressive dyspnoea, fibrosis, and eventually, cor pulmonale. CXR: upper-zone fibrotic masses (1-10cm).

Management:

Avoid exposure to coal dust; claim compensation (as above).

Caplan's syndrome

is the association between rheumatoid arthritis, pneumoconiosis, and pulmonary rheumatoid nodules.

Silicosis

is caused by inhalation of silica particles, which are very fibrogenic. A number of jobs may be associated with exposure, eg metal mining, stone quarrying, sandblasting, and pottery/ceramic manufacture.

Clinical features:

Progressive dyspnoea, ↑incidence of TB, CXR shows diffuse miliary or nodular pattern in upper and mid-zones and egg-shell calcification of hilar nodes. Spirometry: restrictive ventilatory defect.

Management:

Avoid exposure to silica; claim compensation (as above).

Asbestosis

is caused by inhalation of asbestos fibres. Chrysotile (white asbestos) is the least fibrogenic—crocidolite (blue asbestos) is the most fibrogenic. Amosite (brown asbestos) is the least common and has intermediate fibrogenicity. Asbestos was commonly used in the building trade for fire proofing, pipe lagging, electrical wire insulation, and roofing felt. Degree of asbestos exposure is related to degree of pulmonary fibrosis.

Clinical features:

Similar to other fibrotic lung diseases with progressive dyspnoea, clubbing, and fine end-inspiratory crackles. Also causes pleural plaques, ↑risk of bronchial adenocarcinoma and mesothelioma.

Management:

Symptomatic. Patients are often eligible for compensation through the UK Industrial Injuries Act.

Malignant mesothelioma

is a tumour of mesothelial cells which usually occurs in the pleura, and rarely in the peritoneum or other organs. It is associated with occupational exposure to asbestos but the relationship is complex.[41] 90% report previous exposure to asbestos, but only 20% of patients have pulmonary asbestosis. The latent period between exposure and development of the tumour may be up to 45yrs.

Clinical features

include chest pain, dyspnoea, weight loss, finger clubbing, recurrent pleural effusions. If the tumour has metastasized there may be lymphadenopathy, hepatomegaly, bone pain/tenderness, abdominal pain/obstruction (peritoneal malignant mesothelioma).

Tests:

CXR/CT: pleural thickening/effusion. Bloody pleural fluid.

Diagnosis

is made on histology, following a pleural biopsy—Abrams' needle (p752), thoracoscopy. Often the diagnosis is only made post-mortem.

Management:

Symptomatic, with industrial compensation, as above.

Prognosis

is very poor (<2yrs, >650 deaths/yr in the UK).

Obstructive sleep apnoea syndrome

This disorder is characterized by intermittent closure/collapse of the pharyngeal airway which causes apnoeic episodes during sleep. These are terminated by partial arousal.

Clinical features

The typical patient is a obese, middle-aged man (or a post-menopausal woman) who presents because of snoring or daytime somnolence. His partner often describes apnoeic episodes during sleep.

- Snorts loudly in sleep
- Morning headache
- Daytime somnolence
- Decreased libido
- Poor sleep quality
- Cognitive performance↓

Complications

Pulmonary hypertension; Type II respiratory failure (p172). Sleep apnoea is also reported as an independent risk factor for hypertension.[42]

Investigations

Simple studies (eg pulse oximetry, video recordings) may be all that are required for diagnosis. Polysomnography (which monitors oxygen saturation, airflow at the nose and mouth, ECG, EMG chest and abdominal wall movement during sleep) is diagnostic. The occurrence of 15 or more episodes of apnoea or hypopnoea during 1h of sleep indicates significant sleep apnoea.

Management

- Weight reduction
- Avoidance of tobacco and alcohol
- CPAP via a nasal mask during sleep is effective
- Surgical procedures to relieve pharyngeal obstruction (tonsillectomy, uvulopalatopharyngoplasty, or tracheostomy) are occasionally needed, but only after seeing a chest physician.

Cor pulmonale

Cor pulmonale is right heart failure caused by chronic pulmonary hypertension. Causes include chronic lung disease, pulmonary vascular disorders, and neuromuscular and skeletal diseases (see p187).

Clinical features

Symptoms include dyspnoea, fatigue, or syncope. Signs: cyanosis; tachycardia; raised JVP with prominent *a* and *v* waves; RV heave; loud P2, pansystolic murmur (tricuspid regurgitation); early diastolic Graham Steell murmur; hepatomegaly and oedema.

Investigations

FBC*:* Hb and haematocrit↑ (secondary polycythaemia). **ABG***:* hypoxia, with or without hypercapnia. **CXR***:* enlarged right atrium and ventricle, prominent pulmonary arteries. **ECG***:* P pulmonale; right axis deviation; right ventricular hypertrophy/strain.

Management

- ***Treat underlying cause***—eg COPD and pulmonary infections.
- ***Treat respiratory failure***—in the acute situation give 24% oxygen if P_aO_2 <8kPa. Monitor ABG and gradually increase oxygen concentration if P_aCO_2 is stable (p172). In COPD patients, long-term oxygen therapy (LTOT) for 15h/d increases survival (see p168). Patients with chronic hypoxia when clinically stable should be assessed for LTOT.
- ***Treat cardiac failure*** with diuretics such as furosemide, eg 40-160mg/24h PO. Monitor U&E and give amiloride or potassium supplements if necessary. Alternative: spironolactone.
- Consider ***venesection*** if the haematocrit is >55%.
- Consider ***heart-lung transplantation*** in young patients.

Prognosis

Poor. 50% die within 5yrs.

Causes of cor pulmonale

- ***Lung disease***
  Asthma (severe, chronic)
  COPD
  Bronchiectasis
  Pulmonary fibrosis
  Lung resection
- ***Pulmonary vascular disease***
  Pulmonary emboli
  Pulmonary vasculitis
  Primary pulmonary hypertension
  ARDS (p170)
  Sickle-cell disease
  Parasite infestation
- ***Thoracic cage abnormality***
  Kyphosis
  Scoliosis
  Thoracoplasty
- **Neuromuscular disease**
  Myasthenia gravis
  Poliomyelitis
  Motor neurone disease
- ***Hypoventilation***
  Sleep apnoea
  Enlarged adenoids in children
  Cerebrovascular disease

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6

Endocrinology

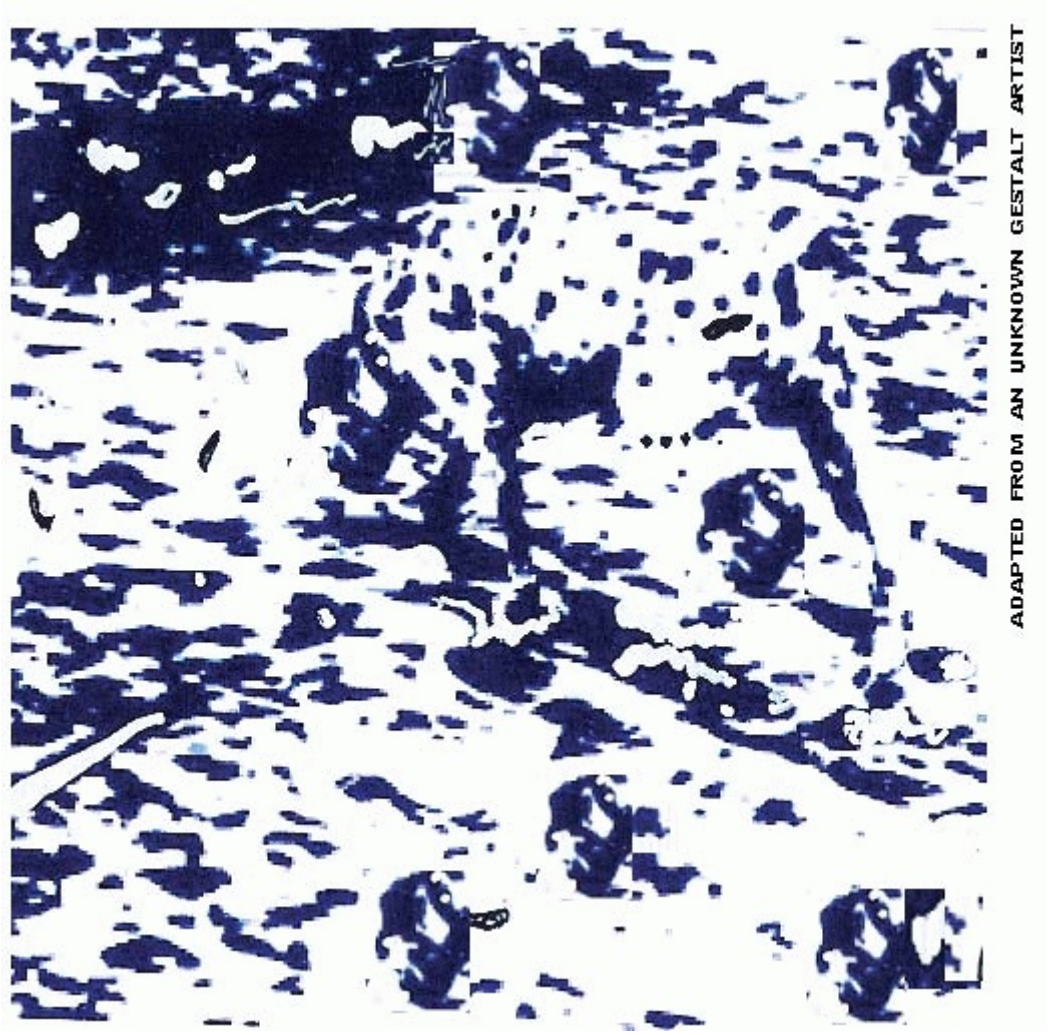


Fig 1. In German, ***Gestalt*** means both *the whole* form (as being more than the sum of its parts) and *the pattern*. A gestalt has come to mean (in WH Auden's words)[1] the place where indiscrete perceptions and extensions meet and new meanings are created. The ideal endocrinologist is a master of gestalt patternrecognition (myxoedema, acromegaly, and the rest—see opposite). On viewing the above, he or she sees the dots and the dog, but does not get *too* carried away by filling in the gaps: he detects the amputated hind-leg—postulating diabetes mellitus (autoimmune, if this Dalmatian has vitiligo).[2]

Nor is he or she put off by missing or paradoxical data (eg *increase* in weight in thyrotoxicosis, seen in up to 30%).[3] Knowing when to stand back and look *holistically*, when to go for *detail*, and when to *count* (how many heads are there in the image?) is a key skill in all of medicine, not just endocrinology.

With **inverse *gestalt*** we deconstruct a familiar picture into its component dots to see what new forms emerge: a useful technique for our most difficult patients.

The essence of endocrinology—for scientists

- Define a clinical syndrome, and match it to a gland malfunction.
- Measure the gland's output in the peripheral blood. Define clinical syndromes associated with too much or too little secretion (*hyper-* and *hypo-* syndromes, respectively; *eu-* means normal, neither ↑ nor ↓, as in *euthyroid*). Note factors that may make measurement variable eg diurnal release of cortisol.
- If suspecting hormone deficiency, test by stimulating the gland that produces it (eg Short ACTH stimulation test or *Synacthen*® test in Addison's disease). If the gland is not functioning normally, there will be a blunted response to stimulation.

- If suspecting hormone excess, test by inhibiting the gland that produces it (eg Dexamethasone suppression test in Cushing's). If there is a hormone secreting tumour then this will fail to suppress via normal feedback mechanisms.
- Find a radiological technique to image the gland. NB: non-functioning tumours or "incidentalomas" may be found in normal subjects, see p208. Imaging alone does not make the diagnosis.
- Aim to halt disease progression. An example is diet and exercise advice which can reduce progression of 'impaired fasting glucose (IFG)' to frank diabetes by 50%..[4] For other glands, halting progression will depend on understanding autoimmunity, and the interaction of endogenous (genetic) and environmental factors. In the case of thyroid autoimmunity (an archetypal autoimmune disease), it is possible to track interactions between genetic and environmental factors (eg smoking and stress) via expression of immunologically active molecules (HLA class I & II, adhesion molecules, cytokines, CD40, and complement regulatory proteins).[5]

The essence of endocrinology—for those doing exams

'What's wrong with *him*?' your examiner asks, baldly. While you apologise to the patient for this rudeness by asking: 'Is it alright if we speak about you as if you weren't there?' think to yourself that if you were a betting man or woman you would wager that the diagnosis will be endocrinological. In no other discipline are *gestalt* impressions so characteristic. To get good at recognizing these conditions, spend time in endocrinology out-patients and looking at collections of clinical photographs. Also, specific cutaneous signs are important, as follows.

Thyrotoxicosis:

Hair loss; pretibial myxoedema (p202); onycholysis (nail separation from the nailbed); bulging eyes (exophthalmos).

Hypothyroidism:

Hair loss; eyebrow loss; cold, pale skin; characteristic face. (You might, perhaps *should*, fail your exam if you blurt out 'Toad-like face'.)

Cushing's syndrome:

Central obesity and wasted limbs (='lemon on sticks'); moon facies; buffalo hump; supraclavicular fat pads; purple abdominal striae.

Addison's disease:

Hyperpigmentation (face, neck, palmar creases).

Acromegaly:

Acral (distal) and soft tissue overgrowth; big jaws (macrognathia), hands and feet; the skin is thick; facial features are coarse.

Hyperandrogenism (♀):

Hirsutism; temporal balding; acne.

Hypopituitarism:

Pale or yellow tinged thinned skin, resulting in fine wrinkling around the eyes and mouth, making the patient look older.

Hypoparathyroidism:

Dry, scaly, puffy skin; brittle nails; coarse, sparse hair.

Pseudohypoparathyroidism:

Short stature, short neck & short 4^{th} & 5^{th} metacarpals.

DM signs:

(There is no gestalt picture). Necrobiosis lipoidica; diabetic dermopathy; acanthosis nigricans (dark patches eg in axillae, neck).[6]

Diabetes mellitus: classification and diagnosis

Essence

Diabetes mellitus (DM) results from a lack (or diminished effectiveness) of endogenous insulin. Hyperglycaemia is just one aspect of a far-reaching metabolic derangement, which may cause serious microvascular (retinopathy, nephropathy, neuropathy) or macrovascular complications (cardiovascular—coronary artery disease, cerebrovascular—stroke, and peripheral vascular disease).

Type 1 DM

(formerly insulin-dependent DM, IDDM): usually juvenile onset but may occur at *any* age.

Cause

Insulin deficiency due to selective destruction of insulinsecreting pancreatic ß cells. Patients *always* need insulin, and are prone to ketoacidosis and weight loss. It is associated with other autoimmune diseases (>90% carry HLA DR3 ± DR4; see index). Concordance is only ~30% in identical twins, indicating environmental influence. 4 genes are important—one (6q) determines islet sensitivity to damage (eg from viruses or cross-reactivity from cows' milk-induced antibodies). Latent autoimmune diabetes of adults (LADA) is a form of Type 1 DM, with slower progression to insulin dependence in later life.

Type 2 DM

(formerly non-insulin dependent DM, NIDDM) appears to be prevalent at 'epidemic' levels in many places, mainly due to changes in lifestyle, but also because of better diagnosis and improved longevity.[7] Higher prevalence occurs in Asians, men, and the elderly (18% in men over 80 in Liverpool).[8] Most are over 40yrs, but teenagers are increasingly getting type 2 DM.

Cause

↓Insulin secretion and insulin resistance. It is associated with obesity, lack of exercise and calorie excess. ≳80% concordance in identical twins, indicating stronger genetic influence than in Type 1 DM. Typically progresses from a preliminary phase of impaired glucose tolerance (IGT) or impaired fasting glucose (IFG), see BOX. (▸This a unique window of opportunity for lifestyle intervention.) Maturity onset diabetes of the young (MODY) is a rare

autosomal dominant form of Type 2 DM affecting young people with a positive family history.

Diagnosis of diabetes mellitus (WHO criteria)

- Symptoms of hyperglycaemia (eg polyuria, polydipsia, unexplained weight loss, visual blurring, genital thrush, lethargy) **AND** raised venous glucose detected once—fasting ≥7mmol/L or random ≥11.1mmol/L **OR**
- Raised venous glucose on 2 separate occasions—fasting ≥7mmol/L, random ≥11.1mmol/L or oral glucose tolerance test—2h value ≥11.1mmol/L.

If there is doubt, use the oral glucose tolerance test (OGTT): look for a 2h level >11.1mmol/L.

How to do a 2h OGTT:

- Fast overnight. Give 75g of glucose in 300mL water to drink in the morning.
- Measure venous plasma glucose before and 2h after the drink.

Hb_{A1c} or capillary glucose levels should not be used to diagnose diabetes. Glycosuria detected on urine dipstick can be a normal finding.

Occasionally it may be difficult to differentiate whether a patient has Type 1 or 2 DM. Features that suggest Type 1 DM include weight loss; persistent hyperglycaemia despite diet and medications; presence of autoantibodies: islet cell antibodies (ICA) and anti-glutamic acid decarboxylase (GAD) antibodies; ketonuria on urine dipstick.

Other causes of diabetes mellitus

- Drug induced: steroids, thiazides.
- Pancreatic: pancreatitis; surgery (where >90% pancreas is removed); trauma; pancreatic destruction (haemochromatosis, cystic fibrosis); pancreatic cancer.
- Endocrine: Cushing's disease; acromegaly; phaeochromocytoma; hyperthyroidism.
- Others: acanthosis nigricans; congenital lipodystrophy with insulin receptor antibodies; glycogen storage diseases.

Other categories of diabetes mellitus

Impaired glucose tolerance (IGT)

Fasting plasma glucose < 7mmol/L and OGTT 2h glucose ≥ 7.8mmol/L but <11.1 mmol/L.

Impaired fasting glucose (IFG)

Fasting plasma glucose ≥ 6.1mmol/L but <7mmol/L. Should have an OGTT to exclude DM.

These denote different abnormalities of glucose regulation (post-prandial and fasting). There may be lower risk of progression to DM in IFG than IGT. Both are managed with lifestyle advice (exercise and diet, p79), and regular review. Giving those with heart failure and IFG ACE-i drugs can prevent progression to DM (3% *vs* 48% over 3yrs).[9]

Gestational diabetes

(OHCS p24) This term includes gestational impaired glucose tolerance (GIGT) and gestational diabetes mellitus (GDM). Use the same diagnostic values as IGT and diabetes above. Glucose tolerance changes during pregnancy. At ≥ 6wks post-partum, do a further 75g OGTT whether she still has diabetes or IGT/IFG. Regardless of this result, these women are at ↑risk of later developing diabetes, with an approximate 50% lifetime risk.

Type 1 versus Type 2 diabetes mellitus

	Type 1 DM	Type 2 DM
Epidemiology	Younger patients	Older patients
Genetics	HLA D3 and D4 linked	No HLA association

Aetiology	Autoimmune ß cell destruction	Insulin resistance, ß cell dysfunction
Presentation	Polydipsia, polyuria, weight loss, ketoacidosis	Often asymptomatic; presents with micro- or macrovascular complications

Causes of insulin resistance

- Obesity
- Asians[1]
- TB drugs
- Metabolic syndrome (syndrome X—see p197): central obesity, hyperglycaemia, hypertension, dyslipidaemia (↑triglycerides, ↓HDL cholesterol).
- Pregnancy
- Acromegaly
- Cushing's
- Renal failure
- Cystic fibrosis
- Polycystic ovarian syndrome
- Werner's syndrome (OHCS p655)

Mechanisms:

- Obesity may cause insulin resistance by ↑ rate of release of nonesterified fatty acids causing post-receptor defects in insulin's action
- Mutation of genes encoding insulin receptors
- Circulating autoantibodies to the extracellular domain of the insulin receptor.

[prescription take] for Syndrome X:
Exercise more; control individual vascular risk factors ie weight↓, statins, antihypertensives, hypoglycaemics (eg glitazones).[10]

Treatment of diabetes mellitus

Enabling patients to manage their own condition, by education and motivation from a multi-disciplinary team of doctors, specialist nurses and dieticians, chiropodists, podiatrists, and patient groups is central to successful treatment. The aim is to maintain near normal glucose control while avoiding hypoglycaemia.

Educate and negotiate

on: Monitoring capillary glucose measurements ('BMs'), regular exercise, diet: p228—saturated fats↓, sugar↓, starch-carbohydrate↑, moderate protein. Give smoking cessation, foot-care (p196), & pre-conception advice (OHCS p2). Care during pregnancy should be shared with an interested obstetrician (OHCS p24). Advise to inform the driving licence authority and not to drive if hypoglycaemic (p145). Loss of awareness of hypoglycaemia may lead to a loss of driving licence (permanent if HGV license)—see below.

Medication

Type 1 DM patients invariably need insulin (see BOX). Type 2 DM patients may be managed initially on diet and exercise alone, but may progress to needing oral hypoglycaemic agents then insulin depending on glycaemic control.

Oral hypoglycaemics

Generally, in Type 2 DM patients, start with metformin if BMI>25. If BMI<25, use either a sulfonylurea or metformin. If this fails to control, combine metformin + sulfonylurea (some, but not NICE,[11] say a glitazone[1] is more appropriate as the 2nd add-in drug).[12] Insulin may be needed if this still does not work (p193).

Biguanides

eg **metformin:** ↑ insulin sensitivity and maintains weight loss. SE: nausea and diarrhoea often transient; *not* hypoglycaemia. Avoid if creatinine ≳ 150µmol/L due to risk of lactic acidosis. *Dose:* 0.5-1g/12h (o.d. MR form may have fewer SE). Stop if tissue morning hypoxia (eg MI, sepsis), morning before GA and contrast medium containing iodine (restart when renal function is OK).[13]

Sulfonylureas

↑insulin secretion. SE: hypoglycaemia, weight gain. **Tolbutamide:** Short-acting (hypoglycaemia is rare); 0.5-1.5g/d in 2-3 doses. **Gliclazide:** Mediumacting; 40-160mg PO, max 160mg/12h). **Glibenclamide:** Long-acting; 2.5- 15mg/24h PO (rarely used as risk of hypoglycaemia).

Thiazolidinediones

↑ insulin sensitivity. SE: hypoglycaemia, fluid retention (caution in CCF), hepatotoxicity: do LFT every 2 months for 1yr, stop if ALT up >3-fold. **Rosiglitazone** 4mg (max 8mg)/24h. **Pioglitazone** 15-30mg/24h. Use if metformin + sulfonylurea combination is problematic: the glitazone replaces whichever is contraindicated or not tolerated.[14]

Other treatments:

Acarbose (*a-glucosidase inhibitor*) decreases breakdown of starch to sugar. Use as an add-on drug,[15] eg 50mg chewed at start of each meal. Start with a once daily dose, max 200mg/8h. SE: wind (often poorly tolerated; less if *slow* dose build-up), abdominal distension/pain, diarrhoea. **Nateglinide** (*sulfonylurea receptor binder*): ↑β-cell insulin release. 60mg ½h before food, increased as needed. Alternative: **repaglinide**. They target post-prandial hyperglycaemia ($t_{½}$ is short[16] —metformin works mostly on fasting glucose). They may have a role in those with irregular mealtimes if glycaemic control is poor.[17]

Monitoring glycaemic control:

1 Patients with Type 1 DM (and selected patients with Type 2 DM) should keep a diary of home fingerstick glucose records, enabling detection of patterns of hypo/hyperglycaemia. 2 Glycated haemoglobin (= Hb_{A1c}) levels relate to mean glucose level over previous 8 wks (ie RBC half-life). The target level is <7.5%, or <6.5% if at increased arterial risk, eg previous MI or stroke (NICE advice). In patients at risk from the effects of hypoglycaemia, eg elderly patients prone to falls, it may be sensible to opt for less tight control. Complications increase with increasing Hb_{A1c}, therefore advise any improvement is beneficial, even if targets are not reached. *Fructosamine* (glycated plasma protein) levels reflect control over 2-3 wks: may be used in pregnancy to assess shorter term control, and in patients with haemoglobinopathies which interfere with Hb_{A1c} tests. 3 History of hypoglycaemic attacks (and whether symptomatic). Hypoglycaemic awareness may diminish if control is too tight, or with time in Type 1 DM, due to ↓glucagon secretion. It may return if control is loosened ie avoiding hypoglycaemia.

Insulin ▸▸Ketoacidosis p814; HONK p816

Educating patients to self-adjust their insulin dose in the light of exercise and calorie intake to achieve normoglycaemia is vital for optimal control.

Subcutaneous insulin

Strength: 100U/mL. There are many types, falling into 6 groups. Delivery devices used to inject the insulin also vary.

1. Ultra-fast acting, eg Humalog® and Novorapid®; inject at start of meal (or immediately after).
2. Soluble insulin eg Humulin S® or Actrapid: inject 15-30min before meals.
3. Intermediate Humulin I® or Insulatard® .
4. Long-acting ('lente'), eg Ultratard® .
5. Long-acting analogue, eg Lantus/insulin glargine, see below.
6. Pre-mixed insulins, eg with ultra-fast component (eg NovoMix® 30); or with soluble insulin (eg Humulin® M3 or Mixtard® 30).

Insulin glargine

is a long-acting recombinant human insulin analogue used once daily at bedtime in type 1 or 2 DM; however, it is not recommended for routine use in type 2 DM (see BNF; NICE guidance).[18] Molecular modification has made an insulin that is soluble at acid pH, but precipitates in subcutaneous tissue and is slowly released from a depot. Given once daily, insulin glargine has comparable efficacy to insulin used twice daily. Its rate of hypoglycaemia is less than that of standard insulins, and there is evidence of less nocturnal hypoglycemia. It may be combined with ultra-short acting insulins given at the times of meals. In type 2 DM, if oral agents are failing, it can be used if a twice-daily dosing is problematic (NICE guidance).[19]

Insulin detemir

has similar characteristics.

Some commonly used subcutaneous insulin regimens

▸ Design the insulin regimen to suit your patient's lifestyle (not *vice versa*).

- 'BD regime': Twice daily premixed insulins by pen injector—useful in type 2 DM or type 1 with regular lifestyle.
- 'QDS regime': Before meals ultra-fast or soluble insulin, with bedtime intermediate- or long-acting analogue: useful in type 1 DM for achieving a flexible life-style (eg for adjusting doses with size of meals, or exercise).
- Once daily before bed intermediate- or long-acting insulin—good initial insulin regimen when switching from tablets in type 2 DM.
- Begin with at least a total daily dose of 1 unit of insulin for every unit of body mass index in adults.

Dose adjustment for normal eating (DAFNE):

One way to optimize control is to use multi-disciplinary teams to fully engage people in self-management, promoting autonomy and independence. The randomized DAFNE study found that training in flexible, intensive insulin dosing improved glycaemic control as well as well-being/quality of life.[20] It is resource-intensive.

Subcutaneous insulin dosing during intercurrent illnesses (eg influenza)

- Illness often increases insulin requirements despite reduced food intake.
- Maintain calorie intake using milk or soft drinks containing sugar.
- Check blood glucose ≥ 4 times a day. Increase insulin doses if glucose rising. Patients should seek advice from a specialist diabetes nurse or GP if concerned, especially if glucose levels are rising or there is ketonuria.

- Admit if the patient is vomiting, dehydrated, or ketotic (see p576).
- Admit early if a child or pregnant.

Inhaled insulin

is being developed: Exubera® is a rapid-acting (before meals) form. It is licensed in Type 2 DM for those poorly controlled on oral drugs, and in adults with Type 1 DM. It has similar efficacy to injected insulin, and improved patient compliance and satisfaction.[21] It is only suitable for non-smokers, and spirometry must be monitored. The inhaler device is bulky and needs careful explanation. Long term safety of inhaled insulin on lung function is unknown.

Helping people with established diabetes

Two prospective studies showed that tight control of hyperglycaemia is key to delaying and preventing complications in Type 1 and 2 DM.[22] Diabetes should not be treated in isolation: do a *global* assessment of vascular risk, eg: BP, cholesterol,[1] obesity and smoking. ▸*Focus on education and lifestyle advice*. Promote exercise (to ↑insulin sensitivity), healthy eating and weight reduction—p228; NICE comments that drugs such as orlistat have a role here if weight loss of >2.5kg has been achieved by lifestyle advice and BMI >28kg/m^2. ▸*Find out what problems are being experienced* (eg glycaemic control, morale, erectile dysfunction—p214).

Assess vascular risk:

BP (BOX). Target is <140/<80mmHg (or <125/<75 with renal disease: ↑creatinine, microalbuminuria—see below, or dipstick proteinuria). BP control is critical for preventing macrovascular disease and mortality.[23] Discuss *smoking* and offer referral to cessation services. Check *cholesterol* (see below).

Look for complications

- Check injection sites for infection or lipohypertrophy (fatty change): advise on rotating sites of injection if present.
- *Vascular disease* Commonest cause of death. MI is 3-5 times commoner in DM and is more likely to be 'silent' (without classic symptoms). Stroke is ~ twice as common. Women are at high risk—DM removes the cardiovascular advantage conferred by the female gender. Address other risk factors—diet, smoking, hypertension (p79). Consider statin therapy, eg simvastatin 40mg nocte esp. if evidence of IHD, peripheral or cerebrovascular disease, or if microalbuminuria (indicates ↑vascular risk). Fibrates are useful for ↑triglycerides and ↓HDL (p682). Aspirin 75mg reduces cardiovascular risk and is recommended as statin co-therapy (safe to use in diabetic retinopathy).
- *Nephropathy* (p301) Microalbuminuria is when urine dipstick is -ve for protein but the urine albumin:creatinine ratio is raised (p306). This reflects early renal disease and is a marker for ↑vascular risk. If microalbuminuria or proteinuria is present, inhibiting the renin-angiotensin system, regardless of BP, protects against worsening renal failure. Use ACE-i (p123) or AT-2 blocker (p301).
- *Diabetic retinopathy* Blindness is uncommon and *preventable*. *Arrange annual fundoscopy or retinal photography for all patients*. Refer to an ophthalmologist if pre-proliferative changes or if any uncertainty at or near the macula (the only place capable of 6/6 vision). ▸Pre-symptomatic screening enables laser photocoagulation to be used, aimed to stop production of angiogenic factors from the ischaemic retina. Indications: maculopathy or proliferative retinopathy. *Background retinopathy:* Microaneurysms (dots), haemorrhages (blots), and hard exudates (lipid deposits). Refer to a specialist if changes are near the macula. *Pre-proliferative retinopathy:* Cotton wool spots (infarcts), haemorrhages, venous beading. These are signs of retinal ischaemia. Refer to a specialist. *Proliferative retinopathy:* New vessels form. Needs *urgent* referral. *Maculopathy:* This is often not visible at an early stage. Suspect if visual acuity↓.

  Pathogenesis: Capillary endothelial change → vascular leak → microaneurysms → capillary occlusion → local hypoxia + ischaemia → new vessel formation. High retinal blood flow caused by hyperglycaemia (& BP ↑ & pregnancy) triggers this, causing capillary pericyte damage. Microvascular occlusion causes ***cotton-wool spots*** (± ***blot haemorrhages*** at interfaces with perfused retina). ***New vessels*** form on the disc or ischaemic areas, proliferate, bleed, fibrose, and can detach the retina. Aspirin[1] (2mg/kg/d) may prevent it: there is no evidence that it ↑ bleeding.
- *Cataracts:* May be juvenile 'snowflake' form, or 'senile'—which occur earlier in diabetic subjects. Osmotic changes in the lens induced in acute hyperglycaemia reverse with normoglycaemia (so wait before buying glasses).
- *Rubeosis iridis:* New vessels on iris: occurs late and may lead to glaucoma.
- *Metabolic complications:* p814. *Diabetic feet:* p196. *Neuropathy:* p196.

Starting insulin in those with type 2 DM

This is indicated when control with oral agents is suboptimal (eg Hb_{A1c} >7.5- 8.0% on maximum oral therapy). Transfer is supervised by a diabetes nurse specialist and dietician. Insulin (p193) may be given initially once or twice a day. Continue metformin to limit weight gain. NICE has commented that long-acting insulin glargine (p193) is not normally needed in this context, unless there is recurrent symptomatic hypoglycaemia or it is necessary to avoid twice daily insulin doses (eg if assistance is needed to inject).

Controlling BP in those with diabetes—3 typical scenarios

1. BP <145/80 and no microalbuminuria and 10yr coronary event risk (CER10, p642) ≤15%, simply check BP every 6 months, or more often.
2. BP ≥ 140/80 and <160/100 and CER10 >15%, but no microalbuminuria, start an antihypertensive (NICE recommends ACE-i, A2A, ß-blocker, or a thiazide). Target BP <140/80. For doses and discussion, see p126.
3. BP ≥ 140/80 and microalbuminuria is present: ensure ACE-i or A2A are part of the approach (unless CI, p123). Target BP: <125/75.

▸Aspirin prophylaxis (75mg/d PO) is indicated, eg if CER10 >15%.[1]

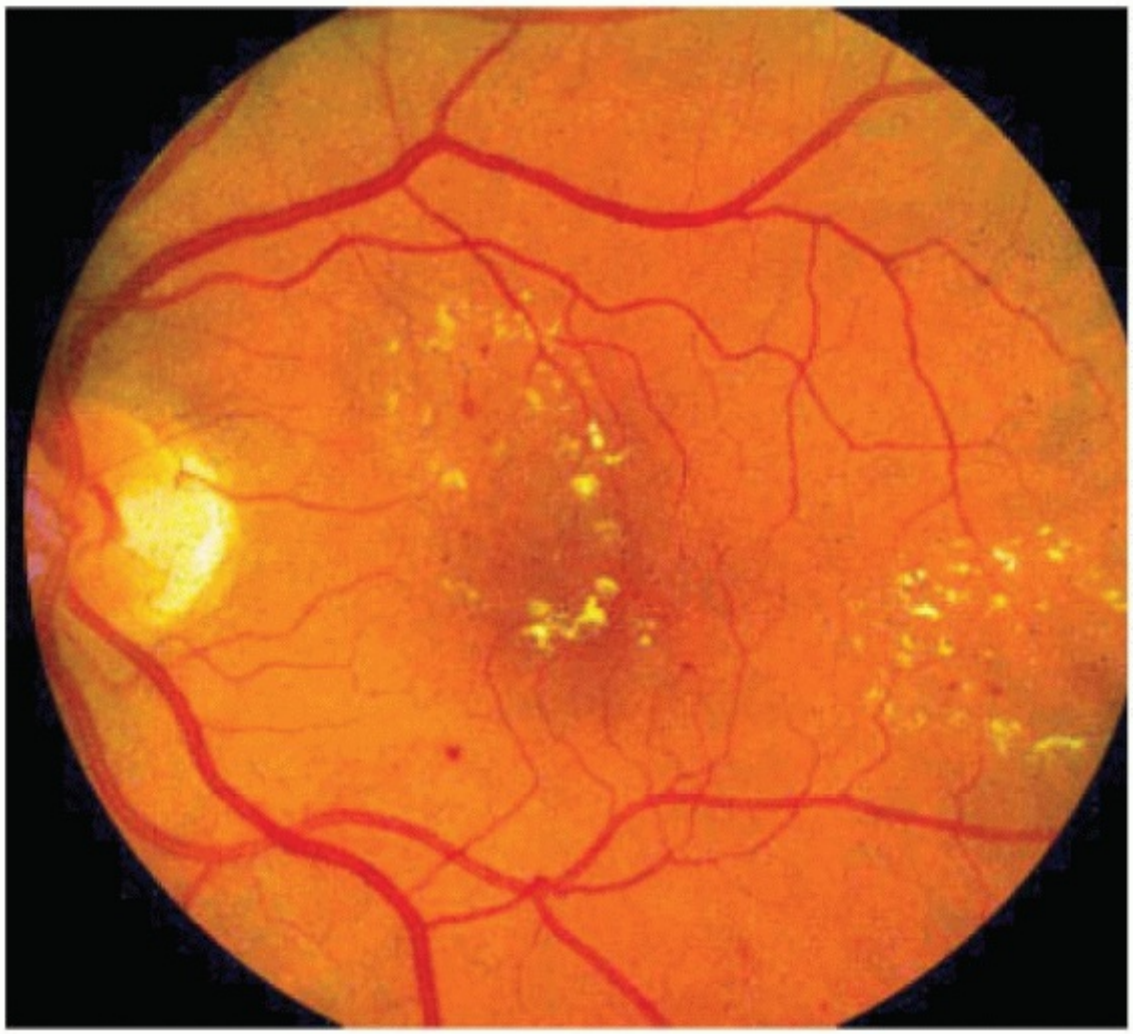


Fig 1. Background retinopathy, with microaneurysms and hard exudates.[24]

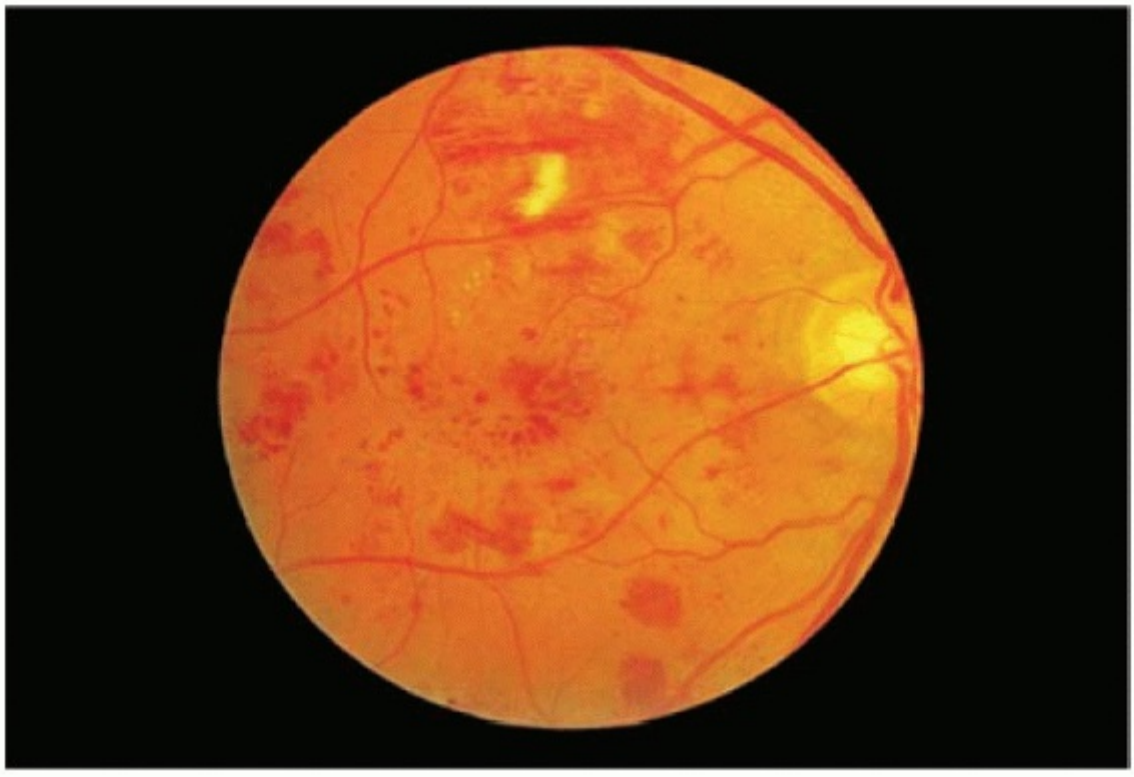


Fig 2. Pre-proliferative retinopathy, with haemorrhages and a cotton-wool spot.

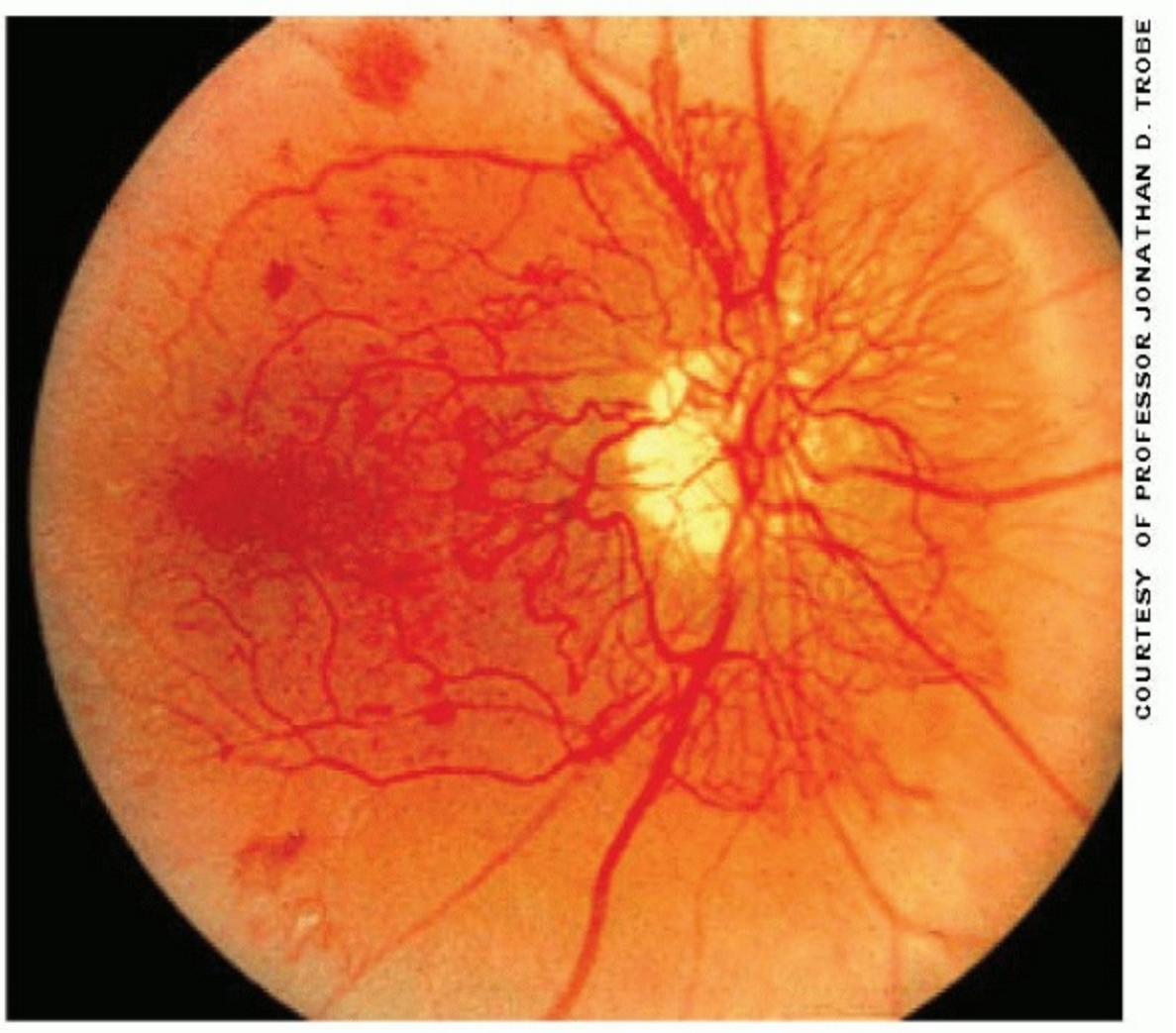


Fig 3. Proliferative retinopathy, with new vessel formation and haemorrhages.[25]

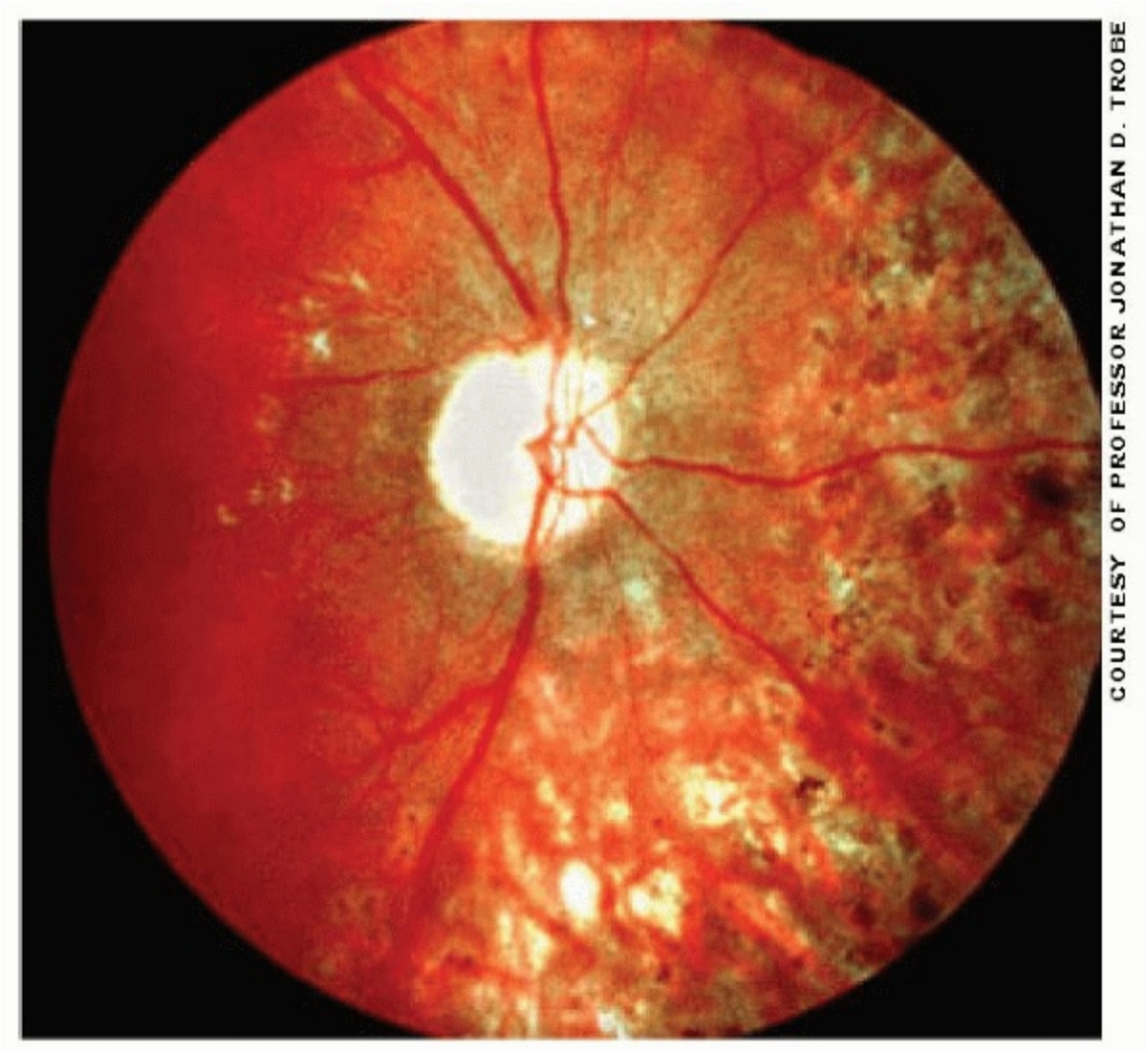


Fig 4. Scars from previous laser photocoagulation.[26]

Diabetic neuropathy and diabetic foot care

▸*Amputation is preventable: good care saves legs*. Examine feet regularly. Distinguish between ischaemia (critical toes ± absent dorsalis pedis pulses) and peripheral neuropathy (injury or infection over pressure points, eg the metatarsal heads). In practice, many have both.

Signs

Neuropathy: Sensation↓ (especially vibration) in 'stocking' distribution, absent ankle jerks, neuropathic deformity: pes cavus, claw toes, loss of transverse arch, rocker-bottom sole. Sensory loss is patchy, so examine all areas using a monofilament. *Ischaemia:* If the foot pulses cannot be felt, do Doppler pressure measurements. Any evidence of neuropathy or vascular disease puts the patient at high risk of foot ulceration. Educate (daily foot inspection; comfortable shoes—ie very soft leather, increased depth, cushioning insoles; weight-distributing cradles; no barefoot walking,[27] no corn-plasters). Regular chiropody to remove callus, as haemorrhage and tissue necrosis may occur below, leading to ulceration. Treat fungal infections (p428).

Foot ulceration

Usually painless, punched-out ulcer in an area of thick callus ± superadded infection. Can lead to cellulitis, abscess and osteomyelitis.

Assess degree of

1 Neuropathy (clinical). 2 Ischaemia (clinical and Dopplers; consider angiography). 3 Bony deformity, eg Charcot joint (clinical, x-ray). 4 Infection (swabs, blood culture, XR for osteomyelitis, probe ulcer to assess depth).

Management

Regular chiropody to remove callus. Relieve high-pressure areas with bedrest ± therapeutic shoes (Pressure Relief Walkers® and similar shoes may be as good as total contact casts[28]); metatarsal head surgery may be needed. If there is cellulitis, admit for IV antibiotics. Common organisms are *staphylococci*, *streptococci* and occasionally anaerobes. Start with benzylpenicillin 1.2g/6h IV and flucloxacillin 1g/6h IV ± metronidazole 500mg/8h IV, refined when microbiology results are known. Normoglycaemia improves healing—treat with IV insulin if needed. Get surgical help.

Absolute indications for surgery

- Abscess or deep infection
- Severe ischaemia—gangrene/rest pain
- Spreading anaerobic infection
- Suppurative arthritis

The degree of peripheral vascular disease, patient's general health, and patient request will determine whether local excision and drainage, vascular reconstruction, and/or amputation (and how much) is appropriate.

Types of neuropathy in diabetes

Sensory neuropathy

Symmetric sensory polyneuropathy—distal numbness ('glove and stocking' distribution), tingling, and pain, often worse at night. *Order of drugs to try*: aspirin/paracetamol → tricyclic (amitriptyline 10-25mg nocte; gradually ↑; max 150mg) → gabapentin. *Alternatives:* carbamazepine (p484); lamotrigine;[29] 0.075% capsaicin cream (a counter-irritant). Decompression may help.[30]

Mononeuritis multiplex

Especially III & VI cranial nerves. Treatment is difficult. If sudden and severe, immunosuppression with corticosteroids, IV immunoglobulins, and ciclosporin has been tried.[31]

Amyotrophy

Painful wasting of quadriceps and other pelvifemoral muscles. Use electrophysiology to show eg lumbosacral radiculopathy, plexopathy, or proximal crural neuropathy.[32] Natural course: variable with gradual but often incomplete improvement. IV immunoglobulins have been used.[33]

Autonomic neuropathy

(p494) Postural BP drop; ↓cerebrovascular autoregulation; gastroparesis; urine retention; erectile dysfunction (ED); diarrhoea. The latter may respond to codeine phosphate (the lowest dose to control symptoms, eg 15mg/8h PO). Gastroparesis (early satiety, post-prandial bloating, nausea/vomiting) is diagnosed by gastric scintigraphy with a ^{99}technetium-labelled meal.[34] It may respond to anti-emetics, or tetracycline if there is bacterial overgrowth. Postural hypotension may respond to fludrocortisone 100-300µg/24h PO (SE: oedema, ↑BP).

Preventing loss of limbs: primary or secondary prevention?

Traditionally prevention involves foot care advice in diabetic clinics (eg 'don't go bare-foot …'), and maintaining good glycaemic and BP control.[1] But despite this, the sight of a diabetic patient minus one limb is not rare: whenever we see such patients we should redouble our commitment to primary prevention—ie stopping those at risk from ever getting diabetes. In one randomized prospective study of those with impaired glucose tolerance (IGT) and other risk factors, after 3 yrs, the incidence of diabetes per 100 person-years was 5 in those receiving simple exercise and diet advice, 8 in a group given metformin, and 11 in the placebo group. Advice and metformin decreased incidence of diabetes by 58% (NNT ≈7) and 31% (NNT ≈14), respectively, compared with placebo.[35] One vital group to focus on are those with the metabolic syndrome.[2]

[2] **Metabolic syndrome** is central obesity or BMI >30 plus any 2 of: • Triglycerides ≥1.7mmol/L • HDL <1.03 • BP ≥130/85mmHg • Fasting glucose ≥5.6mmol/L or type 2 DM. There is also insulin resistance, but it is hard to measure, and is not part of the operational definition (nor is a glucose tolerance test essential). See K Alberti 2006 *Diabetic Medicine* 23 469-80

Waist circumference for central obesity

Europeans	♂ ≥94cm; ♀ ≥80cm
South (S) Asians	♂ ≥90cm; ♀ ≥80cm
Chinese	♂ ≥90cm; ♀ ≥80cm
Japanese	♂ ≥85cm; ♀ ≥90cm

S & Central Americans use S Asian *pro tem*

Africans + Middle East use European *pro tem*

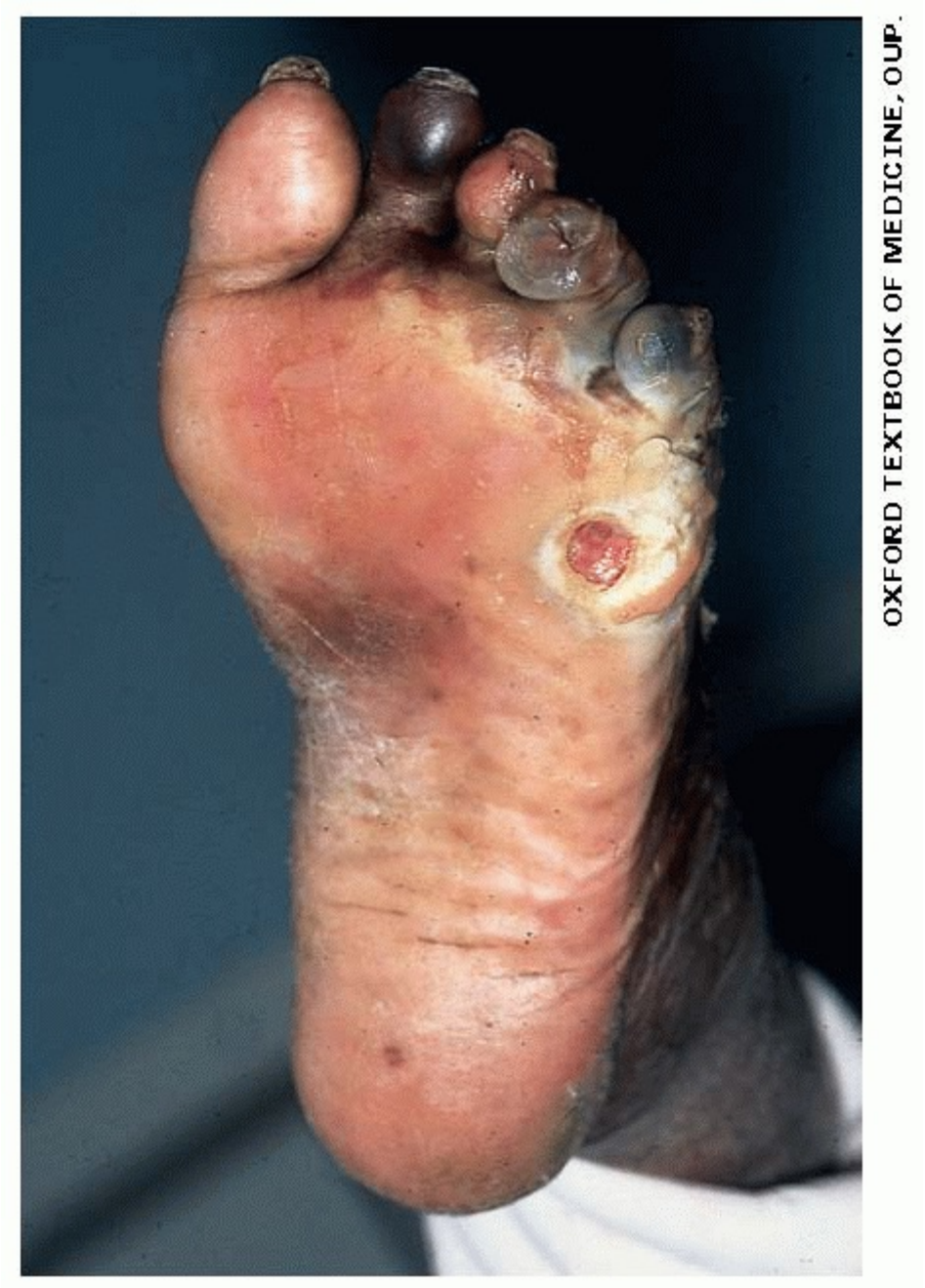


Fig 1. Diabetic foot: a typical punched-out neuropathic ulcer on the lateral sole, with gangrene of toes 2, 4, and 5.

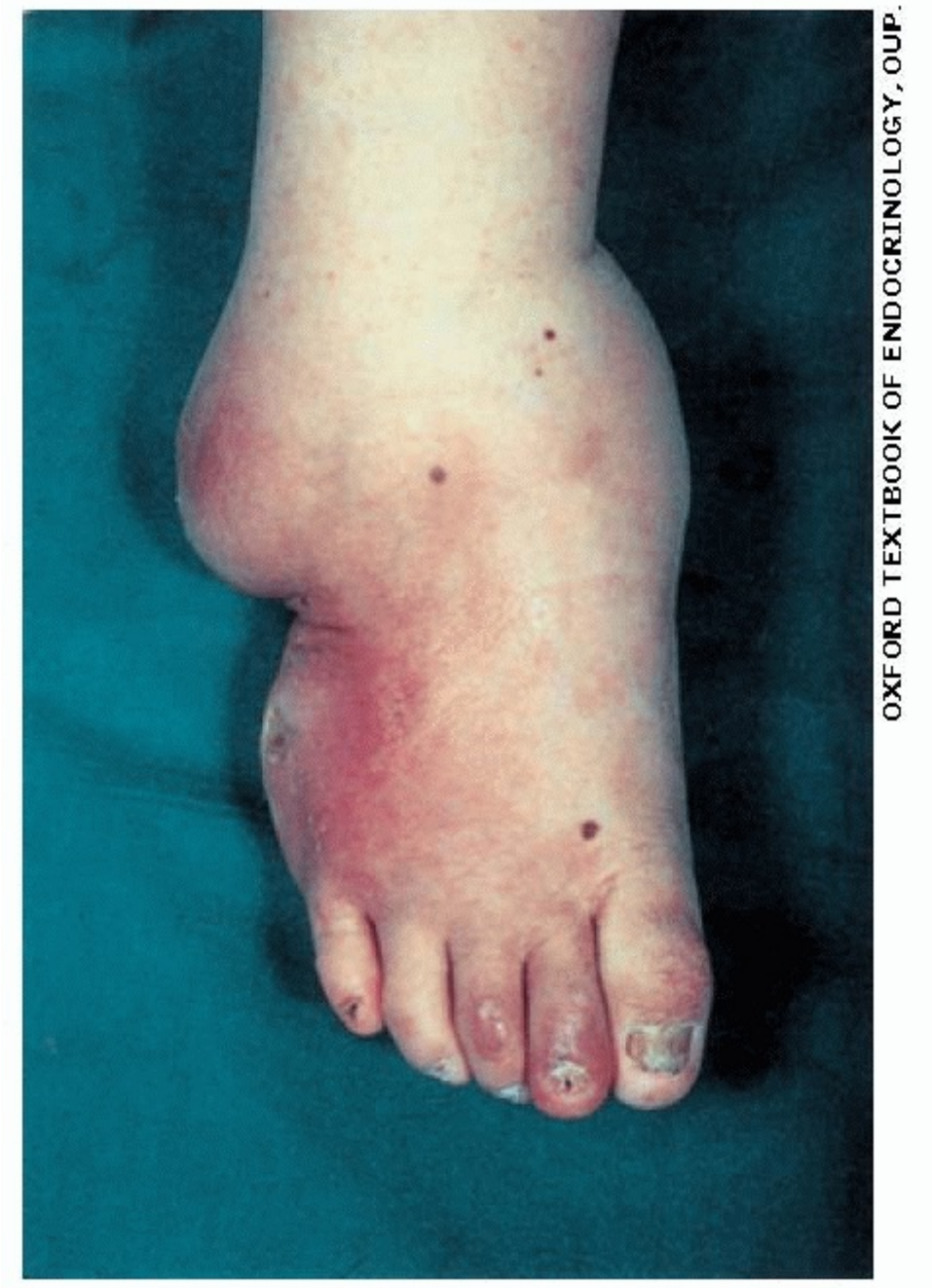


Fig 2. Charcot (neuropathic) joint, caused by loss of pain sensation, leading to ↑mechanical stress (unimpeded by pain) and repeated joint injury. Swelling, instability and, eventually, deformity, may develop, as seen here. ▸Early recognition is essential. Treatment: rest (bed rest or non-weight bearing crutches) and immobilisation by a total contact cast until oedema and local warmth reduce and bony repair is complete (~2-3 months). The role of bisphosphonates is under investigation. Charcot joints are also seen in tabes dorsalis, syringomyelia, and leprosy. For an X-ray, see p526.

Hypoglycaemia

▸This is the commonest endocrine emergency—see p816. Prompt diagnosis and treatment is essential—brain damage & death can occur in severe prolonged cases.

Definition

Plasma glucose <3mmol/L. Individual threshold for symptoms varies.

Symptoms

- *Autonomic*—Sweating, anxiety, hunger, tremor, palpitations.
- *Neuroglycopenic*—Confusion, drowsiness, seizures, coma. Rarely focal symptoms, eg transient hemiplegia. Mutism, personality change, restlessness and incoherence may lead to misdiagnosis of alcohol intoxication or even psychosis.[36]

Two types:

Fasting hypoglycaemia

(requires full investigation if documented).

Causes:

By far the commonest cause is insulin or sulfonylurea treatment in a known diabetic eg with ↑activity, missed meal, accidental or non-accidental overdose. In the *non-diabetic* subject with fasting hypoglycaemia, the following mnemonic is useful: **EXPLAIN**

Exogenous drugs, eg *insulin*, *oral hypoglycaemics* (p192). Does he/she have access to these (diabetic in the family)? Body-builders may misuse insulin to improve stamina.  *Alcohol*, eg alcoholic on binge with no food. Also: *aspirin poisoning; pentamidine; quinine sulfate; aminoglutethamide*.

Pituitary insufficiency.

Liver failure, plus some rare inherited enzyme defects.

Addison's disease.

Islet cell tumours (insulinoma, see below) and immune hypoglycaemia (eg anti-insulin receptor antibodies in Hodgkin's disease).

Non-pancreatic neoplasms (especially retroperitoneal fibrosarcomas and haemangiopericytomas, typically due to IGF-1 secretion).

Diagnosis and investigations

- Document hypoglycaemia by taking finger-prick (on filter-paper at home for later analysis) during attack and lab glucose if in hospital (monitors are often not reliable at low readings).
- Take a drug history and exclude liver failure.
- Admit for 72h fast. Take blood samples for glucose, insulin, C-peptide and plasma ketones if symptomatic.

Interpreting results

- Hypoglycaemia with high or normal insulin and no elevated ketones. *Causes:* Insulinoma, sulfonylureas, insulin administration (no detectable C-peptide — only released with endogenous insulin).
- Insulin low or undetectable, no excess ketones. *Causes:* Non-pancreatic neoplasm; anti-insulin receptor antibodies.
- Insulin↓, ketones↑. *Causes:* Alcohol, pituitary insufficiency, Addison's disease.

Post-prandial hypoglycaemia

May occur after gastric surgery (‘dumping’, p636), and in type 2 diabetes.

Investigation:

Prolonged OGTT (5h, p190).

Treatment

▸▸See p816. Treat with oral sugar, and a long-acting starch (eg toast); If cannot swallow, 25-50ml 50% glucose IV (via large vein with 0.9% saline flush to prevent phlebitis) or glucagon 1mg IM if no IV access (short duration of effect so repeat after 20min and *follow with oral carbohydrate*). If episodes are often, advise many small high-starch meals. If post-prandial glucose↓, give slowly absorbed carbohydrate (high fibre). In diabetics, rationalise insulin therapy (p193).

Insulinoma

This pancreatic islet cell tumour is associated with MEN-1 (p207), and is usually benign. It presents as fasting hypoglycaemia, with Whipple's triad: 1 Symptoms associated with fasting or exercise 2 Recorded hypoglycaemia with symptoms 3 Symptoms relieved with glucose.

Screening test:

Hypoglycaemia + plasma insulin ↑ during a long fast.

Suppressive tests:

Give IV insulin and measure C-peptide. Normally exogenous insulin suppresses C-peptide production, but this does not occur in insulinoma.

Imaging:

CT/MRI ± endoscopic pancreatic US (all fallible, so don't waste too much time before proceeding to intra-operative visualization[38] ± intra-operative ultrasound).[39]

Treatment:

Surgical excision.

Thyroid function tests (TFTs)

Physiology

The hypothalamus secretes thyrotrophin releasing hormone (TRH), a tripeptide, which stimulates production of thyroid stimulating hormone (TSH), a glycoprotein, from the anterior pituitary. TSH ↑production and release of thyroxine (T4) and triiodothyronine (T3) from the thyroid, which exert negative feedback on TSH production. The thyroid produces mainly T4, which is 5-fold less active than T3. 85% of T3 is formed from peripheral conversion of T4. Most T3 and T4 in plasma is protein bound, mainly to thyroxine-binding globulin (TBG). The *unbound* portion is the active part. T3 and T4 ↑cell metabolism, via nuclear receptors, and are thus vital for growth and mental development. They also ↑catecholamine effects.

Thyroid hormone abnormalities are usually due to problems in the thyroid gland itself, and rarely caused by the hypothalamus or the anterior pituitary.

Basic tests

Measurement of free T4 and T3 levels is more useful than total T4 and T3 levels as the latter are affected by TBG. Total T4 and T3 are ↑ when TBG is ↑ and vice versa. Free T3 and T4 levels are unaffected. TBG is ↑ in pregnancy, oestrogen therapy (HRT, oral contraceptive pill) and hepatitis. TBG is ↓ in nephrotic syndrome and malnutrition (protein loss), drugs (eg androgens, corticosteroids, phenytoin), chronic liver disease and acromegaly.

- *Hyperthyroidism suspected:* Ask for T3, T4, and TSH. In hyperthyroidism, all will have ↓TSH (except for the rare phenomenon of a TSH-secreting pituitary adenoma). Most have raised T4, but ~1% have only raised T3.
- *Hypothyroidism suspected or monitoring replacement treatment:* Ask for only T4, and TSH. Measuring T3 does not add any extra information.

↑TSH, ↓T4	Hypothyroidism
↑TSH, normal T4	Treated hypothyroidism or subclinical hypothyroidism
↑TSH, ↑T4	TSH secreting tumour or thyroid hormone resistance
↓TSH, ↑T4 or ↑T3	Hyperthyroidism
↓TSH, normal T4 & T3	Subclinical hyperthyroidism
↓TSH, ↓T4 and ↓T3	Sick euthyroidism (below) or pituitary disease
Normal TSH, abnormal T4	Consider changes in thyroid-binding globulin, assay interference, amiodarone or pituitary TSH tumour

Sick euthyroidism

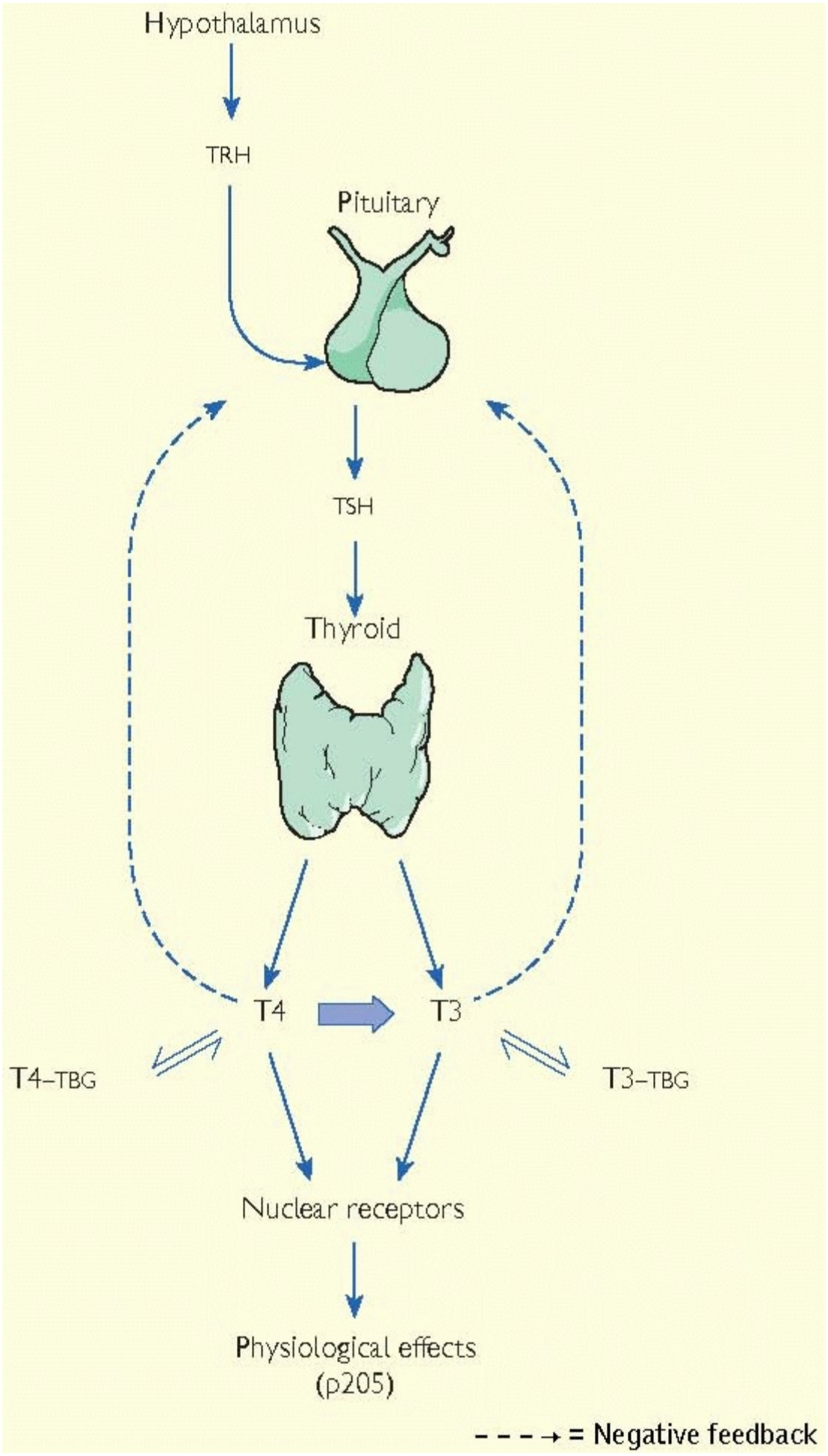
In any systemic illness, TFTs may become deranged. The typical pattern is for ‘everything to be low’. The test should be repeated after recovery.

Assay interference

is caused by antibodies in the serum, interfering with the test.

Other tests

- *Thyroid autoantibodies:* Antithyroid peroxidase (TPO) antibodies or antithyroglobulin antibodies may be increased in autoimmune thyroid disease: Hashimoto's or Graves' disease. If +ve in Graves', there is an increased risk of developing hypothyroidism at a later stage.
- TSH *receptor antibody:* May be ↑ in Graves' disease (useful in pregnancy).
- *Serum thyroglobulin:* Useful in monitoring the treatment of carcinoma (p622), and in detection of factitious (self-medicated) hyperthyroidism, where it is low.
- *Ultrasound:* This distinguishes cystic (usually, but not always, benign) from solid (possibly malignant) nodules. If there is a solitary large nodule, or dominant nodule in a multinodular goitre, a fine needle aspiration should be performed to look for thyroid carcinoma. See **fig 2**, p623.
- *Isotope scan:* (^{123}Iodine or ^{99}Technetium pertechnetate). Useful for determining the cause of hyperthyroidism. Also used to detect retrosternal goitre, ectopic thyroid tissue or thyroid metastases (using whole body CT scan). If there are suspicious nodules, the main question is: does the area have increased (hot), decreased (cold), or the same (neutral) uptake of isotope as the remaining thyroid? 20% of ‘cold’ nodules are malignant. Few neutral and almost no hot nodules are malignant. See also p724.



Screening thyroid function[40]

The following should be screened for abnormalities in thyroid function:

- Patients with atrial fibrillation.
- Patients with hyperlipidaemia (4-14% have hypothyroidism).
- Diabetes mellitus—on annual review.

- Women with Type 1 DM during 1st trimester and post delivery (3-fold rise in incidence of postpartum thyroid dysfunction).
- Patients on amiodarone or lithium (6 monthly).
- Patients with Down's or Turner's syndrome, or Addison's disease (yearly).

Thyrotoxicosis

Symptoms

Weight loss despite increased appetite (**NB:** paradoxical weight gain in 10-30%), heat intolerance, sweating, diarrhoea, tremor, irritability, frenetic activity, emotional lability, psychosis, itch, oligomenorrhoea—may cause infertility.

Signs

Pulse↑, AF, warm peripheries, fine tremor, palmar erythema, hair thinning, lid lag (eyelid lags behind eye's descent as patient watches your finger descend slowly), lid retraction (exposure of sclera above iris, causing 'stare'). There may be goitre (**fig 2**), thyroid nodules or bruit depending on the cause.

Graves' disease

only: 1 *Eye disease* (see BOX): exophthalmos, ophthalmoplegia. 2 *Pretibial myxoedema*: oedematous swellings above lateral malleoli: the term *myxoedema* is confusing here 3 *Thyroid acropachy*: extreme manifestation, with clubbing, painful finger and toe swelling, and periosteal reaction in limb bones.[41]

Tests

TSH↓ (suppressed), T4 and T3↑. There may be mild normocytic anaemia, mild leucopenia, ESR↑, Ca^{2+}↑, LFT↑.

Also:

Check thyroid autoantibodies. Isotope scan if the cause is unclear, to detect nodular disease or subacute thyroiditis. If ophthalmopathy, test visual fields, acuity, and eye movements (see BOX).

Causes

Thyrotoxicosis is the clinical and biochemical effect of excess thyroid hormone. This is usually due to hyperthyroidism, hyperfunction of the thyroid itself:

• *Graves' disease:* ♀:♂~9:1. Common between 30-50yrs. This is an autoimmune disease caused by stimulatory TSH-receptor antibodies (which also react with orbital autoantigens.[42]) There is diffuse thyroid enlargement. Patients are often hyperthyroid but may be, or become, hypo- or euthyroid. It is associated with other autoimmune diseases: vitiligo, type 1 DM, Addison's disease, p210.

• *Toxic multinodular goitre:* Seen in the elderly and in iodine-deficient areas.[43] There are nodules that secrete thyroid hormones. [prescription take]: Control the thyrotoxicosis first with medication, then follow with radioiodine. Surgery is indicated if there are compressive symptoms from the enlarged thyroid (dysphagia or dyspnoea).[44]

• *Toxic adenoma:* There is a solitary nodule producing T3 and T4. On isotope scan, the nodule is 'hot' (p200), and the rest of the gland is suppressed. [prescription take]: Radioiodine.

Others

(not hyperthyroidism) •*Subacute (de Quervain's) thyroiditis:* A self-limiting viral infection with painful goitre, fever and ↑ESR. There is low isotope uptake on scan. [prescription take]: NSAIDS. •*Drugs:* Amiodarone (p204), lithium (hypothyroidism is commoner.[45]) •*Exogenous:* Thyroxine intoxication causes ↑T4, ↓T3 and ↓thyroglobulin. Rarely seen with iodine excess eg contrast media, food contamination.[46] • *Ectopic thyroid tissue:* Metastatic follicular thyroid cancer[47], choriocarcinoma or struma ovarii: ovarian teratoma containing thyroid tissue.

Treatment

1. *Drugs:* ß-blockers (eg propranolol 40mg/6h) for rapid control of symptoms. *Anti-thyroid medication:* 2 strategies: 1 *Titration* eg carbimazole 20-40mg/24h PO for 4wks, reduce according to TFTs every 1-2 months. 2 *Blockreplace*: Give carbimazole and thyroxine simultaneously (less risk of iatrogenic hypothyroidism). In Graves', maintain on either regime for 12-18 months then withdraw. ~50% will relapse, requiring radioiodine or surgery. Carbimazole SE: agranulocytosis (↓↓neutrophils, can lead to life-threatening sepsis; rare (0.03% of patients) but serious—warn to stop and get an urgent FBC if signs of infection, eg fever, sore throat or mouth ulcers. Alternative: propylthiouracil.
2. *Radioiodine (^{131}I):* Most become hypothyroid post-treatment. There is no evidence for ↑cancer, birth defects or infertility in women. CI: pregnancy, lactation. Caution in active hyperthyroidism as risk of thyroid storm (p817).
3. *Thyroidectomy*: Carries a risk of damage to recurrent laryngeal nerve (hoarse voice) and hypoparathyroidism. Patients may become hypo- or hyperthyroid.
4. *In pregnancy and infancy*: Get expert help. See OHCS p25.

Complications

Heart failure (thyrotoxic cardiomyopathy, ↑ in elderly),[48] angina, AF (seen in 10-25%: control hyperthyroidism and warfarinize if no contraindication), osteoporosis, ophthalmopathy, gynaecomastia. ▸▸Thyroid storm (p817).

Thyroid eye disease

Thyroid eye disease is associated with Graves' disease in 25-50% of people with the condition. The main known risk factor is smoking. The eye disease may not correlate with thyroid disease and the patient can be euthyroid, hypothyroid, or hyperthyroid at presentation. Eye disease may be the first presenting sign of Graves' disease, and can also be worsened by treatment, typically with radioiodine (usually a transient effect). Retro-orbital inflammation and lymphocyte infiltration results in swelling of the orbit.

Symptoms

Eye discomfort, grittiness, excess tear production, photophobia. Diplopia, decreased acuity or an afferent pupillary defect (p68) may mean optic nerve compression: ▸*Seek expert advice immediately as decompression may be needed.* Nerve damage does not necessarily go hand-in-hand with protrusion. Indeed, if the eye cannot protrude for anatomical reasons, optic nerve compression is more likely—a paradox!

Signs

Exophthalmos—appearance of protruding eye; proptosis—eyes protrude beyond the orbit (look from above in the same plane as the forehead); conjunctival oedema; corneal ulceration; papilloedema; loss of colour vision. Ophthalmoplegia (especially of upward gaze) occurs due to muscle swelling and fibrosis.

Tests

Diagnosis is clinical. CT/MRI of the orbits may reveal enlarged eye muscles.

Management

Eye disease should be managed by a specialist. Treat hyper- or hypothyroidism. Advise to stop smoking as this worsens prognosis.[49] Most have mild disease which can be treated symptomatically ie artificial tears, sunglasses, avoid dust, elevate bed when sleeping to reduce periorbital oedema. Diplopia may be managed with a Fresnel prism stuck to one lens of a spectacle, so allowing for easy changing as the exophthalmos changes.

A minority experience more severe disease with ophthalmoplegia or gross oedema, and are treated with steroids, started at high dose (prednisolone 80mg/day PO), decreased gradually according to symptoms. Surgical decompression is used for severe sight-threatening disease, or for cosmetic reasons once the activity of eye disease has reduced. This is usually done by an inferior orbital approach, using space in the ethmoidal, sphenoidal, and maxillary sinuses. Eyelid surgery may improve cosmesis and function. Orbital radiotherapy can be used to treat ophthalmoplegia but has little effect on proptosis.

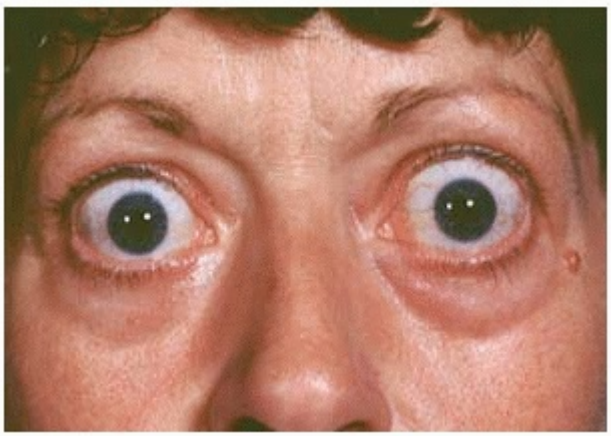


Fig 1. Thyroid eye disease: lid retraction causing a ‘staring’ appearance.

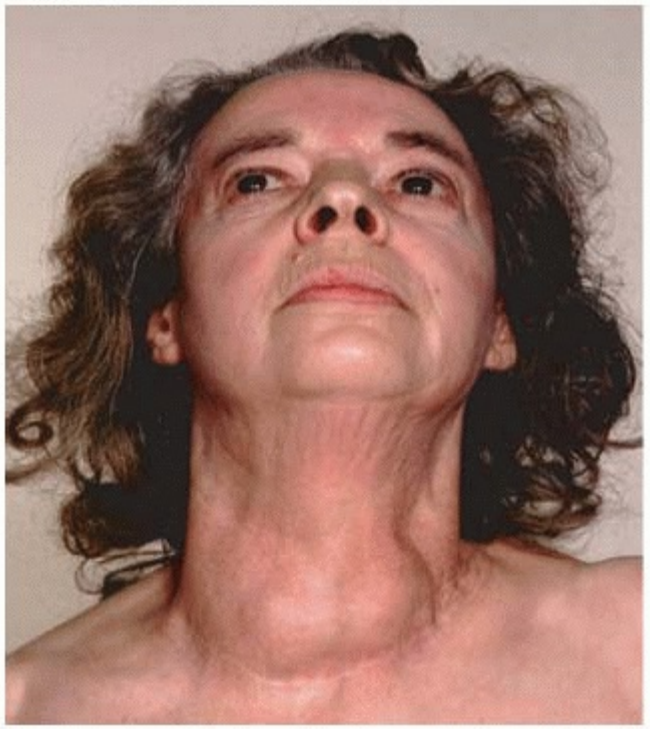


Fig 2. Goitre

Causes of goitre
Diffuse

- Physiological
- Graves' disease
- Hashimoto's thyroiditis
- Subacute (de Quervain's) thyroiditis (painful)

Nodular

- Multinodular goitre
- Adenoma
- Carcinoma

Hypothyroidism (myxoedema)

This is common and easy to treat. ▸*As it is insidious, both the patient and the doctor may not realize anything is wrong*, so be alert to subtle and non-specific symptoms, particularly in women over 40yrs old.

Symptoms

Tiredness, lethargy, depression, dislike of cold, weight gain, constipation, menorrhagia, hoarse voice, poor cognition/dementia, myalgia.

Signs

Bradycardia, dry skin and hair, non-pitting oedema (eyelids, hands, feet), cerebellar ataxia, slow relaxing reflexes, peripheral neuropathy, 'toad-like face'. There may be goitre depending on the cause, or signs of CCF or pericardial effusion.

Diagnosis

TSH↑, T4↓ (in secondary hypothyroidism: T4↓ and ↓ or normal TSH due to lack from the pituitary, p216). Cholesterol and triglyceride may be ↑. Occasionally normochromic macrocytic anaemia. See also p200.

Causes of primary hypothyroidism

(1) Autoimmune

- *Primary atrophic hypothyroidism:* ♀:♂~6:1. Common. Diffuse lymphocytic infiltration of the thyroid, leading to atrophy, hence no goitre.
- *Hashimoto's thyroiditis:* Autoimmune disease as above plus goitre due to lymphocytic and plasma cell infiltration. Commoner in older women, aged 60-70yrs. May be hypothyroid or euthyroid—occasionally initial period of hyperthyroidism ('Hashitoxicosis'). Autoantibody titres are very high.

Both are associated with other autoimmune diseases: Type 1 DM, Addison's disease, pernicious anaemia (p320).

(2) Acquired

- *Iodine deficiency:* Poor intake, commonest cause world-wide.
- *Post-thyroidectomy or radioiodine treatment.*
- *Drug-induced:* Antithyroid drugs, amiodarone, lithium, iodine.
- *Subacute thyroiditis:* Temporary hypothyroidism after hyperthyroid phase.

Secondary hypothyroidism

(from hypopituitarism, p216) is very rare.

Associations with hypothyroidism:[50]

Turner's syndrome, Down's syndrome, cystic fibrosis, primary biliary cirrhosis, POEMs syndrome (**p**olyneuropathy, **o**rganomegaly, **e**ndocrinopathy, **m**-protein band from a plasmacytoma + **s**kin pigmentation/ tethering).

Genetic:

Dyshormonogenesis: genetic (mostly autosomal recessive) defect in hormone synthesis. One form is Pendred's syndrome (with deafness): there is ↑uptake on isotope scan, which is displaced by potassium perchlorate.

Treatment

- *If healthy and young:* Levothyroxine (T4), 50-100μg/24h PO; review at 12wks. Adjust 6 weekly by clinical state and to normalize but not suppress TSH. Thyroxine's *t½* is ~7 days , so any change in dosage will take ~4 weeks to be assessed accurately by checking TSH.[51] Once normal, check TSH yearly. Metabolism of levothyroxine is increased by enzyme-inducers (p681).
- *If elderly or ischaemic heart disease:* Start with 25μg/24h; ↑dose by 25μg/ 4wks according to TSH (▸cautiously, as thyroxine may precipitate angina or MI).
- *If diagnosis is in question and* T4 *already given:* Stop T4; recheck TSH in 6wks.

The effects of amiodarone

on the thyroid are complex: it can cause both hypo- and hyperthyroidism. Effects are due both to the drug and the iodine contained within it. Hypothyroidism is caused by iodine excess, inhibiting thyroid hormone synthesis and release. Thyrotoxicosis is caused either by iodine excess, resulting in increased hormone synthesis, or by direct toxic effect causing thyroiditis and release of hormones. 2% of patients on amiodarone have clinically detectable thyroid abnormalities. Seek expert help. The *t½* of amiodarone is long (40-100d), so problems persist after withdrawal. If on amiodarone, check TFTs 6 monthly.

Thyroid disease in pregnancy and neonates

See OHCS p25.

Why are symptoms of thyroid disease so many, so various, and so subtle?

Almost all our cell nuclei have receptors showing a high affinity for T3: that known as TRα-1 is abundant in muscle and fat; TRα-2 is abundant in brain; and TRß-1 is abundant in brain, liver, and kidney. These receptors, via their influence on various enzymes, affect the following processes:

- The metabolism of substrates, vitamins, and minerals.
- Modulation of all other hormones and their target-tissue responses.
- Stimulation of O_2 consumption and generation of metabolic heat.
- Regulation of protein synthesis, and carbohydrate and lipid metabolism.
- Stimulation of demand for co-enzymes and related vitamins.

Subclinical thyroid disease [52]

Subclinical hypothyroidism

suspect if TSH↑, with normal T4 and T3, and no obvious symptoms. It is common: ~10% of those >55yrs old have a raised TSH. The risk of progression to

frank hypothyroidism is ~2%, and increases as TSH↑; risk doubles if thyroid autoantibodies are present, and is also increased in men.

Management:

- Confirm that raised TSH is persistent (recheck in 2-4 months).
- Recheck the history: if any non-specific features (eg depression), discuss benefits of treating (p204) with the patient: they may simply feel better, without realizing that they were not functioning optimally.
- One approach is to treat (with thyroxine) those with a TSH >10, positive thyroid autoantibodies, previously treated Graves' disease, or other organ-specific autoimmunity (Type 1 DM, myasthenia, pernicious anaemia, vitiligo), as these patients are more likely to progress to clinical hypothyroidism.[53] If the patient does not fall into any of these categories, monitor TSH annually.
- Risks from well-monitored treatment of subclinical hypothyroidism are small (but there is an ↑risk of atrial fibrillation and osteoporosis if over-treated).

Subclinical hyperthyroidism

occurs when TSH↓, with normal T4 and T3. Again, there is no consensus regarding management, with ongoing trials to assess whether treatment prevents subsequent complications of clinical hyperthyroidism (especially AF and osteoporosis).

Management:[54]

- Confirm that suppressed TSH is persistent (recheck in 2-4 months).
- Check for a non-thyroidal cause: illness, pregnancy, pituitary or hypothalamic insufficiency (suspect if T4 or T3 are in the lower end of the reference range), use of TSH suppressing medication eg thyroxine, steroids.
- If TSH <0.1, treat on an individual basis eg with symptoms of hyperthyroidism, AF, unexplained weight loss, osteoporosis, goitre.
- Options are antithyroid medication (carbimazole or propylthiouracil) or radioiodine therapy.
- If no symptoms, recheck 6 monthly.

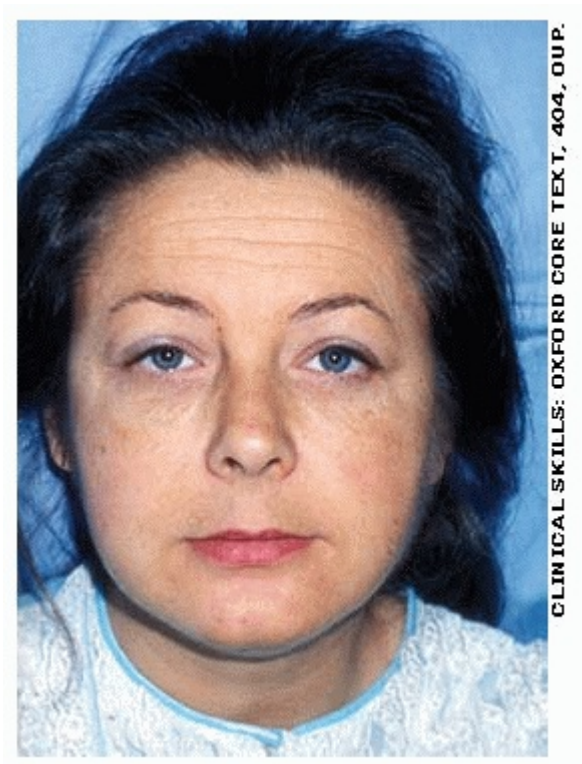


Fig 1. Facial appearance in hypothyroidism.

Parathyroid hormone and hyperparathyroidism

Parathyroid hormone (PTH) is normally secreted in response to low ionised Ca^{2+} levels, by 4 parathyroid glands situated posterior to the thyroid (p670). The glands are controlled by -ve feedback via Ca^{2+} levels. PTH acts by: • ↑ osteoclast activity releasing Ca^{2+} & PO_4^{3-} from bones; • ↑Ca^{2+} & ↓PO_4^{3-} reabsorption in the kidney; •Active 1,25dihydroxy-vitamin D_3 production is ↑. Overall effect is ↑Ca^{2+} & ↓PO_4^{3-}.

Primary hyperparathyroidism

Causes:

~80-85% solitary adenoma, ~15-20% hyperplasia of all glands, <0.5% parathyroid carcinoma.

Presentation:

Often asymptomatic, with ↑Ca^{2+} on routine tests. Symptoms relate to ↑Ca^{2+} (p672): weakness, tiredness, depression, dehydration[55], polyuria and polydipsia, renal stones, abdominal pain, pancreatitis, ulcers (duodenal: gastric ≈ 7 : 1; MEN1 can cause ↑PTH and Zollinger-Ellison syndrome).[56] Bone resorption effects of PTH can cause pain, fractures and osteopenia/osteoporosis. Also, there may be BP↑, and if untreated, long-term ↑cardiovascular risk and ↑mortality.[57]

Associations with multiple endocrine neoplasia (MEN):

See BOX.

Tests:

Ca^{2+}↑ & PTH↑ (or inappropriately normal). Differentials with these tests: thiazide diuretics, lithium, familial hypocalciuric hypercalcaemia, tertiary hyperparathyroidism. Also PO_4^{3-} ↓ (unless there is renal failure), alk phos↑ from bone activity, 24h urinary Ca^{2+}↑. *DEXA bone scan* to assess for osteoporosis (p674). **Osteitis fibrosa cystica** is bone marrow fibrosis and cyst formation, due to severe resorption (seen rarely now). *Appearances:* brown tumours, subperiosteal erosions of distal phalanges on hand x-ray, pepper-pot skull on skull x-ray.

Treatment:

Surgical excision, of the adenoma or of all 4 hyperplastic glands, prevents fractures and peptic ulcers.[58] *Indications:* high serum or urinary Ca^{2+}, bone disease, osteoporosis, renal calculi, ↓renal function, age $\leq$50y.[59] *Complications:* Hypoparathyroidism, recurrent laryngeal nerve damage (hoarse voice), post-op symptomatic Ca^{2+}↓ (hungry bones syndrome; check Ca^{2+} daily ≥14d post-op). Pre-op ultrasound & MIBI (methoxyisobutyl isonitrile) isotope scan may localise an adenoma; intra-operative PTH sampling is used to confirm removal.[60] *Recurrence:* ~8% of patients in 10yrs.[61] Mild symptoms may not merit surgery: advise ↑fluid intake to prevent stones, avoid thiazides or high Ca^{2+} & vit D intake, review 6 monthly. Cinacalcet is a new drug, which ↑sensitivity of the parathyroid cell to Ca^{2+} (∴ ↓PTH secretion); monitor Ca^{2+} within 1wk of any dose change; SE: myalgia; testosterone↓.

Secondary hyperparathyroidism

Ca^{2+}↓, PTH↑ (appropriately). *Causes:* As for hypocalcaemia (p670), eg low vitamin D intake, chronic renal failure (p294).

Tertiary hyperparathyroidism

Ca^{2+}↑, ↑↑PTH (inappropriately). Occurs after prolonged secondary hyperparathyroidism, causing glands to act autonomously having undergone hyperplastic or adenomatous change. This causes Ca^{2+}↑ from ↑↑secretion of PTH unlimited by feedback control. Seen in chronic renal failure.

Malignant hyperparathyroidism

Parathyroid-related protein (PTHrP) is produced by some squamous cell lung cancers, breast and renal cell carcinomas. This mimics PTH resulting in Ca^{2+}↑ (PTH is ↓, as PTHrP is not detected in the assay).

Hypoparathyroidism

Primary hypoparathyroidism

PTH secretion is ↓ due to gland failure.

Tests:

Ca^{2+}↓, PO_4^{3-}↑ or normal, alk phos normal.

Symptoms:

As in hypocalcaemia (p670).

Causes:

Autoimmune (associated with other autoimmune disorders—BOX 2), also congenital: Di George syndrome (OHCS p642).

[prescription take]:

Alfacalcidol.

Secondary hypoparathyroidism

Radiation, surgery (thyroidectomy, parathyroidectomy), hypomagnesaemia (magnesium is required for PTH secretion).

Pseudohypoparathyroidism

Failure of target cell response to PTH.

Signs:

Short metacarpals (esp 4th and 5th), round face, short stature, mental retardation.

Tests:

Ca^{2+}↓, ↑PTH, alk phos ↔ or ↑.

Treatment:

As for 1° hypoparathyroidism.

Pseudopseudohypoparathyroidism

The morphological features of pseudohypoparathyroidism, but with normal biochemistry. The cause for both is genetic.[62]

Multiple endocrine neoplasia (MEN)

The **MEN** syndromes are a group of genetic syndromes inherited in an *autosomal dominant* manner, where there are functioning hormone-producing tumours in multiple organs.[63] They comprise of:

- MEN1 & 2
- Neurofibromatosis (p506)
- Von Hippel Lindau syndrome (p704).
- Peutz-Jeghers' syndrome (p700).[64]
- Carney complex: This consists of spotty skin pigmentation, schwannomas, myxoma of skin, mucosa or heart (especially atrial myxoma), and endocrine tumours: eg pituitary adenoma, adrenal hyperplasia, testicular tumour.[65]

MEN type-1 (=MEN1):

Parathyroid hyperplasia/adenoma (~95%; most ~Ca^{2+}).

Pancreatic endocrine tumours (~70%)—usually gastrinoma (p708) or insulinoma (p198), rarely, somatostatinoma,[1] glucagonomas or VIPoma (p238).

Pituitary adenoma (~50%)—usually prolactinoma or GH secreting tumour (acromegaly: p218).

Also, adrenal and carcinoid tumours are associated.

The MEN1 gene is a tumour suppressor gene. Menin, its protein, alters transcription activation.[66] Many are sporadic, presenting in the 3rd-5th decades.

MEN2a:

Thyroid: Medullary thyroid carcinoma (seen in ~100%, p622)

Adrenal: Phaeochromocytoma (~50%, usually benign and bilateral)

Parathyroid hyperplasia (~80%, but less than 20% have ↑Ca^{2+}).[67][68]

MEN2b[69]

has similar features to MEN2a plus mucosal neuromas and Marfanoid appearance (p698), but no hyperparathyroidism.[70] Mucosal neuromas consist of 'bumps' on: lips, cheeks, tongue, glottis, eyelids, and visible corneal nerves.[71]

The gene involved in MEN2a and b is the *ret* proto-oncogene, a receptor tyrosine kinase. Tests for *ret* mutations are revolutionizing MEN2 treatment by enabling a prophylactic thyroidectomy to be performed before neoplasia occurs, usually done before 3 yrs of age.[72] **NB:** *ret* mutations rarely contribute to sporadic parathyroid tumours.

Autoimmune polyendocrine syndromes [73]

Autoimmune disorders cluster into two defined syndromes:

Type 1:

Autosomal recessive, rare.

Cause:

Mutations of **AIRE** (**A**uto **I**mmune**RE**gulator) gene on chromosome 21.

Features:

- Addison's disease
- Chronic mucocutaneous candidiasis
- Hypoparathyroidism.

Also associated with primary hypogonadism, pernicious anaemia, autoimmune primary hypothyroidism, chronic active hepatitis, vitiligo, alopecia.

Type 2:

HLA D3 and D4 linked, common.

Cause:

Polygenic.

Features:

- Addison's disease
- Type 1 diabetes mellitus (in 20%).
- Autoimmune thyroid disease—hypothyroidism or Graves' disease.

Also associated with primary hypogonadism, vitiligo, alopecia, pernicious anaemia, chronic atrophic gastritis, coeliac disease, dermatitis herpetiformis.

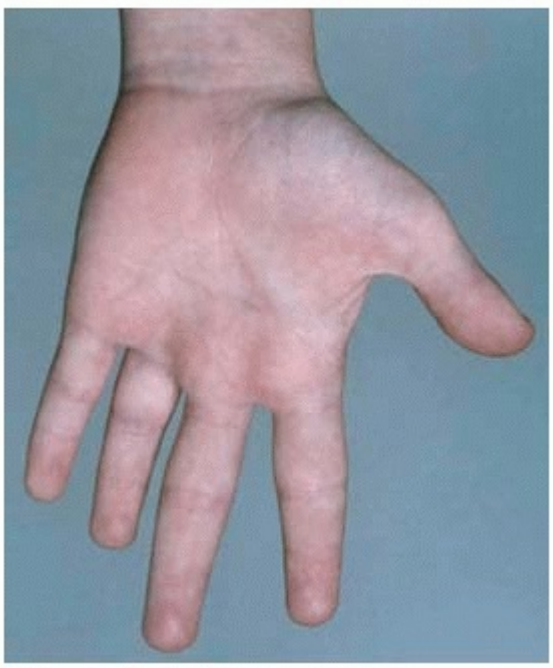


Fig 1. Pseudohypoparathyroidism: short 4th & 5th metacarpals.

Adrenal cortex and Cushing's syndrome

Physiology

The adrenal cortex produces steroids: 1 *Glucocorticoids* (eg cortisol), which affect carbohydrate, lipid and protein metabolism, 2 *Mineralocorticoids*, which control sodium and potassium balance (eg aldosterone, p664), and 3 *Androgens*, sex hormones which have weak effect until peripheral conversion to testosterone and dihydrotestosterone. Corticotrophin-releasing factor (CRF) from the hypothalamus stimulates ACTH secretion from the pituitary, which in turn stimulates cortisol and androgen production by the adrenal cortex. Cortisol is excreted as urinary free cortisol and various 17-oxogenic steroids.

Cushing's syndrome

This is chronic glucocorticoid excess. The commonest cause is steroid treatment. Endogenous causes are much rarer: 85% are due to ↑ACTH, of these a pituitary adenoma (Cushing's disease) is the commonest cause.

1 ACTH-dependent causes: (↑ACTH)

- *Cushing's disease* Bilateral adrenal hyperplasia due to an ACTH secreting pituitary adenoma (usually a microadenoma, p218). ♀:♂>1. Peak age: 30-50yrs.
- *Ectopic* ACTH *production* Especially small cell lung cancer and carcinoid tumours, p270. Specific features: pigmentation (due to ↑↑ACTH), hypokalaemic metabolic alkalosis (↑↑cortisol leads to mineralocorticoid activity), weight loss, hyperglycaemia. Classical features of Cushing's are often absent.
- Rare: *Ectopic* CRF *production*—reported with medullary thyroid carcinoma and prostate carcinoma. *Iatrogenic* ACTH administration.

2 ACTH-independent causes: (↓ACTH due to -ve feedback)

- *Iatrogenic* Pharmacological doses of steroids (common).
- *Adrenal adenoma* or *carcinoma* Carcinoma may be associated with abdominal pain and virilization in women (p214).

- *Adrenal nodular hyperplasia*
- Rare: *Carney complex* p207. *McCune Albright syndrome* OHCS p650.

The patient

Symptoms:

Weight↑, mood change (depression, lethargy, irritability), proximal weakness, gonadal dysfunction: ♂: impotence. ♀: irregular menses, hirsutism, acne.

Signs:

Central obesity, moon face, neck (buffalo hump) and supraclavicular fat distribution, thin skin, bruising, purple abdominal striae, osteoporosis (±fractures), hypertension, impaired glucose tolerance or overt diabetes mellitus (30%), predisposition to infection, slow wound healing.

Tests

See BOX. *Pitfalls:* (1) Random cortisol measurements are of no value, as levels are affected by diurnal variation, stress (including venepuncture), and illness. (2) Imaging cannot be relied on alone to localise the cause: Non-functioning 'incidentalomas' occur in ~5% on adrenal CT and ~10% on pituitary MRI. Also, MRI detects only ~70% of pituitary tumours causing Cushing's, as they may be too small.

Treatment

Depends on the cause.

- *Iatrogenic:* Stop medications if possible.
- *Cushing's disease:* Selective removal of pituitary adenoma via a transsphenoidal approach. Bilateral adrenalectomy if the source cannot be located, or recurrence post-surgery (complications include *Nelson's syndrome*: post adrenalectomy development of a locally aggressive pituitary tumour (corticotrophinoma) due to lack of -ve feedback, p700). Pituitary radiotherapy is effective in children, and is used in adults to prevent Nelson's syndrome.
- *Adrenal adenoma or carcinoma:* Adrenalectomy: curative for adenoma, rarely for carcinoma. Radiotherapy & adrenolytic drugs (mitotane) follow if carcinoma.
- *Ectopic* ACTH: Surgery if the tumour can be located and has not spread.
- Medical treatment, eg metyrapone or ketoconazole, are used to reduce cortisol secretion pre-surgery or while awaiting radiation to become effective.

Prognosis

Untreated Cushing's syndrome has an increased mortality rate, due to cardiovascular complications.[74] Treated Cushing's syndrome has a good prognosis, usually with resolution of physical features and psychological disorders. However, osteoporosis, hypertension, obesity, subtle mood changes, glucose intolerance or diabetes mellitus may persist, which require follow up and addressing individually.

Investigation of suspected Cushing's syndrome[75]

First, confirm the diagnosis (a raised cortisol), then localize the source on the basis of laboratory testing. Use imaging studies to confirm the likely source.

(1) 1st line screening tests

- The *overnight dexamethasone suppression test* is a useful outpatient test. Give dexamethasone 1mg PO at midnight; check serum cortisol before, and at 8AM. In normal patients, this high dose of steroid causes -ve feedback, ↓ACTH and ↓cortisol secretion to <50nmol/L. In Cushing's syndrome, there is a failure to suppress cortisol secretion. False -ve rate: <2%; **False +ves**: 2% normal, 13% obese and 23% of hospital inpatients.
- *24*h *urinary free cortisol* (normal: <280nmol/24h) is an alternative.

NB : False +ves ('Pseudocushing's') are seen in depression, obesity, alcohol excess, and inducers of liver enzymes which ↑ the rate of dexamethasone metabolism (eg phenytoin, phenobarbital, and rifampicin, p681).

(2) 2nd line screening tests, if above abnormal:

- The *48*h *dexamethasone suppression test:* Give dexamethasone 0.5mg/6h PO for 2d. Measure cortisol at 0 and 48h (last test at 6h after last dose). Again, in Cushing's syndrome, there is a failure to suppress cortisol secretion.
- *Midnight cortisol:* Requires admission. Often inaccurate due to difficulties in measurement. Normal circadian rhythm (cortisol *lowest* at midnight, *highest* early in the morning) is lost in Cushing's syndrome. Cortisol level is taken at midnight, via a cannula whilst the patient is asleep, and is ↑ in Cushing's.

(3) Localization tests (where is the lesion?)—If the above are positive.

- *Plasma* ACTH: If ACTH is undetectable, an adrenal tumour is likely → CT adrenal glands. If no mass is seen, proceed to adrenal vein sampling or adrenal scintigraphy (radiolabelled cholesterol derivative). If ACTH is detectable, distinguish a pituitary cause from ectopic ACTH production by the following:
  - *High-dose dexamethasone suppression test:* Give dexamethasone 2mg/6h PO for 2d. Measure plasma and urinary cortisol at 0 and 48h.

Complete or partial suppression indicates Cushing's disease as the pituitary retains some feedback control. An ectopic source is not under feedback control.

- Or *corticotrophin releasing hormone test:* 100µg ovine or human CRH IV.[76] Measure cortisol at 120min. Cortisol rises with pituitary disease but not with ectopic ACTH production. CRH is corticotrophin-relasing hormone.

If tests indicate that cortisol responds to manipulation, Cushing's disease is likely. Image the pituitary (MRI). If no mass is seen, *bilateral inferior petrosal sinus sampling* may help in confirming a pituitary adenoma, where the sinuses are sampled for ACTH release from the pituitary.

If tests indicate that cortisol does not respond to manipulation, hunt for the source of ectopic ACTH production. CT ± MRI of neck, thorax and abdomen should be performed to detect small ACTH secreting carcinoid tumours.

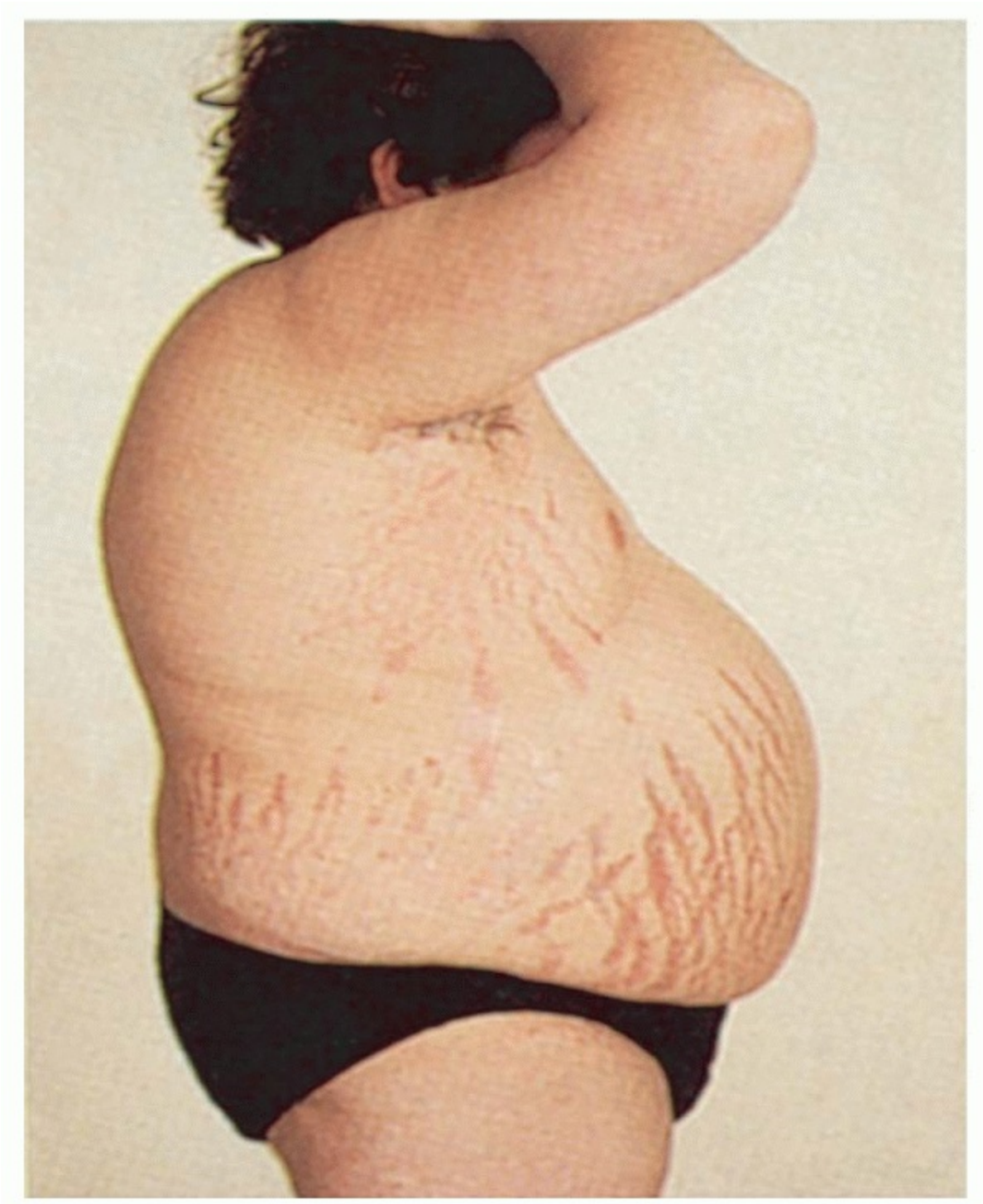


Fig 1. Signs of Cushing's include central obesity and purple abdominal striae.

Addison's disease (adrenal insufficiency)

▸▸Anyone on prednisolone for long enough to suppress the pituitary-adrenal axis or has overwhelming sepsis, or has metastatic cancer may suddenly develop adrenal insufficiency with deadly hypovolaemic shock.[77] ▸▸See p818.

Primary adrenocortical insufficiency

(Addison's disease) is rare (~0.8 /100,000), but can be fatal. Destruction of the adrenal cortex leads to glucocorticoid (cortisol) and mineralocorticoid (aldosterone) deficiency. Signs are capricious: it is *'the unforgiving master of non-specificity and disguise'*.[78] You may diagnose a viral infection or anorexia nervosa in error (K+ is ↓ in the latter but ↑ in Addison's).

Cause

80% are due to an autoimmune cause in the UK. *Other causes:* TB (commonest cause worldwide), adrenal metastases (eg from lung, breast, renal Ca), lymphoma[79], opportunistic infections in HIV (eg CMV, *Mycobacterium avium*, p399); adrenal haemorrhage (▸▸Waterhouse-Friederichsen syndrome p706; antiphospholipid syndrome; SLE)[80], congenital (late-onset congenital adrenal hyperplasia).

Symptoms

Often diagnosed late: Fatigue, weakness, anorexia, weight loss, dizziness, fainting, myalgia, arthralgia. *Mood:* depression, psychosis[81], low selfesteem.[1] GI: nausea or vomiting, abdominal pain, diarrhoea or constipation. *Think of Addison's in all those with unexplained abdominal symptoms.*[82]

Signs

Hyperpigmentation due to ↑ACTH (cross-reacts with melanin receptors): palmar creases, buccal mucosa. Postural hypotension. Vitiligo may be associated. ▸▸*Signs of critical deterioration* (p818): Shock (↓BP, tachycardia), fever, coma.

Tests

Na^+↓ & K^+↑ (due to ↓mineralocorticoid), glucose ↓ (due to ↓cortisol). Also: uraemia, Ca^{2+}↑, eosinophilia, anaemia.

Diagnosis

Short ACTH *stimulation test (Synacthen® test):* Do plasma cortisol before and 30 minutes after tetracosactide (=Synacthen®) 250µg IM. Addison's is excluded if 2nd cortisol >550nmol/L. Steroid drugs may interfere with this assay—check with lab. **NB:** in pregnancy or the oral contraceptive pill, cortisol levels may be reassuring but falsely↑, due to ↑cortisolbinding globulin.

Also

• ACTH: In Addison's disease, 9 a.m. ACTH is raised (>300ng/L: inappropriately high). It is low in secondary causes (see below). • *21-Hydroxylase adrenal autoantibodies:* +ve in autoimmune disease in >80%. • *Plasma renin and aldosterone:* To assess mineralocortocoid status.

AXR/CXR:

Any signs of past TB eg upper zone fibrosis or calcification of adrenals? If autoantibodies are negative, consider further tests (eg adrenal CT) to look for TB or metastatic disease.

Treatment

Replace steroids: ~15-25mg *hydrocortisone* daily, in 2-3 divided doses eg 10mg on waking, 5mg lunchtime. Avoid giving late in the day, as it can cause insomnia. Mineralocorticoid replacement may be needed eg if postural hypotension, Na^+↓, K^+↑ or plasma renin↑: *fludrocortisone* PO from 50-200µg daily. Adjust both on clinical grounds. If there is a poor response to treatment, suspect an associated autoimmune disease (check thyroid, do coeliac serology: p272).[83]

Steroids

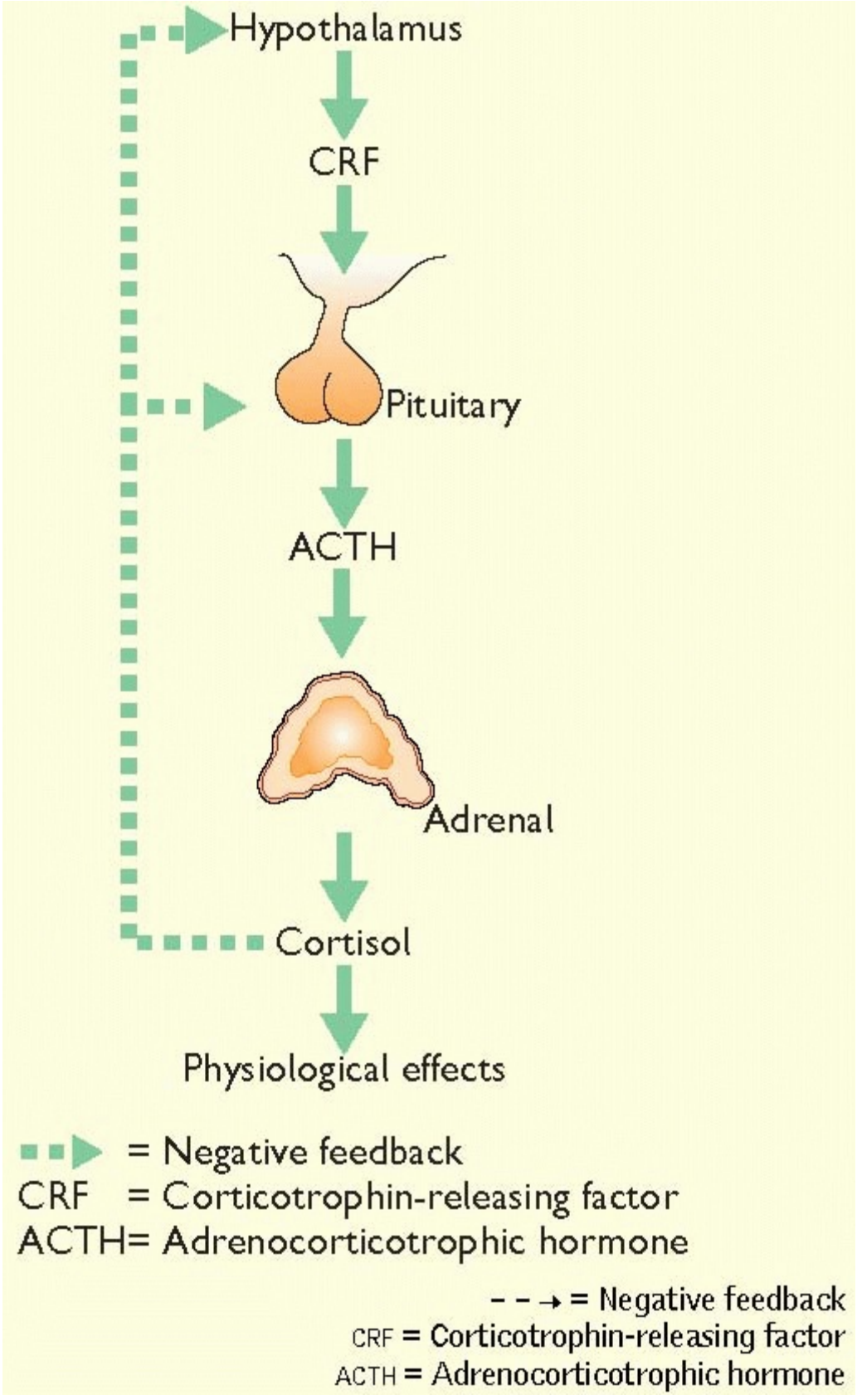
Warn against abruptly stopping steroids. Emphasize that prescribing doctors/dentists/surgeons *must* know of steroid use: give *steroid card*, advise wearing a bracelet declaring steroid use. Add 5-10mg hydrocortisone to daily intake before strenuous activity/exercise. Double steroids in febrile illness, injury or stress. Patients should be given syringes and in-date IM hydrocortisone, and shown how to inject themselves in case vomiting prevents oral intake. If vomiting, take hydrocortisone 100mg IM, and seek medical help; admit for IV fluids if dehydrated.

Follow-up

Yearly (BP, U&E). Prognosis is good: watch for autoimmune diseases.

Secondary adrenal insufficiency

The commonest cause is iatrogenic, due to long term steroid therapy leading to suppression of the pituitary-adrenal axis. This only becomes apparent on withdrawal of the steroids. Other causes are rare and include hypothalamic-pituitary disease leading to ↓ACTH production. Mineralocorticoid production remains intact, and there is no hyperpigmentation as ↓ACTH.



Hyperaldosteronism

Primary hyperaldosteronism

is excess production of aldosterone, independent of the renin-angiotensin system, causing ↑sodium and water retention, and ↓renin release. Consider with the following features: hypertension, hypokalaemia or alkalosis in someone not on diuretics. Sodium tends to be mildly raised or normal.

Symptoms

Usually asymptomatic. May present with features of hypokalaemia (p668): weakness, cramps, paraesthesiae, polyuria, polydipsia.

Causes

Around 2/3 are due to a solitary aldosterone-producing adenoma (***Conn's syndrome***). ~1/3 are due to bilateral adrenocortical hyperplasia. Rare causes: adrenal carcinoma or glucocorticoid-remediable aldosteronism (**GRA**). In GRA, the ACTH regulatory element of the 11ß-hydroxylase gene fuses to the

aldosterone synthase gene, increasing aldosterone production, and bringing it under the control of ACTH.

Tests

(see BOX) U&E (ideally not on diuretics, hypotensives, steroids, K^+, or laxatives for 4 wks). Do not rely on a low K^+, as >20% are normokalaemic. For GRA (suspect if there is a family history of early hypertension), genetic testing is available. NB: Renal artery stenosis is a more common cause of refractory ↑BP and ↓K^+ (p300).

Treatment

• *Conn's:* Surgery—laparoscopic adrenalectomy. Spironolactone is used up to 300mg per 24h PO for 4wks pre-op, to control hypertension and to treat ↓K^+. • *Hyperplasia:* Treated medically: spironolactone, amiloride, or eplerenone: a newer selective aldosterone receptor antagonist, which does not cause gynaecomastia. • *GRA*: dexamethasone 1mg/24h PO for 4wks, normalizes biochemistry but not always BP. If BP is still ↑, use spironolactone as an alternative. • *Adrenal carcinoma:* Surgery ± post-operative adrenolytic therapy with mitotane—prognosis is poor.

Secondary hyperaldosteronism

Due to a high renin from ↓renal perfusion eg in renal artery stenosis, accelerated hypertension, diuretics, CCF or hepatic failure.

Bartter's syndrome

This is a major cause of congenital (autosomal recessive) salt wasting—via a sodium and chloride leak in the loop of Henle via a defective channel. Presents in childhood with failure to thrive, polyuria and polydipsia. BP is *normal*. Sodium loss leads to volume depletion, causing ↑renin and aldosterone production, leading to hypokalaemia and metabolic alkalosis, ↑urinary K^+ and Cl^-.

Treatment:

K^+ replacement, NSAIDs (to inhibit prostaglandins), and ACE-inhibitors.

Phaeochromocytoma

These are rare catecholamine-producing tumours. They arise from sympathetic paraganglia cells (=phaeochrome bodies), which are collections of adrenalinesecreting chromaffin cells. They are usually found within the adrenal medulla. Extra-adrenal tumours (paragangliomas) are rarer, often found by the aortic bifurcation (the organs of Zuckerkandl). Phaeochromocytomas *roughly* follow the 10% rule: 10% are malignant, 10% are extra-adrenal, 10% are bilateral, and 10% are familial. They are a dangerous but treatable cause of hypertension (in <0.1%).

Associations

~90% are sporadic. 10% are part of a hereditary cancer syndrome (p207) eg MEN2a and 2b, neurofibromatosis, von Hippel-Lindau syndrome.[84]

The patient

Episodic hypertension, anxiety, chest tightness, etc.—see BOX.

Tests

• *Screening:* 3 × 24h urinary collections for free catecholamines. A clonidine suppression test is done in some centres for borderline cases. • *Localisation:* Abdominal CT/MRI, or meta-iodobenzylguanidine (MIBG—chromaffin-seeking isotope) scan: useful for detection of extra-adrenal tumours, see p725.

Treatment

Surgery, α- & ß-blockade pre-op: phenoxybenzamine (α-blocker) is used *before* ß-blocker to avoid crisis from unopposed α-adrenergic stimulation. ▸Consult the anaesthetist. *Post-op:* Do 24h urine catecholamines 2wks post-op, monitor BP (risk of BP↓↓). ▸▸Emergency [prescription take]: p818. In malignant disease, chemotherapy may be used.[85]

Follow-up

Lifelong: malignant recurrence may present late.[86]

Hypertension: a common context for hyperaldosteronism tests

Think of Conn's in these contexts: • Hypertension associated with hypokalaemia • Refractory hypertension eg despite three antihypertensive drugs • Hypertension occurring before 40yrs of age (especially in women).[87]

The approach to investigation remains controversial. The **aldosterone/renin ratio** (**ARR**) is a good initial screening test. It is ideally measured when the patient has been upright or sitting for 2h, as posture affects results. Antihypertensives should be withheld for 2 weeks (spironolactone for 6 weeks) if possible. α-blockers can be used to control hypertension, as they do not affect the test. A raised ratio ie ↑aldosterone and ↓renin, indicates hyperaldosteronism. Additional **suppression tests** are done in some centres with fludrocortisone or saline, to test their ability to suppress aldosterone production.

Further investigation is needed to differentiate the cause of hyperaldosteronism. One method is to assess the effect of posture. Renin, aldosterone and cortisol are measured after the patient has been lying overnight, then repeated after being upright for 4 hours. Renin production increases on standing, causing ↑aldosterone production. This is exaggerated in bilateral hyperplasia, but there is no effect in Conn's, as aldosterone production is autonomous.

CT or MRI of the adrenals is done to localise the cause. This should be done after hyperaldosteronism is proven, due to the high number of adrenal

incidentalomas. If imaging shows a unilateral adenoma, surgical excision is indicated. If no nodules or bilateral nodules are seen, a **trial of glucocorticoids** (eg dexamethasone) may be used to test for GRA. In GRA, dexamethasone causes ↓ACTH production by negative feedback, and therefore ↓aldosterone production.

If the above are inconclusive, **adrenal vein sampling** may then be performed, where venous blood is sampled from both adrenals. If one side demonstrates increased aldosterone production compared to the other, an adenoma is likely. **Adrenal scintigraphy** is an alternative, where increased unilateral uptake of the isotope indicates adenoma.

The clinical features of phaeochromocytoma

Phaeochromocytomas present with sustained or episodic hypertension, not controlled by treatment, or vague *episodic* features eg:

- General features, such as sweating, heat intolerance, pallor, flushing, a feeling of apprehension, or pyrexia.
- *Neurological:* Headaches, visual disturbances, seizures
- *Cardiovascular:* Palpitations, chest tightness, dyspnoea, faints (postural BP drop), pulmonary oedema.
- *Gastrointestinal:* Abdominal pain, nausea, constipation.

Symptoms may be precipitated by straining, exercise, stress, pressure on the abdomen, surgery, or parturition—or by agents such as ß-blockers, IV contrast agents, or the tricyclic you so kindly prescribed, thinking that the patient's bizarre symptoms were only explicable by psychopathology, such as depression. The site of the phaeochromocytoma may determine precipitants, eg if pelvic, precipitants include sexual intercouse, parturition, and micturition. These crises may last minutes to days. Suddenly patients feel 'as if about to die'—and then get better, or go on to develop a stroke or cardiovascular collapse. On examination, there may be no signs, or hypertension (± signs of cardiomyopathy or heart failure), thyroid swelling (episodic), glycosuria during attacks, or terminal haematuria from a bladder phaeochromocytoma.

Complications:

Heart failure, dilated cardiomyopathy, arrhythmias, stroke and death due to hypertensive crisis.

Hirsutism, virilism, gynaecomastia & impotence/ED

Hirsutism

is common (10% of women) and usually benign. It implies hair growth in women, in the male pattern. Causes are familial, idiopathic or are due to ↑ androgen secretion by the *ovary* (eg polycystic ovarian syndrome, ovarian cancer, OHCS p252), the *adrenal gland* (eg late-onset congenital adrenal hyperplasia, OHCS p134, Cushing's syndrome, adrenal cancer), or *drugs* (eg steroids).

Polycystic ovarian syndrome (PCOS)

causes secondary oligo- or amenorrhoea, infertility, obesity, acne and hirsutism (OHCS p252).

Tests:

Ultrasound shows bilateral polycystic ovaries. Blood tests: ↑testosterone, ↓sex-hormone binding globulin, ↑LH:FSH ratio (not consistent).

[prescription take]:

Metformin may restore regular cycles and fertility in some, as it counteracts insulin resistance found in this condition.

Management:

▸Be supportive.

- Local measures: Shaving; depilation: wax, creams (eg eflornithine), or electrolysis (expensive and time-consuming, but *effective*); bleach (1:10 hydrogen peroxide).
- Oestrogens help by ↑serum sex hormone-binding globulin and therefore ↓free androgens; but always combine with a progesterone (eg as in contraceptive pill) to prevent an excess risk of uterine neoplasia. An alternative is cyproterone acetate, an anti-androgen and progestogen, eg up to 100mg on days 1-11, with oestrogen on days 1-21. It is teratogenic so advise contraception. Cyproterone is also present in Dianette® (but this is now not licensed as a contraceptive pill).
- Clomifene is used for infertility (a fertility expert should prescribe).

Virilism

is rare but is associated with androgen-secreting adrenal and ovarian tumours and therefore needs investigation. It is the development of male secondary sexual characteristics in the female, characterized by a rapid onset of amenorrhoea, clitoromegaly, deep voice, temporal hair recession, and hirsutism.

Gynaecomastia

implies an abnormal amount of breast tissue in males, but may occur in normal puberty. It is unrelated to galactorrhoea (which is due to ↑prolactin). There is an increase in the oestrogen/androgen ratio.

Causes:

Hypogonadism (see BOX), liver cirrhosis (oestrogens↑), hyperthyroidism, drugs: oestrogens, spironolactone, digoxin, cimetidine, testosterone, marijuana; tumours: *oestrogen-producing* eg testicular, adrenal; *hCG-producing* eg testicular, bronchial.

Erectile dysfunction

(ED = impotence—the inability of an adult male to sustain an adequate erection for penetration.) It is common in old age, and is often multifactorial. A psychological element is common and is more likely if ED occurs only in some situations, if there is a clear stress to account for its onset, and if early morning 'incidental' erections still occur (these also persist at the onset of organic disease). Psychological causes may exacerbate organic causes.

- *Organic causes:* The major causes are smoking, alcohol, and diabetes. Also: *Endocrine*: hypogonadism, hyperthyroidism, ↑prolactin; *Neurological*: spinal cord lesions, MS, autonomic neuropathy (eg in DM); *Pelvic surgery* eg bladder-neck, prostate surgery; *radiotherapy*; *peripheral vascular disease*; *renal* or *hepatic failure*; *prostatic hypertrophy*; *penile abnormalities* eg post-priapism, Peyronie's.
- *Drug causes:* Antihypertensives (especially ß-blockers and diuretics), digoxin, major tranquillizers, alcohol, oestrogens, antidepressants, cimetidine, steroids.

Tests:

U&E, LFT, glucose, TFT, LH, FSH, cholesterol, testosterone, prolactin. Nocturnal tumescence studies are not usually needed. Doppler may show ↓blood flow, but is rarely needed as vascular reconstruction is difficult.

Treatment:

• Treat causes • Counselling • Oral phosphodiesterase (PDE5) inhibitors act by ↑ cyclic guanosine monophosphate (GMP). Erection isn't automatic (depends on stimuli). **Sildenafil** (Viagra®) 25-100mg ½-1h pre-sex (food & alcohol upset absorption).[88][89] SE: headache (16%); flushing (10%); dyspepsia (7%); nasal congestion (4%); transient blue-green tingeing of vision (inhibition of retinal PDE6).[90] CI: See BOX. **Tadalafil** (Cialis®; long *t*½,) 10-20mg ½-36h pre-sex. Don't use >once daily. SE: headache, dyspepsia, myalgia; ?no visual SEs. **Vardenafil** (Levitra® 5-20mg).[91] Vacuum aids, intracavernosal injections, transurethral pellets, and implants are used less.

Contraindications[ci]/cautions to Viagra® and other oral ED agents

- Concurrent use of nitrates[ci]
- BP↑↑ or ≲90/50mmHg;[ci] arrhythmias
- Myocardial infarction <90d ago[ci]
- Degenerative retinal disorders,[ci] eg retinitis pigmentosa (for sildenafil)
- Unstable angina[ci]
- Stroke in last 6 months[ci]
- Bleeding disorders (sildenafil)
- Active peptic ulceration (sildenafil)
- Marked renal or hepatic impairment

Other cautions

- Angina (especially if during intercourse).
- Peyronie's disease or cavernosal fibrosis.
- Risk of priapism (sickle-cell anaemia, myeloma, leukaemia).
- Concurrent complex antihypertensive regimens.
- Dyspnoea on minimal effort (sexual activity may be unsupportable).

Use in coronary disease has been a question, but in one good study, no adverse cardiovascular effects were detected even in severe coronary artery disease.[92]

Interactions:

Processed by the cytochrome p450 system: Macrolides, anti-HIV drugs, theophylline, ketoconazole, rifampicin, phenytoin, carbamazepine, phenobarbital, grapefruit juice (↑bioavailability).

When does a lifestyle malcontent become a disease?

'When should health providers pay for erectile treatment?' In the UK, the NHS will pay (write 'SLS'/selected list substances on the prescription) if ED is causing *severe* distress,[1] or there has been:

- Prostatectomy
- Prostate cancer
- Dialysis or a renal transplant
- Spinal cord or pelvic injury

- Radical pelvic surgery[2]
- Diabetes mellitus
- Multiple sclerosis
- Parkinson's disease
- Spina bifida
- Single gene neurological disease
- Poliomyelitis and its after-effects

It is easy to criticise politicians who produce these rather arbitrary-looking criteria by recourse to clever counter-examples, but they really need our support because they are making rationing (which is an inescapable fact of clinical life) *overt*, *open*, *available to scrutiny*, and *rational modification*. All too often rationing is covert, and no source takes responsibility for it.

IRATIONING IN ACTION: YOU CAN ONLY AVOID POLITICS IF YOU AVOID LIFE.

Causes of hypogonadism

Hypogonadism is the failure of testes to produce testosterone, spermatozoa or both. The testes are small, with symptoms of reduced libido, impotence and loss of secondary sexual hair. There are many causes which are divided into:

Primary hypogonadism:

Due to testicular failure. *Causes*: • Local trauma, torsion, chemotherapy or irradiation •Post-orchitis eg mumps, HIV, brucellosis, leprosy • Renal failure, liver cirrhosis or alcohol excess (toxic to Leydig cells). • Chromosomal abnormalities eg Klinefelter's syndrome (47XXY)—delayed sexual development, small testes and gynaecomastia.

Secondary hypogonadism:

Due to ↓gonadotrophins (LH and FSH). *Causes*: • Hypopituitarism • Kallman's syndrome—isolated gonadotrophin releasing hormone deficiency, often with anosmia and colour blindness • Systemic illness • Also: Laurence-Moon-Biedl syndrome, Prader-Willi syndrome.

Hypopituitarism

Hypopituitarism is the diminished secretion of the anterior pituitary hormones. They are affected in the following order: growth hormone (GH), gonadotrophins: follicle-stimulating hormone (FSH) and luteinizing hormone (LH), prolactin (PRL), thyroid-stimulating hormone (TSH), and adrenocorticotrophic hormone (ACTH). Panhypopituitarism is deficiency of all anterior hormones, usually caused by irradiation, surgery or pituitary tumour.

Causes

are from 3 levels 1 *Hypothalamus:* Kallman's syndrome (p215), tumour, inflammation, infection (eg meningitis, TB), ischaemia. 2 *Pituitary stalk:* Trauma, surgery, mass lesion (eg craniopharyngioma—p218), meningioma, carotid artery aneurysm. 3 *Pituitary:* Tumour, irradiation, inflammation, infiltration (haemochromatosis, amyloidosis, metastatic Ca), ischaemia (pituitary apoplexy: p218, Sheehan's syndrome[1]).

Features

are due to 1↓ Hormone: • GH *lack:* Central obesity, atherosclerosis, dry wrinkly skin, strength↓, balance↓, well-being↓, exercise ability↓, cardiac output↓, osteoporosis, glucose↓.$_{93}$ • *Gonadotrophin (*FSH*;* LH*) lack:* ♀**:** Few, scant, or no menses (oligomenorrhoea or amenorrhoea), fertility↓, libido↓, osteoporosis, breast atrophy, dyspareunia. ♂**:** Erectile dysfunction, libido↓, muscle bulk↓, hypogonadism (↓hair, all over; small testes; ejaculate volume↓; spermatogenesis↓). • *Thyroid lack:* As for hypothyroidism (p204). • *Corticotrophin lack:* As for adrenal insufficiency (p210). NB: no ↑ skin pigmentation as ↓ACTH. • *Prolactin lack:* Rare— failure of lactation.

2 Cause: eg pituitary tumour (p218), causing mass effect, or hormone secretion with ↓secretion of other hormones—eg prolactinoma, acromegaly, rarely Cushing's.

Tests

(The triple stimulation test is now rarely done.)

- *Basal:* **LH & FSH** (↓ or ↔), **testosterone** or **oestradiol** (↓); **TSH** (↓ or ↔), **T4** (↓); **prolactin** (may be ↑, due to loss of dopamine from the hypothalamus which normally inhibits its release), **insulin-like growth factor-1 (IGF-1;** ↓—used as measure of GH axis, see p222), **cortisol** (↓). Thyroid, gonadotrophin and prolactin hormone secretion are adequately assessed on basal tests. Also U&E (Na^+↓ ∴ dilution), Hb↓ (normochromic, normocytic).
- *Dynamic tests:* 1 **Short Synacthen® test:** (p210) to assess the adrenal axis.$_{94}$ 2 **Insulin tolerance test (ITT):** Done in specialist centres to assess the adrenal and GH axes. CI: epilepsy, heart disease, adrenal failure. Consult lab first. It involves IV insulin to induce hypoglycaemia, causing stress to ↑cortisol and GH secretion. It is done in the morning (water only taken from 22:00h the night before). Have 50% glucose & hydrocortisone to hand and IV access. Glucose must fall below 2.2mmol/L and the patient should become symptomatic when cortisol and GH are taken. Normal: GH >20mU/L, and peak cortisol >550mmol/L. 3 **Arginine + growth hormone releasing hormone test** and 4 **Glucagon stimulation test** are alternatives when ITT is contraindicated.
- *Investigate cause:* MRI scan to look for a hypothalamic or pituitary lesion.

Treatment

involves hormone replacement and treatment of underlying cause.

- *Hydrocortisone* for secondary adrenal failure (p210).
- *Thyroxine* if hypothyroid (p204, but TSH is useless for monitoring).
- Hypogonadism (for symptoms and to prevent osteoporosis). ♂: Options include testosterone enanthate 250mg IM every 3 weeks, daily topical gels or buccal mucoadhesive tablets. Patches or tablets are used less often. ♀: (*premenopausal*) *Oestrogen:* Transdermal oestradiol patches, oestradiol implants or oral therapy. The oral contraceptive pill exceeds replacement requirement. Gonadotrophin therapy is needed to induce fertility in both men and women.
- The importance of GH deficiency in adults has been increasingly recognised, with effects on protein and fat metabolism. GH deficiency impairs physical fitness, quality of life, promotes insulin resistance and dyslipidaemia.[95] If GH deficiency is suspected, refer to an endocrinologist for insulin tolerance testing. See BOX.

NICE guidelines on giving somatropin (GH) in those >25yrs old

Somatropin is produced by DNA technology; it has the same sequence as human GH. It should only be used if all the following criteria are fulfilled:[96]

1. There is severe GH deficiency, defined by peak GH response of <9mU/L (3ng/mL) during an ITT (or equivalent).
2. There is impaired quality of life (QoL), as measured by QoL-AGHDA questionnaires (assessment of hormone deficiency in adults score ≥ 11 points).[1]
3. The person is already receiving treatment for other pituitary hormone deficiencies, as required.

Achieving adult bone mass is a valid indication for somatropin in adults <25yrs old who fulfil criteria 1 but not 2. (Maximum GH secretion is during adolescence; then secretion normally falls by ~14% per decade.)

Self-injection

0.15-0.3mg/d; needs decrease with age. Dose titration (1st 3 months of therapy) is done by an endocrinologist. **SE***:* dose related fluid retention may cause oedema, carpal tunnel syndrome, myalgia, congestive heart failure, BP↑, ICP↑ (rare). IGF-1 levels increase with GH replacement. High IGF-1 levels have been linked with an increased risk of colon, breast and prostate cancer, but an increase in rates of cancer in adults on GH replacement has not been proven— long term data is lacking.[97] **CI***:* malignancy, pregnancy, renal transplant, closed epiphyses.

Somatropin should be stopped after 9 months if QoL-AGHDA does not improve by 7 points or more.[1] ***Using* GH *in children:*** See OHCS p180.

Pituitary tumours

Pituitary tumours (almost always benign adenomas) account for 10% of intracranial tumours. They may be divided by size: a microadenoma is a tumour <1cm, and a macroadenoma is >1cm. There are 3 histological types.

1. *Chromophobe*—70%. Some are non-secretory, but cause hypopituitarism. Half produce prolactin (PRL); a few produce ACTH or GH. Local pressure effect in 30%.
2. *Acidophil*—15%. Secrete GH or PRL. Local pressure effect in 10%.
3. *Basophil*—15%. Secrete ACTH. Local pressure effect rare.

Classification by hormone secreted

(may be revealed by immunohistology)

PRL only (→prolactinoma)	35%	ACTH (→Cushing's disease)	7%
GH only (→acromegaly)	20%	LH/FSH/TSH	≥1%[1][98]
PRL and GH	7%	No obvious hormone	30%[2]

[1] Sensitive methods of TSH measurement have improved recognition of TSH-secreting tumours. These are now more frequently found at microadenoma stage, medially located, and *without* associated hormone hypersecretion. In these tumours, somatostatin analogues (p222) are very helpful.

[2] Many produce an alpha-subunit which may serve as a tumour marker.

Symptoms are caused by local pressure, hormone secretion, or hypopituitarism (p216). FSH secreting tumours can cause macro-orchidism in men, but are rare.

Features of local pressure

Headache, visual field defects (bilateral temporal hemianopia, due to compression of the optic chiasm), palsy of cranial nerves III, IV, VI (pressure or invasion of the cavernous sinus). Also, diabetes insipidus (DI) (p224; more likely from hypothalamic disease); disturbance of hypothalamic centres of T°, sleep, and appetite; erosion through floor of sella leading to CSF rhinorrhoea.

Investigations

Pituitary MRI (defines intra- and supra-sellar extension); accurate assessment of visual fields; screening tests: PRL, IGF-1 (p222), ACTH, cortisol, TFTs, LH/FSH, testosterone in ♂, short Synacthen® test. Glucose tolerance test if acromegaly suspected (p222). If Cushing's disease suspected, see p209. Water deprivation test if DI is suspected (p224).

Treatment

Start hormone replacement as needed. Ensure steroids are given before thyroxine, as thyroxine may precipitate an adrenal crisis. For Cushing's disease see p209, prolactinoma p220, acromegaly p222.

- *Surgery:* Most pituitary surgery is trans-sphenoidal, but if there is supra-sellar extension, a trans-frontal approach may be required. **NB:** for prolactinoma, first line treatment is medical with a dopamine agonist, see p220. *Pre-op:* Ensure hydrocortisone 100mg IV/IM pre-op. Subsequent cortisol replacement and reass-essment varies with local protocols—ask advice. *Post-op:* Retest pituitary function (p216) to assess replacement needs. Wait 6-8 weeks post-op before repeating dynamic tests for adrenal function.
- *Radiotherapy:* Post-op if complete removal of the tumour has not been possible.

Post-op

Recurrence may occur late after surgery, so life-long follow up is required. Fertility should be discussed: this may be reduced post-op due to ↓ gonadotrophins.

Pituitary apoplexy

Rapid pituitary enlargement due to haemorrhage into a tumour may cause sudden mass effects, cardiovascular collapse due to acute hypopituitarism, and death. $_{99}$ Suspect if acute onset of headache, meningism, ↓GCS, ophthalmoplegia and visual field defects, especially in someone with a known tumour (may present like subarachnoid haemorrhage).

Treatment:

Urgent steroids (hydrocortisone 100mg IV) and surgery.

Craniopharyngioma

Not strictly a pituitary tumour: it originates from Rathke's pouch so is situated between pituitary and the 3rd ventricle floor. They are rare, but are the commonest childhood intracranial tumour. Over 50% present in childhood with growth failure; adults may present with amenorrhoea, ↓libido, hypothalamic symptoms (eg diabetes insipidus, hyperphagia, sleep disturbance) or tumour mass effect, see above.

Tests:

CT/MRI (calcification in 50%, may also be seen on skull XR).

Treatment:

Surgery ± post-op radiation; test pituitary function post-op.

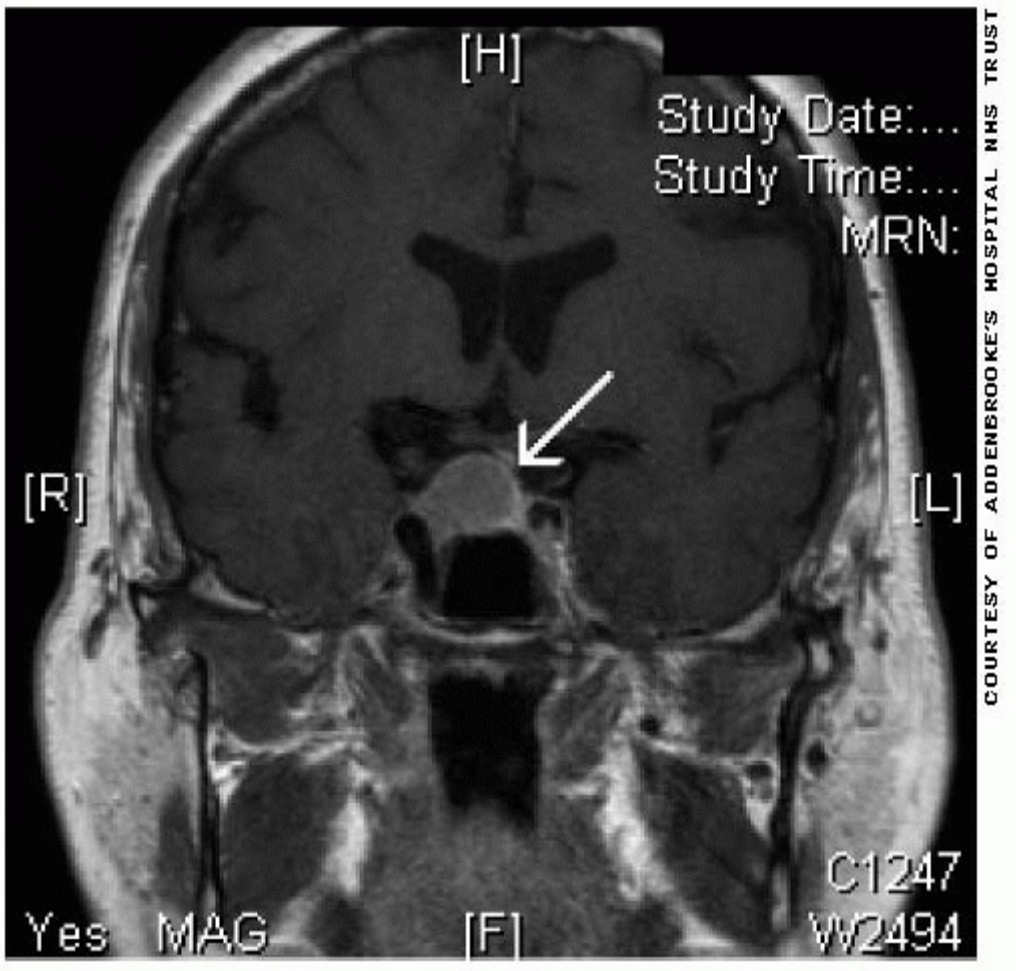


Fig 1. Sagittal T1 weighted MRI of the brain post IV gadolinium showing a pituitary adenoma.

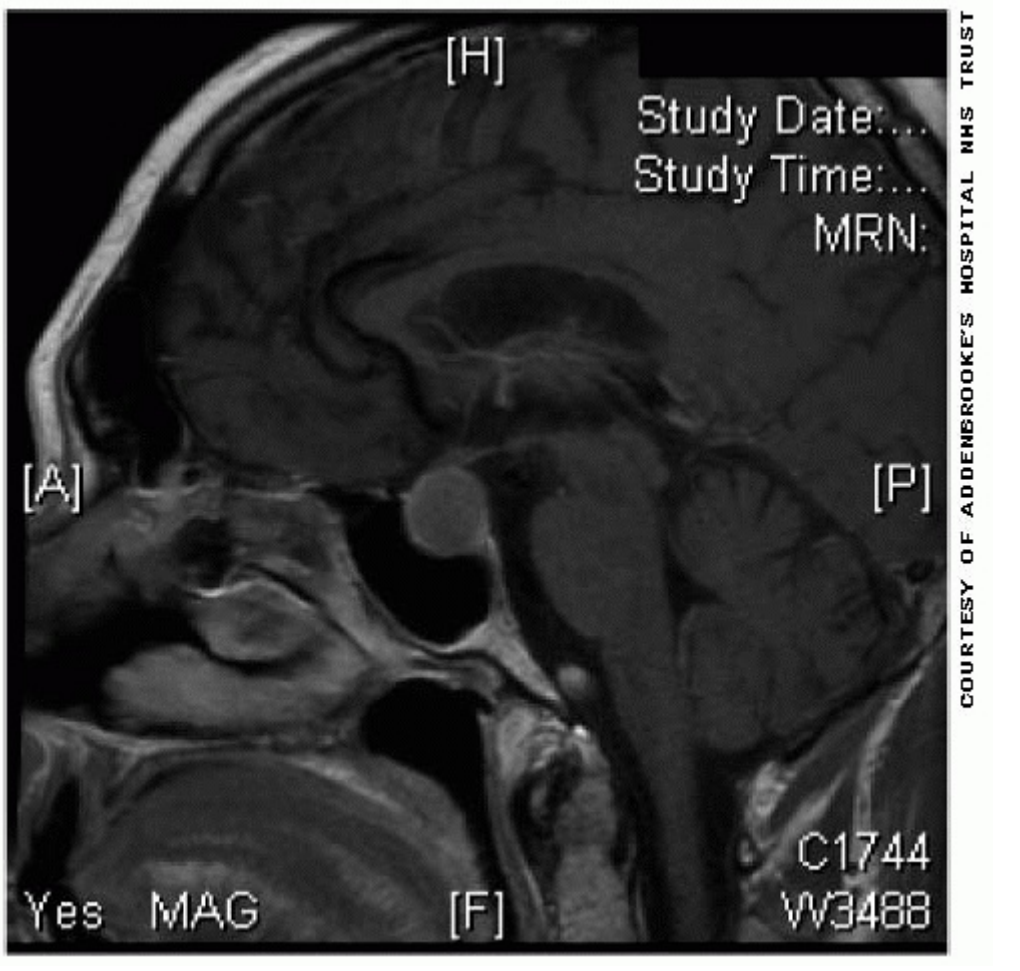


Fig 2. Coronal T1 weighted MRI of the brain post IV gadolinium showing a pituitary adenoma.

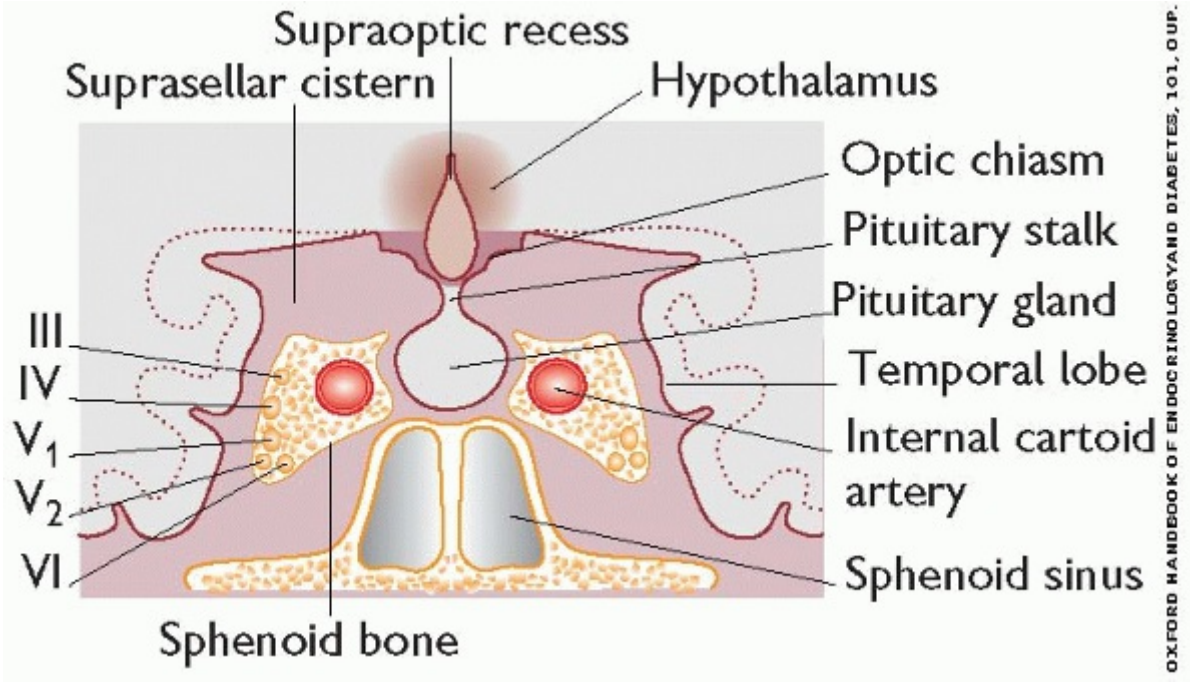


Fig 3. Diagram of the pituitary gland, with its relation to surrounding structures and cranial nerves III, IV, V, and VI.

Hyperprolactinaemia

This is the most common biochemical disturbance of the pituitary. It presents earlier in women (due to menstrual disturbance) but late in men. Prolactin stimulates lactation. Raised levels lead to secondary hypogonadism, and therefore infertility and osteoporosis, by inhibiting secretion of gonadotrophin releasing hormone, resulting in low LH/FSH and low testosterone or oestrogen levels.

Causes of raised basal plasma prolactin (PRL)

(>390mU/L) PRL is secreted from the anterior pituitary and release is inhibited by dopamine produced in the hypothalamus. Hyperprolactinaemia may result from **1** Excess production from the pituitary, eg prolactinoma. **2** Disinhibition, by compression of the pituitary stalk, reducing local dopamine levels or **3** Administration of a dopamine antagonist. A PRL of 1000-5000mU/L may result from any, but >5000 is likely to be due to a prolactinoma, with macroadenomas (>10mm) having the highest levels, eg 10,000-100,000.

- *Physiological:* Pregnancy; breast-feeding; stress eg post-seizure.
- *Drugs (most common cause):* Phenothiazines; metoclopramide; haloperidol; α-methyldopa; oestrogens.
- *Diseases: Prolactinoma:* micro- or macroadenoma; *Stalk damage:* pituitary adenomas, surgery, trauma; *Hypothalamic disease:* craniopharyngioma, other tumours; *Other:* hypothyroidism (due to ↑TRH), chronic renal failure (↓excretion).

Symptoms ♀:

Amenorrhoea or oligomenorrhoea; infertility; galactorrhoea. Also: libido↓, weight↑, dry vagina. ♂: Impotence, reduced facial hair, galactorrhoea. May present late with osteoporosis or local pressure effects from the tumour (p218).

Tests

Basal PRL: non-stressful venepuncture between 09.00 and 16.00h. Do a pregnancy test, TFT, U&E. MRI pituitary if other causes are ruled out.

Management

Dopamine agonists (bromocriptine or cabergoline) are 1st line.

Microprolactinomas:

A tumour <10mm on MRI (NB: ~25% of the population have asymptomatic microprolactinomas). Bromocriptine, a dopamine agonist, ↓PRL secretion, restores menstrual cycles and ↓tumour size. Dose is titrated up:1.25mg PO; increase weekly by 1.25-2.5mg/d until ~2.5mg/12h. SE: Nausea, depression, postural hypotension (minimise by giving at night). If pregnancy is planned in ♀ patients, use barrier contraception until two periods have occurred. If subsequent pregnancy occurs, bromocriptine should be stopped after the first missed period.[100] An alternative dopamine agonist is cabergoline: more effective and less SE, but there is less data on safety during pregnancy.

Trans-sphenoidal surgery may be considered if intolerant of dopamine agonists. It has a high success rate, but there are risks of permanent hormone deficiency and prolactinoma recurrence, and so is usually reserved as a second-line treatment.

Macroprolactinomas:

A tumour >10mm diameter on MRI. Macroprolactinomas should be initially treated with a dopamine agonist (bromocriptine if fertility is the goal). Surgery is indicated if there are visual symptoms or pressure effects which fail to respond quickly to medical treatment, or if pregnancy is contemplated as ~25% of macroadenomas will expand during pregnancy. Bromocriptine, and in some cases radiation therapy, may be required post-op as complete surgical resection is uncommon. Pre-op assessment is often difficult: familiarize yourself with case-histories to show complexities of this aspect of endocrinology.[1]

[1] Harms E 2003 *Dtsch Med Wochenschr* **128** 667. A 46yr-old lady had galactorrhoea for 7yrs, and a ↑prolactin (3133mU/L) and intact pituitary function with no eye signs. MRI showed a 1.9cm pituitary tumour with extrasellar extension. Is trans-sphenoidal resection needed for a presumed macroadenoma with functional hyperprolactinaemia, or should there be a dopamine-agonist trial? *One possible answer:* try drugs, and monitor MRI if initial prolactin ≥ 2000mU/L.

Follow up:

Monitor PRL levels. If headache or visual loss occur, check fields and consider MRI. Medication can be decreased after 2 years of treatment, although recurrence of hyperprolactinaemia and expansion of the tumour may occur, and so these patients should be monitored carefully.

Acromegaly

This disease is due to hypersecretion of GH (growth hormone) from a pituitary tumour in >99% of cases, and is rarely associated with ectopic production of GHreleasing hormone eg from a carcinoid tumour. ♀:♂=1:1. It mainly presents between 30-50yrs old. Prevalence is ~40-60 per million. ~5% are associated with MEN1. GH stimulates soft tissue and skeletal growth through ↑secretion of insulin-like growth factor-1 (IGF-1), and its secretion is inhibited by somatostatin.

Clinical features

Onset is insidious.

- *Excessive soft tissue growth:* Growth of hands and feet: ie ↑ring size, thick spade-like hands and ↑shoe size; coarsening of facial features: prominent supraorbital ridge, prognathism, wide-spaced teeth; large tongue (macroglossia); headache; excess sweating; hoarse voice and obstructive sleep apnoea (soft tissue swelling in the larynx); arthralgia, osteoarthritis, proximal muscle weakness; carpal tunnel syndrome (p495).
- *Features of a pituitary tumour:* Hypopituitarism ± local mass effect (p218).

Complications

- Impaired glucose tolerance (40%), DM (20%), as GH is counter-regulatory to insulin.
- Vascular: BP↑, left ventricular hypertrophy, cardiomyopathy. There is ↑risk of ischaemic heart disease and stroke, due to ↑BP and insulin resistance.
- Malignancy: Controversy exists over the extent of ↑risk of colonic polyps and development of colon cancer; guidelines suggest colonoscopy at 50yr.[101]
- Mortality is increased (2-3 fold), mainly due to cardiovascular risk.

Investigations

- Random GH measurements are not helpful as GH is secreted in a markedly pulsatile manner. During peaks, levels can overlap between normal subjects and acromegalic patients. GH is ↑ in stress, sleep, and puberty, and ↓ in pregnancy.
- Serum IGF-1 (p216) is used as a screening test for acromegaly. Levels correlate with GH secretion over the preceding 24h, and so are ↑ with excessive GH secretion. But in up to 25% of cases, IGF-1 remains normal with ↑GH secretion.
- The definitive test is the oral glucose tolerance test (OGTT) with GH measurement, as described on p190. The test is done at 09.00, with fasting from midnight. Collect samples for GH and glucose at: 0, 30, 60, 90, 120, 150min. *Interpretation:* normally GH secretion is inhibited by a rise in glucose, and GH should be undetectable (<0.5mU/L—check with lab for reference level). In acromegaly there is failure to suppress GH release. False +ves for this test are seen in puberty, pregnancy, hepatic and renal disease, anorexia nervosa and DM.
- MRI scan of pituitary fossa.
- Test pituitary function (p216)—hypopituitarism?
- Visual fields and acuity.
- ECG, echocardiogram. Obtain old photos if possible.

Treatment

- *Trans-sphenoidal surgery:* Usually the treatment of choice. Cure rate ~80% microadenomas, and ~40% macroadenomas. At 3 months post-op, measure GH day curve (4-5 samples during day, aim for mean GH <5mU/L) or repeat OGTT, measure IGF-1, and do pituitary function tests (p216) to check for hypopituitarism. If GH remains high, adjuvant medical or radiotherapy may be needed.
- *Medical:* Somatostatin analogues eg *octreotide* (Sandostatin Lar®, given monthly IM), and *lanreotide* (Somatuline LA®) are replacing dopamine agonists. SE include: pain at the injection site; gastrointestinal: abdominal cramps, flatulence, loose stools, ↑gallstones; impaired glucose tolerance. Control of GH and IGF-1 levels occurs in up to 60%. Pegvisomant, a recombinant GH analogue, acts as a GH receptor antagonist. It suppresses IGF-1 to normal in 90%, but GH levels rise. Occasionally tumour size increases, so monitor closely. We await long term data.
- *Radiotherapy:* If surgery inappropriate or as adjuvant; may take years to work.

Follow-up:

Yearly, GH and IGF-1 measurement ± OGTT; visual fields; clinical photos; cardiovascular assessment. Aim serum GH <5mU/L to reverse mortality risk.[102]

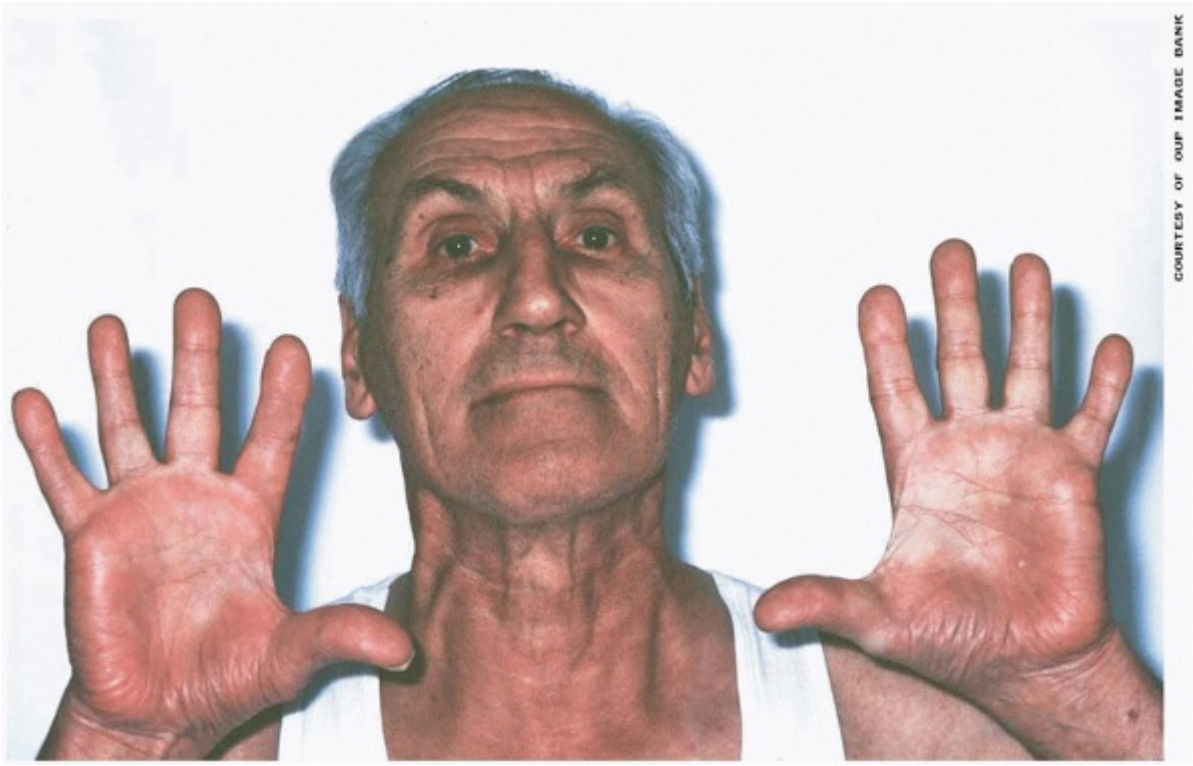


Fig 1. Coarsening of facial features and growth of hands in acromegaly.

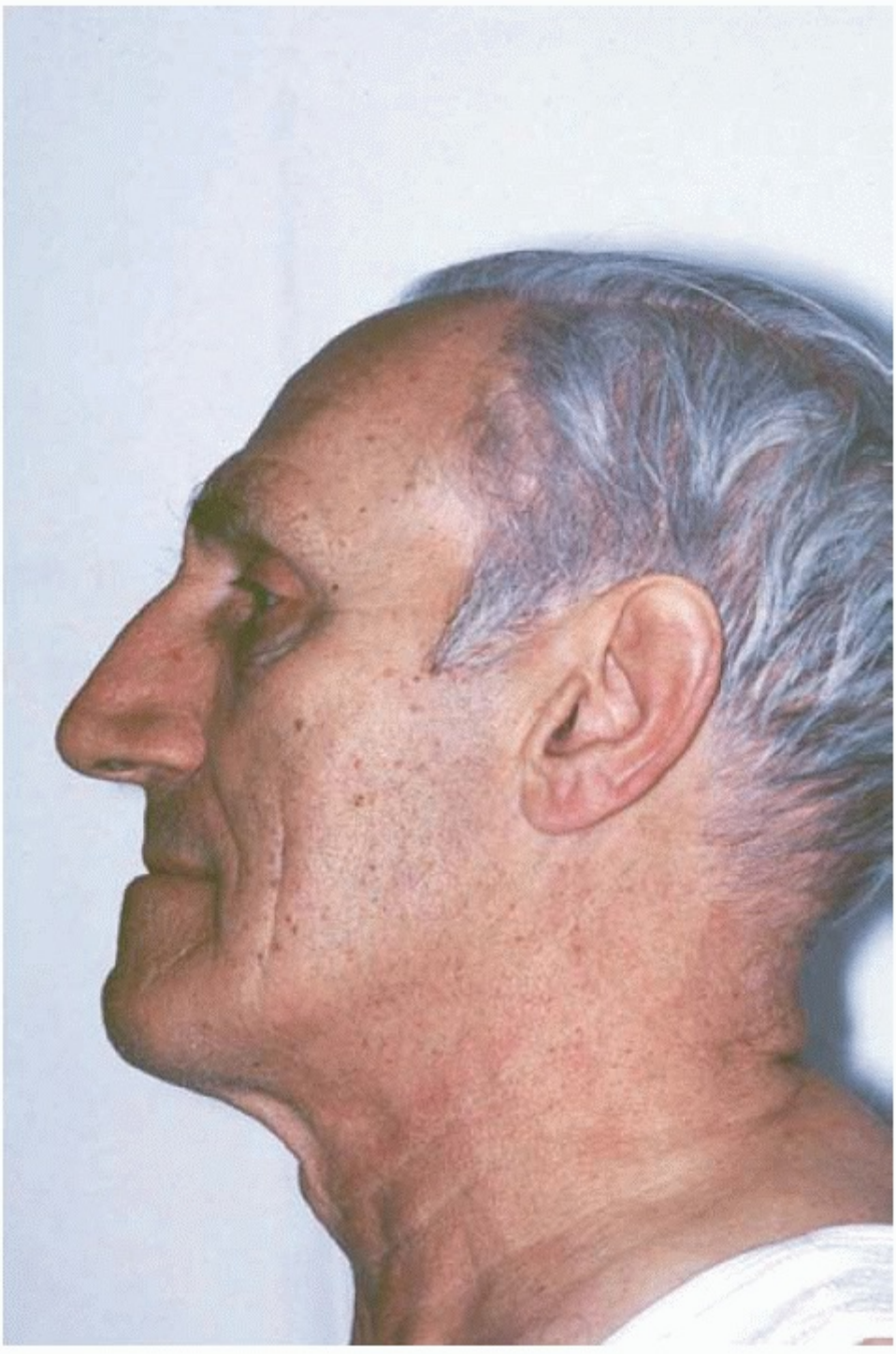


Fig 2. Prognathism: abnormal protrusion of the jaw, due to increased growth of the mandible.

Diabetes insipidus (DI)

This is the passage of big volumes (>3L/day) of dilute urine due to impaired water resorption by the kidney, because of reduced ADH secretion from the posterior pituitary (cranial DI), or impaired response of the kidney to ADH (nephrogenic DI).

Symptoms

Polyuria; polydipsia; dehydration; symptoms of hypernatraemia (p666). Polydipsia can be uncontrollable, with the patient drinking anything *and everything* to hand: in such cases, if beer is on tap, disaster will ensue.[103]

Causes of cranial DI

• *Idiopathic* (≲50%) • *Congenital:* defects in ADH gene, **DIDMOAD** syndrome[1] • *Tumour:* craniopharyngioma, metastases, pituitary tumour (rare) • *Trauma:* hypophysectomy, head injury • *Infiltration:* histiocytosis, sarcoidosis[2] • *Vascular:* Sheehan's syndrome,[3] haemorrhage •*Infection:* meningoencephalitis.

Causes of nephrogenic DI

• Inherited • *Metabolic:* Low potassium, high calcium • *Drugs:* lithium, demeclocycline • Chronic renal disease • Post-obstructive uropathy.

Tests

U&E, Ca^{2+}, glucose (exclude DM), serum and urine osmolalities. Serum osmolality estimate≈2×(Na^+ + K^+) + urea + glucose (all in mmol/L). It is normally tightly controlled between 285-295mOsmol/kg. In DI, urine osmolality is low (usually <400mOsmol/kg) as it cannot be concentrated and so plasma osmolality rises. Serum sodium rises, due to fluid loss. In primary polydipsia there may be dilutional hyponatraemia—and as hyponatraemia may itself cause mania,[104] be cautious in using terms such as 'water intoxication from psychogenic polydipsia'.

Diagnosis

The *water deprivation test* aims to test the ability of kidneys to concentrate urine for diagnosis of DI, and then to localise the cause. See BOX. **NB:** it is often difficult to differentiate primary polydipsia from partial DI. **OTM4 3.207**

ΔΔ: DM; diuretics or lithium use; *primary polydipsia*—this causes symptoms of polydipsia & polyuria with dilute urine. Its cause is poorly understood;[4] it may be associated with schizophrenia or mania (±Li^+ therapy[105]), or, rarely, hypothalamic disease (neurosarcoid; tumour; encephalitis; brain injury; HIV encephalopathy).[106]

As part of this syndrome, the kidneys may lose their ability to fully concentrate urine, due to a wash-out of the normal concentrating gradient in the renal medulla.

Treatment

Cranial DI:

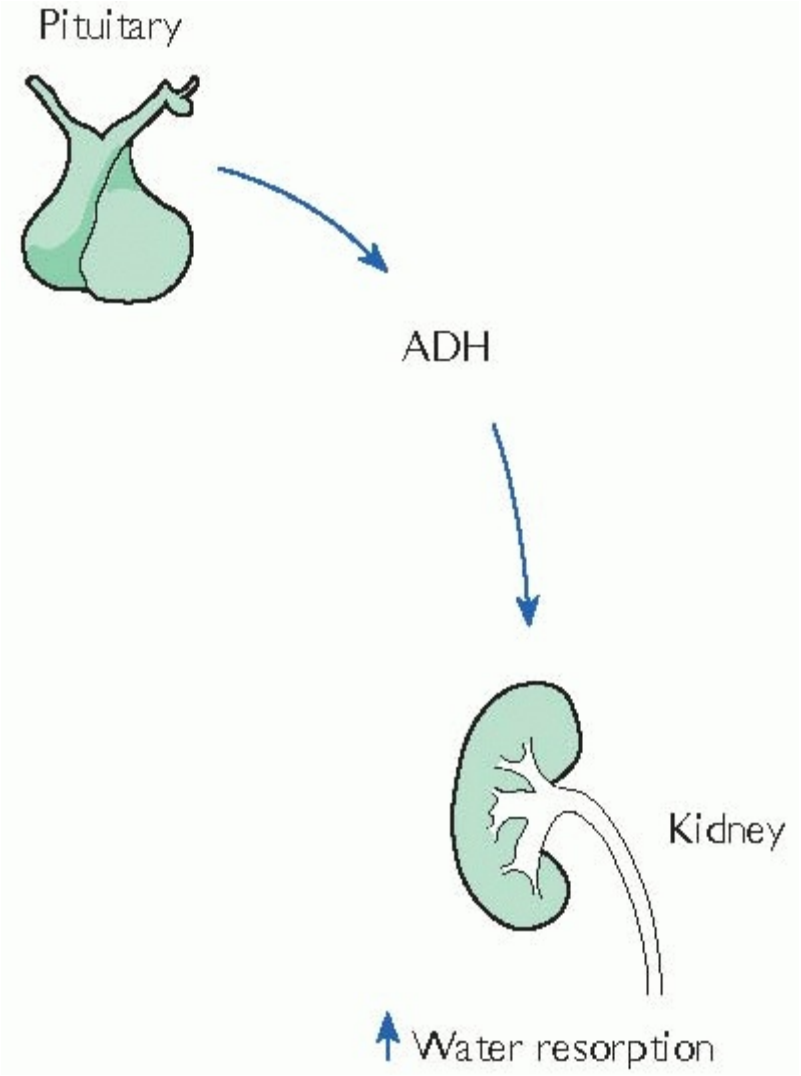
Find the cause—MRI (head); test anterior pituitary function (p216). Give desmopressin, a synthetic analogue of ADH. Dose: 10-20µg/12-24h intranasally (smallest dose that controls polyuria: higher doses ↑risk of hyponatraemia). An oral formulation is available but dosing is difficult due to differences in bioavailability.

Nephrogenic:

Treat the cause. If it persists, try bendroflumethiazide 5mg PO/24h. NSAIDS lower urine volume and plasma Na^+ by inhibiting prostaglandin synthase: prostaglandins locally inhibit the action of ADH.[107]

▸▸*Emergency management*

- Do urgent plasma U&E, and serum and urine osmolalities. Monitor urine output carefully and check U&E twice a day initially.
- IVI to keep up with urine output. If severe hypernatraemia, do not lower Na^+ rapidly as this may cause cerebral oedema and brain injury. If Na^+ is ≥ 170, use 0.9% saline initially—this contains 150mmol/L of sodium. Aim to reduce Na^+ at a rate of less than 12mmol/L per day. Use of 0.45% saline can be dangerous.
- Desmopressin 2µg IM (lasts 12-24h) may be used as a therapeutic trial.



Water deprivation test

The purpose of this test is to see if the kidneys persist in producing dilute urine despite dehydration, and then to localise the cause. Do not do the test before establishing that urine volume >3L/d (output less than this with normal plasma Na^+ and osmolality excludes significant disturbance of water balance).

- Stop test if urine osmolality >600mOsmol/kg in Stage 1 (DI is excluded).
- Free fluids until 07.30. Light breakfast at 06.30, no tea, no coffee, no smoking.

Stage 1

Fluid deprivation (0-8h): For diagnosis of DI. Start at 08.00.

- Empty bladder, then no drinks and only dry food.
- Weigh hourly. If >3% weight lost during test, order urgent serum osmolality. If >300mOsmol/kg, proceed to Stage 2. If <300, continue test.
- Collect urine every 2 hours; measure its volume and osmolality.
- Venous sample for osmolality every 4 hours.
- Stop test after 8h (16.00) if urine osmolality >600mOsmol/kg (ie normal).

Stage 2

Differentiate cranial from nephrogenic DI.

- Proceed if urine still dilute—ie urine osmolality <600mOsmol/kg.
- Give desmopressin 20µg intranasally (or 2µg IM). Water can be drunk now.
- Measure urine osmolality hourly for the next 4 hours.

Interpreting the water deprivation test	

• Normal	Urine osmolality >600mOsmol/kg in Stage 1 (normal concentrating ability).
• Primary polydipsia	Urine concentrates, but less than normal, eg >400- 600mOsmol/kg.
• Cranial DI	Urine osmolality increases to >600mOsmol/kg *after* desmopressin.
• Nephrogenic DI	No increase in urine osmolality after desmopressin.

[4] Most of us could drink 20L/d and not get hyponatraemic; some get hyponatraemic drinking 5L/d; they may have the **P**sychosis, **I**ntermittent hyponatraemia, and **P**olydipsia (**PIP** syndrome, ?from ↑intravascular volume leading to ↑atrial natriuretic peptide, hence natriuresis & hyponatraemia).

Acknowledgements

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Title: *Oxford Handbook of Clinical Medicine, 7th Edition*

7

Gastroenterology

Fig 1. What shall be our guiding light through the twists and turns of the tunnelous GI tract? Perhaps more so than in any field, GI symptoms can be vague and nonspecific (eg dyspepsia, p234), often leaving us with little choice but turn to invasive procedures, which we know are not without risk (p248). Yet if we leave pathology in the dark, be it benign or malignant, we may be doing a disservice. But not every symptom needs illuminating by a scan or gadget: ▸get used to listening to patients' stories; ▸get good at dealing with uncertainty, and ▸know that in time you will learn the right level of illumination to use to reveal the subtle nuances and shades of gastrointestinal phenomena.

Lumen

We learn about gastroenterological diseases as if they were separate entities, independent species collected by naturalists, each kept in its own dark matchbox—collectors' items collecting dust in a desiccated world on a library shelf. But this is not how illness works. Otto had diabetes, but refused to see a doctor until it was far advanced, and an amputation was needed. He needed looking after by his wife Aurelia. But she had her children Warren and Sylvia to look after too. And when Otto was no longer the bread-winner, she forced herself to work as a teacher, an accountant, and at any other job she could get. Otto's illness manifested in Aurelia's duodenum—as an ulcer. The gut often bears the brunt of other people's worries. Inside every piece of a gut is a lumen[1]—the world is in the gut, and the gut is in the world. But the light does not always shine. So when the lumen filled with Aurelia's blood, we can expect the illness to impact on the whole family. Her daughter knows where blood comes from ('straight from the heart… pink fizz'). After Otto died, Sylvia needed long-term psychiatric care, and Aurelia moved to be near her daughter. The bleeding duodenal ulcer got worse when Sylvia needed electroconvulsive therapy. The therapy worked and now, briefly, Sylvia, before her own premature death, is able to look after Aurelia, as she prepares for a gastrectomy.

The story of each illness told separately misses something; but even taken in its social context, this story is missing something vital—the poetry, in most of our patients lived rather than written—tragic, comic, human, and usually obscure— but in the case of this family not so obscure. Welling up, as unstoppable as the bleeding from her mother's ulcer,[1] came the poetry of Sylvia Plath.[2]

Healthy, enjoyable eating

> *'There's a lot of people in this world who spend so much time watching their health that they haven't the time to enjoy it.'* Josh Billings (1818-85).

There are no good or bad **foods**, and no universally good or bad **diets**. We must not consider diet out of context with a desired lifestyle, and nor should we assume that everyone wants to be thin, healthy, and live for ever. If we are walking to the South Pole, our bodies need a diet as full of energy-rich fat as possible: taking any other food would be a waste of space. But if we live a sedentary life, the converse is not necessarily true. After decades of research, we still do not know who should eat what, or when. Are 3 meals a day healthier than 1? Is fat bad if weight is normal? Is a balanced diet (see BOX) best? Should we eat 3, 5, 7, or 9 fruits per day? The latter is one recommendation for men, but recent studies find no benefit beyond 3.[2] The traditional answer to these questions is 'Yes'—and the more fruit the better—but evidence is far from complete, not just because of the paucity of randomized trials, but because of complex interactions between eating and health. All diets have unintended consequences: eg the 'good' antioxidant epicatechin (a flavonoid) in dark chocolate is annulled by taking milk at the same time.[3] Randomized trials show how an Atkins-type diet (low in carbohydrate Ì ↑fat & ↑protein) can improve lipid profiles and insulin resistance, but with possible SEs of renal problems and excessive calcium excretion.RCT[4] [5] To complicate matters futher, diet is also confounded by lifestyle—whilst some studies have shown that vegetarians may may be less likely to die from ischaemic heart disease,[6] is this effect because vegetarians in the UK are more likely to be non-smokers?[7]

Current recommendations must take into account 3 facts:

- Obesity is an escalating epidemic costing health services as much as smoking—1 in 4 adults in the UK are now classified as obese.[8]
- Diabetes mellitus is burgeoning: in some places prevalence is >7% (p190).
- Past advice has not changed eating habits in large sections of the population.

Advice is likely to focus on the following

- *Body mass index (BMI):* see TABLE; aim for 20-25; ie **eat less**. Controlling quantity may be more important than quality. In hypertension, eating the 'right' things lowered BP by 0.6mmHg, but controlling weight (OHCS p529) caused a 3.7mmHg reduction in 6 months in 1 RCT.RCT[9]
- *Oily fish:* Rich in omega-3 fatty acid (eg mackerel, herring, pilchards, salmon— but benefits are not fully substantiated).[10] If tinned fish, avoid those in unspecified oils. Nuts are also valuable: walnuts lower total cholesterol and have one of the highest ratios of polyunsaturates to saturates (7:1). Soya protein lowers cholesterol, low-density lipoproteins, and triglycerides.
- *Refined sugar:* (See BOX for its deleterious effects.) Use fruit to add sweetness. Have low-sugar drinks: a 330mL can of non-diet carbonated soft drink can have up to 10 teaspoons (40g) of refined sugar. Don't add sugar to drinks or cereals. (In a thin, active, elderly, normoglycaemic person, sugar may be no great evil.)
- *Eat enough fruit and fibre:* See BOX and *reduce salt intake.*
- *Enjoy moderate alcohol use (adults):* ♀: <15U/wk; ♂: <20U/wk (higher levels are controversial)—taken regularly, not in binges. Alcohol inhibits platelet aggregation and is an antioxidant (Ì cardioprotective). There is no evidence that spirit or beer drinkers should switch to wine. There is evidence that the benefit accrues **only** to those whose LDL cholesterol is ≳5.25mmol/L.[11]

▸*Avoid this diet if:* • <5yrs old • Need for low residue (eg Crohn's, UC, p266) or special diet (coeliac disaese, p272) • Weight loss is expected. *Emphasis may be different in:* Dyslipidaemia (p682); DM (p190); obesity; constipation (p240); liver failure (p250); chronic pancreatitis (p272); renal failure (less protein); BP↑.[12]

Difficulties

It is an imposition to ask us to change our diet (children often refuse point-blank); a more subtle approach is to take a meal we enjoy (eg Coke® and crisps) and make it healthier (eg fresh fruit juice, low-salt crisps made from jacket potatoes, and fried in sunflower oil).

Traditional low-fat nutritional advice: *the balance of good health*

A low-fat diet may not only be for the sake of good health, as it can can also help control symptoms, eg as in gallstone disease, and while it is unrealistic to expect all our patients' troubles to drift away as the weight comes off, we **can** offer the incentive of an improvement in both symptoms and health as encouragement.

Starchy foods:

Bread, rice, pasta, potatoes, etc. form the main energy source (especially wholemeal). ↑Fluid intake with a diet high in non-starch polysaccharide (NSP)—eg 8 cups (1-2½ pints) daily. Warn about bulky stools. NSP ↓calcium and iron absorption, so restrict main intake to 1 meal a day.

Fruit, vegetables:

eg >6 different pieces of fruit (ideally with skins)[13] or portions of pulses, beans, or lightly cooked greens per day. This probably ↓cardiovascular and cancer mortality.[14] The term **fibre** is imprecise. Most is NSP—the preferred term.

Meat and alternatives:

Meat should be cooked without additional fat. Lower fat alternatives, such as white meat (poultry, without skin), white fish, and vegetable protein sources (eg pulses, soya) are encouraged.

Dairy foods:

Low-fat semi-skimmed milk/yoghurt; edam or cottage cheese.

Fat and sugary foods:

Avoiding extra fat in cooking is advised ('grill, boil, steam, or bake, but don't fry'). Fatty spreads (eg butter) are kept to a minimum and snack foods (crisps, sweets, biscuits, or cake) are avoided.

Loosing weight—why and how?

The risks of too much sugar

Excess sugar causes caries, diabetes, obesity— which itself contributes to osteoarthritis, cancer,[15] hypertension,[16] and ↑oxidative stress—so raising cardiovascular mortality) [17] and much more.

Loosing weight

Consider referral to a dietician—a needs-specific diet may be more effective. In conjunction with exercise and diet strategies, targeted weight-loss can also be achieved successfully with psychotherapy.[18]

Drugs for obesity?

The most desirable treatment for obesity is still primary prevention, but pharmacotherapy does work.[19] ***Orlistat*** lowers fat absorption (hence SE of oily faecal incontinence). ***Sibutramine*** increases post-ingestive satiety (SE hypertension and tachycardia)—see OHCS p529.[1]

Surgery for obesity?

See p579.

Calculating BMI

BMI is calculated as (weight in kg)/(height in m)^2

BMI	State	Some implications within the categories
<18.5	Underweight	<17.5 is one of the criteria for anorexia nervosa
18.5-25	Target	
25-30	Overweight	Weight loss should be considered
30-40	Obesity	>32 is unsuitable for day-case general surgery
>40	Extreme/morbid obesity	>40 is an indication for bariatric surgery

▸Caveats: BMI does not take into account the distribution of body fat, and is harder to interpret for children and adolescents. **Waist circumference** >94cm in men and >80cm in women reflects omental fat and correlates better with risk than does BMI. For ethnic variations, see p197.

The mouth

Leucoplakia

White thickening of the tongue or oral mucosa of unknown cause (**fig 1**). It is premalignant. Oral hairy leucoplakia is a shaggy white patch on the side of the tongue seen in HIV, caused by EBV. ▸When in doubt, refer all intra-oral white lesions (see MINIBOX).

Aphthous ulcers

(**fig 2**) 20% of us get these shallow, painful ulcers on the tongue or oral mucosa that heal without scarring. *Causes of severe ulcers:* Crohn's & coeliac disease; Behçet's (p686); trauma; erythema multiforme; lichen planus; pemphigus; pemphigoid; infections (herpes simplex, syphilis, Vincent's angina, p704). *Treatment* is difficult: ***hydrocortisone*** lozenges held on the ulcer may help, as may ***tetracycline*** mouthwash. ▸Biopsy any ulcer not healing after 3 weeks to exclude malignancy; refer to an oral surgeon if uncertain.

White intra-oral lesions

- Idiopathic keratosis
- Carcinoma
- Leucoplakia
- Hairy oral leucoplakia
- Lichen planus
- Lupus erythematosus
- Poor dental hygiene
- Smoking
- Candidiasis

- Aphthous stomatitis
- Squamous papilloma
- Secondary syphilis

Candidiasis (thrush)

(**fig 3**) causes white patches or erythema of the buccal mucosa. Patches may be hard to remove and bleed if scraped. *Risk factors:* extremes of age; DM; antibiotics; immunosuppression (long-term corticosteroids, including inhalers; cytotoxics; malignancy; HIV). ▸Oropharyngeal candidiasis in an apparently fit patient may suggest underlying HIV infection. *Treatment:* ***Nystatin*** suspension or pastilles or ***amphotericin*** lozenges. ***Fluconazole*** for oropharyngeal candidiasis.

Cheilitis (angular stomatitis)

Fissuring of the mouth's corners is caused by denture problems, candidiasis (above), or deficiency of iron or riboflavin (vitamin B_2).

Gingivitis

Gum inflammation ± hypertrophy occurs with poor oral hygiene, drugs (phenytoin, ciclosporin, nifedipine), pregnancy, vitamin C deficiency (scurvy, p270), acute myeloid leukaemia (p340), or Vincent's angina (p704).

Microstomia

(**fig 4**) The mouth is too small, eg from thickening and tightening of the perioral skin after burns or in epidermolysis bullosa (destructive skin and mucous membrane blisters ± ankyloglossia) or systemic sclerosis (p538).

Oral pigmentation

Perioral brown spots characterize Peutz-Jeghers' (p700). Pigmentation anywhere in the mouth suggests Addison's disease or drugs (eg antimalarials). Consider malignant melanoma. *Telangiectasia:* Systemic sclerosis; Osler-Weber-Rendu syndrome (p700). *Fordyce glands* (creamy yellow spots at the border of the oral mucosa and the lip vermillion) are sebaceous cysts, common and benign. *Aspergillus niger* colonisation may cause a black tongue.

Teeth

A blue line at the gum-tooth margin suggests lead poisoning. Prenatal or childhood tetracycline exposure causes a yellow-brown discolouration.

Tongue

This may be furred or dry (xerostomia) in dehydration, if on tricyclics, etc.,[1] after radiotherapy, in Crohn's disease, Sjögren's (p702) and Mikulicz's syndrome.[21]

- *Glossitis* means a smooth, red, sore tongue, eg caused by iron, folate, or B_{12} deficiency (**fig 1**, p321). If local loss of papillae leads to ulcer-like lesions that change in colour and size, use the term **geographic tongue** (harmless migratory glossitis).
- *Macroglossia:* The tongue is too big. Causes: myxoedema; acromegaly; amyloid. A *ranula* is a bluish salivary retention cyst to one side of the frenulum, named after the bulging vocal pouch of frogs' throats (genus *Rana*).
- *Tongue cancer* typically appears on its edge as a raised ulcer with firm edges and environs. Main risk factors are smoking and alcohol.[2] Examine under the tongue and ask patient to deviate his extended tongue sideways. Spread: anterior 1/3 of the tongue drains to the submental nodes; middle 1/3 to the submandibular nodes; posterior 1/3 to the deep cervical nodes (see BOX, p621).

  Treatment: Surgery or radiotherapy. 5yr survival (early disease): 80%. ▸When in doubt, refer a tongue ulcer.

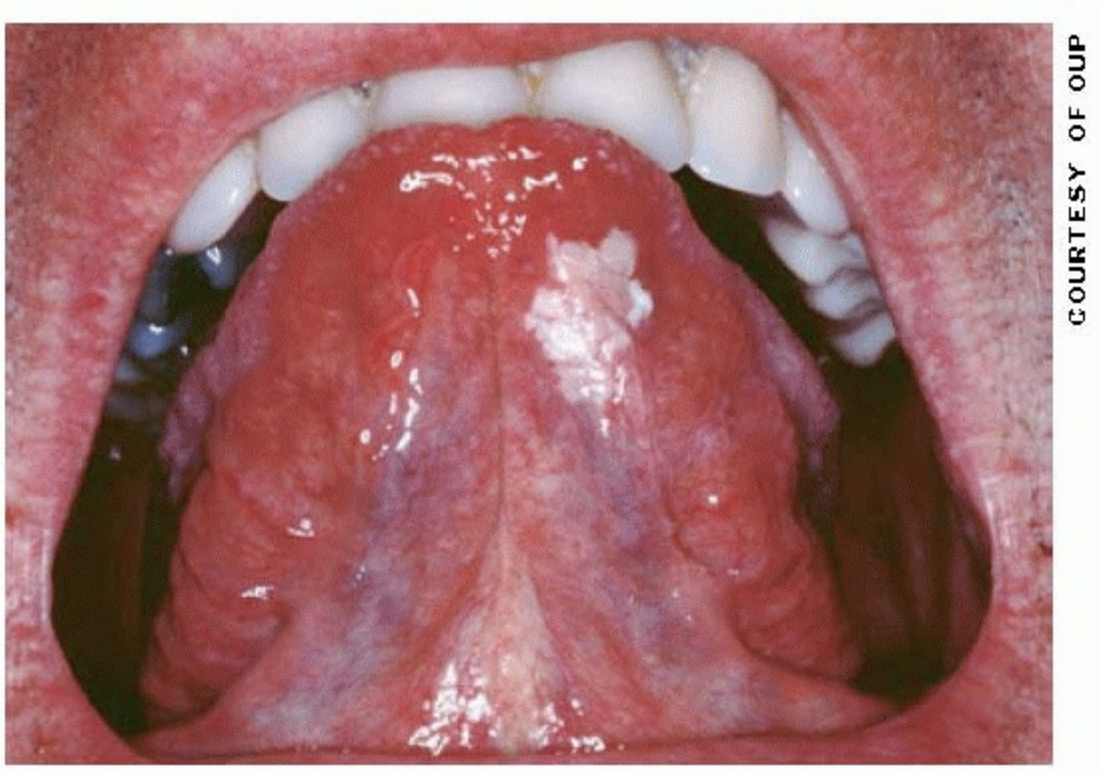


Fig 1. Leucoplakia on the underside of the tongue. It is important to refer leucoplakia because it is a premalignant.

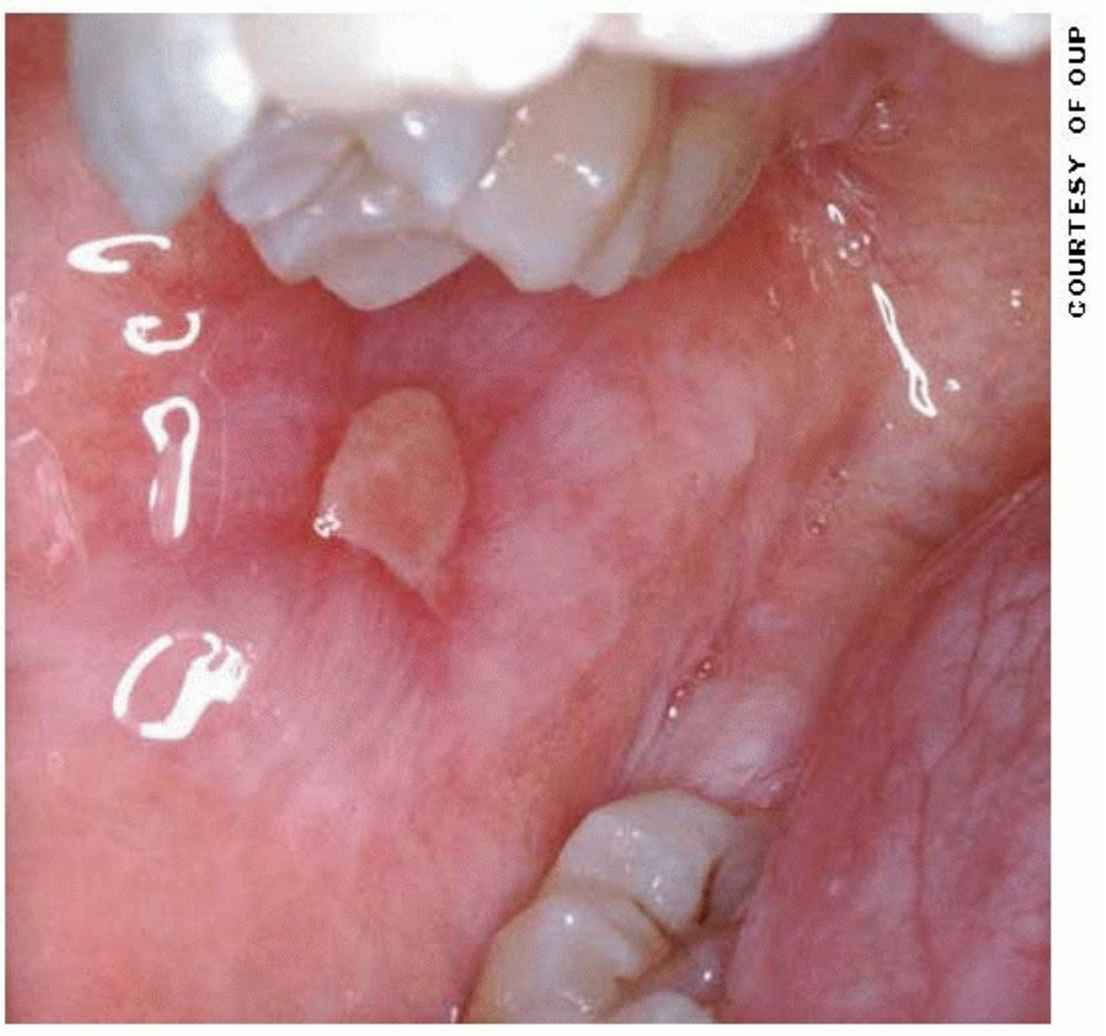


Fig 2. An aphthous ulcer in the buccal mucosa. The name is tautological, literally meaning an ulcer-like ulcer—the adjective aphthous comes from the latinised Greek noun *aphtha*, meaning ulceration. This is a fine example of the (sometimes unnessecary) complexity of language that has historically

pervaded medicine. A light grasp of the classical languages can help but it is by no means prerequisite!

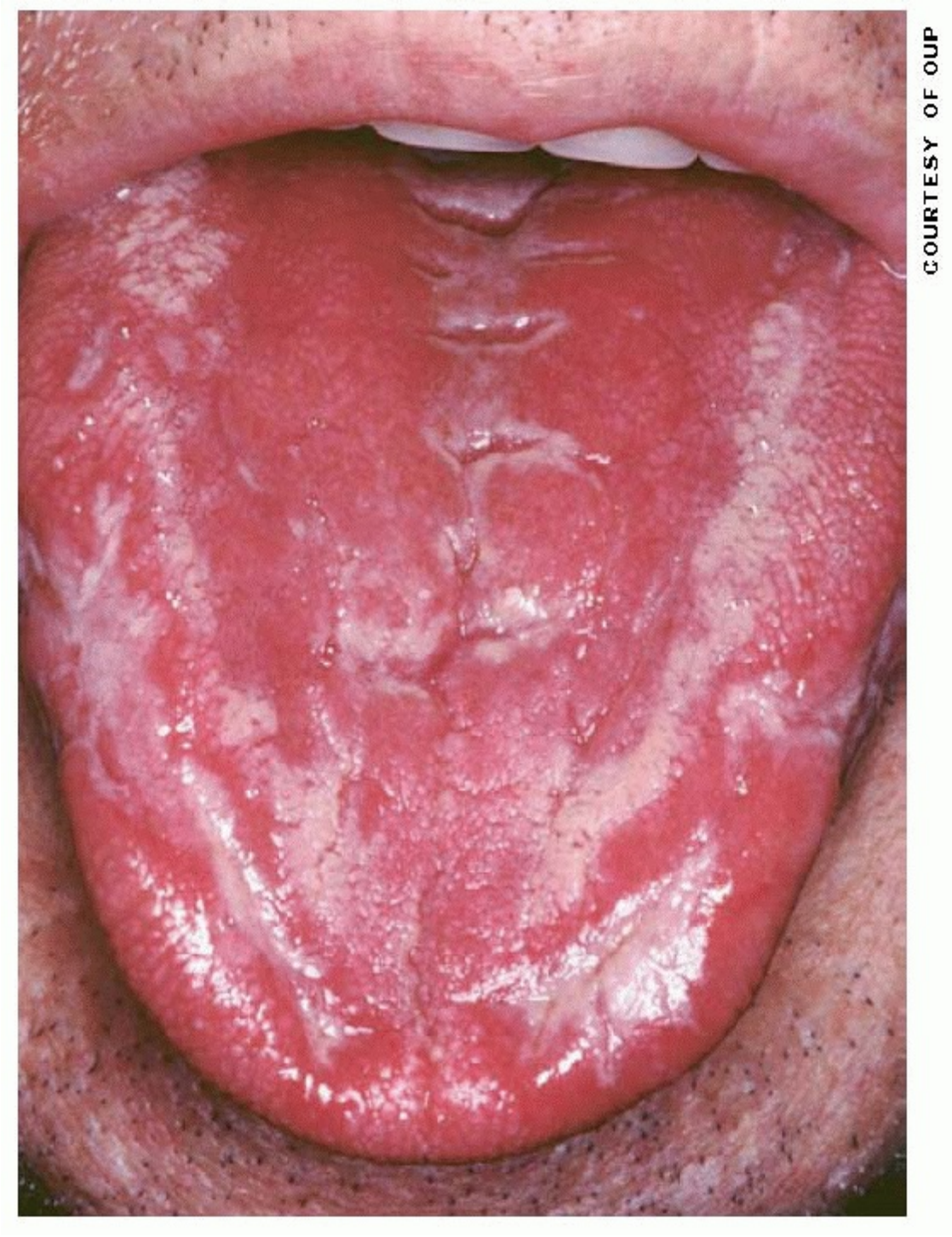


Fig 3. White fur on an erythematous tongue caused by oral candidiasis.

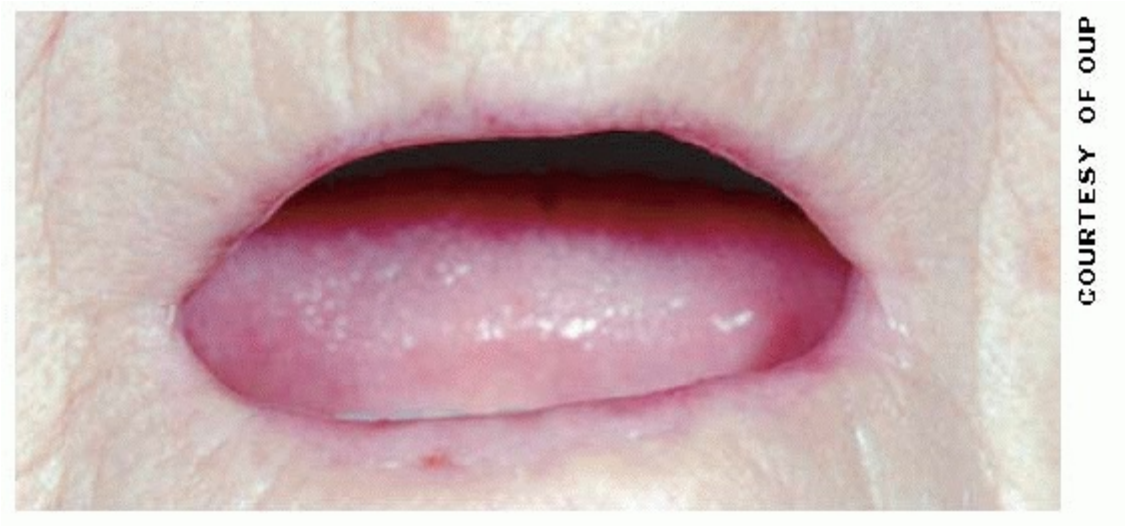


Fig 4. Microstomia (small, narrow moth), eg from hardening of the skin around the mouth which causes the oral opening to close in scleroderma. It can be both cosmetically and functionally disabling.[22]

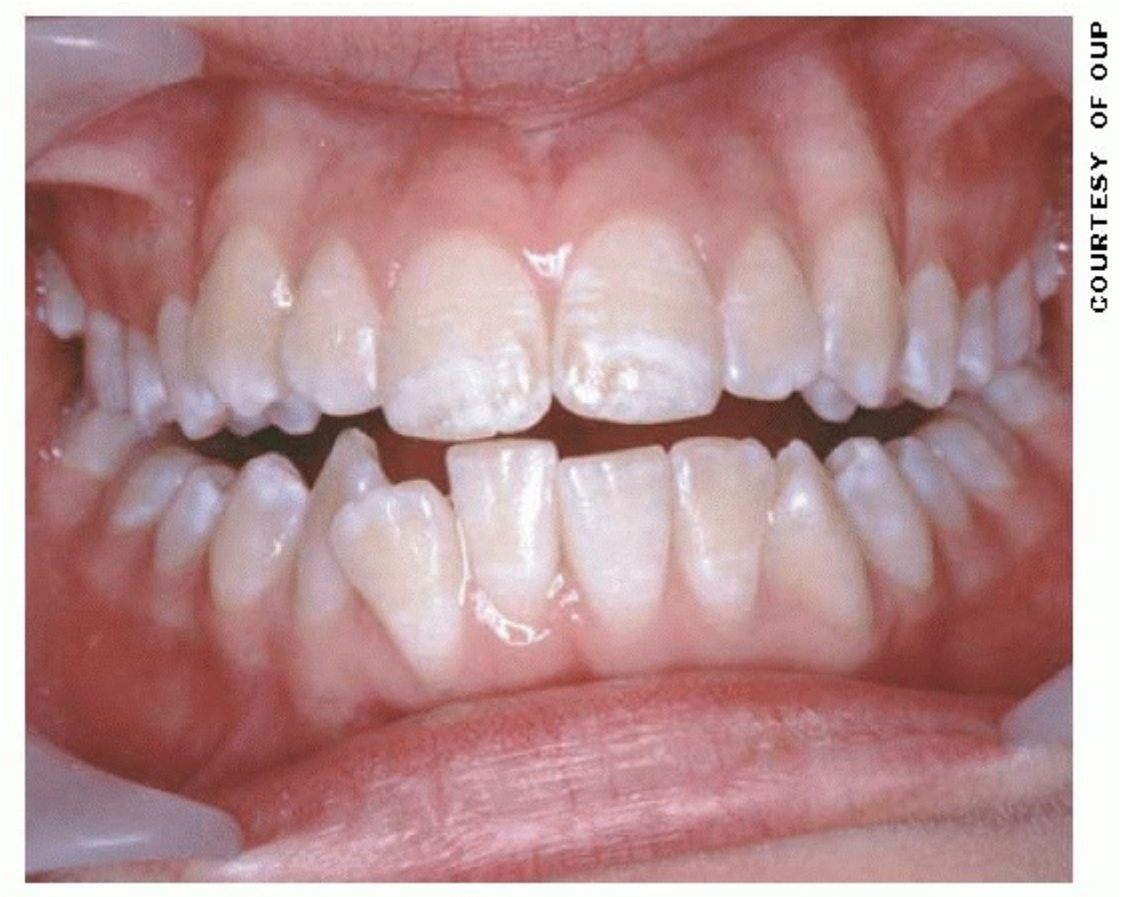


Fig 5. White bands on the teeth can be caused by excessive fluoride intake.

[2] Betel nut (*Areca catechu*) chewing, common in South Asia, may be an independent risk factor.

Dysphagia

Dysphagia is difficulty in swallowing and always needs investigating to exclude malignancy. If symptoms are progressive or prolonged then **urgent** investigation is required.

Causes

Oral, pharyngeal, or oesophageal? Mechanical or motility related (see BOX)?

Clinical features

There are a number of key questions to ask:

1. Was there difficulty swallowing solids **and** liquids from the start?

   Yes: Motility disorder (achalasia, neurological), or pharyngeal causes.

   No: Solids **then** liquids: suspect a stricture (benign or malignant).

2. Is it difficult to make the swallowing movement?

   Yes: Suspect bulbar palsy, especially if he coughs on swallowing.

3. Is swallowing painful (odynophagia)?

   Yes: Suspect cancer, severe oesophagitis, achalasia, or oesophageal spasm.

4. Is the dysphagia intermittent or is it constant and getting worse?

   Intermittent: Suspect oesophageal spasm.

   Constant and worsening: Suspect malignant stricture.

5. Does the neck bulge or gurgle on drinking?

   Yes: Suspect a pharyngeal pouch (see **fig 1**, p621).

Signs

Is the patient cachectic or anaemic? Examine the mouth; feel for supraclavicular nodes (left supraclavicular node = Virchow's node—suggests intra-abdominal malignancy); look for signs of systemic disease, eg systemic sclerosis, CNS disease.

Investigations

FBC (anaemia); U&E (dehydration); CXR (mediastinal fluid level, absent gastric bubble, aspiration); barium swallow (**fig 1**) +/- video fluoroscopy; upper GI endoscopy and biopsy. Further investigations: oesophageal manometry (if normal barium swallow); ENT opinion if suspected pharyngeal cause.

Specific conditions

Oesophagitis

p236.

Diffuse oesophageal spasm

causes intermittent dysphagia ± chest pain. Barium swallow: abnormal contractions, eg corkscrew oesophagus.[1]

[1] Non-propulsive contractions manifest as tertiary contractions or **'corkscrew oesophagus'** and suggest a motility disorder and may lead to impaired acid clearance. Symptoms and radiology do not necessarily correlate. *Nutcracker oesophagus* denotes distal peristaltic contractions >180mmHg. It can cause pain, eg relieved by nitrates, sublingual ***nifedipine***, or the smooth muscle relaxant ***sildenafil*** (p316).

Achalasia:

Failure of relaxation of the lower oesophageal sphincter (due to degeneration of the myenteric plexus) causes dysphagia, regurgitation, substernal cramps, and ↓weight. Barium swallow: dilated tapering oesophagus. Treatment: endoscopic balloon dilatation, or Heller's cardiomyotomy— then proton pump inhibitors (PPIs, p236). Botulinum toxin injection is an alternative if unsuitable for an invasive procedure.[23]

Benign oesophageal stricture:

Caused by gastro-oesophageal reflux disease (GORD, p236), corrosives, surgery, or radiotherapy. Treatment: endoscopic balloon dilatation. *Oesophageal cancer:* (p614) Associations: û; GORD,[24] tobacco, alcohol, Barrett's oesophagus (p686), achalasia, tylosis (palmar hyperkeratosis), Paterson-Brown-Kelly syndrome.

Paterson-Brown-Kelly (Plummer-Vinson) syndrome:

Post-cricoid web + iron-deficiency.

Nausea and vomiting Causes: p74

Tests

Bloods:

FBC, U&E, LFT, Ca^{2+}, glucose, and amylase.

ABG:

A metabolic (hypochloraemic) alkalosis from loss of gastric contents (pH >7.45, ↑HCO_3^-) indicates severe vomiting. Request a plain

AXR

if suspected bowel obstruction—see p716 for AXR findings in obstruction. Consider upper GI endoscopy (p248) if persistent vomiting. Identify and **treat the underlying cause** if possible.

Treatment

See TABLE. Try to use pre-emptive therapy, eg pre-operatively for post-operative symptoms. When possible to try the oral route first. Roughly 1/3 of patients with nausea will require a second-line anti-emetic, so be prepared to prescribe more than one on occasions, but avoid drugs in pregnancy and children. Give IV fluids with K^+ replacement if severely dehydrated or nil by mouth and monitor electrolytes and fluid balance.

Causes of dysphagia
Mechanical block

- Malignant stricture (**fig 1**)
  - Oesophageal cancer
  - Gastric cancer
  - Pharyngeal cancer
- Benign strictures
  - Oesophageal web or ring p232
  - Peptic stricture
- Extrinsic pressure
  - Lung cancer
  - Mediastinal lymph nodes
  - Retrosternal goitre
  - Aortic aneurysm
  - Left atrial enlargement
- Pharyngeal pouch

Motility disorders

- Achalasia
- Diffuse oesophageal spasm
- Systemic sclerosis (p538)
- Myasthenia gravis (p504)
- Bulbar palsy (p498)
- Pseudobulbar palsy (p498)
- Syringobulbia (p508)
- Bulbar poliomyelitis (p420)
- Chagas' disease (p426)

Others

- Oesophagitis (p236) Ð
  - Infection (*Candida*, HSV)
  - Reflux oesophagitis
- Globus hystericus

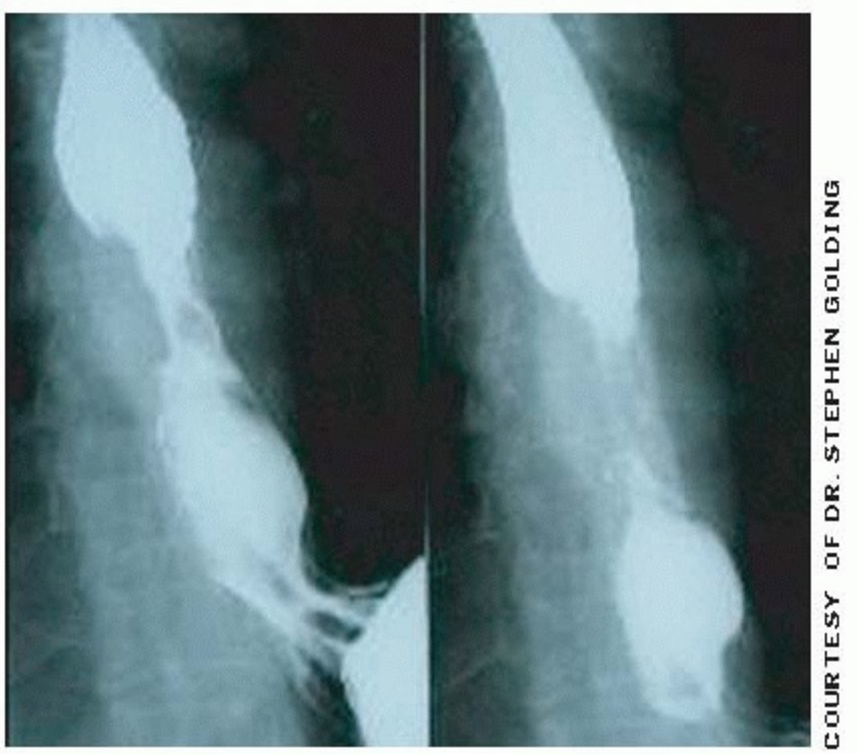


Fig 1. A malignant lower oesophageal stricture shown on barium swallow. The shouldered edges of the stricture produce an 'apple core' effect with an irregular mucosal pattern. On video fluoroscopy there would be no peristalsis visible in this segment. A benign stricture would have a more funnelled appearance with a normal mucosal pattern. Note the normal but similar appearance of the gastro-oesophageal junction inferiorly.

Ad nauseam…

Jumping into the sea is a certain cure for seasickness. John Ruskin (1819-1900) Nausea is often described by patients as their most intolerable symptom when they are unwell (especially by those enduring palliative care). It can be an equally difficult symptom to help control. Not all anti-emetics will work for everyone, so it is worthwhile persevering with your options to help alleviate such a disparaging and sometimes intractable symptom, since not everyone is able to jump ship so easily.

Remembering your anti-emetics

One way of recalling anti-emetics involves using (simplified) pharmacology.

Receptor	Antagonist	Dose	Notes
H_1	***Cyclizine***	50mg/8h PO/IV/IM	GI causes
	Cinnarizine	30mg/8h PO	Vestibular disorders
D_2	***Metoclopramide***	10mg/8h PO/IV/IM	GI causes; also prokinetic
	Domperidone	60mg/12h PR 20mg/6h PO	Also prokinetic

	Prochlorperazine	12.5mg stat IM 25mg stat PR 5mg/8h PO	Vestibular/GI causes
	Haloperidol	1.5mg bd PO	Chemical causes eg opioids
$5HT_3$	***Ondansetron***	4mg/8h IV	Doses can be much higher for eg emetogenic chemotherapy
others	***Hyoscine butylbromide***	20mg stat IM/IV	Antimuscarinic Ì also antispasmodic and antisecretory (don't prescribe with a prokinetic)
	Dexamethasone	6-10mg/d PO/SC	Unknown mode of action; as adjuvant therapy
	Midazolam	2-4mg/d IV	Unknown action; anti-emetic effect outlasts sedative effectRCT_{25}

▸All anti-dopaminergics can cause dystonias and oculogyric crisis, especially in younger patients.

Dyspepsia (indigestion) & peptic ulcer disease (PUD)

Dyspepsia is a non-specific group of symptoms related to the upper GI tract.

Non-specific symptoms

Epigastric pain eg related to hunger, eating specific foods, or time of day; may be associated with bloating ± fullness after meals; heartburn (retrosternal pain with demonstrable acid reflux). Alarm symptoms: Anaemia (iron deficiency); loss of weight; anorexia; recent-onset of progressive symptoms; melaena or haematemesis; swallowing difficulty. Signs Tender epigastrium (non-specific). Any abdominal mass; supraclavicular nodes ± hepatomegaly?

△△ ***of dyspepsia***

- Non-ulcer dyspepsia
- Duodenal ulcer
- Duodenitis
- Gastritis/gastric ulcer
- Gastric malignancy
- GORD (reflux, p236)
- Oesophagitis

Managing new dyspepsia

See FLOWCHART/NICE advice. *If ≤55yrs old:* test for *Helicobacter pylori*; treat if +ve.[1] 'Test and treat' is more effective at reducing symptoms and recurrence than acid suppression alone (eg with ***lansoprazole*** 30mg/24h PO for 4 weeks; SE: D&V, oedema, bronchospasm, Stevens-Johnson syndrome, toxic epidermal necrolysis, alopecia, photosensitivity, interstitial nephritis, LFT↑, agranulocytosis).[26] When choosing anti-acid therapy, PPIs are better than H_2-receptor antagonists (H_2RA) at controlling symptoms in those with uninvestigated dyspepsia. The most accurate non-invasive test for *H. pylori* is the ^{13}C breath test (see TABLE). ▸*If≥55* (and **new** dyspepsia not accounted for by NSAID use and persisting for >4-6 weeks) **or** *alarm symptoms*, refer for urgent endoscopy (p248). Platelets↑, ESR↑ ± LFT↑ suggest organic causes.[27]

Duodenal ulcers (DU)

are 4-fold commoner than GU.

Major risk factors:

H. pylori (~90%); drugs (aspirin; NSAIDs; steroids).

Minor:

↑Gastric acid secretion; ↑gastric emptying (↓duodenal pH); blood group O; smoking. The role of stress is controversial.

Symptoms:

Epigastric pain typically before meals or at night, relieved by eating, or drinking milk. 50% are asymptomatic; others experience recurrent episodes.

Signs:

Epigastric tenderness.

Diagnosis:

Upper GI endoscopy (stop PPI 2 weeks before), see **fig 1**, p245. Test for *H. pylori*. Measure gastrin concentrations whilst off PPIs if Zollinger-Ellison syndrome (p709) is suspected.

△△

Non-ulcer dyspepsia; duodenal Crohn's; TB; lymphoma; pancreatic cancer (p268).

Gastric ulcers (GU)

occur mainly in the elderly, on the lesser curve. Ulcers elsewhere are more often malignant.

Risk factors: H. pylori

(~80%); smoking; NSAIDs; reflux of duodenal contents; delayed gastric emptying; stress, eg neurosurgery (Cushing's ulcers) or burns (Curling's ulcers).

Symptoms:

Asymptomatic or epigastric pain (related to meals ± relieved by antacids) ± weight↓.

Tests:

Upper GI endoscopy to exclude malignancy (stop PPI 2weeks before); take multiple biopsies from the ulcer's rim & base (histology, *H. pylori*) and brushings (cytology).

Treating peptic ulcers

Lifestyle

Avoid food that worsens symptoms; stop smoking (smoking slows healing in GU and ↑relapse rates in DU).

H. pylori eradication:

Triple therapy is 80-85% effective at eradication.[1]

Drugs to reduce acid:

PPIs are the most effective, eg ***lansoprazole*** 30mg/24h PO for 4 (DU) or 8 (GU) weeks. H2RAs may have a place for individual responders, eg ***ranitidine*** 300mg nocte PO or ***cimetidine*** 800mg nocte PO for 8 weeks.

NSAID-associated ulcers:

Stop NSAID if possible (if not, use H_2RA, PPI, or ***misoprostol*** for prevention). If symptoms persist, re-endoscope, recheck for *H. pylori*, and reconsider the differential diagnosis.

Surgery:

p638.

Complications

Bleeding, ▸▸(p244), perforation, ▸▸(p580), malignancy, gastric outflow obstruction, (p638).

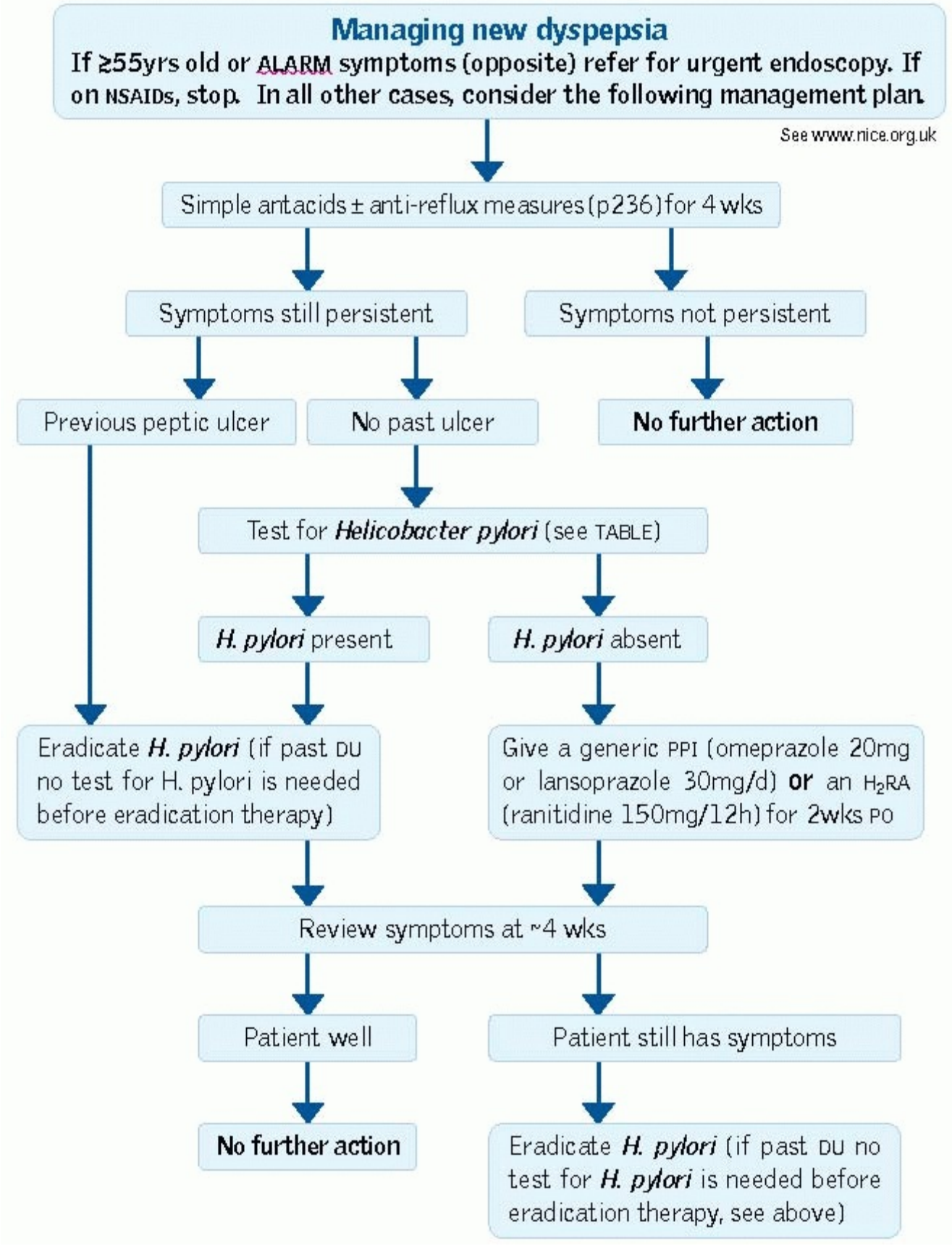
Treatment of non-ulcer dyspepsia

H. pylori eradication

may be beneficial in relieving symptoms and preventing ulcers, MET_{28} but we do not know enough about the long-term effects of such a strategy (SE include ↑reflux) for authoritative advice, and so we start eradication therapy for *H. pylori* only after a +ve result.

Medical therapy:

Prokinetic agents (eg ***metoclopramide*** 10mg/8h PO) may relieve symptoms. PPIs or H2RAs are unlikely to be beneficial.$_{29}$



See www.nice.org.uk

Why do we use the ^{13}C breath test to detect *Helicobacter pylori*?

Of all the non-invasive tests, the 13C breath test is the most accurate.

Test	Sensitivity	Specificity
Invasive		

	CLO test	95%	95%
	Histology	95%	95%
	Culture	90%	100%
Non-invasive			
	^{13}C breath test	95%	96%
	Stool antigen	95%	94%
	Serology	92%	83%
NB: Stop PPI 2 weeks before ^{13}C breath and stool antigen testing, as well 2 weeks before endoscopy.			

Gastro-oesophageal reflux disease (GORD)

Dysfunction of the lower oesophageal sphincter predisposes to the gastro-oesophageal reflux of acid. If reflux is prolonged or excessive, it may cause oesophagitis, benign oesophageal stricture, or Barrett's oesophagus (p686).

Associations

Smoking; alcohol; hiatus hernia (see below); pregnancy; obesity; big meals; surgery in achalasia; drugs (tricyclics, anticholinergics, nitrates); systemic sclerosis; *Helicobacter pylori*?[1] GORD can also contribute to asthma.

Symptoms

Heartburn (burning, retrosternal discomfort related to meals, lying down, stooping, and straining, relieved by antacids); belching; acid brash (acid or bile regurgitation); waterbrash (excessive salivation); odynophagia (painful swallowing, eg from oesophagitis or ulceration); nocturnal asthma (cough/wheeze with apparently minimal inhalation of gastric contents).

Complications

Oesophagitis, ulcers, benign stricture, Barrett's oesophagus, oesophageal adenocarcinoma, and rarely iron deficiency anaemia.

△△*:*

Oesophagitis (corrosives, NSAID); infection (CMV, herpes, *Candida*); DU; gastric ulcers or cancers; non-ulcer dyspepsia.

Tests

Isolated symptoms do not require investigation.

Indications for upper GI endoscopy:

Age >55yrs; symptoms >4 wks; dysphagia; persistent symptoms despite treatment; relapsing symptoms; weight↓.

Endoscopic classification:

See BOX. At endoscopy, record complications of GORD (above) as *present* or *absent*. Barium swallow may show hiatus hernia. 24h oesophageal pH monitoring ± oesophageal manometry help diagnose GORD when endoscopy is normal.

Treatment

- *Lifestyle:* **Encourage:** Weight loss; smoking cessation; raise the bed head; small, regular meals. **Avoid:** Hot drinks, alcohol, and eating <3h before bed. Avoid drugs affecting oesophageal motility (nitrates, anticholinergics, tricyclic antidepresssants, calcium channel blockers—relax the lower oesophageal sphincter) or that damage the mucosa (NSAIDs, K^+ salts, bisphosphonates).
- *Drugs:* Antacids eg ***magnesium trisilicate mixture*** (10mL/8h) or alginates eg ***Gaviscon®*** (10-20mL/8h PO) relieve symptoms. If symptoms persist for >4 weeks (or weight↓; dysphagia; excessive vomiting; GI bleeding), refer for GI endoscopy. If oesophagitis confirmed, try a PPI (the most effective and most expensive drug option) eg ***lansoprazole*** 30mg/24h PO.[30] Prokinetic drugs: These help gastric emptying (eg ***metoclopramide*** 10mg/8h PO; dystonias can be a serious side-effect). ***Cisapride*** is no longer licensed in the UK.
- *Surgery:* (eg Nissen fundoplication, p638) is not indicated unless symptoms are severe, refractory to medical therapy **and** there is pH-monitoring evidence of severe reflux. Laparoscopic repairs are gaining favour.[31]

Hiatus hernia

The proximal stomach herniates through the diaphragm into the thorax. See **fig 3**. *Sliding hiatus hernia* (80%) is where the gastro-oesophageal junction slides up into the chest—see BOX. *Rolling hiatus hernia* (20%) is where the gastro-oesophageal junction remains in the abdomen but a bulge of stomach herniates up into the chest alongside the oesophagus—see BOX and **fig 3**.

Clinical features

Common: 30% of patients >50yrs, especially obese women. 50% have symptomatic gastro-oesophageal reflux.

Imaging

Barium swallow is the best diagnostic test; upper GI endoscopy allows visualization of the mucosa (?oesophagitis) but cannot reliably exclude a hiatus hernia.

Management

Lose weight. Treat reflux symptoms (see above). Indications for surgery (eg Nissen, see above): intractable symptoms; recurrent stricture.

The Los Angeles (LA) classification of GORD

Minor diffuse changes (erythema, oedema; friability) are not included, and the term **mucosal break** (a well-demarcated area of slough/erythema) is used to encompass the old terms erosion and ulceration. There are 4 grades:[32]

1. One or more mucosal breaks <5mm long, not extending beyond 2 mucosal fold tops.
2. Mucosal break >5mm long limited to the space between 2 mucosal fold tops.
3. Mucosal break continuous between the tops of 2 or more mucosal folds but which involves less than 75% of the oesophageal circumference.
4. Mucosal break involving ³75% of the oesophageal circumference. Useful though the grading is, it is still important to document the actual findings at endoscopy.

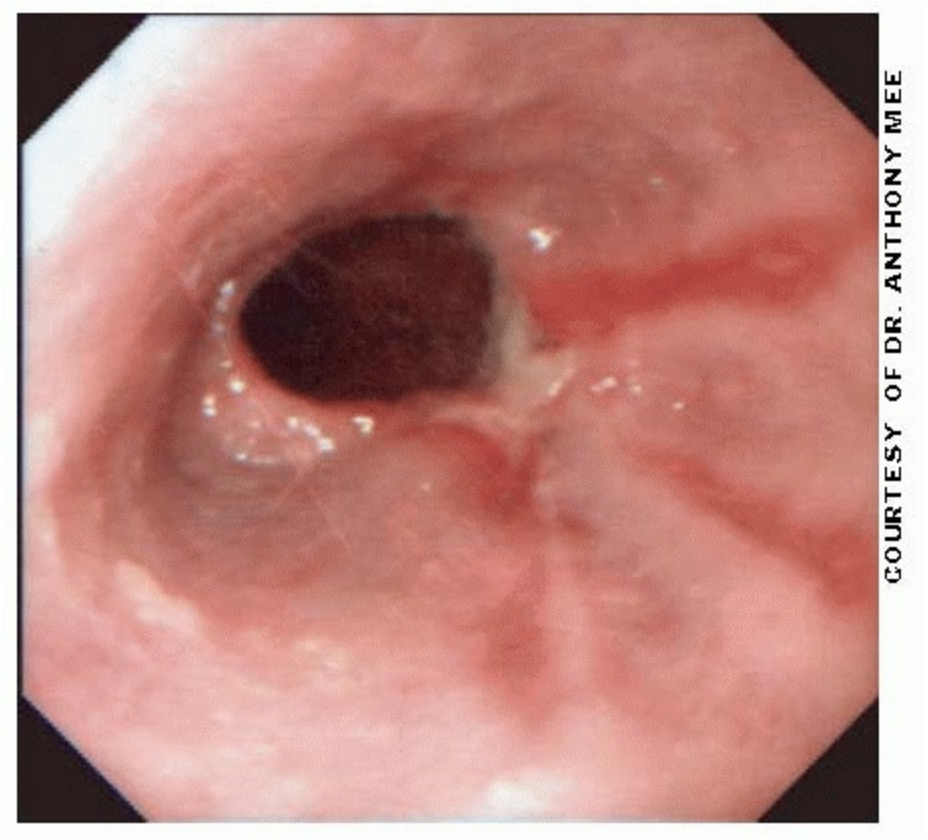


Fig 1. Upper GI endoscopy showing longitudinal mucosal breaks in severe oesophagitis.

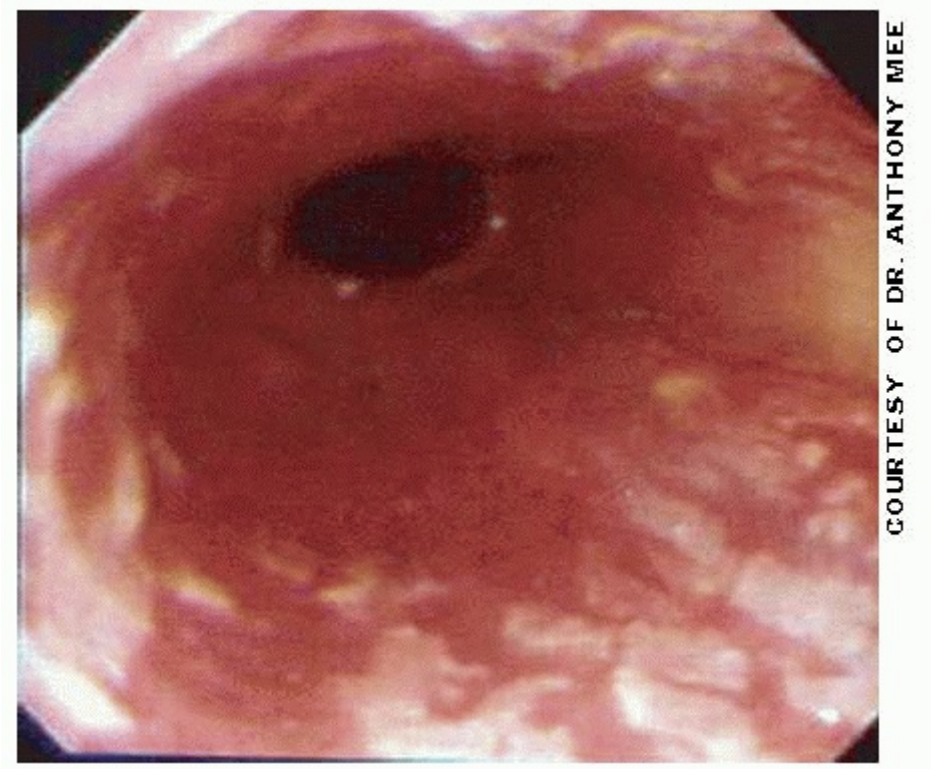
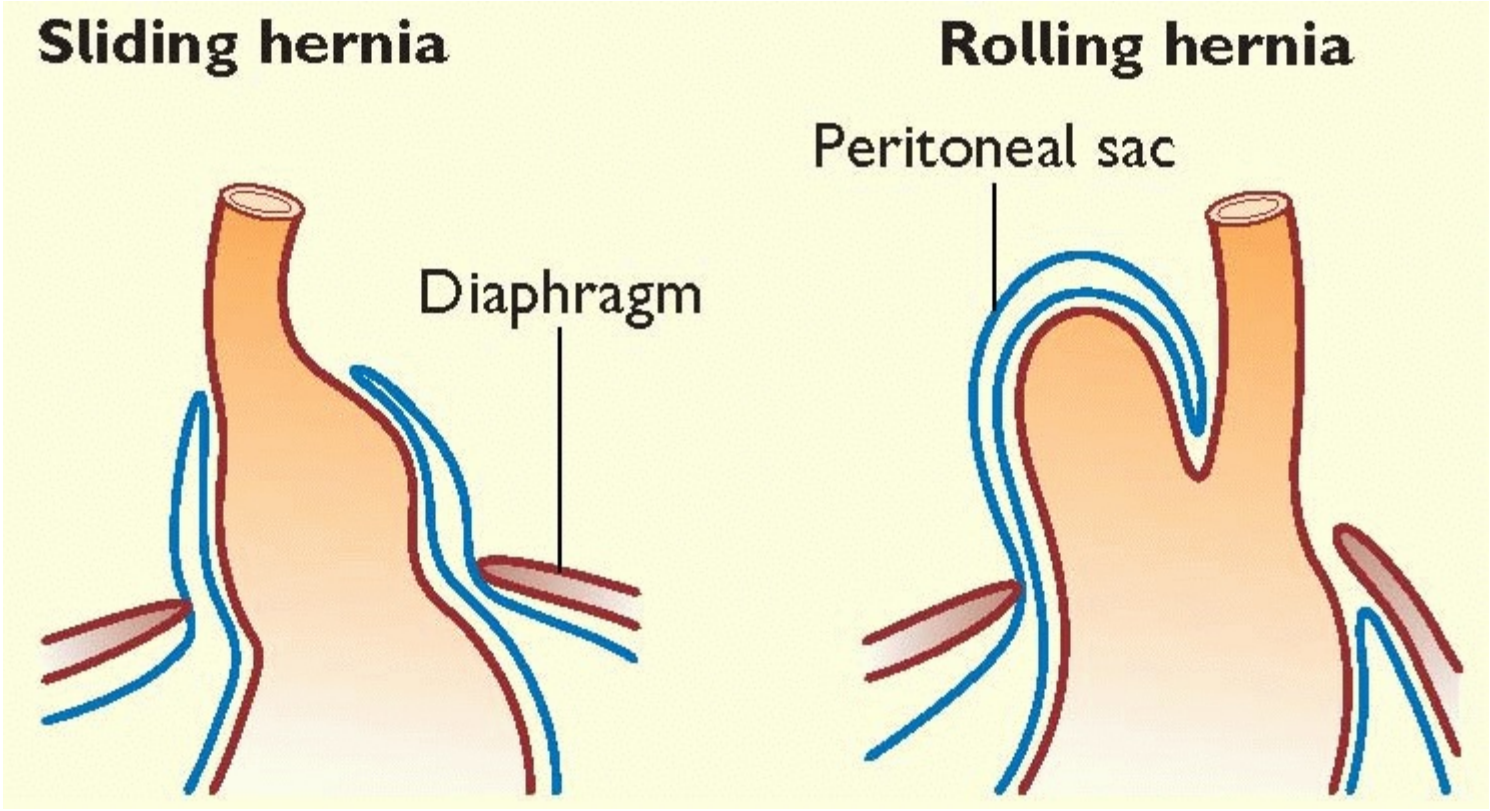


Fig 2. Barrett's oesophagus on upper GI endoscopy, in which the epithelium of the distal oesophagus undergoes metaplasia from squamous to columnar type. Endoscopic appearance can be described as a 'velvety' epithelium, and it is usually an incidental finding at endoscopy. See p686.

Hiatus hernia—sliding and rolling



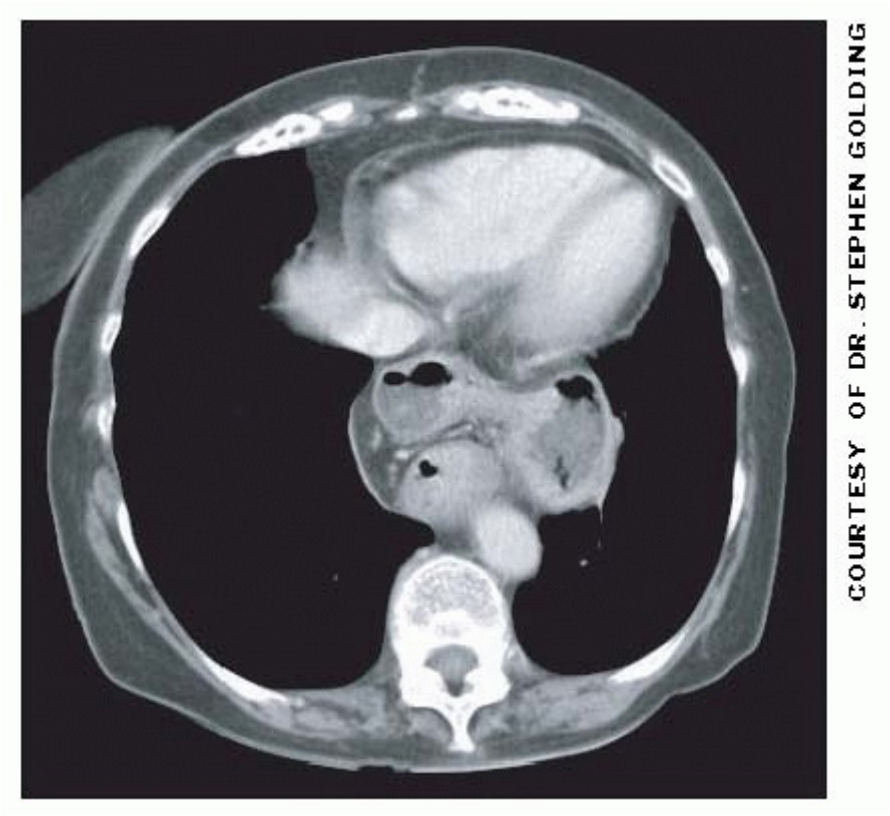


Fig 3. CT chest with IV contrast showing the rolling components of a hiatus hernia anterior to the oesophagus. Between the oesophagus and the vertebral coloumn on the left hand side, is the aorta.

Diarrhoea Traveller's diarrhoea p367

Diarrhoea means increased stool water (hence ↑stool volume, eg >200mL daily), and this increases stool frequency and the passage of liquid stool. If it is the stool's fat content which is increased, use the term **steatorrhoea** (=pale, malodorous stool that is difficult to flush away, p272). Distinguish both from faecal urgency (which suggests rectal pathology eg cancer, UC).[34]

Clinical features

Take a detailed history:

- *Acute or chronic?* If acute suspect gastroenteritis. Ask about travel, change in diet, and contact history. Chronic diarrhoea alternating with constipation suggests irritable bowel (p248). Anorexia, weight↓, nocturnal diarrhoea & anaemia suggest an organic cause.
- *Bloody diarrhoea: Campylobacter*, *Shigella*, *Salmonella*, *E. Coli*, amoebiasis, UC, Crohn's disease, colorectal cancer (p612), colonic polyps, pseudomembranous colitis, ischaemic colitis (p488).
- *Fresh* PR *bleeding:* See p594.
- *Mucus* occurs in IBS, colorectal cancer, and polyps.
- *Pus* suggests IBD (inflammatory bowel disease), diverticulitis, or a fistula/abscess.
- *Large bowel symptoms:* Watery stool ± blood or mucus; pelvic pain relieved by defecation; tenesmus; urgency.
- *Small bowel symptoms:* periumbilical (or RIF) pain not relieved by defecation; watery stool or steatorrhoea.
- *Non-*GI *causes:* Antibiotics; PPIs; cimetidine; propranolol, cytotoxics; NSAIDs; digoxin; alcohol; laxative abuse); **medical conditions:** thyrotoxicosis; autonomic neuropathy; Addison's disease; carcinoid syndrome.

Examination

Look for weight↓, clubbing, anaemia, oral ulcers (p230), rashes and abdominal scars. Assess severity of dehydration (dry mucous membranes, ñskin turgour and capillary refill >2s). **Feel** for an enlarged thyroid or an abdominal mass. Do a rectal examination for masses (eg rectal carcinoma), or impacted faeces (overflow diarrhoea). Test for faecal occult blood.

Common causes

- Gastroenteritis
  - Viral
  - Bacterial
  - Parasites/protozoa
- IBS (p268)
- Drugs (see below)
- Colorectal cancer
- Ulcerative colitis (UC)
- Crohn's disease
- Coeliac disease

Uncommon causes

- Microscopic colitis[1]
- Chronic pancreatitis
- Bile salt malabsorption
- Thyrotoxicosis
- Laxative abuse
- Lactose intolerance
- Ileal/gastric resection
- Overflow diarrhoea
- Bacterial overgrowth
- Pseudomembranous colitis[2]

Rare causes

- Autonomic neuropathy[33]
- Addison's disease
- Ischaemic colitis
- Amyloidosis
- Tropical sprue
- Gastrinoma

- VIPoma[3]
- Carcinoid syndrome
- Medullary thyroid CA
- Pellagra

Tests

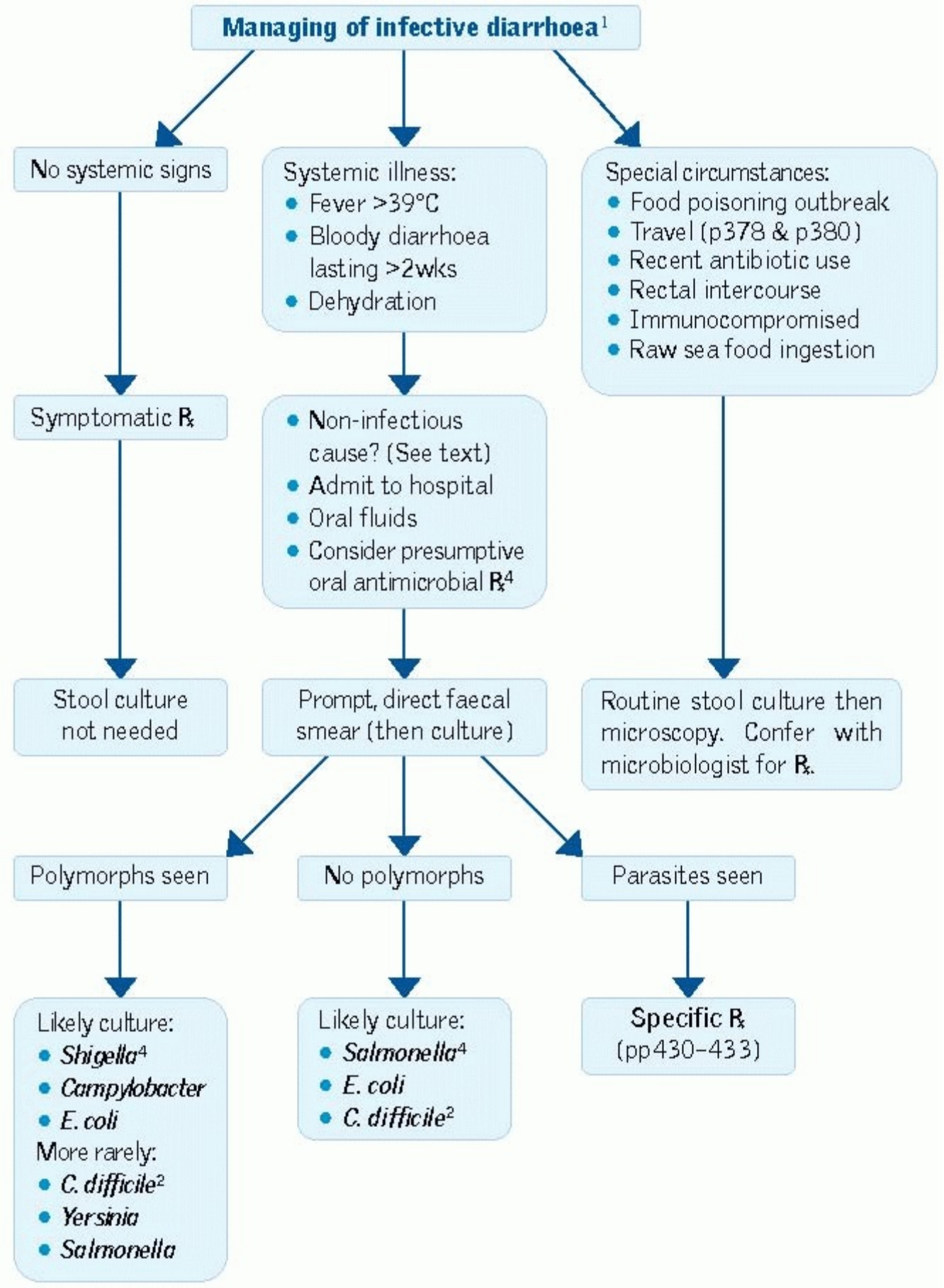
Bloods:

FBC (iron deficiency; MCV↑ in coeliac disease, ↑alcohol use, ileal Crohn's); U&E (K^+↓); ESR↑ (cancer, IBD); CRP↑ (infection, IBD). TSH↓ (thyrotoxicosis); coeliac serology (p272 ± duodenal biopsy).

- *Stool* Test for pathogens & *C. difficile* toxin (pseudomembranous colitis).[2] Faecal fat excretion or ^{13}C-triolein (highly labelled triolein) breath test (nicer and reliable) if symptoms of chronic pancreatitis, malabsorption, or steatorrhoea.[35]
- *Rigid sigmoidoscopy* with biopsy of normal and abnormal looking mucosa: ~15% of patients with Crohn's disease have macroscopically normal mucosa.
- *Colonoscopy/Barium enema:* To exclude malignancy and in colitis (▸but **not** during an acute episode). If normal, consider small bowel radiology (eg Crohn's disease) ± ERCP (eg chronic pancreatitis).

Management

Treat causes. ***Oral rehydration*** is better than IV rehydration; if impossible, give 0.9% saline + 20mmol K^+/L IVI. ***Codeine phosphate*** 30mg/6h PO or ***loperamide*** 2mg PO after each loose stool (max 16mg/day) reduce stool frequency.[36] Avoid antibiotics except in infective diarrhoea causing systemic illness (see p239 CHART)—because of the risk of developing antibiotic resistance.



Constipation

Always ask the patient exactly what he means by 'constipation'—bowel habit varies greatly between individuals and according to diet. There are various formal and different definitions of constipation but the infrequent passage of stool (<3 times weekly) or difficulty in defecation, with straining or discomfort, is a reasonably practical working definition. The causes of constipation are numerous (see BOX).

Clinical features

Ask about frequency, nature, and consistency of the stool. Is there blood or mucus in/on the stools? Is there diarrhoea alternating with constipation? Has there been a recent change in bowel habit? Ask about diet and drugs. ▸**PR examination** is essential.

Tests

Most do not need investigation, especially young, mildly affected patients. Indications for investigation: age >40yrs; change in bowel habit; associated symptoms (weightñ, PR mucus or blood, tenesmus). *Blood tests:* FBC, U&E, Ca^{2+}, TFT. *Sigmoidoscopy* and biopsy of abnormal mucosa. *Barium enema* or *colonoscopy* if suspected colorectal malignancy. Special investigations (eg transit studies; anorectal physiology) are occasionally needed.

Treatment

Treat causes (BOX). Advise exercise and a good fluid intake (a high-fibre diet is often advised, but may cause bloating without helping constipation).[37] ▸Consider drugs only if these measures fail, and try to use them for short periods only.[1] Often, a stimulant such as ***senna*** ± a bulking agent is more effective and cheaper than agents such as ***lactulose***.[38]

Bulking agents

↑Faecal mass, so stimulating peristalsis. They must be taken with plenty of fluid and may take a few days to act. CI: difficulty in swallowing; intestinal obstruction; colonic atony; faecal impaction. ***Bran*** powder 3.5g 2-3 times/d with food (may hinder absorption of dietary trace elements if taken with every meal).[39] ***Ispaghula husk***, eg 1 Fybogel® 3.5g sachet after a meal, mixed in water and swallowed promptly (or else it becomes an unpleasant sludge). ***Methylcellulose***, eg Celevac® 3-6 500mg tablets/12h with ≥;300mL water. ***Sterculia***, eg Normacol® granules, 10mL sprinkled on food daily.

Stimulant laxatives

increase intestinal motility, so do not use in intestinal obstruction or acute colitis. Avoid prolonged use as it **may** cause colonic atony and hypokalaemia (but there are no good long-term data). Abdominal cramps are an important SE. Pure stimulant laxatives are ***bisacodyl*** tablets (5-10mg at night) or suppositories (10mg in the mornings) and ***senna*** (2-4 tablets at night). ***Docusate sodium*** and ***danthron***[2] (=dantron) have stimulant and softening actions. ***Glycerol*** suppositories act as a rectal stimulant. ***Sodium picosulfate*** (5-10mg up to 12h beforehand) is useful for rapid bowel evacuation prior to procedures.

Stool softeners

are particularly useful when managing painful anal conditions eg fissure. ***Arachis oil*** enemas lubricate and soften impacted faeces. ***Liquid paraffin*** should not be used for a prolonged period (SE: anal seepage, lipoid pneumonia, malabsorption of fat-soluble vitamins).

Osmotic laxatives

retain fluid in the bowel. ***Lactulose***, a semisynthetic disaccharide, produces osmotic diarrhoea of low faecal pH that discourages growth of ammoniaproducing organisms. It is useful in hepatic encephalopathy (initial dose: 30-50mL/12h). SE: bloating Ì it has a limited role in the treatment of constipation. ***Magnesium salts*** (eg magnesium hydroxide; magnesium sulfate) are useful when rapid bowel evacuation is required. ***Sodium salts*** (eg Microlette® and Micralax® enemas) should be avoided as they may cause sodium and water retention. ***Phosphate enemas*** are useful for rapid bowel evacuation prior to procedures.

[1] Risks of laxative abuse are overemphasized ('cathartic colon' is a questionable entity); stimulant laxatives may be used chronically on those who do not respond to bulk or osmotic laxatives alone.

What if laxatives don't help?

A multi-disciplinary approach with behaviour therapy, psychological support, habit training ± sphincter-action biofeedback may help. $5HT_4$ agonists, which induce peristalsis by systemic rather than luminal means, are under trial (***tegaserod*** and ***prucalopride***: neither currently licensed in UK).[40]

Causes of constipation

General

- Poor diet
- Inadequate fluid intake or dehydration
- Immobility (or lack of exercise)
- Irritable bowel syndrome (p268)
- Old age
- Post-operative pain
- Hospital environment (lack of privacy, having to use a bed pan)
- Distant, squalid, or otherwise unsatisfactory toilets

Anorectal disease

- Anal fissure (p626)
- Anal stricture
- Rectal prolapse

Intestinal obstruction

- Colorectal carcinoma (p612)
- Strictures (eg Crohn's disease)

- Pelvic mass (eg fetus, fibroids)
- Diverticulosis (rectal bleeding is a commoner presentation)
- Pseudo-obstruction (p598)

Metabolic/endocrine

- Hypercalcaemia (p672)
- Hypothyroidism (can cause constipation, but rare in those presenting with constipation—p204)
- Hypokalaemia (p668)
- Porphyria
- Lead poisoning

Drugs
(anticipate the potential effect and give dietary advice)

- Opiate analgesics (eg morphine, codeine)
- Anticholinergics (tricyclics, phenothiazines)
- Iron

Neuromuscular
(slow transit with ↓propulsive activity)

- Spinal or pelvic nerve injury (eg trauma, surgery)
- Aganglionosis (Chagas' disease, Hirschsprung's disease)
- Systemic sclerosis
- Diabetic neuropathy

Other causes

- Chronic laxative abuse (rare—diarrhoea is commoner)
- Idiopathic slow transit
- Idiopathic megarectum/colon
- Psychological (eg associated with depression or abuse as a child).

NB: Constipation alone is unlikely to be a symptom of serious organic disease and therefore can be met with reassurance.

Jaundice

Jaundice (**icterus**) refers to yellow pigmentation of skin, sclerae, and mucosae due to ↑plasma bilirubin (visible at >35μmol/L—not always easy to spot when mild). Jaundice is classified by the site of the problem (pre-hepatic, hepatocellular, or cholestatic/obstructive) or by the type of circulating bilirubin (conjugated or unconjugated). **Kernicterus** is seen in infants with unconjugated hyperbilirubinaemia and involves deposition of jaundice in the basal ganglia, which can cause **opisthotonus**.

Bilirubin metabolism (see BOX)

Bilirubin is formed from the breakdown of haemoglobin. It is conjugated with glucuronic acid by hepatocytes, making it water soluble. Conjugated bilirubin is secreted into the bile and passes out into the gut. Some is taken up again by the liver (via the enterohepatic circulation) and the rest is converted to urobilinogen by gut bacteria. Urobilinogen is either reabsorbed and excreted by the kidneys, or converted to stercobilin, which colours faeces brown.

Pre-hepatic jaundice

If there is ↑bilirubin production (haemolysis), ↓liver uptake or ↓conjugation, unconjugated bilirubin enters the blood. As it is water insoluble, it does not enter urine resulting in **unconjugated (acholuric) hyperbilirubinaemia**.

Causes:

Physiological (neonatal); haemolysis; dyserythropoiesis; glucuronyl transferase deficiency (Gilbert's, p692, & Crigler-Najjar syndromes, p688).

Hepatocellular jaundice

There is hepatocyte damage, usually with some cholestasis.

Causes:

Viruses: hepatitis (p394, eg A, B, C, etc.), CMV (p392), EBV (p389); drugs (see TABLE); alcoholic hepatitis; cirrhosis; liver metastases/abscess; haemochromatosis; autoimmune hepatitis (AIH); septicaemia; leptospirosis; α1-antitrypsin deficiency (p256); Budd-Chiari (p688); Wilson's disease (p257); failure to excrete conjugated bilirubin (Dubin-Johnson, p690, and Rotor syndromes, p702); right heart failure; toxins, eg carbon tetrachloride; fungi

(*Amanita phalloides*, **fig 1**).

Cholestatic (obstructive) jaundice

If the common bile duct is blocked, conjugated bilirubin overspills into the blood causing a **conjugated hyperbilirubinaemia**. Being water soluble, it is excreted in urine, making it dark. Less conjugated bilirubin enters the bowel and the faeces become pale. When severe, it can be associated with an intractable pruritus which is best treated by relief of the obstruction.

Causes:

Common bile duct gallstones; pancreatic cancer; lymph nodes at the porta hepatis; drugs (see BOX); cholangiocarcinoma; primary sclerosing cholangitis; primary biliary cirrhosis; choledochal cyst; biliary atresia; Mirrizi's syndrome (obstructive jaundice secondary to compression of the common hepatic duct by a gallstone impacted in the cystic duct, often associated with cholangitis).

Clinical features

Ask

about blood transfusions, intravenous drug use, body piercing, tattoos, sexual activity, travel abroad, jaundiced contacts, family history, alcohol consumption, and **all** medications (eg old drug charts; GP records).

Examine

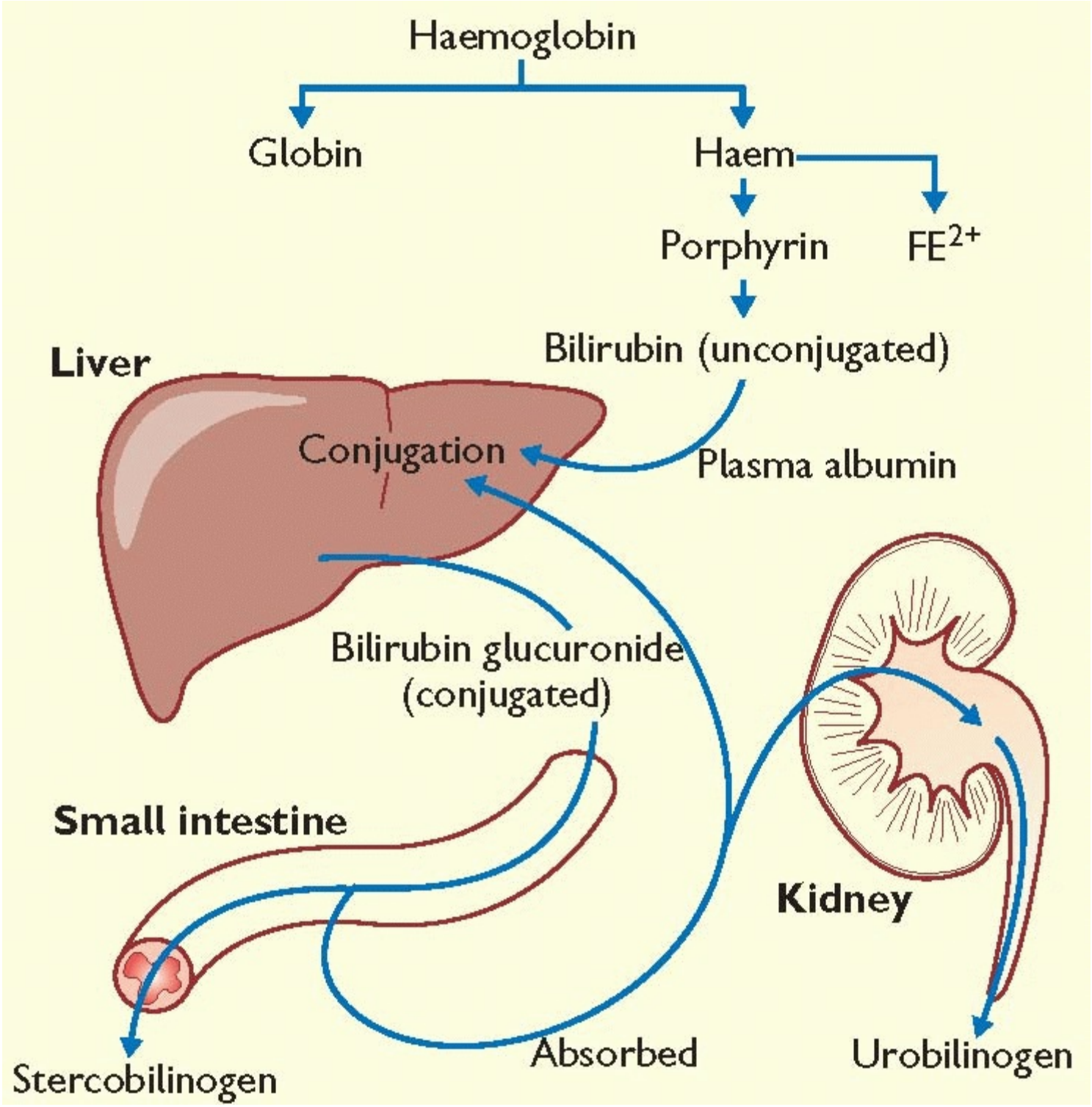
for signs of chronic liver disease (p252), hepatic encephalopathy (p250), lymphadenopathy, hepatomegaly, splenomegaly, ascites and a palpable gall bladder (which in conjunction with painless jaundice suggests a cause other than gallstones—Courvoisier's 'law'). Pale stools with dark urine ≈ obstructive jaundice.

Tests

See BOX (p257) for screening tests in suspected liver disease. *Urine:* Bilirubin is absent in pre-hepatic causes, hence 'acholuric' jaundice; urobilinogen is absent in obstructive jaundice. *Haematology:* FBC, clotting, blood film, reticulocyte count, Coomb's test. *Biochemistry:* U&E, LFT[1] (bilirubin, ALT, AST, alk phos, γ-GT, total protein, albumin).[41] *Ultrasound:*

Are the bile ducts dilated >6mm (obstruction—see **fig 3**, p723)? Are there gallstones, hepatic metastases or a pancreatic mass? *ERCP* (p728) if bile ducts are dilated and LFT not improving. MRCP (p729) or endoscopic ultrasound (EUS) if conventional ultrasound shows gallstones but no definite common bile duct stones. Perform a *liver biopsy* (p248) if the bile ducts are normal. Consider abdominal CT or MRI if abdominal malignancy is suspected clinically.

The pathway of bilirubin metabolism



After www.rcsi.ie

Causes of jaundice in a previously stable patient with cirrhosis

- Sepsis: especially emanating from UTI, pneumonia, or SBP (see p252).
- Alcohol
- Drugs: see TABLE
- Malignancy: eg hepatocellular carcinoma
- GI bleeding

Look for signs of decompensation: ascites; dilated abdominal veins; neurological upset; peripheral oedema.

Drug-induced jaundice

1	•	Antimalarials

Haemolysis		
	•	Dapscine
2 Hepatitis	•	***Paracetamol*** overdose (p828)
	•	Anti-TB (***isoniazid***, ***rifampicin***, ***pyrazinamide***)
	•	Statins (BOX, p101)
	•	***Sodium valproate***
	•	Monoamine oxidase inhibitors
	•	***Halothane*** (any recent anaesthetics?)
3 Cholestasis	•	Antibiotics (***flucloxacillin***—may occur weeks after treatment, ***fusidic acid***, ***co-amoxiclav***, ***nitrofurantoin***)
	•	Anabolic steroids
	•	Oral contraceptives
	•	***Chlorpromazine***
	•	***Prochlorperazine***
	•	Sulfonylureas

	•	***Gold***

Fig 1.[42] *Amanita phalloides*, or the 'death cap', is a lethal cause of jaundice—it is, in fact, the most lethal mushroom in the world. Its hepatotoxic effects are mediated by amatoxins that induce hepatic necrosis.[43] Ingestion (usually as a result of misidentification from its benign appearance) can result in death through acute liver failure, though cases have been treated successfully with liver transplantation. **NB:** Not to be used for identification purposes.

Upper gastrointestinal bleeding: 1

Haematemesis is vomiting of blood. It may be bright red or look like coffee grounds.

Melaena (from the Greek *melas* = black) means black motions, often like tar, and has a characteristic smell of altered blood. Both indicate upper GI bleeding.

▸Take a brief history and examine to assess severity.

History

Ask about previous GI bleeds; dyspepsia or known ulcers (p234); known liver disease or oesophageal varices (p246); dysphagia; vomiting; weight loss. Check drugs (see MINIBOX) and alcohol consumption. Is there serious co-morbidity (bad for prognosis) eg cardiovascular disease, respiratory disease, hepatic or renal impairment, or malignancy?

Examination

Look for signs of chronic liver disease (p252) and do a PR to check for melaena. Is the patient shocked? "Do you feel faint when you sit up?"

- Peripherally shut down (cool and clammy); capillary refilling (CR) time >2s.
- ↓GCS (may be tricky to assess in decompensated liver disease) or signs of encephalopathy (p251).
- Poor urine output, eg <25mL/h or <½mL/kg/h.

- Tachycardic (pulse >100bpm, and JVP not raised).
- Hypotensive (systolic BP <100mmHg)
- Postural drop in BP (>20mmHg systolic).

Calculate the *Rockall risk score* (see TABLE).

Common causes

- Mallory-Weiss tear
- Oesophagitis
- Oesophageal varices
- Peptic ulcers
- Gastritis/gastric erosions
- Duodenitis
- Malignancy
- Drugs (NSAIDs, aspirin, steroids, thrombolytics, anticoagulants)
- No obvious cause

Rare causes

- Bleeding disorders
- Portal hypertensive gastropathy
- Aorto-enteric fistula[1]
- Angiodysplasia
- Haemobilia
- Dieulafoy lesion[2]
- Meckel's diverticulum
- Peutz-Jeghers' syndrome
- Osler-Weber-Rendu synd.

Acute management

(see p778). In summary:

▸▸ Protect airway and give high-flow oxygen.

▸▸ Insert 2 large-bore (14-16G) IV cannulae and take blood for FBC (an early Hb may be normal because haemodilution has not yet taken place), U&E (↑urea out of proportion to creatinine is indicative of a massive blood meal), LFT, clotting, and cross-match 4-6 units (give 1 unit per g/dL <14g/dL).

▸▸ Give IV crystalloid to restore intravascular volume while waiting for blood to be crossmatched.MET_{44} In a dire emergency—ie haemodynamically deteriorating despite fluid resuscitation measures—give group O Rh-ve blood.

▸▸ Insert a urinary catheter and monitor hourly urine output.

▸▸ Organize a CXR, ECG, and check ABG.

▸▸ Consider a CVP line to monitor and guide fluid replacement.

▸▸ Transfuse (with crossmatched blood) until haemodynamically stable.

▸▸ Correct clotting abnormalities (***vitamin K***, FFP, platelets).

▸▸ Monitor pulse, BP, and CVP (keep >5cm H20) at least hourly until stable.

▸▸ Arrange an urgent *endoscopy*, preferably at a dedicated endoscopy unit.$_{45}$

▸▸ Inform surgeons of all severe bleeds on admission.

Further management

- Re-examine after 4h and give FFP if >4 units transfused.
- Monitor pulse, BP, CVP, and urine output hourly; ↓frequency to 4hrly if haemodynamically stable.
- Transfuse to keep Hb >10g/dL; always keep 2 units of blood in reserve.

- Give ***omeprazole*** 40 mg IV **after** endoscopy (reduces risk of rebleeding and need for surgery, but not mortality, in peptic ulcer bleeding).MET[46]
- Check FBC, U&E, LFT, and clotting daily.
- Keep nil by mouth for 24h. Allow clear fluids after 24h and light diet after 48h, as long as there is no evidence of rebleeding (p246).

▸▸See p246 for additional management in suspected variceal beeding.

Rockall risk-scoring for upper GI bleeds

	0 pts	1 pt	2 pts	3 pts
Pre-endoscopy				
Age[I]	<60yrs	60-79yrs	≥80yrs	
Shock: systolic BP pulse rate[I]	BP >100mmHg <100/min	BP >100mmHg Pulse >100/min	BP<100mmHg	
Co-morbidity[I]	Nil major	Cardiac failure Ischaemic heart disease	Renal failure Liver failure	Metastases
Post-endoscopy				
Diagnosis[F]	Mallory-Weiss tear; no lesion; no sign of recent bleeding	All other diagnoses	Upper GI malignancy	
Signs of recent haemorrhage on endoscopy[F]	None, or dark red spot		Blood in upper GI tract; adherent clot; visible vessel	

[I] These criteria make up the initial Rockall score, which is a more reliable predictor of mortality in peptic ulcer bleeding than the final score.[47]

[F] Added to the initial score, these criteria make up the final Rockall score.

Prediction of rebleeding and mortality from the Rockall score

Rockall scores help predict risk of rebleeding and mortality after upper GI bleeding.[48] An initial score >6 is said to be an indication for surgery, but decisions relating to surgery are rarely taken on the basis of Rockall scores alone (p246).

	Mortality	
Score	Initial score	Final score (after endoscopy)
0	0.2%	0%
1	2.4%	0%
2	5.6%	0.2%
3	11.0%	2.9%
4	24.6%	5.3%
5	39.6%	10.8%
6	48.9%	17.3%
7	50.0%	27.0%
8+	-	41.1%

Table adapted from *Mangement Guidelines of Haematemesis and/or Malaena 2004*, at

http://static.oxfordradcliffe.net/med/gems/HMGuidelines04.pdf.

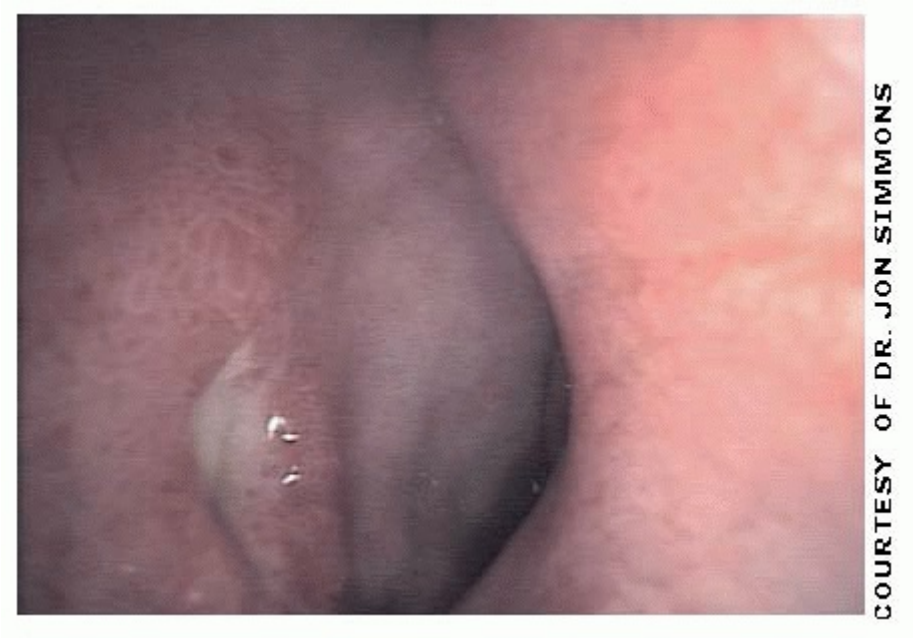


Fig 1. Upper GI endoscopy image of a duodenal ulcer. See p234 for the topic of peptic ulceration and 'Lumen' BOX, p227, for possible enlightenment. OURTESY OF DR. JON SIMMONS

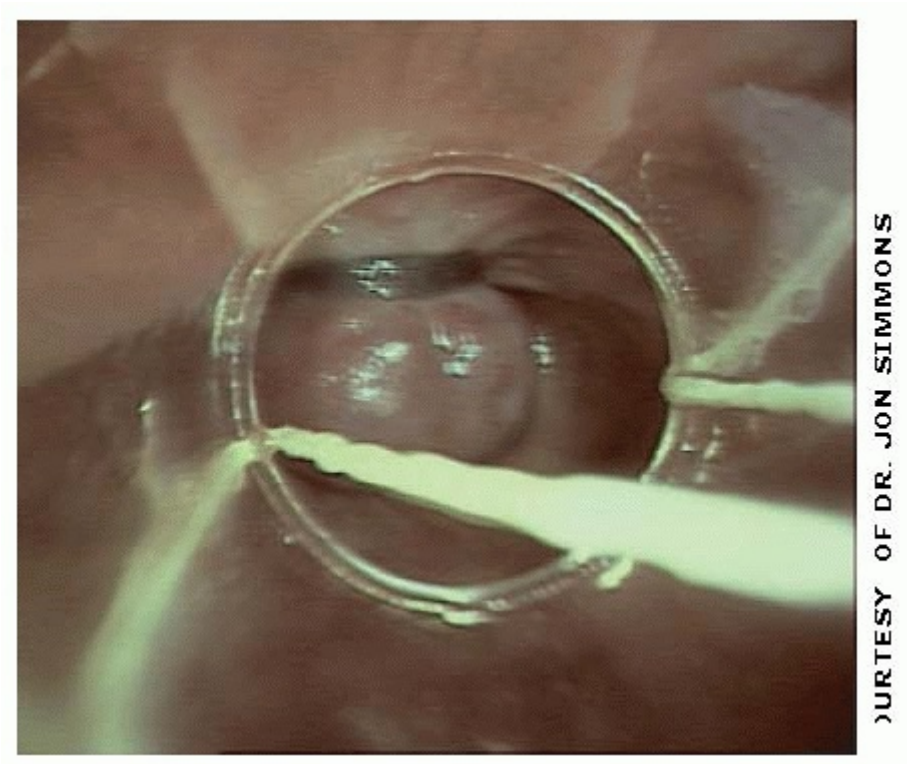


Fig 2. Upper GI endoscopy image of variceal banding. The technique involves sucking up a varix into the transparent banding chamber, then placing an elastic band around the varix. After a few days the banded varix starts to slough, leaving behind scar tissue in a shallow ulcer. See also p246.

Upper GI bleeding: 2 and ▸▸bleeding varices

Endoscopy

should be arranged after resuscitation, within 4h of a suspected variceal haemorrhage, or when bleeding is ongoing within 24h of admission. It can identify the site of bleeding, be used to estimate the risk of rebleeding, and to administer treatment, preferably 2 of: eg ***adrenaline***, sclerotherapy, variceal banding (**fig 2**, p245) or argon plasma coagulation (for superficial lesions).[49]

Endoscopic signs associated with risk of rebleeding:

active arterial bleeding (80% risk); visible vessel (50% risk); adherent clot/black dots (30% risk).

Rebleeding

40% of rebleeders die of complications. Identify high-risk patients (TABLE, p245) and monitor closely for signs of rebleeding. IV ***omeprazole*** has a preventive role. Get help; **inform a surgeon at once if:** ÊHaematemesis with melaena • ↑pulse rate; • ↓CVP (assess via JVP or CVP line) • ↓BP; • ↓urine output.

Indications for surgery (p638)

▸Contact the surgical team at the onset

- Severe bleeding or bleeding despite transfusing 6U if >60yrs (8U if <60yrs)
- Rebleeding
- Active or uncontrollable bleeding at endoscopy
- Initial Rockall score ≥3 or final Rockall score >6 (but see TABLE, p245).

Varices

Portal hypertension causes dilated collateral veins (varices) at sites of portosystemic anastomosis. Varices most commonly occur in the lower oesophagus, but may also be found in the stomach around the umbilicus (*caput medusae* is rare) and in the rectum. Varices develop in patients with cirrhosis once portal pressure (measured by hepatic venous pressure gradient) is >10mmHg; if >12mmHg variceal bleeding may develop—associated with a mortality of 30-50% per episode.[50]

Other causes of portal hypertension

Pre-hepatic:

Portal vein thrombosis; splenic vein thrombosis.

Intrahepatic:

Cirrhosis (80% in UK); schistosomiasis (commonest worldwide); sarcoidosis; myeloproliferative diseases; congenital hepatic fibrosis.

Post-hepatic:

Budd-Chiari syndrome (p688); right heart failure; constrictive pericarditis; veno-occlusive disease.

Risk factors for variceal haemorrhage:

↑Portal pressure, variceal size, endoscopic features of the variceal wall (eg haematocystic spots) and Child-Pugh score ≥8 (see TABLE, P253).[51]

Suspect varices as a cause of GI bleeding

if there is alcohol abuse or cirrhosis. Look for signs of chronic liver disease, encephalopathy, splenomegaly, ascites, hyponatraemia, coagulopathy and thrombocytopaenia.

Prophylaxis

Primary

Without treatment ~30% of cirrhotic patients with varices bleed—reducible to 15% by: 1 non-selective Ò-blockade (***propranolol*** 40-80mg/12h PO) 2 Repeat endoscopic banding ligation. One recent study showed that banding had significantly better outcome than Ò-blocker therapy in patients with cirrhosis.[52] Endoscopic sclerotherapy is not used as complications (eg stricturing) may outweigh benefits.[53]

Secondary

After an initial variceal bleed, risk of further bleeding is high—80% will rebleed within 2 years. Options are 1 and 2 as above + transjugular intrahepatic portosystemic shunting (TIPSS)[1] for varices resistant to banding **or** surgical shunts if TIPSS is impossible for technical reasons. Endoscopic banding may be better than sclerotherapy (lower bleeding rates & fewer complications).MET$_{54}$

[1] TIPSS works by shunting blood away from the portal circulation through an artificial side-to-side portosystemic anastamosis created in the liver; also used in uncontrolled variceal haemorrhage.

Acute variceal bleeding

Get help at the bedside from your senior.

▸▸ Resuscitate until haemodynamically stable (do not give 0.9% saline).

▸▸ Correct clotting abnormalities with ***vitamin K*** and FFP.

▸▸ Start IVI of ***terlipressin*** 2mg bolus, then 2mg/4h for ≤3d; relative risk of death ↓ by 34%).$_{55}$ Somatostatin analogues are no longer used in the UK. MET$_{56}$

▸▸ Endoscopic banding (p245, **fig 2**) or sclerotherapy should be tried (banding may be impossible because of limited visualization).

▸▸ If bleeding uncontrolled, a Minnesota tube or Sengstaken-Blakemore tube (see BOX) should be placed by someone with experience; get anaesthetist's help.

Balloon tamponade with a Sengstaken-Blakemore tube

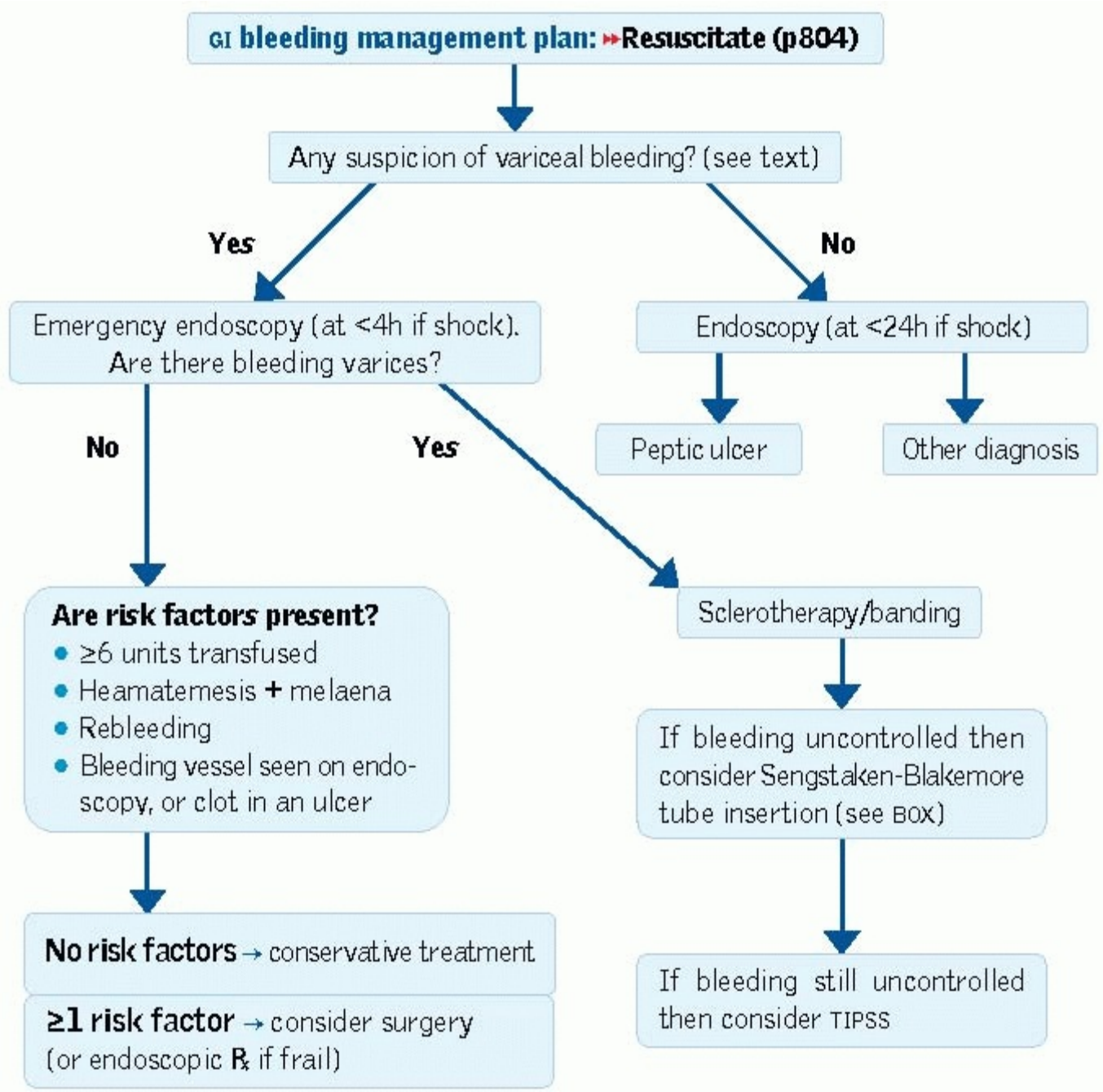
In life-threatening variceal bleeding, this can buy time to arrange transfer to a specialist liver centre or for surgical decompression. It uses balloons to compress gastric and oesophageal varices. Before insertion, inflate balloons with a measured volume (120-300mL) of air giving pressures of 60mmHg (check with a sphygmomanometer).

- Deflate, and clamp exits.
- Pass the lubricated tube (try to avoid sedation) and inflate the gastric balloon with the predetermined volume of air. Cooling the tube beforehand probably doesn't make it any easier to pass.$_{57}$

▸ Check position with a portable x-ray before inflating the oesophageal balloon.

- Check pressures (should be 20-30mmHg greater than on the trial run). This phase of the procedure is dangerous: do not over inflate the balloon because of the risk of oesophageal necrosis or rupture).
- Tape to patient's forehead to ensure the gastric balloon impacts gently on the gastro-oesophageal junction.
- Place the oesophageal aspiration channel on continuous low suction and arrange for the gastric channel to drain freely.
- Leave *in situ* until bleeding stops. Remove after <24h.

Various other techniques of insertion may be used, and tubes vary in structure. ▸**Do not try to pass one yourself if you have no or little experience:** ask an expert; if unavailable, transfer urgently to a specialist liver centre.



Endoscopy and biopsy

▸**Consent** is required for all these interventions and procedures—see p554.

Upper GI endoscopy

Indications:

See TABLE.

Pre-procedure:

Stop anti-acid therapy for 2 weeks beforehand if possible—these mask diagnosis of up to ~30% of adenocarcinomas.[58] Nil by mouth for 8h (but water up to 4h pre-op may be OK). Advise the patient not to drive for 24h if sedation is being given. Arrange follow-up.

Procedure:

Sedation may be given (eg ***midazolam*** 1-5mg IV; monitor O2 saturation with a pulse oximeter). The pharynx is sprayed with local anaesthetic and a flexible endoscope is passed. Continuous suction must be available to prevent aspiration.

Complications:

Transient sore throat; amnesia following sedation; perforation (<0.1%); cardiorespiratory arrest (<0.1%).

Duodenal biopsy

is the gold standard for diagnosing coeliac disease (p272). It is also useful in investigating unusual causes of malabsorption, eg giardiasis, lymphoma, Whipple's disease, amyloid, or microscopic colitis (p238).

Sigmoidoscopy

views the rectum; rigid or flexible sigmoidoscopy should precede barium enema in suspected colorectal cancer. Flexible sigmoidoscopes gain better access than rigid ones (→splenic flexure), but ~25% of colon cancers are still out of reach. It can be used therapeutically (±insertion of a flatus tube) for decompression of sigmoid volvulus (Box, p599).

Preparation:

Give 2 ***phosphate enemas***.

Procedure:

PR examination is performed first. Do biopsies—macroscopic appearances may be normal in some diseases, eg IBD, amyloidosis, microscopic colitis.

Colonoscopy

Indications:

See TABLE.

Preparation:

Prescribe ***sodium picosulfate*** (Picolax®) 1 sachet for the morning and afternoon of the day before the procedure.

Procedure:

PR examination is performed first. Sedation (monitor O_2 saturation with a pulse oximeter) and analgesia are given before a flexible colonoscope is passed and guided around the colon.

Complications:

Abdominal discomfort; incomplete examination; perforation (0.1%); haemorrhage after biopsy or polypectomy.

Capsule endoscopy

Indications:

Assessment of small bowel disease, especially in Crohn's (after exclusion of strictures with a small bowel contrast study) or obscure/occult GI bleeding. Also now able to image the oesophagus, despite quick transit time.[60]

Pre-procedure:

Clear fluids only the evening before and then nil by mouth from 10pm.

Procedure:

A pillsized capsule (**fig 1**) transmits video images via radiowaves to pads on the skin. Information is stored in a device worn on the belt. Normal activity can take place during the examination.

Complications:

Capsule retention (occurs in 1%: endoscopic or surgical removal is required); obstruction (usually in the terminal ileum or site of a stricture); incomplete examination (eg battery failure, slow transit, achalasia).

Disadvantages:

Unable to perform therapeutic intervention and gives poor localisation of lesions.

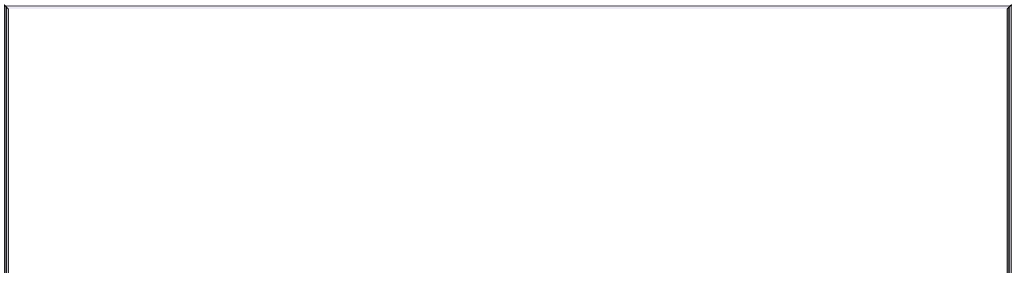


Fig 1. The size of a capsule in comparison to a £1 coin.[59]

Liver biopsy

This may be done percutaneously (if clotting is normal) or via the transjugular route with FFP cover.

Indications:

Abnormal LFT, chronic viral hepatitis; alcoholic hepatitis; autoimmune hepatitis (AIH); suspected cirrhosis; suspected carcinoma; biopsy of hepatic lesions; investigation of PUO. Now usually performed with US/CT guidance.

Pre-procedure:

Nil by mouth for 8h. Check clotting (INR <1.5) and platelet count (>100 × 10^9/L). Prescribe analgesia.

Procedure:

Sedation may be given. If not done under US guidance, the liver borders are percussed out and where there is dullness in the mid-axillary line in expiration, local anaesthetic (***lidocaine*** 2%) is infiltrated down to the liver capsule. Breathing is rehearsed and a needle biopsy is taken with the breath held in expiration. Afterwards the patient lies on the right side for 2h, then in bed for 6h while regular pulse and BP observations are taken.

Complications:

Local pain; pneumothorax; bleeding (<0.5%); death (<0.1%).

Indications for upper GI endoscopy
Diagnostic indications

- Haematemesis
- Dyspepsia (>55yrs old p234)
- Gastric biopsy (?cancer)
- Duodenal biopsy
- Persistent vomiting
- Iron deficiency anaemia

Therapeutic indication

- Treatment of bleeding lesions
- Variceal banding and sclerotherapy
- Stricture dilatation
- Palliation eg stent insertion, laser therapy
- Argon plasma coagulation for suspected vascular abnormality

Indications for colonoscopy
Diagnostic indications

- Rectal bleeding—when settled, if acute
- Iron deficiency anaemia
- Persistent diarrhoea
- Biopsy of lesion seen on barium enema
- Assessment or suspicion of IBD
- Colon cancer surveillance
- *Streptococcus bovis* endocarditis.[1]

Therapeutic indication

- Polypectomy
- Angiodysplasia (argon plasma photocoagulation)
- Decompression
- Pseudo-obstruction
- Volvulus

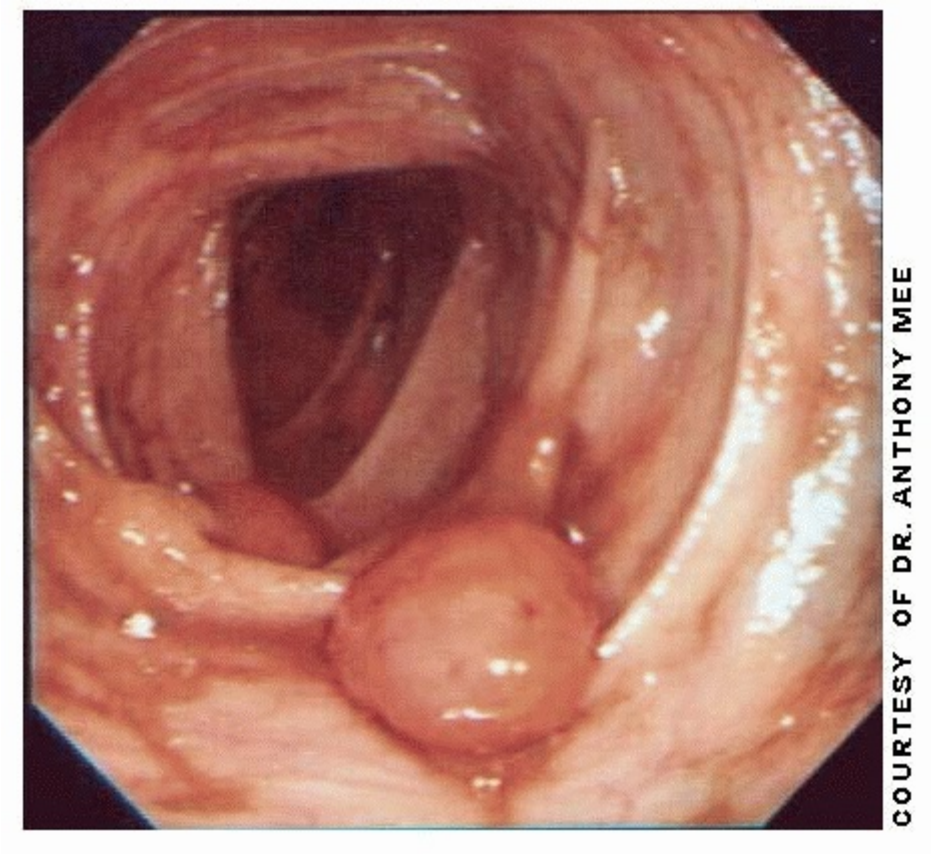


Fig 1. Colonoscopy image of a large colonic polyp. An advantage of colonoscopy over barium enema is the ability to perform biopsy or intervention at the same time—in this case, polypectomy.

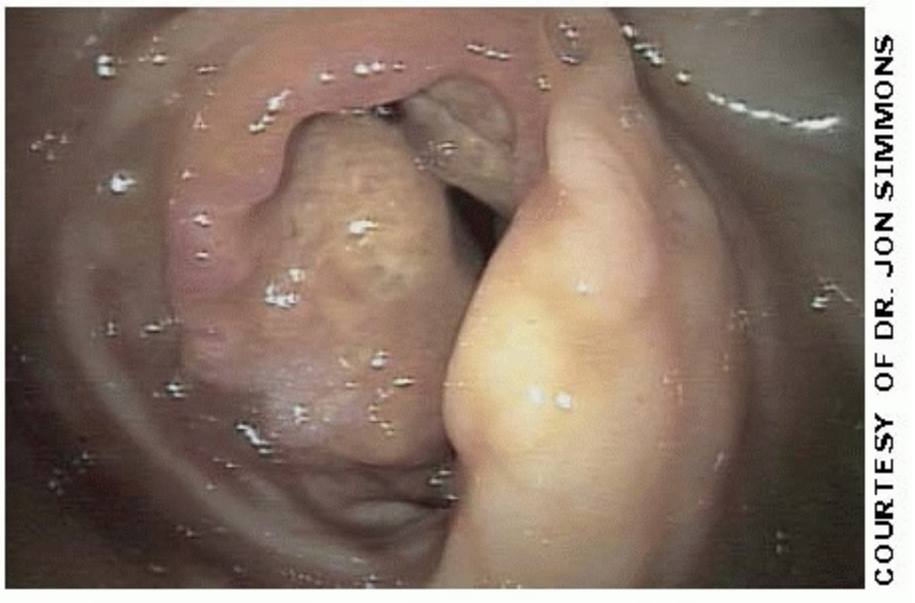


Fig 2. Colonoscopy image of a colonic adenocarcinoma— see p612. Compared to a colonic polyp (**fig 1**), the carcinoma is irregular in shape and colour, larger and more aggressive.

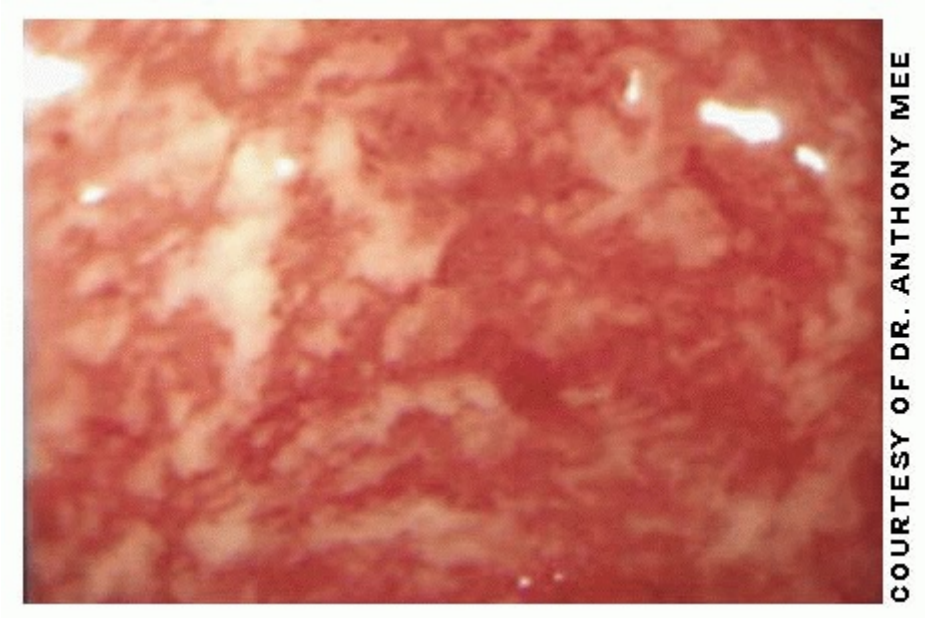


Fig 3. Colonoscopy image of the colonic mucosa in active ulcerative colitis (UC). The mucosa is red, inflamed and can be friable (bleed on touching). In more severe disease there may also be endoscopic findings of mucopurulent exudate, mucosal ulceration, and spontaneous bleeding. In quiescent disease there may only be a distorted or absent mucosal vascular pattern. See p264 for the topic of UC.

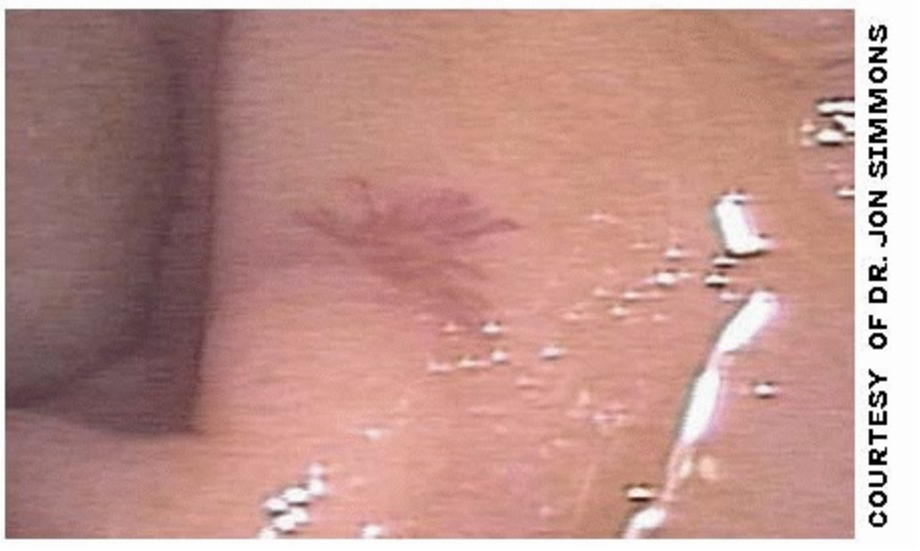


Fig 4. Colonoscopy image of a small angiodyplasia lesion in the colonic mucosa. Argon plasma coagulation is a common treatment for this condition—see p588.

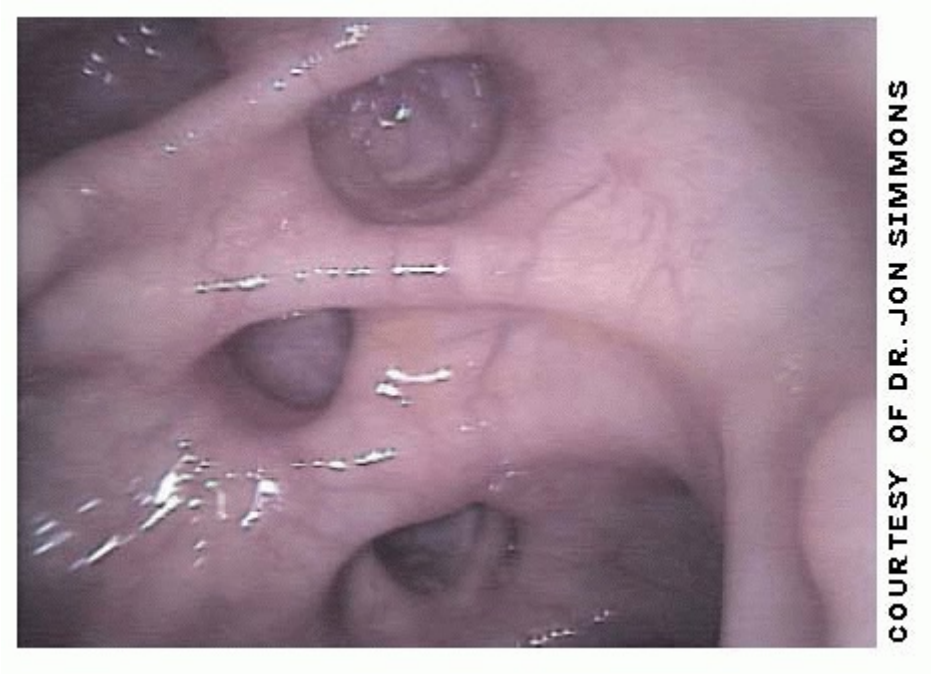


Fig 5. Colonoscopy image showing diverticulosis of the colon. Navigating safely through the colon, avoiding the false lumina of the diverticula can be a challenge. Endoscopy is avoided if the diverticula are acutely inflamed in an attack of diverticulitis because of the risk of perforation. See p588 for the topic of diverticular disease.

Further endoscopy images:

See www.gastrosource.com/kisweb/atlas.htm

Liver failure

Definitions

Liver failure may occur suddenly in the previously healthy liver: **acute hepatic failure**. More commonly it occurs as a result of decompensation of chronic liver disease = **acute-on-chronic hepatic failure**. **Fulminant hepatic failure** is a clinical syndrome resulting from massive necrosis of liver cells leading to severe impairment of liver function: **hyperacute** = encephalopathy within 7d of onset of jaundice; **acute** = within 8-28d; **subacute** = within 5-26 weeks. There is decreasing risk of cerebral oedema as the onset of encephalopathy is increasingly delayed.

Causes

Infections:

Viral hepatitis, yellow fever, leptospirosis.

Drugs:

Paracetamol overdose, halothane, isoniazid.

Toxins:

Amanita phalloides mushroom (**fig 1**, p243), carbon tetrachloride.

Vascular:

Budd-Chiari syndrome (p688), veno-occlusive disease.

Others:

Alcohol hepatitis, primary biliary cirrhosis, haemochromatosis, autoimmune hepatitis, α_1-antitrypsin deficiency, Wilson's disease, fatty liver of pregnancy (OHCS p26), malignancy.

Signs

Jaundice, hepatic encephalopathy (see TABLE), *fetor hepaticus* (smells like pear drops), asterixis, constructional apraxia (ask the patient to draw a 5-pointed star). Signs of chronic liver disease (p252) suggest acute-on-chronic hepatic failure.

Tests

Blood:

FBC (?infection,[1] ?GI bleed), U&E,[2] LFT, clotting (↑PT/INR), glucose, paracetamol level, hepatitis, CMV & EBV serology, ferritin, α_1-antitrypsin, caeruloplasmin, autoantibodies (p539).

Microbiology:

Blood culture; urine culture; ascitic tap for M,C+S of ascites—neutrophils >250/mm^3 indicates spontaneous bacterial peritonitis (p252).

Radiology:

CXR; abdominal ultrasound; Doppler flow studies of the portal vein (& hepatic vein in suspected Budd-Chiari syndrome, p688).

Neurophysiology:

EEG, evoked potentials (and neuroimaging) have a limited role.[61]

Management

▸▸Beware **sepsis**, **hypoglycaemia**, and **encephalopathy**:

- Nurse with a 20° head-up tilt in ITU. Protect the airway with intubation and insert an NG tube to avoid aspiration and remove any blood from stomach.
- Insert urinary and central venous catheters to assess fluid status.
- Monitor T°, respirations, pulse, BP, pupils, urine output hourly. Daily weights.
- Check FBC, U&E, LFT, and INR daily.
- 10% dextrose IV, 1L/12h to avoid hypoglycaemia. Do blood glucose every 1-4h.
- Treat the cause, if known (eg paracetamol poisoning, p828). N-acetylcysteine probably does not help in non-paracetamol liver failure.[62]
- If malnourished, get dietary help because good nutrition ↓ mortality (eg diet rich in carbohydrate- and protein-derived calories, preferably orally).[63] Give thiamine and folate supplements.
- Haemofiltration or haemodialysis, if renal failure develops (see BOX).
- Avoid sedatives or other drugs with hepatic metabolism (see BOX and BNF), but treat seizures with ***lorazepam***.[64]
- Consider PPI as prophylaxis against stress ulceration eg ***omeprazole*** 40mg/d IV.
- Liaise early with nearest transplant centre regarding appropriateness—see BOX.

Treat complications

Bleeding:

Vitamin K 10mg/d IV for 3d, platelets, FFP + blood as needed.

Infection:

Until sensitivities are known, give ***ceftriaxone*** 1-2g/24h IV. ▸Avoid ***gentamicin*** (↑risk of renal failure).

Ascites:

Fluid restriction, low-salt diet, daily weights, diuretics (see p252).

Hypoglycaemia:

Check blood glucose regularly and give 50mL of 50% glucose IV if levels fall below 2mmol/L or symptomatic.

Encephalopathy:

Avoid sedatives; 20° head-up tilt in ITU; ***lactulose*** 30-50mls/8h PO + regular enemas to ↓numbers of nitrogen-forming bowel organisms. Aim for 2-4 soft stools/d.

Cerebral oedema:

Give 20% ***mannitol*** IV; hyperventilate.

Prognosis

Poor prognostic factors: Grade III or IV encephalopathy, age >40yrs, albumin <30g/L, ↑INR, drug-induced liver failure, late-onset hepatic failure worse than fulminant failure. 65% survival post-transplantation.

Hepatic encephalopathy

As the liver fails, nitrogenous waste (as ammonia) builds up in the circulation and passes to the brain, where astrocytes clear it (by processes involving the conversion of glutamate to glutamine). This excess glutamine causes an osmotic imbalance and a shift of fluid into these cells—hence cerebral oedema.[65]

Grade I	Altered mood/behaviour; sleep disturbance (eg reversed sleep pattern)
Grade II	Increasing drowsiness; confusion, slurred speech
Grade III	Stupor; incoherence; restlessness, significant confusion
Grade IV	Coma

▸ Other causes of reduced conscious level should always be ruled out when considering hepatic encephalopathy—eg sepsis, trauma, hypoglycaemia or seizure activity.

What is hepatorenal syndrome (HRS)?

HRS is not well understood. It occurs in ~18% of cirrhotic patients with ascites, showing splanchnic arterial vasodilatation, ↓effective circulatory volume, (↓venous return and cardiac output),[66] intense renal vasoconstriction, ↓glomerular filtration rate, and **normal** renal histology. Raised neuropeptide Y (NPY) and activation of the renin-angiotensin-aldosterone axis occur, further worsening renal vasoconstriction. ADH levels also ↑ in an attempt to restore intravascular volume. ▸ It is important to make the diagnosis only after other causes of renal impairment have been excluded. Two types of HRS have been described: ***HRS 1*** is a rapidly progressive deterioration in circulatory and renal function (median survival <2weeks); ***HRS 2*** is a more steady deterioration (median survival ~6 months). Other factors in cirrhosis may contribute to poor renal function (p253).

Treatment is IV ***albumin*** + arterial vasocontrictors eg ***terlipressin*** to replenish the depleted volume. Haemodialysis (as supportive therapy) and TIPSS (p246) may be required. Liver transplantation remains treatment of choice, even after improvement in renal function, since prognosis is so poor.[67]

Prescribing in liver failure

Avoid opiates, diuretics (↑risk of encephalopathy), oral hypoglycaemics, and saline-containing IVIs. ***Warfarin*** effects are enhanced.

Hepatotoxic drugs include:

Paracetamol, methotrexate, phenothiazines, isoniazid, azathioprine, oestrogen, 6-mercaptopurine, salicylates, tetracycline, mitomycin.

King's College Hospital[UK] criteria for liver transplantation

Paracetamol liver failure	• Arterial pH <7.3 24h after ingestion **Or all of the following:** • Prothrombin time (PT) >100s • Creatinine >300μmol/L • Grade III or IV encephalopathy
Non-paracetamol liver failure	• PT >100s **Or 3 out of 5 of the following:** **1** Drug-induced liver failure **2** Age <10 or >40 yrs old **3** >1wk between onset of jaundice and encephalopathy **4** PT >50s **5** Bilirubin >300μmol/L

Fulfilment of the criteria is a good predictor of poor outcome in acute liver failure, but failure to meet the criteria does not predict survival. Transplantation is either **cadaveric** (heart-beating or non-heart-beating)[1] or from **live donors** (right lobe)—may cause a biliary fistula. Gaining **valid consent** from the donor is difficult (see BOX, p555). See also BOX, p255 for indications in chronic disease.

[1] There has been a recent renewed interest and ↑ in the number of non-heart-beating cadaveric donors.

Cirrhosis

Cirrhosis (Greek *kirrhos* = yellow) implies irreversible liver damage. Histologically, there is loss of normal hepatic architecture with fibrosis and nodular regeneration.

Causes

Most commonly chronic alcohol abuse, HBV, and HCV infection. Others: see BOX.

Signs

May be none (just ↑LFT) or decompensated end-stage liver disease.

Chronic liver disease:

Leuconychia: white nails with lunulae undemarcated, from hypoalbuminaemia; Terry's nails—white proximally but distal 1/3 reddened by telangiectasias; [68] clubbing; palmar erythema; hyperdynamic circulation; Dupuytren's contracture; spider naevi (**fig. 1**); xanthelasmata; gynaecomastia; atrophic testes; loss of body hair; parotid enlargement; hepatomegaly, or small liver in late disease.

Complications

Hepatic failure:

Coagulopathy (↓factors II, VII, IX, & X causes ↑INR); encephalopathy—ie liver flap (asterixis) + confusion/coma; hypoalbuminaemia (oedema, leuconychia); sepsis (pneumonia; septicaemia); spontaneous bacterial peritonitis (SBP); hypoglycaemia.

Portal hypertension:

Ascites (**fig 2**); splenomegaly; portosystemic shunt including oesophageal varices (± life-threatening upper GI bleed) and *caput medusae* (enlarged superficial periumbilical veins).

HCC:

↑risk.

Tests

Blood:

LFT: ↔ or ↑bilirubin, ↑AST, ↑ALT, ↑alk phos and ↑γGT. Later, with loss of synthetic function, look for ↓albumin ± ↑PT/INR. ↓wcc and ↓platelets indicate hypersplenism. ***Find the cause:*** Ferritin, iron/total iron-binding capacity (p254); hepatitis serology; immunoglobulins (p258); autoantibodies (ANA, AMA, SMA, p539); α-fetoprotein (p262); caeruloplasmin in patients <40yrs old (p257); α_1-antitrypsin (p256).

Liver ultrasound + duplex

may show a small liver or hepatomegaly, splenomegaly, focal liver lesion(s), hepatic vein thrombus, reversed flow in the portal vein, or ascites.

MRI:

Caudate lobe size↑, smaller islands of regenerating nodules, and the presence of the right posterior hepatic notch are more frequent in alcoholic cirrhosis than in virus-induced cirrhosis.[69] MRI scoring systems based on spleen volume, liver volume, and presence of ascites or varices/collaterals can quantify severity of cirrhosis in a way that correlates well with Child grades (see BOX).[70]

Ascitic tap

should be performed and fluid sent for urgent MC+S— neutrophils >250/mm^3 indicates spontaneous bacterial peritonitis (see below for treatment).

Liver biopsy

(p248) confirms the clinical diagnosis.

Management

General:

Good nutrition is vital; low-salt diet (if ascites). Alcohol abstinence. Avoid NSAIDs, sedatives, and opiates. ***Colestyramine*** may help pruritus (4g/12h PO, 1h after other drugs). Consider ultrasound and α-fetoprotein every 3-6 months to screen for HCC, p262.[71]

Specific:

Interferon-α (± ***ribavirin***) improves LFT and may slow development to HCC in HCV-induced cirrhosis (p394). There may be some benefit of high dose ***ursodeoxycholic acid*** in PBC (see p258)—it can normalise LFT, though may have no effect on longterm disease progression.[MET][72] ***Penicillamine*** for Wilson's disease (p257).

Ascites:

Bedrest, fluid restriction (<1.5L/d), low-salt diet (40-100mmol/d). Give ***spironolactone*** 100mg/24h PO; ↑dose every 48h, to 400mg/24h—it counters the deranged renin-angiotensin-aldosterone (RAA) axis. Chart daily weight and aim for weight loss of ≤½kg/d. If response is poor, add in ***furosemide*** ≤120mg/24h PO; do U&E often. Therapeutic paracentesis with concomitant albumin infusion (6-8g/L fluid removed) may be tried.

Spontaneous bacterial peritonitis (SBP):

▸ Must considered in any patient with ascites who deteriorates suddenly (may be asymptomatic). Common organisms are *E. coli*, *Klebsiella*, and *Streptococcus*.[73] Treatment: eg ***cefotaxime*** 2g/6h or ***tazocin*** 4.5g/8h (consult the datasheet) for 5 days or until sensitivities known (+ ***metronidazole*** 500mg/8h IV if there has been instrumentation to the ascites). Give prophylaxis for high risk patients (↓albumin, ↑PT/INR, low ascitic albumin) or those who have had a previous episode: eg ***norfloxacin*** 400mg PO daily.

Prognosis

Overall 5yr survival is ~50%. Poor prognostic indicators: encephalopathy; serum Na^+ <110mmol/L; serum albumin <25g/L; ↑INR.

Liver transplantation

is the only definitive treatment for cirrhosis (p255). This increases 5yr survival from ~20% in end-stage disease to ~70%.[74]

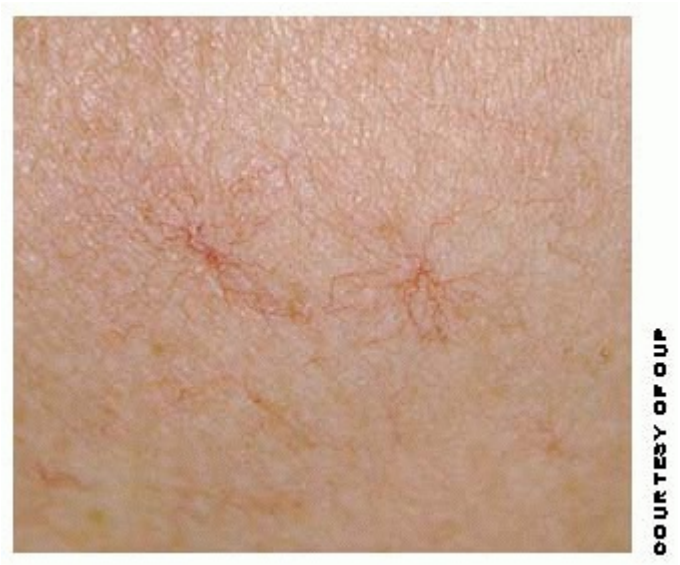


Fig 1. Spider naevi. These consist of a central arteriole, from which numerous vessels radiate (like the legs of a spider). These fill from the centre as opposed to telangiectasias that fill from the edge. They occur most commonly in skin drained by the superior vena cava. Up to 5 are said to be normal (they are common in young ♀). Causes include liver disease, contraceptive steroids, and pregnancy (ie changes in oestrogen metabolism).

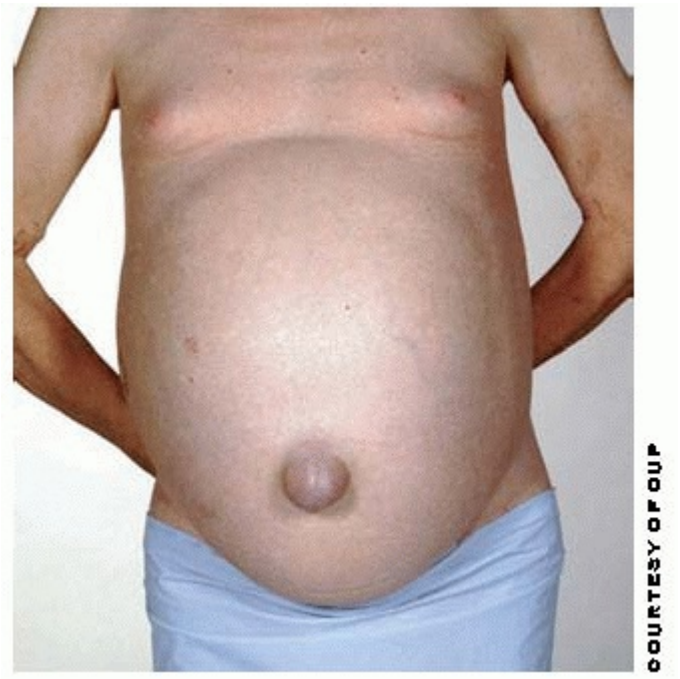


Fig 2. Gross ascites. Note the umbilical hernia (see p631) and a mild degree of gynaecomastia. There are veins visible on the anterior abdominal wall, though they are not in the pattern of caput medusae.

Causes of cirrhosis

- Chronic alcohol abuse.
- Chronic HBV or HCV infection[1]
- Autoimmune disease: PBC (p258); PSC (p259); AIH (p260).
- Genetic disorders: Haemachromatosis (p254); α_1-antitrypsin deficiency (p256); Wilson's disease (p257).
- Others: can be cryptogenic in up to 20%; Budd-Chiari syndrome (p688, hepatic vein thrombosis).
- Drugs: eg amiodarone, methyldopa, methotrexate.

[1] Clues as to which patients with chronic HCV will get cirrhosis: platelet count ≤140 x 10^9/L, globulin/albumin ratio ≥1, and AST/ALT ratio ≥1—100% +ve predictive value but lower sensitivity (~30%).

Child-Pugh grading and risk of variceal bleeding

The severity of cirrhosis can be graded according to the score. Grade A = 5-6, grade B = 7-9, grade C >10, with the risk of variceal bleeding ↑↑ if score is >8. The grading can also be used to predict mortality and quantify the need for liver transplantation (see p255).

	1 point	2 points	3 points
Bilirubin (μmol/L)	<34	34-51	>51
Albumin (g/L)$_{75}$	<35	28-35	<28
Prothrombin time (seconds > normal)	1-3	4-6	>6
Ascites	none	slight	moderate
Encephalopathy (p251)	none	1-2	3-4

Cirrhosis and deteriorating renal function

In cirrhosis reduced hepatic clearance of immune complexes leads to their trapping in the kidney (∴ IgA nephropathy ± hepatic glomerulosclerosis). HCV can cause cryoglobulinaemia and membranoproliferative glomerulonephritis, HBV may cause membranous nephropathy and PAN and membranoproliferative glomerulonephritis can occur in α_1-antitrypsin deficiency.$_{76}$ See p251 for hepatorenal syndrome (HRS).

Hereditary haemochromatosis (HH)

This is an inherited disorder of iron metabolism in which increased intestinal iron absorption leads to deposition in multiple organs (joints, liver, heart, pancreas, pituitary, adrenals and skin). Middle-aged males are more frequently and severely affected than women, in whom the disease tends to present ~10yrs later (menstrual blood loss is protective).

Genetics

HH is one of the commonest inherited disease in those of Northern European (especially Celtic) ancestry (carrier rate of ~1 in 10 and a frequency of homozygosity of ~1: 200-400). The gene responsible for most HH is called HFE, found on the short arm of chromosome 6. The 2 major mutations are termed C282Y and H63D. C282Y accounts for 60-90% of HH, and H63D accounts for 3-7%, with compound heterozygotes accounting for 1-4%. Penetrance is unknown but is <100%.[77]

Clinical features

Asymptomatic early on—then tiredness and arthralgia (MCP and large joints). Later, look for: slate-grey skin pigmentation; diabetes mellitus ('bronze diabetes'); signs of chronic liver disease (p252); hepatomegaly; cirrhosis; cardiac failure (dilated cardiomyopathy); hypogonadism (p216) from pituitary dysfunction↓ or via cirrhosis (not from testicular iron deposition); associated osteoporosis.[78] Other endocrinopathies include hyporeninaemic hypoaldosteronism. [79]

Tests

Blood:

LFT↑, ↑serum ferritin; ↑serum iron; ↓TIBC; transferrin saturation >80%.[1] HFE genotyping. Blood glucose (?DM). ***Joint x-rays*** may show chondrocalcinosis.

Liver biopsy:

Perl's stain quantifies iron loading (hepatic iron index (HII)[2] >1.9μmol/kg/yr) and assesses disease severity. **MRI** can be used to estimate hepatic iron loading—haemosiderin and ferritin have a paramagnetic quality that affects T1 and T2 relaxation times (p720).[80] Do **ECG** & ***ECHO*** if you suspect cardiomyopathy.

[2] The HII aims to separate HH from other causes of hepatic siderosis (eg HBV; alcoholic cirrhosis). It is less used now that genotyping is available. HII in μmol iron/gram liver/year = [Iron concentration (μg iron per gram dry weight of liver)/55.846 (atomic weight of Fe)]/patient's age. HII >1.9 in a non-cirrhotic liver strongly suggests HH. ▸*Caveats*: • ~7% of those with HH have a HII <1.9. Using a threshold hepatic iron concentration of 71μmol/g as well as HII can detect most of these.[81] • Cirrhotic livers can rapidly accumulate iron in non-HH liver disease making HII >1.9. Some say that an HII cut-off of ~4.2 is best in diagnosing HH in cirrhotics.[81] • Iron is not uniformly distributed in the liver (sampling variation). •Correlation among HII, phenotypic HH, & genotypic HH is not 100%.[81]

Management

Venesect

~1 unit/wk, until mildly iron-deficient. Iron will continue to accumulate, so maintenance venesection is needed for life (1U every 2-3 months). Aim to maintain haematocrit <0.5, serum ferritin <100micrograms/L, TIBC >50μmol/L, and transferrin saturation <40%.

Other monitoring:

Diabetes (p190). Hb_{A1c} levels may be falsely low as venesection reduces the time available for Hb glycosylation.[81]

Over-the-counter self-medication:

Make sure that vitamin preparations etc. contain no iron.

Dietary intake:

Maintaining a well-balanced lowiron diet may help. Drinking tea, coffee or red wine with meals reduces iron absorption, but fruit and fruit juice (high in vitamin C) and white wine increase absorption.

Screening:

Test serum ferritin and genotype in 1st-degree relatives. Prevalence of iron overload in asymptomatic C282Y homozygotes is ≤4.5 per 1000 persons screened. How many will go on to develop iron overload is unknown.

Prognosis

Venesection returns life expectancy to normal if non-cirrhotic and non-diabetic. Arthropathy may improve or worsen. Gonadal failure is irreversible. In non-cirrhotic patients, venesection may improve liver histology. ▸Cirrhotic patients have >10% chance of developing HCC. Sources vary on the exact risk: some authorities quote 30%, others 22%.[82] One cause of variability is varying co-factors: age over 50yrs ↑risk by 13-fold; being HBsAg +ve by 5-fold and alcohol abuse by 2-fold. [83]

Secondary haemochromatosis

may occur in any haematological condition where many transfusions (~40L in total) have been given.[84] To reduce need for transfusions, find out if the haematological condition responds to erythropoietin or marrow transplantation before irreversible effects of iron overload become too great. See iron management in thalassaemia, p328.

A bit about iron metabolism

The average daily diet contains ~180-270μmol (~3-4g) of iron, with red meats, liver, seafoods, enriched breakfast cereals and pulses and even some spices (eg paprika) being particularly iron-rich. Most dietary iron is Fe^{3+}, which is reduced by low gastric pH and ascorbic acid (vitamin C) to better-absorbed Fe^{2+}. Absorption occurs mainly in the duodenum and jejunum, though very small amounts are absorbed in the stomach and ileum. Regulation of iron levels (by an unknown mechanism) is based mainly on absorption, while iron excretion is in the form of uncontrolled shedding of the gut lining.[85] The majority (60-70%) of body iron circulates in haemoglobin, though it is also found in myoglobin, bound to enzymes and proteins (such as the β-globulin, transferrin), in mitochondria, and in hepatocytes—as ferritin and haemosiderin. Iron requirements are greater for women (menstrual loss), when growing, in pregnancy and in chronic infection.

In HH the total body iron is up to 10-fold that of a normal person, with loading found particularly in the liver and pancreas (×100). Hepatic disease classically starts with fibrosis, progressing to cirrhosis as a late feature.

Liver transplantation in chronic liver disease

The first ever liver transplantation was performed by Starzl in Denver, USA, in 1963. The first in the UK was in 1968 at Addenbrooke's Hospital, Cambridge.[86] Between 1996 and 2000 there were ~3,400 liver transplants performed in the UK and Ireland and the limiting step for the procedure is now the waiting-list for a donor organ (live or cadeveric—see p251). The indications for transplantation in chronic disease (see TABLE) are generally because of advanced cirrhosis (p252), the grading of which has been used as a selection criterion.[1]

Indications	Contraindications
• Advanced cirrhosis secondary to:	• Extrahepatic malignancy
• Alcoholic liver disease	• Multiple primary or secondary tumours
• Hepatitis B & C	
• PBC (p258)	• Severe cardiorespiratory disease
• AIH (p260)	• Systemic sepsis
• Wilson's disease	• HIV infection
• α_1-antitrypsin deficiency	• Non-compliance with drug therapy
• PSC (p259)	
• HCC (1 nodule <5cm or 2-3 nodules <3cm)	

The post-operative period involves 12-24h on ITU, with enteral feeding starting as soon as possible and close monitoring of LFT. Immunosuppressant protocols usually involve a combination of ***ciclosporin*** or ***tacrolimus*** together with ***azathioprine*** or ***mycophenolate mofetil*** and ***prednisolone***. Hyperacute rejection is a result of ABO incompatabilty. Acute rejection (T-cell mediated) occurs in about 50% at 5-10 days, with the patient feeling unwell and developing pyrexia and tender hepatomegaly—it can usually be managed by increasing or altering the immunosuppressant regime. Other complications include sepsis (especially gram -ve), hepatic artery thrombosis, CMV infection, chronic rejection (at 6-9 months), disease recurrence,[87] and very rarely, graft-versus-host disease.[88] The average patient survival at 1yr is ~80% and at 5yrs is 60-90%, though this varies between different patients with different diseases. Poor pre-transplant renal function has been identified as a predictor of poor outcome.[89] (See also BOX, Indications for transplantation in acute liver failure, p251.)

[1] The incredibly difficult selection of patients for liver transplantation can also be made according to the Model for End-stage Liver Disease (MELD).

α_1-antitrypsin deficiency

The glycoprotein α_1-antitrypsin is one of a family of **ser**ine **p**rotease **in**hibitors (deficiency is termed a '**serpin**opathy') controlling inflammatory cascades. It is synthesized in the liver, making up 90% of serum α_1-globulin on electrophoresis (p679). α_1-antitrypsin deficiency is the chief genetic cause of liver disease in children. In adults, its lack causes emphysema in ~75% (p168),[1] chronic liver disease in and HCC (p262). *Other associations:* Asthma, pancreatitis, gallstones, Wegener's (p706). *Prevalence:* 1:2000-7000

Genetics

The gene for this autosomal recessive disorder is found on chromosome 14; carrier frequency of 1:10. Genetic variants are typed by electrophoretic mobility as **medium** (M), **slow** (S), or **very slow** (Z). S and Z types are due to single amino acid substitutions at positions 264 and 342, respectively. These result in ↓production of α_1-antitrypsin (S=60%, Z=15%). The normal genotype is PiMM, the homozygote is PiZZ; heterozygotes are PiMZ & PiSZ (at low risk of developing liver disease).

Clinical features

Symptomatic patients usually have the PiZZ genotype: dyspnoea from emphysema; cirrhosis; cholestatic jaundice. **NB**: cholestasis often remits in adolescence.

Tests

Serum α_1-antitrypsin levels↓. *Liver biopsy:* (p248) Periodic acid Schiff (PAS) +ve; diastase-resistant globules. ***Phenotyping*** by isoelectric focusing requires expertise to distinguish SZ and ZZ phenotypes. ***Prenatal diagnosis*** is possible by DNA analysis of chorionic villus samples obtained at 11-13wks' gestation. DNA tests are likely to find greater use in the future.[90] Measuring lung density with **CT** may be better than lung function tests at predicting disease progression and mortality.[91]

Management

Mostly supportive for emphysema and liver complications. Quit smoking. Consider **augmentation therapy** with ***α_1-antitrypsin*** pooled from human plasma if FEV_1 <80% of predicted and if not smoking (it is very expensive!).[2] Plasma levels of >0.7g/L are considered protective. ***Liver transplantation*** (p251) is treatment of choice in decompensated cirrhosis.

Prognosis

Male gender and obesity may predispose to advanced liver disease.[92] Emphysema is the cause of death in most, liver disease in ~5%. In adults, cirrhosis ± HCC affect 25% of α_1-antitrypsin-deficient adults >50yrs.

Wilson's disease/hepatolenticular degeneration

A rare inherited disorder with toxic accumulation of copper (Cu) in the liver and CNS (especially basal ganglia, eg globus pallidus hypodensity ± putamen cavitation) due to failure of biliary copper excretion. It is treatable, so screen all young patients with cirrhosis. *Prevalence:* 3:100,000.

Genetics

It is an autosomal recessive disorder of a gene on chromosome 13 that codes for a copper transporting ATPase, ATP7B. Many mutations are known (>200) with HIS1069GLU being the commonest in European populations.

Clinical features

Children usually present with ***liver disease*** (hepatitis, cirrhosis, fulminant liver failure); young adults often start with CNS *signs:* tremor; dysarthria, dysphagia; dyskinesias; dystonias; purposeless stereotyped movements (eg hand clapping); dementia; parkinsonism; micrographia; ataxia/clumsiness.

Affective features:

Depression/mania; labile emotions; libido↑↓; personality change. ▸Ignoring these may cause years of needless misery.

Cognitive/behavioural:

Memory↓; quick to anger; slow to solve problems; IQ↓; delusions; mutism.

Kayser-Fleischer rings:

Cu deposits in iris (Descemet's membrane), pathognomonic but not invariable; may need slit lamp to see.

Also:

Haemolysis; blue lunulae (nails); polyarthritis; hypermobile joints; grey skin; abortions; hypoparathyroidism.

Tests

Serum copper and caeruloplasmin usually↓. 24h urinary copper excretion↑ (>100µg/24h, normal <40µg). Molecular genetic testing can confirm the diagnosis.

Liver biopsy:

↑hepatic copper content.

MRI:

Basal ganglia degeneration (± fronto-temporal, cerebellar, and brain stem atrophy).[93]

Management

Chelation:

Lifelong ***penicillamine*** (500mg/6-8h PO for 1yr, maintenance: 0.75-1g/d). SE: nausea, rash, WCC↓, Hb↓, platelets↓ haematuria, nephrosis, lupus. Monitor FBC & urinary Cu (and protein) excretion. Say 'report sore throat, T°↑, or bruising at once' in case WCC/platelets↓↓. Stop if WCC <2.5×10^9/L or platelets falling (or <120×10^9/L). Alternative: ***Trientine dihydrochloride*** 600mg/6-12h PO (SE: rash; sideroblastic anaemia).

Liver transplantation

(p255) if severe liver disease.

Screen siblings

as asymptomatic homozygotes need treatment.

Prognosis

Pre-cirrhotic liver disease is reversible, though neurological damage is less so. There are no clear clinical prognostic indicators.[94] Death occurs from liver failure, variceal haemorrhage (p246), or infection.

Screening tests for suspected liver disease

- EBV, CMV, HAV, HBV, & HCV serologies—see p394.
- Iron studies for haemochromatosis: ↑ferritin, ↑iron, ↓TIBC—see p254.
- α_1-antitrypsin deficiency (plasma for genetics)—see opposite.
- Wilson's disease: ↓serum copper, ↓caeruloplasmin—see above.
- PBC: ↑AMA—see p258.
- PSC: ANA, AMA & ANCA may be +ve—see p259.
- AIH: ↑ANA + ↑ASMA; ↑IgG—see p260.
- Check all immunoglobulins: IgA (↑ in alcoholic liver disease); IgG (↑ in AIH) & IgM (↑ in PBC).
- HCC: ↑α-fetoprotein—see p262.
- Conjugated and unconjugated bilirubin.

[2] 120mg/kg IV every 2wks is conveniently self-given via SC intravenous injection port systems.

Primary biliary cirrhosis (PBC)

Interlobular bile ducts are damaged by chronic granulomatous inflammation causing progressive cholestasis, cirrhosis, and portal hypertension.

Cause:

Possibly an autoimmune response triggered by environmental factors, with genetic predisposition thought to be of importance.

♀:♂

≈ 9:1.

Prevalence:

≲4/100,000.

Peak presentation:

~50yrs old.

Associations with PBC

- Thyroid disease
- Rheumatoid arthritis
- Sjögren's syndrome
- Keratoconjunctivitis sicca
- Systemic sclerosis
- Renal tubular acidosis
- Membranous glomerulonephritis

Clinical features

Often asymptomatic and diagnosed after finding ↑alk phos on routine LFT. Lethargy and pruritus may occur, and can precede jaundice by months to years.

Signs:

Jaundice; skin pigmentation; xanthelasma (p682); xanthomata; hepatomegaly; and splenomegaly.

Complications:

Osteoporosis is common. Malabsorption of fat-soluble vitamins (A, D & K) results in osteomalacia and coagulopathy. Other complications include: portal hypertension; ascites; variceal haemorrhage; hepatic encephalopathy; HCC (p262). See MINIBOX for associations.

Tests

Blood tests:

↑Alk phos, ↑γGT, and mildly ↑AST and ALT; late disease: ↑bilirubin, ↓albumin, ↑prothrombin time. 98% are antimitochondrial antibody (AMA) M_2 subtype +ve (highly specific). Other autoantibodies (p539) may occur in low titres (see BOX). Immunoglobulins are ↑ (especially IgM). TSH and cholesterol may be ↑.

Radiology:

US & ERCP (p728) to exclude extrahepatic cholestasis.

Liver biopsy:

Granulomas around the bile ducts, progressing to cirrhosis.[1]

Treatment

Symptomatic:

Pruritus: try ***colestyramine*** 4-8g/24h PO; ***naltrexone*** and ***rifampicin*** may also help. Diarrhoea: ***codeine phosphate***, eg 30mg/8h PO. Osteoporosis prevention: p674.

Specific:

Fat-soluble vitamin prophylaxis: vitamin A, D, and K. Consider high dose ***ursodeoxycholic acid (UDCA)***, 10-15mg/kg/d in 2-4 divided doses. One review claimed that it had a marginal therapeutic effect with improvement of ascites, jaundice and LFT, but no long term effect on mortality or need for liver transplantation, though others have suggested a trend towards improved survival and a lower transplantation rate… A main benefit was the paucity of SE.[95]

Liver transplantation

(p251) is the last recourse for patients with end-stage disease (eg bilirubin >100μmol/L) or intractable pruritus. Recurrence in the graft has been histologically estimated at 17% after ~5 years, and although graft failure can occur as a result of recurrence, this is rare and not predictable. [96]

Prognosis

Once jaundice develops, survival is <2yrs. In one study, at 2yrs post-transplant, predicted survival without transplant was 55% and actual survival was 79%. At 7yrs, these figures were 22% and 68%, respectively. [97]

Testing for autoantibodies—entering a minefield?

The conditions in the next few pages all include the measurement of autoantibodies—with their varying sensitivities and specificities—as part of an investigative work-up. But dare we tread our way precariously through this dangerous minefield scattered with duds and tripwires, just to reach the other side in some degree of greater diagnostic certainty? Although we do measure some autoantibodies in the routine screen for suspected liver disease (p257), just how far should we go into this minefield with our patients before we think about the consequences? The best approach is most likely a combination of experience, close attention to the latest medical evidence, and individual circumstances.

Primary sclerosing cholangitis (PSC)

PSC is a disorder of unknown cause characterized by inflammation, fibrosis, and strictures of the intra- and extrahepatic bile ducts. Immunological mechanisms have been implicated.

Associations with PSC

- Ulcerative colitis[1]
- HLA-A1, B8, & DR3
- Crohn's disease (much rarer)
- HIV infection

The Patient

Chronic biliary obstruction and secondary biliary cirrhosis lead to liver failure and death (or transplantation) over ~10yrs.

Symptoms:

Patients may be asymptomatic and found incidentally after finding alk phos↑ on LFT; or else symptoms may fluctuate, eg: jaundice; pruritus; abdominal pain; fatigue.

Signs:

Jaundice; hepatomegaly; portal hypertension.

Complications:

Bacterial cholangitis; cholangiocarcinoma (20-30%); ↑risk of colorectal cancer. 30% of patients in some series had an overlap syndrome with type 1 AIH (p260).[2] See MINIBOX for associations.

Tests

Blood:

↑Alk phos initially followed by ↑bilirubin; hypergammaglobulinaemia; AMA negative, but ANA, SMA, & ANCA may be +ve, see p539. ***ERCP*** (see **fig 1**) shows multiple strictures of the biliary tree with a characteristic 'beaded' appearance. **MRCP** (see **fig 2**) is cost effective and accurate in diagnosis in comparison to ERCP. *Liver biopsy* shows a fibrous, obliterative cholangitis.

Management

Drugs:

Colestyramine 4-8g/24h PO for pruritus (***naltrexone*** and ***rifampicin*** may also help). ***Ursodeoxycholic acid*** improves cholestasis but has no clear clinical effects.[98] Antibiotics for bacterial cholangitis. ***Endoscopic stenting*** helps symptomatic dominant strictures. Yearly ***ultrasound*** screening may help detect cholangiocarcinoma, with cholecystectomy advocated for gallbladder polyps. ***Liver transplantation*** (p251) is indicated in end-stage disease. Recurrence occurs in up to 30%; 5yr graft survival is >60%. Prognosis is worse for those with concomitant IBD, as 5-10% develop colorectal cancer post-transplant.[99] *Colonoscopy screening* should be performed yearly for patients with UC to because of the increased risk of colorectal carcinoma.

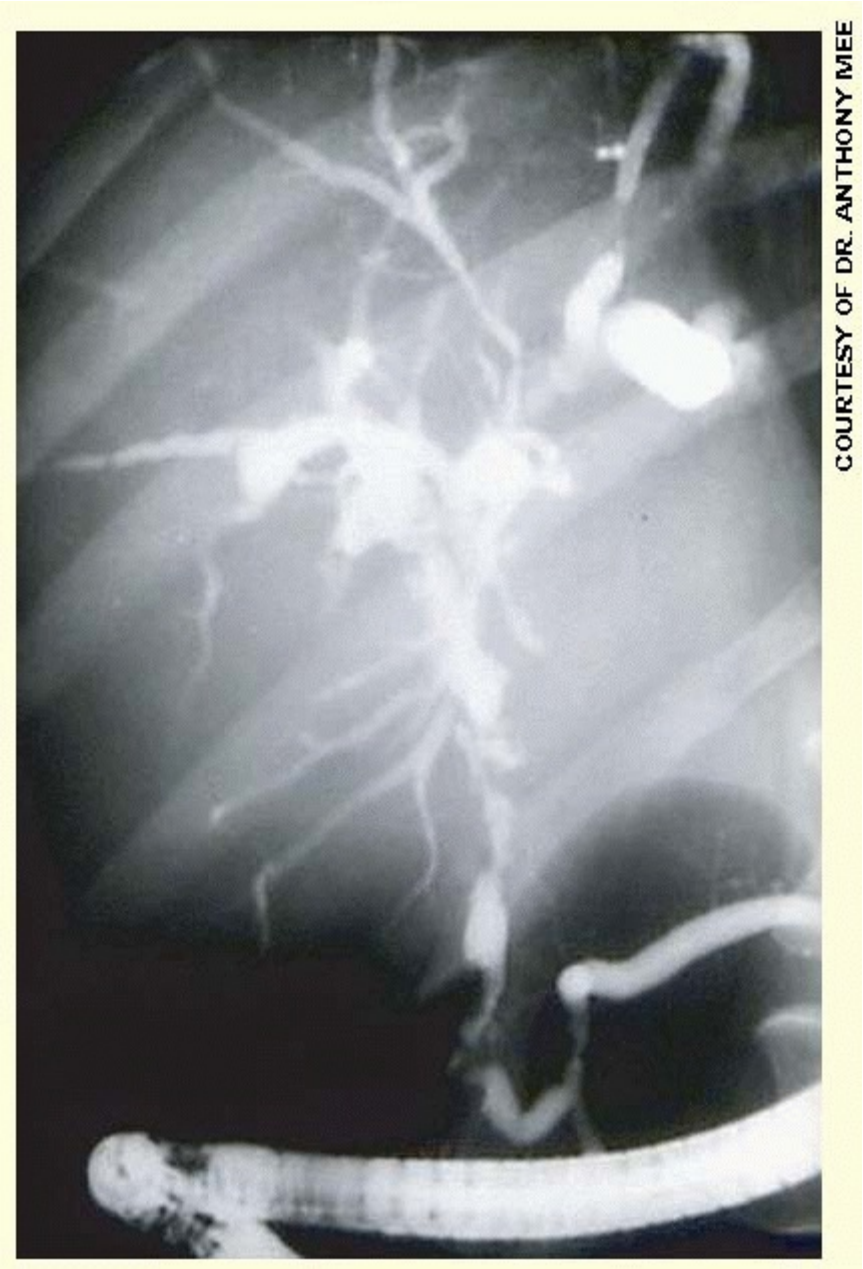


Fig 1. ERCP showing the features of PSC.

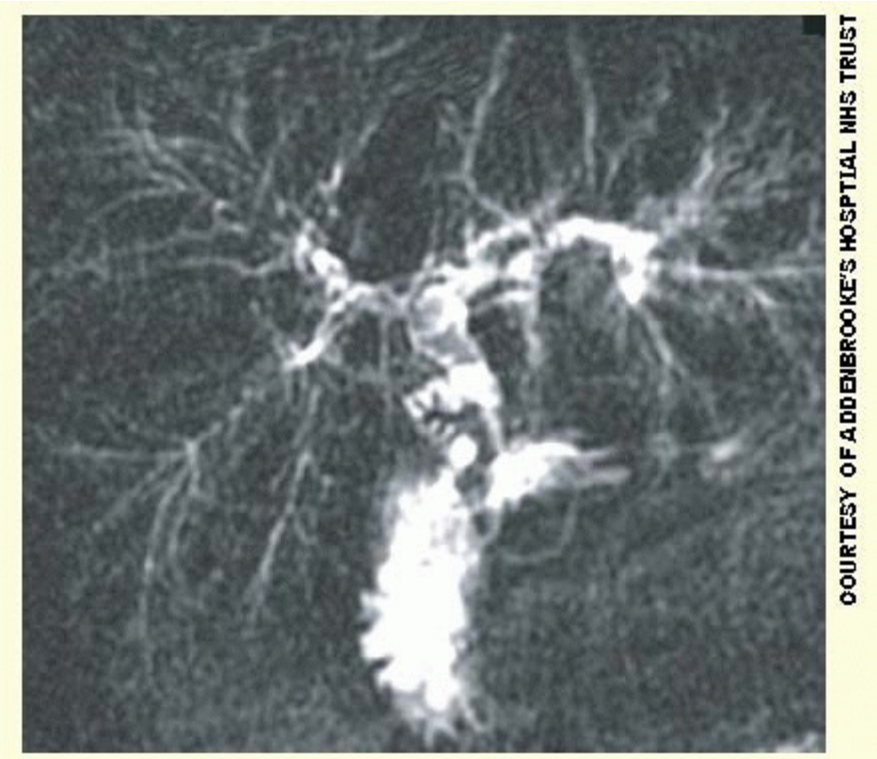


Fig 2. MRCP showing features of PSC. The intra- and extrahepatic ducts show extensive multifocal strictures. MRCP = magnetic resonance choleangiopancreatography.

[1] 3% of those with UC have PSC, but 80% of those with PSC have UC/Crohn's associated with PSC has a higher rate of backwash ileitis and rectal sparing—it may be a distinct IBD-phenotype.

[2] Do anti-mitochondrial, anti-nuclear, anti-smooth muscle, anti-liver kidney microsomal type 1, anti-liver cytosol type 1, perinuclear anti-neutrophil nuclear, & anti-soluble liver antigen antibodies.

Autoimmune hepatitis (AIH)

An inflammatory liver disease of unknown cause[1] characterized by suppressor T-cell defects with autoantibodies directed against hepatocyte surface antigens. Two types have been distinguished by the presence of circulating autoantibodies (see TABLE).

Associations

- Pernicious anaemia
- AI haemolysis
- Ulcerative colitis
- Diabetes mellitus
- Glomerulonephritis
- PSC
- AI thyroiditis
- HLA A1, B8, & DR3 haplotype

Clinical features

Predominantly affects young and middle-aged women. 25% present with acute hepatitis and features of an autoimmune disease, eg fever, malaise, urticarial rash, polyarthritis, pleurisy, pulmonary infiltration, or glomerulonephritis. The remainder present insidiously or are asymptomatic and diagnosed incidentally with signs of chronic liver disease. Amenorrhoea is common and disease tends to attenuate during pregnancy.

Complications:

those associated with cirrhosis (p252) and drug therapy. See MINIBOX for associations.

Tests

Abnormal LFT (AST↑), hypergammaglobulinaemia (especially IgG), +ve autoantibodies (ANA, SMA, or LKM1). Other autoantibodies, eg anti-soluble liver antigen (SLA) and antimeasles virus may be seen. Anaemia, WCC↓, and platelets↓ indicate hypersplenism. *Liver biopsy* (p248) shows mononuclear infiltrate of portal and periportal areas + piecemeal necrosis, fibrosis, or cirrhosis. MRCP (p729) helps exclude PSC if alk phos disproportionately↑.

Diagnosis

depends on excluding other diseases as there is no pathognomonic sign or laboratory test. There is genuine overlap with other chronic liver disease: eg PBC (p258), PSC (p259) and chronic viral hepatitis.[100] Diagnostic criteria exist but are not fully validated (eg the revised IAHG system).[2]

Management

- *Immunosuppressant therapy*: ***Prednisolone*** 30mg/d PO for 1 month; ↓by 5mg a month to a maintenance dose of 5-10mg/d PO. Corticosteroids can sometimes be stopped after 2yrs but relapse occurs in 50-86%. ***Azathioprine*** (50-100mg/d PO) may be used as a steroid sparing agent. Remission is achievable in 80% of patients within 3yrs. 10- and 20yr survival rates are >80%.[101]
- *Non-standard proposed therapies* to avoid steroid SE: ***Ciclosporin***, ***budesonide***, ***tacrolimus***, ***mycophenolate mofetil***, ***ursodeoxycholic acid***, ***methotrexate***, ***cyclophosphamide***, ***mercaptopurine***, and free radical scavengers.[102]
- *Liver transplantation* (p251) is indicated for decompensated cirrhosis or there is if failure to respond to medical therapy, but recurrence may occur. It is effective (actuarial 10yr survival is 75%).

Prognosis

appears not to matter whether symptomatic or asymptomatic at presentation (10yr survival ~80% for both). The presence of cirrhosis at presentation reduces 10yr survival from 94% to 62%.[103]

Types of autoimmune hepatitis

Type I

- Affects adults or children (bimodal distribution)
- Anti-smooth muscle antibodies (SMA) +ve in 80%[104]
- Antinuclear antibody (ANA) +ve in 10%.

Type II

- Affects children
- More commonly progresses to cirrhosis
- Anti-liver/kidney microsomal type 1 (LKM1) antibodies.

[1] Hepatotropic viruses (eg measles, herpes viruses) and some drugs appear to trigger AIH in genetically predisposed individuals exposed to a hepatotoxic *milieu intérieur*. Viral interferon can inactivate cytochrome P-450 enzymes (∴ ↓ metabolism of ex- or endogenous hepatotoxins). Putative examples of exogenous agents: monosodium glutamate (MSG; E621) and aspartame (E951), which, if regularly consumed in excess, may promote formation of salt bridges between amino acids. These compounds then act as autoantigens causing CD4 T-helper cell activation.

[2] International Autoimmune Hepatitis Group (revised) 1999.

Liver tumours

The commonest (90%) liver tumours are secondary (metastatic) tumours eg from breast, bronchus, or the gastrointestinal tract (see TABLE). Primary hepatic tumours are much less common and may be benign or malignant (see TABLE).

Symptoms

Fever, malaise, anorexia, weight↓, RUQ pain (Á liver capsule stretch). Jaundice is late, except with cholangiocarcinoma. Benign tumours are often asymptomatic. Tumours may rupture causing intraperitoneal haemorrhage.

Signs

Hepatomegaly (smooth, or hard and irregular, eg metastases, cirrhosis, HCC). Look for signs of chronic liver disease (p252) and evidence of decompensation (jaundice, ascites). Feel for an abdominal mass. Listen for a bruit over the liver (HCC).

Tests

Blood:

FBC, clotting, LFT, hepatitis serology, α-fetoprotein (↑ in 80% of HCC, though it is a poor prognostic indicator,[105] and may be normal if tumour <3cm).

Imaging:

US (**fig 1**) or CT to identify lesions and guide diagnostic biopsies. MRI is better for distinguishing benign from malignant lesions. ERCP (p728) and biopsy should be performed for suspected cholangiocarcinoma.

Liver biopsy

(p248) may achieve a histological diagnosis; ▸careful multidisciplinary discussion is required if potentially resectable, as seeding along the biopsy tract can occur. Other investigations for metastases (eg CXR, mammography, endoscopy, colonoscopy, CT, MRI, marrow biopsy) are tailored according to the suspected primary.

Liver metastases

signify advanced disease. Treatment and prognosis vary with the type and extent of primary tumour. Chemotherapy may be effective (eg lymphomas, germ cell tumours). Small, solitary metastases may be amenable to resection (eg colorectal carcinoma).[106] In most, treatment is palliative.

Prognosis:

<6 months.

Hepatocellular carcinoma (HCC)

A malignant tumour of hepatocytes, accounting for 90% of primary liver cancers. Common in China & sub-Saharan Africa (40% of cancers), rare in the West (~2% of cancers).

Causes:

Viral hepatitis (persistent HCV or HBV, especially if >2.3×10^4 virions/mL);[1] cirrhosis (alcohol, haemochromatosis, PBC); aflatoxin; parasites (*Clonorchis sinensis*); anabolic and contraceptive steroids.

Management:

Resection of solitary tumours <3cm diameter improves 3yr survival rate (59% from 13%), though ~50% have recurrence by 3yrs. Applying the Milan criteria for liver transplantation gives a 5yr survival rate of 70%.[2] Chemotherapy, percutaneous ablation, and tumour embolization are also options.[107]

Prognosis:

Often <6 months, with a 95% 5yr mortality. Fibrolamellar HCC, which occurs in children/young adults, has a better prognosis (60% 5yr survival).

Prevention

is vital. ▸Ensure HBV vaccination (see BOX). ▸Don't reuse needles. ▸Screen blood products. ▸Reduce exposure to aflatoxins (anti-humidity measures such as sundrying to ↓spread of this common fungal contaminant in stored maize); this is most important for those who harbour HBV (risk is highly synergistic).[108]

Screening

using ultrasound and α-fetoprotein levels needs further evaluation.[109]

[1] 2.3×10^4 virions/mL by PCR is a low level, so almost all are at risk.

Cholangiocarcinoma

= biliary tree malignancy; ~10% of liver primaries.

Causes:

Flukes (*Clonorchis*, p433) in the East; PSC (p259); congenital biliary cysts; biliary-enteric drainage surgery;[110] N-nitroso toxins.[111]

The patient:

Fever, abdominal pain (±ascites), malaise, ↑bilirubin; ↑↑alk phos.

Pathology:

Usually slow-growing. Most are distal extrahepatic or perihilar.

Management:

70% are unsuitable for surgical resection. Of those that are, 76% recur. **Surgery:** eg major hepatectomy + extrahepatic bile duct excision + caudate lobe resection. 5yr survival is ~30%.[112] Specific post-op complications include liver failure, bile leak and GI bleeding.[113] **Palliative stenting** of an obstructed extrahepatic biliary tree, percutaneously or via ERCP (p728), improves quality of life.

Prognosis:

~5 months.

Benign tumours

Haemangiomas

are the commonest benign liver tumours. They are often an incidental finding on ultrasound or CT scan and do not require treatment. Biopsy should be avoided!

Adenomas

are common. Causes: Anabolic steroids, the oral contraceptive pill; pregnancy. Only treat if symptomatic.

Primary liver tumours
Malignant

- HCC
- Cholangiocarcinoma
- Angiosarcoma
- Hepatoblastoma
- Fibrosarcoma
- Leiomyosarcoma

Benign

- Cysts
- Haemangioma
- Adenoma
- Focal nodular hyperplasia
- Fibroma
- Leiomyoma

Origins of secondary liver tumours
Common in ♂

- Stomach
- Lung
- Colon

Common in ♀

- Breast
- Colon
- Stomach
- Uterus

Less common (either sex)

- Pancreas
- Leukaemia
- Lymphoma
- Carcinoid tumours

Preventing of hepatitis B, hepatitis B-associated cirrhosis, chronic hepatitis, and hepatic neoplasia
Use hepatitis B vaccine, Engerix B®, 1mL into deltoid; repeat at 1 & 6 months (child: 0.5mL × 3 into the anterolateral thigh).
Indications:
Everyone (WHO advice, even in areas of 'low' endemicity).[114] This strategy is expensive, but not as expensive as trying to rely on the ultimately unsuccessful strategy of vaccinating at-risk groups—health workers (eg GPs, dentists, nurses, etc.), IV drug users, sexual adventurers, male or immigrant prostitutes (homo- or heterosexual), those on haemodialysis, and the sexual partners of known HB_e antigen +ve carriers. The immunocompromised and others may need further doses. Serology helps time boosters and finds poor or non-responders (correlates with older age, smoking, and ♂ sex). ▸**Know your own antibody level!**

Anti-HBs (IU/L)	Actions and comments: (UK advice: USA advice is different)
>1000	Good level of immunity; retest in ~4yrs.
100-1000	Good level of immunity; if level approaches 100, retest in 1yr.
<100	Inadequate; give booster and retest.
<10	Non-responder; give booster and retest; if <10 get consent to check hepatitis B status: HBsAg +ve means chronic infection; anti-HB core +ve represents past infection and immunity.

NB: Protective immunity begins about 6 weeks after the 1st immunizing dose, so it is inappropriate if exposure is recent; here, specific anti-hepatitis B immunoglobulin is the best option if not already immunized.

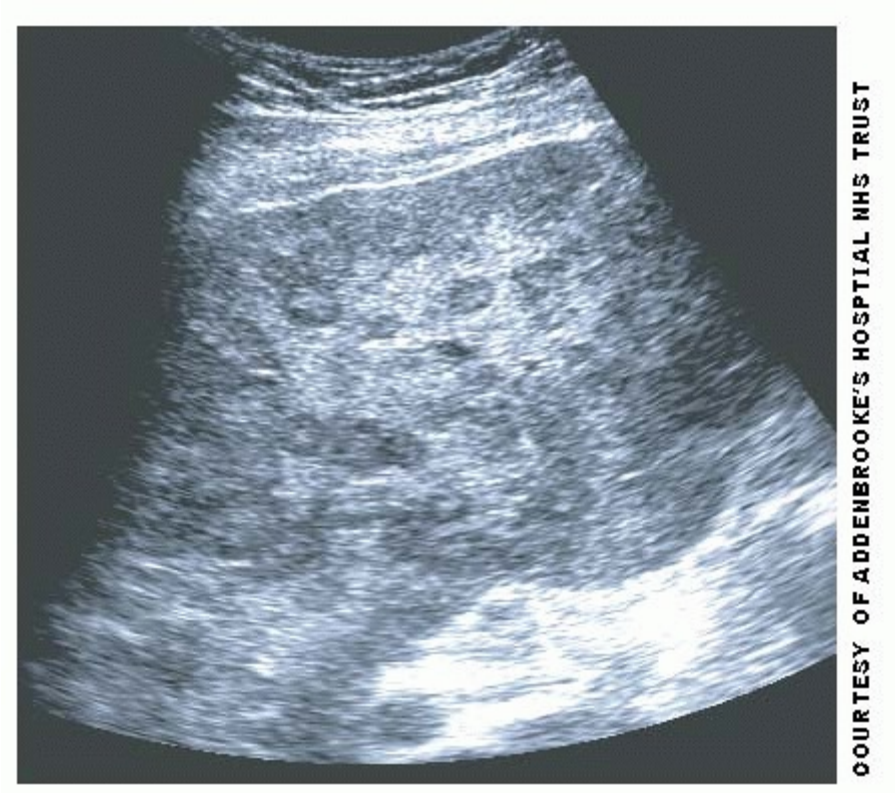


Fig 1. Ultrasound of the liver showing multiple heterogeneous lesions suggestive of hepatic metastasis.

Ulcerative colitis (UC)

UC is a relapsing and remitting inflammatory disorder of the colonic mucosa. It may affect just the rectum (proctitis, as in ~50%) or extend proximally to involve part of the colon (left-sided colitis, in ~30%) or all of the colon (pancolitis, in ~20%). It 'never' spreads proximally to the ileocaecal valve (except for backwash ileitis).

Cause:

Unknown;[1] there is some genetic susceptibility.

Pathology:

Hyperaemic/ haemorrhagic granular colonic mucosa ± pseudopolyps formed by inflammation. Punctate ulcers may extend deep into the lamina propria—inflammation is normally not transmural.

Histology:

See biopsy, below.

Prevalence:

100-200/100,000.

Incidence:

10-20/100,000/yr. ♀/♂ ***>1***. Most present aged 15-30yrs. UC is 3-fold as common in non-smokers (the opposite is true for Crohn's disease)—symptoms may relapse on stopping smoking.

Symptoms

Gradual onset of diarrhoea ± blood & mucus. Crampy abdominal discomfort is common; bowel frequency is related to severity of disease (see TABLE). Systemic symptoms are common during attacks, eg fever, malaise, anorexia, weight↓. Urgency and tenesmus occur with rectal disease.

Signs

May be none. In acute, severe UC there may be fever, tachycardia, and a tender, distended abdomen.

Extraintestinal signs:

Clubbing; aphthous oral ulcers; erythema nodosum (p267); pyoderma gangrenosum; conjunctivitis; episcleritis; iritis; large joint arthritis; sacroiliitis; ankylosing spondylitis; fatty liver; PSC (p259); cholangiocarcinoma; renal stones; osteomalacia; nutritional deficits; amyloidosis.[115]

Tests

Blood:

FBC, ESR, CRP, U&E, LFT, and blood cultures.

Stool MC+s

and ***CDT*** (p238) to exclude infections (*C. difficile, Salmonella, Shigella, Campylobacter, E. coli, amoebae*).

AXR:

No faecal shadows; mucosal thickening/islands (**fig 4**, p716); colonic dilatation (below).

Erect CXR:

Perforation.

Sigmoidoscopy:

Inflamed, friable mucosa.

Rectal biopsy:

Inflammatory infiltrate; goblet cell depletion; glandular distortion; mucosal ulcers; crypt abscesses.

Barium enema:

Loss of *haustra*; granular mucosa; shortened colon. ▸**Never do a barium enema during a severe acute attack or as a diagnostic test.** ***Colonoscopy*** shows disease extent and allows biopsy (**fig 3**, p248).

Assessing severity in UC: the Truelove and Witts criteria

Parameter	Mild	Moderate	Severe
Motions/day	<4	4-6	>6
Rectal bleeding	Small	Moderate	Large
Temperature at 6am (p26)	Apyrexial	37.1-37.8°C	>37.8°C
Pulse rate (beats/min)	<70	70-90	>90

Haemoglobin	>11g/dL	10.5-11g/dL	<10.5g/dL
ESR	<30mm/h		>30mm/h

Complications

▸Perforation and bleeding are 2 serious dangers, also:

- Toxic dilatation of colon (mucosal islands, colonic diameter >6cm).
- Venous thrombosis—consider prophylaxis (p334) during hospital admission.[116]
- Colonic cancer: risk ≈15% with pancolitis for 20yrs; surveillance colonoscopy may be used (eg 2-4yearly), but proving this saves lives has been difficult.[117] [118]

Inducing remission

Mild UC:

If <4 motions/d and the patient is well, give ***prednisolone*** (eg 20-40mg/d PO) + ***mesalazine***, eg Pentasa® (modified-release 500mg tabs; up to 1g/6h) or Asacol MR® (400mg tabs; in an acute attack 2tabs/8h).[119] For mild distal disease use twice-daily steroid foams PR (eg ***hydrocortisone*** as Colifoam®), or ***prednisolone*** 20mg **retention enemas** (Predsol®). If symptoms improve, ↓steroids gradually. If no improvement after 2wks, treat as moderate UC.

Moderate UC:

If 4-6 motions/d, but otherwise well, give oral ***prednisolone*** 40mg/d for 1wk, then 30mg/d for 1wk, then 20mg for 4 more weeks + a 5-aminosalycilic acid (5-ASA) + and twice-daily steroid enemas.[2] If improving, ↓steroids gradually. If no improvement after 2 weeks, treat as a severe UC.

Severe UC:

If systemically unwell and passing >6 motions/d, admit for:

- Nil by mouth and IV maintenance hydration (eg 1L of 0.9% saline + 2L dextrosesaline/ 24h, + 20mmol K^+/L; less if elderly).
- ***Hydrocortisone*** 100mg/6h IV.
- Rectal steroids, eg ***hydrocortisone*** 100mg in 100mL 0.9% saline/12h PR.
- Monitor T°, pulse, and BP—and record stool frequency/character on a stool chart.
- Twice-daily exam: document distension, bowel sounds and tenderness.
- Daily FBC, ESR, CRP, U&E ± AXR.
- Consider the need for blood transfusion (if Hb <10g/dL). Parenteral nutrition is only very rarely required (eg if severely malnourished).
- If improving in 5d, transfer to ***prednisolone*** PO (40mg/24h) with a 5-ASA (below, eg ***sulfasalazine*** 500mg/6h) to maintain remission.
- If on day 3 CRP >45 or stool frequency >6, consider ***ciclosporin***/***infliximab***/surgery.

Topical therapies:

Proctitis may respond to ***suppositories*** (***prednisolone*** 5mg or ***mesalazine***, eg Asacol® 250mg/8h or Pentasa® 1g at bedtime). Topical 5-ASAs work better than topical steroids.[MET][120] Procto-sigmoiditis may respond to ***foams*** PR (20mg Predfoam®/12-24h or 5-ASA, eg Asacol® 1g/d); disposable applicators aid accurate delivery. Retention enemas may be needed in left-sided colitis.

Surgery:

~20% will require surgery at some stage.

Procedures:

Proctocolectomy + terminal ileostomy (may be possible to retain the ileocecal valve, and hence reduce liquid loss);[121] colectomy with later ileo-anal pouch.

Surgical mortality:

2-7%, ↑ to 50% if perforation. Pouchitis can be successfully treated with antibiotics (eg ***metronidazole*** + ***ciprofloxacin*** for 2wks) and immunosuppressants.[122]

Indications for surgery

- Perforation
- Massive haemorrhage
- Toxic dilatation
- Failure to respond to medical therapy

Novel therapies:

A short course of ***ciclosporin*** (eg 2mg/kg IV per day) may help obtain remission quickly in patients with steroid-refractory UC, although it is markedly nephrotoxic and not suitable for long courses (▸monitor levels, do U&E, LFT and BP often—stop if raised and get expert help).[123] Oral ***tacrolimus*** may also help in steroid-refractory disease. ***Infliximab*** (see p267) may be effective as rescue therapy in UC, though evidence is scarce.[124] Transdermal ***nicotine*** is superior to placebo for induction of remission, but SEs are common (eg dizziness, nausea).[125]

Maintaining remission:

All *5-ASAs* ↓relapse rate from 80% to 20% at 1yr— examples are ***sulfasalazine***, ***mesalazine***, and ***olsalazine***.[1] Maintenance is continued for life. ***Sulfasalazine*** (500mg/6h PO) remains 1st-line. SEs related to sulfapyridine intolerance include headache, nausea, anorexia, and malaise. Other SEs: fever, rash, haemolysis (▸monitor FBC), hepatitis, pancreatitis, paradoxical worsening of colitis, and reversible oligospermia.[126]

Newer 5-ASAs

(eg ***Mesalazine*** 400-800mg/8h PO or ***olsalazine*** 500mg/12h PO) are just as effective at maintaining remission, have fewer SEs, but are more expensive. They are indicated in ***sulfasalazine*** intolerance and young men in whom fertility is a concern (less effect on sperm).[127] ***Azathioprine*** (2-2.5mg/kg/d PO after food) is indicated as a steroid-sparing agent in those with steroid side-effects or those who relapse quickly when steroids are reduced. Treat for several months, and monitor FBC every 4-6 weeks.

Indeterminate colitis

This is a diagnosis reserved for cases of IBD that have been fully investigated and cannot be definitely recognised as either UC or Crohn's disease. It tends to resemble UC more than Crohn's disease, and some cases may be due to lack of recognition of unusual variants of UC that involve transmural inflammation or skip lesions. Regarding surgical management, it is probably appropriate to perform colectomy + pouch formation, if indicated (see MINIBOX), though pouch failure rate is higher than in UC.[128]

[1] UC & Crohn's *may* involve adhesin-expressing strains of *E. coli* capable of inducing interleukin-8 production and transepithelial migration of WBCs—see OTM 2.613.

[2] ***Budesonide*** (Entocort) enemas, 1 nocte, may have fewer SEs Á ↓suppression of plasma cortisol.

Crohn's disease

Crohn's disease[1] is a chronic inflammatory GI disease characterized by transmural granulomatous inflammation. It may affect any part of the gut, but favours the terminal ileum (in 50%) and proximal colon. Unlike UC, there is unaffected bowel between areas of active disease (skip lesions).

Cause:

Unknown.[2] Mutations of the NOD2/CARD15 gene ↑risk.

Prevalence:

50-100/100,000.

Incidence:

5-10 per 100,000/yr.

Associations:

High sugar, low-fibre diet; anaerobes; mucins; altered cell-mediated immunity. Smoking ↑risk ×3-4 and NSAIDs may exacerbate disease.

Symptoms

Diarrhoea, abdominal pain, and weight loss are common (failure to thrive in children). Fever, malaise, anorexia occur with active disease.

Signs

Aphthous ulceration; abdominal tenderness; right iliac fossa mass; perianal abscesses/fistulae/skin tags; anal/rectal strictures.

Extraintestinal signs:

Clubbing, erythema nodosum (**fig 1**), pyoderma gangrenosum, conjunctivitis, episcleritis, iritis, large joint arthritis, sacroiliitis, ankylosing spondylitis, fatty liver, PSC, cholangiocarcinoma, renal stones,[3] osteomalacia, malnutrition, amyloidosis.

Complications

Small bowel obstruction; toxic dilatation (colonic diameter >6cm); abscess formation (abdominal, pelvic, or ischiorectal); fistulae (present in ~10%), eg colovesical (bladder), colovaginal, perianal, enterocutaneous; perforation; rectal haemorrhage; colonic carcinoma (rarer than in UC).

Tests

Blood:

FBC, ESR, CRP, U&E, LFT, blood culture. Serum iron, B_{12}, and red cell folate if anaemia. *Markers of activity:*

Hb↓; ↑ESR; ↑CRP; ↑WCC; ↓albumin. ***Stool* MC + S** and ***CDT*** (p238) to exclude infectious diarrhoea (*C. difficile*, *Salmonella*, *Shigella*, *Campylobacter*, *E. coli*). Do ***sigmoidoscopy*** + ***rectal biopsy*** if the mucosa looks normal (20% have microscopic granulomas). ***Small bowel enema*** detects ileal disease (strictures, proximal dilatation, inflammatory mass; fistulae). ***Capsule endoscopy*** (p248) also has an important and growing role in assessing small bowel disease. ***Barium enema*** may show cobblestoning, 'rose thorn' ulcers, and colon strictures with rectal sparing. ***Colonoscopy*** is preferred to barium enema to assess disease extent and enables biopsies to be taken. **MRI** assesses pelvic disease.

Management

Severity is harder to assess than in UC, but T°↑; pulse↑; ↑ESR; ↑CRP; ↑WCC; ↓albumin reflect severity and merit admission.

Mild attacks:

Patients are symptommatic but systemically well. ***Prednisolone*** 30mg/d PO for 1wk, then 20mg/d for 1 month. See in clinic every 2-4 weeks. If symptoms resolve, ↓prednisolone by 5mg every 2-4 weeks; stop steroids when parameters are normal.

Severe attacks:

Admit for IV steroids, nil by mouth, and IV hydration (eg 1L 0.9% saline + 2L dextrose-saline/24h, + 20mmol K^+/L, less if elderly). Then:

- ***Hydrocortisone*** 100mg/6h IV.
- Treat rectal disease with topical steroids (eg ***hydrocortisone*** 100mg in 100mL 0.9% saline/12h PR).
- ***Metronidazole*** 400mg/8h PO, or 500mg/8h IV, helps (esp. in perianal disease or superadded infection). SEs: alcohol intolerance; irreversible neuropathy.
- Monitor T°, pulse, BP, and record stool frequency/character on a stool chart.
- Physical examination twice daily. Daily FBC, ESR, CRP, U&E, and plain AXR.
- Consider need for blood transfusion (if Hb <10g/dL) and parenteral nutrition.
- If improving after 5d, transfer on to oral ***prednisolone*** (40mg/d).
- If no response (or deterioration) during IV therapy, seek surgical advice.

Perianal disease

occurs in about 50%. MRI and examination under anaesthetic (EUA) are an important part of assessment. Treatment includes oral antibiotics, immunosuppressant therapy ± ***infliximab***, and local surgery ± seton insertion.[129]

Additional therapies in Crohn's disease

Azathioprine

(2-2.5mg/kg/d PO) is effective therapy and useful as a steroid-sparing agent, eg for those with steroid SEs or if experiencing multiple/rapid relapses. It takes 6-10 weeks to work.[130]

Sulfasalazine

other 5-ASAs (p264) are not regarded as useful for the maintenance of remission in Crohn's disease.[131]

Elemental diets

(eg E028®) are made by mixing single amino acids and are antigen free. They are not as good as steroids at inducing remission in active disease but do have a beneficial effect.[132] A **low residue diet** may help control disease activity, though diet alone is not effective at inducing remission.

Methotrexate

A Cochrane review found good evidence from a single large RCT on which to recommend 25mg IM weekly for induction of remission and complete withdrawal from steroids in patients with refractory Crohn's disease. NNT ≈ 5—see p650. There was no evidence for lower doses, and no substantial SE were reported. [133]

Surgery

50-80% need ≥1 operation in their life. In the severely affected, it can become a devastating cycle of deterioration. Indications for surgery:

- Failure to respond to drugs (most commonly)
- Intestinal obstruction from strictures
- Intestinal perforation
- Local complications (fistulae, abscesses).

Surgery is never curative. The aims are **1** to defunction (rest) distal disease eg with a temporary ileostomy or **2** limited resection of the worst areas—short bowel syndrome can be a complication (p566).[134] <1m of small bowel in the absence of a colon may require regular parenteral nutrition (p574). Bypass and pouch surgery is **not** done in Crohn's (Á ↑risk of recurrence).

Infliximab

This is an anti-tumour necrosis factor monoclonal antibody which can ↓Crohn's disease activity. It counters neutrophil accumulation and granuloma formation, activates complement, and causes cytotoxicity to CD4+ T-cells, thus clearing cells driving the immune response. A single dose (5mg/kg) of ***infliximab*** given by IVI over 2h is effective at inducing remission.[135] NNT ≈ 3-4 (see p650). Response may be short-lived, but it may be repeated at 8 weeks. Some trials have also shown it to be effective as maintenance therapy.[136] CI: Sepsis, ↑LFT >3-fold above top end of normal, concurrent ***ciclosporin*** or ***tacrolimus***. SE: rash. It should be avoided in people with known underlying malignancy.[137] Cost per QALY: (see p12) £6700 (higher in fistulizing Crohn's).[138]

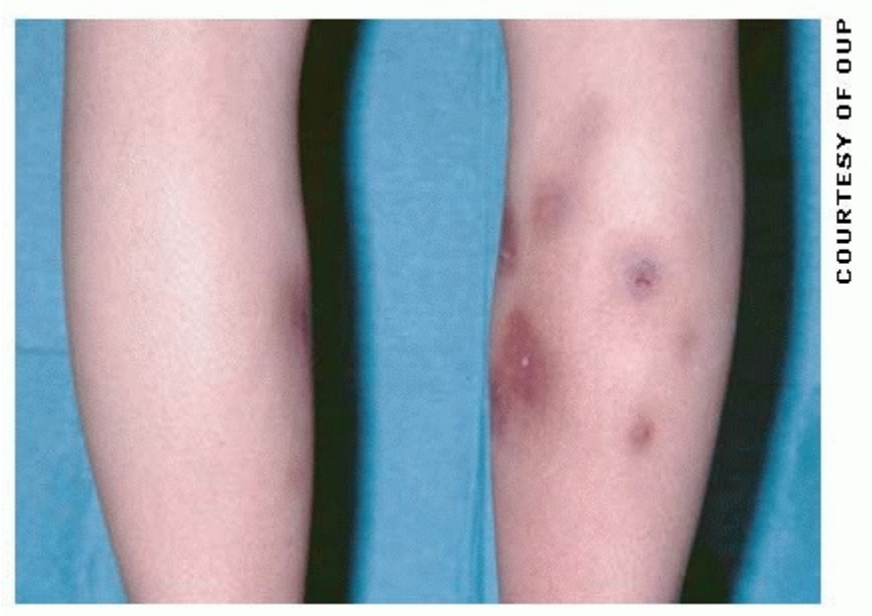


Fig 1. Erythema nodosum is an extraintestinal manifestation of Crohn's disease and UC, presenting as painful purplish nodules usually over the shins. They regress after a few weeks, leaving behind a bruised appearance. Other causes include sarcoidosis, drugs, streptococcal infection, and TB.[139]

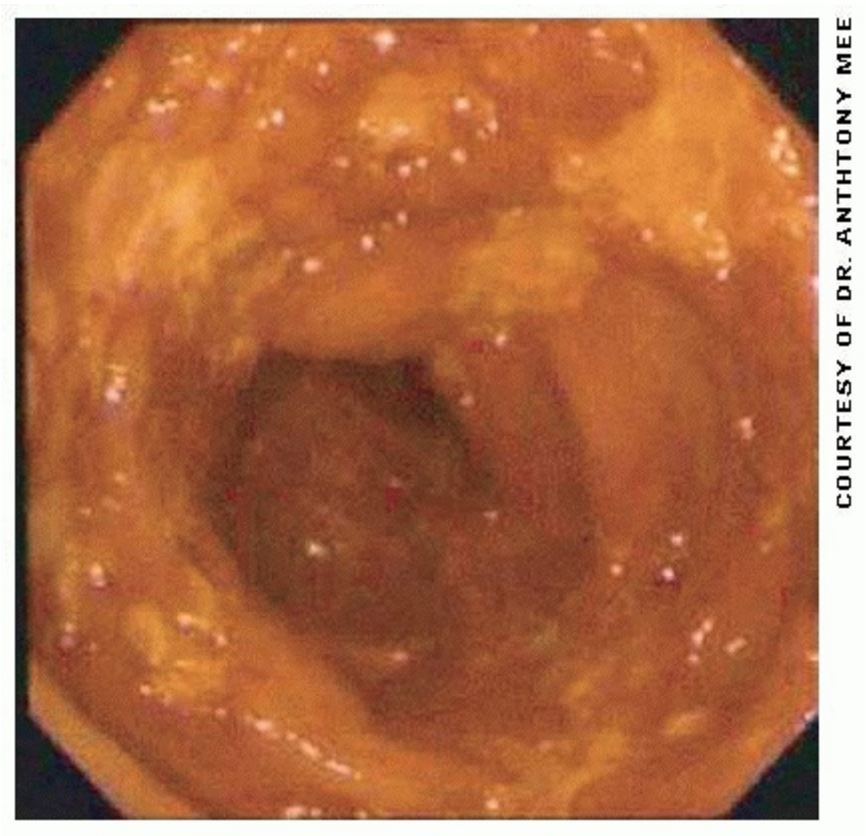


Fig 2. Colonscopy image showing deep fissured ulcers of the colonic mucosa in Crohn's disease.

[1] Burrill B. Crohn was a US gastroenterologist (1884-1983). The original paper was penned in 1932.

[2] **Environmental agents** are implicated. **Genetics:** Colon involvement goes with ↑CARD15 gene expression in macrophages & intestinal epithelial cells. **Dysregulated immune responses** might be primary or from infecting gut commensals, eg *Mycobacterium avium paratuberculosis; E. coli* adhesins, p264, may have a role.

Irritable bowel syndrome (IBS)

IBS is used to describe a heterogeneous group of abdominal symptoms for which no organic cause can be found. Most are probably due to disorders of intestinal motility or enhanced visceral perception (the 'brain-gut' axis: see BOX). Several diagnostic criteria exist that evaluate symptoms and their duration (eg Manning, Rome II),[140] but they are not always helpful in clinical practice.

Clinical features

Patients are usually 20-40yrs; ♀>♂.[1]

Symptoms:

Central or lower abdominal pain (relieved by defecation); abdominal bloating; altered bowel habit (constipation alternating with diarrhoea); tenesmus; mucus PR. Less commonly: nausea; dyspareunia; pain in the back, thigh, or chest; urinary frequency; depression. Symptoms are chronic (>6 months), and exacerbated by stress, menstruation, or gastroenteritis.

Signs:

Examination is often normal, but generalized abdominal tenderness is common. Insufflation of air during sigmoidoscopy may reproduce the pain.

Markers suggesting a disease other than IBS:

Age >40yrs; history <6 months; anorexia; weight↓; waking at night with pain/diarrhoea; mouth ulcers; abnormal investigations (eg ↑CRP, ↓Hb);
▸Investigate PR bleeding urgently.

Management

see BOX.

Carcinoma of the pancreas

Epidemiology:

≤2% of all malignancy; ~6500 deaths/yr (UK). UK incidence is rising.

Typical patient:

♂ >60yrs old.

Risk factors:

Smoking, alcohol, diabetes, chronic pancreatitis.

Pathology:

Mostly ductal adenocarcinoma (metastasize early; present late). 60% arise in the pancreas head, 25% in the body, 15% the tail. A few arise in the Ampulla of Vater (ampullary tumour) or pancreatic islet cells (insulinoma, gastrinoma, glucagonomas, somatostatinomas (p207), VIPomas); both have a better prognosis.

Genetics:

~95% have mutations in the KRAS2 gene.

Symptoms & signs

Tumours in the head of the pancreas present with **painless obstructive jaundice**. 75% of tumours in the body and tail present with epigastric pain (radiates to back and relieved by sitting forward). Either may cause anorexia, weight loss, diabetes or acute pancreatitis.

Rarer features:

Thrombophlebitis migrans (eg an arm vein becomes swollen and red, then a leg vein); $Ca^{2+}\uparrow$; marantic endocarditis; portal hypertension (splenic vein thrombosis); nephrosis (renal vein metastases).

Signs:

Jaundice + palpable gall bladder (Courvoisier's 'law': see p242); epigastric mass; hepatomegaly; splenomegaly; lymphadenopathy; ascites.

Tests

Blood:

Cholestatic jaundice. CA 19-9↑ (p680) is non-specific, but may help assess prognosis.

Imaging:

US or CT can show a pancreatic mass[2] ± dilated biliary tree ± hepatic metastases. They are also used to guide biopsy and provide staging prior to surgery/stent insertion. MRI & MRCP have an increasing role in diagnosis.[141] ERCP (p728) shows the biliary tree anatomy and may localize the site of obstruction.

[2] Endoscopic US is the most accurate diagnostic tool available for pancreatic tumours.

Treatment

Most ductal carcinomas present with metastatic disease; <10% are suitable for radical surgery.

Surgery:

Consider pancreatoduodenectomy (Whipple's, p271) if fit and the tumour <3cm with no metastases. Post-op morbidity is high (mortality <5% in experienced hands) and non-curative resections confer no survival benefit. *Post-op chemotherapy* delays disease progression.

Palliation of jaundice:

Endoscopic or percutaneous stent insertion may help jaundice and anorexia. Rarely, palliative bypass surgery is done for duodenal obstruction or unsuccessful ERCP.

Pain relief:

Disabling pain may require opiates in large doses, p560, or radiotherapy. Coeliac plexus infiltration with alcohol may be done at the time of surgery, or percutaneously. Referral to a palliative care team is essential.

Prognosis

Dismal. Mean survival <6 months. 5yr survival: <2%. Overall 5yr survival after Whipples' procedure 5-14%. Prognosis is better if: tumour <3cm; no nodes involved; -ve resection margins at surgery; ampullary or islet cell tumours.

Management of IBS

The 1st step is to exclude other diagnoses, so:

- If young, with a classic history, FBC, ESR, LFT, coeliac serology (p272), and urinalysis ± sigmoidoscopy with rectal biopsy is sufficient investigation.
- If the patient is aged ≤45yrs or has **any** marker or organic disease, request colonoscopy (barium enema if unavailable).
- If diarrhoea is prominent, do: LFT; stool culture; B_{12}/folate; antiendomysial antibodies (p272); TSH; consider referral ± barium follow-through (if symptoms suggest small bowel disease) ± rectal biopsy.
- Further investigation should be guided by symptoms and include:
  - Upper GI endoscopy (dyspepsia, reflux)
  - Duodenal biopsy (coeliac disease), eg if antiendomysial antibodies +ve
  - Giardia tests, p424 (it often triggers IBS; anti-parasitic [prescription take] may not help)[142]
  - Small bowel radiology (Crohn's disease)
  - ERCP (p728, eg chronic pancreatitis) or MRCP, p259 if active pancreatitis.
  - Transit studies and anorectal physiological studies—rarely used.

Refer:

1 If equivocal diagnosis. **2** If changing symptoms in 'known IBS'. **3** *To surgeon* if rectal mucosal prolapse. **4** *To dietician* if food intolerance. **5** *To psychiatrists* if stress/depression is pronounced.[1] **6** *To gynaecologist* if cyclical pain (endometriosis, OHCS p288) or if difficult pelvic infection, p406.

Treatment

Rarely 100% successful (especially medical therapy) so be pragmatic.[143] Careful explanation and reassurance are vital, as is developing a good relationship with your patient.

- *Food intolerance:* Try exclusion diets (difficult; may lead to obsessions).
- *Constipation:* See p240; ↑fibre intake gradually (can paradoxically worsen flatulence/bloating). Fybogel® (***ispaghula***) or Celevac® (***methylcellulose***; start with 3-6 tabs night and morning with >300mL fluid) have non-fermentable fibre—and are better than ***lactulose*** which ferments (↑gas production is hard to distinguish from bloating).[144] A recent RCT showed that the $5HT_4$ agonist ***tegaserod***[1] was successful at relieving constipation in women and was tolerated well (SE: ↑diarrhoea)—it is not yet licensed in the UK.[145]
- *Diarrhoea:* Bulking agent ± ***loperamide*** 2mg after each loose stool; max 16mg/d; SEs: colic, nausea, dizziness, constipation, bloating, ileus.
- *Colic and bloating:* Antispasmodics may help (eg ***mebeverine*** 135mg/8h PO (available over the counter); ***alverine citrate*** 60-120mg/8h PO; ***dicycloverine*** 10-20mg/8h PO).
- *Dyspeptic symptoms:* May respond to ***metoclopramide*** or antacids.
- *Psychological therapy:* Emphasize positive aspects and prognosis: in 50% symptoms go or improve after 1yr; <5% worsen. Symptoms are still troublesome in the rest at 5yrs. Tricyclic antidepressants (low dose) are often helpful, eg ***amitriptyline*** 10-50mg at night (SEs: constipation, dry mouth, etc., OHCS p340). Psychotherapy (OHCS p370), cognitive-behavioural therapy (OHCS p372), and gut-focused hypnotherapy[2] all have roles. Explain that all forms of stress (sexual, physical, or verbal abuse) perpetuate IBS.

The future

Much interest is being expressed in modulating the 'brain-gut' axis by neurotransmitter manipulation.

Visceral hypersensitivity:

Those with IBS have lower visceral pain thresholds, and since 5HT antagonists increase pain tolerance, highly selective $5HT_3$ receptor antagonists (eg ***alosetron***) are under trial. ***Alosetron*** 1mg/12h PO[2] can ↓symptoms in non-constipated IBS female patients, but its efficacy is unclear in males. SE: ~25% may get constipated; ▸it may be associated with ischaemic colitis, which has raised questions on its place in practice. It is not currently available in the UK.[146]

[2] 12wks of hypnosis helps abnormal sensory perception: ▸Do not think of hypnosis as dubious; it is a neat way to influence the brain-gut axis, reducing doctor dependency and stopping patients from being patients (passive recipients of suffering). Benefits may last ≤5yrs.

Nutritional disorders (also see TABLE, p273)

▸Always consider that more than one nutritional disorder is likely to be present.

Scurvy

This is due to lack of vitamin C in the diet.[1] Is the patient poor, pregnant, or on an odd diet?

Signs:

1 Listlessness, anorexia, cachexia (p54). **2** Gingivitis, loose teeth, and foul-smelling breath (halitosis). **3** Bleeding from gums, nose, hair follicles, or into joints, bladder, gut.

Diagnosis:

No test is completely satisfactory. WBC ascorbic acid↓.

Treatment:

Dietary education; ***ascorbic acid*** ≥250mg/24h PO.

Beriberi

There is heart failure with general oedema (wet beriberi) or neuropathy (dry beriberi) due to lack of vitamin B_1 (thiamine). For treatment and diagnostic tests, see Wernicke's encephalopathy (p706).

Pellagra

= lack of nicotinic acid. Classical triad: **d**iarrhoea, **d**ementia, **d**ermatitis (± neuropathy, depression, insomnia, tremor, rigidity, ataxia, fits). It may occur in carcinoid syndrome and anti-TB drugs (isoniazid). It is endemic in China and Africa.

Treatment:

Education, electrolyte replacement, ***nicotinamide*** 100mg/4h PO.[147]

Xerophthalmia

This vitamin A deficiency syndrome is a major cause of blindness in the Tropics. Conjunctivae become dry and develop oval or triangular spots (Bitôt's spots). Corneas become cloudy and soft. See OHCS p450. Give ***vitamin A*** 200,000 IU stat PO, repeat in 24h and a week later (halve dose if <1yr old; quarter if <6 months old); ▸get special help if pregnant: vitamin A embryopathy must be avoided. Re-educate and monitor diet.

[1] The link of diet (oranges and lemons) with the symptoms of 'the scurvy' is accredited to the naval surgeon James Lind, as described in his *Treatise* of 1753.

Carcinoid tumours

A diverse group of tumours of enterochromaffin cell (neural crest) origin, by definition capable of producing 5HT. Common sites: appendix (45%), ileum (30%) or rectum (20%).[2] They also occur elsewhere in the GI tract, ovary, testis, and bronchi. 80% of tumours >2cm across will metastasize (ie consider all as malignant).

Symptoms & signs:

Initially few. GI tumours can cause appendicitis, intussusception, or obstruction. Hepatic metastases may cause RUQ pain. Tumours may secrete bradykinin, tachykinin, substance P, VIP, gastrin, insulin, glucagon, ACTH (∴ Cushing's syndrome), parathyroid, and thyroid hormones. 10% are part of MEN1 syndrome (p207) and 10% occur with other neurendocrine tumours.[148]

Carcinoid syndrome

occurs in ~5% and implies hepatic involvement.

Symptoms and signs:

Bronchoconstriction; paroxysmal flushing especially in upper body (± migrating weals); diarrhoea; CCF (tricuspid incompetence and pulmonary stenosis from 5HT-induced fibrosis).

CNS effects:

Many, eg **enhanced** ability to learn new stimulus-response associations.[149]

▸*Carcinoid crisis:*

(see EMERGENCY BOX).

Diagnosis

24h urine 5-hydroxyindoleacetic acid↑ (5HIAA, a 5HT metabolite; levels change with drugs and diet: discuss with lab). If liver metastases are not found, try to find the primary (CXR; chest/pelvis MRI/CT).

New tests:

Plasma chromogranin A (reflects tumour mass);[150] 111Indium octreotide scintigraphy (octreoscan);[151] positron emission tomography (p472) techniques are alse being developed.

Treatment

Carcinoid syndrome:

Octreotide (somatostatin analogue) blocks release of tumour mediators and counters peripheral effects. Effects lessen over time. Other options: ***loperamide*** or ***cyproheptadine*** for diarrhoea;[152] ***interferon-a*** as add-in therapy with ***octreotide***.[153]

Tumour therapy:

Curative resection is possible, so it is important to identify the primary (see above); at surgery the tumours have an intense yellow appearance. Surgical debulking (eg enucleating), embolization, or radiofrequency ablation of hepatic metastases can ↓symptoms. These require ***octreotide*** cover to avoid precipitating a massive carcinoid crisis.

Median survival:

5-8yrs; 38 months if metastases are present, but may be **much longer** (~20 yrs); so beware of giving up too easily, even if metastases are present.[154]

Food mountains, the pellagra paradox, and the sorrow that weeping cannot symbolize[1]

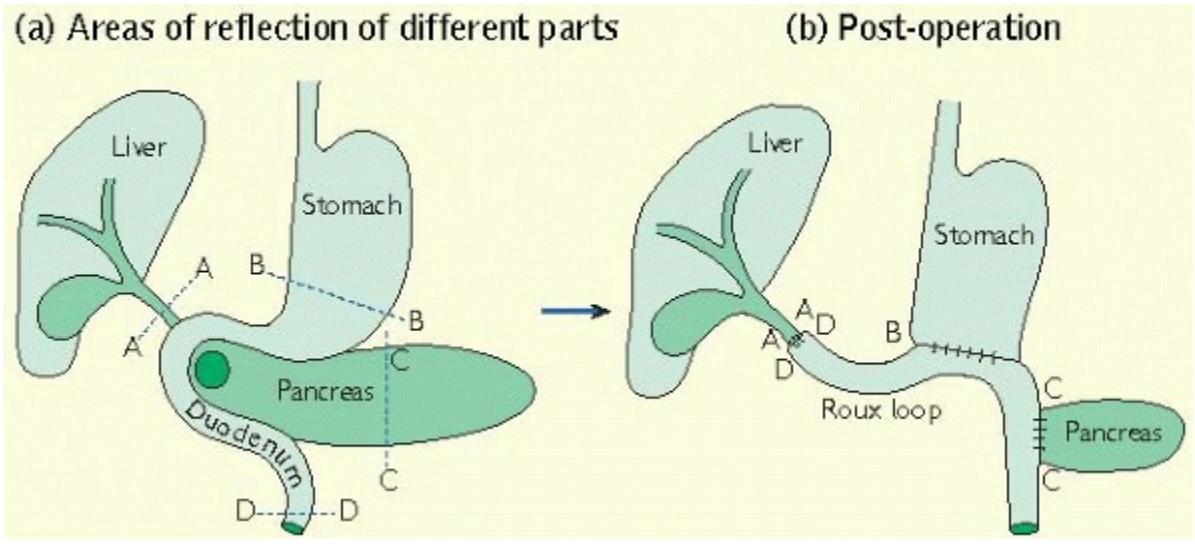
'The sweet smell is a great sorrow on the land. Men who can graft the trees and make the seed fertile and big can find no way to let the hungry people eat their produce … The works of the roots of the vines, of the trees, must be destroyed to keep up the price …

There is a crime here that goes beyond denunciation. There is a sorrow here that weeping cannot symbolize. There is a failure here that topples all our success. The fertile earth, the straight tree rows, the sturdy trunks, and the ripe fruit. And children dying of pellagra must die because a profit cannot be taken from an orange. And coroners must fill in the certificates—died of malnutrition—because the food must rot, must be forced to rot.

The people come with nets to fish for potatoes in the river, and the guards hold them back; they come in rattling cars to get the dumped oranges, but the kerosene is sprayed. And they stand still and watch the potatoes float by, listen to the screaming pigs being killed in a ditch and covered with quicklime, watch the mountains of oranges slop down to a putrefying ooze; and in the eyes of the people there is a failure; and in the eyes of the hungry there is a growing wrath. In the souls of the people the grapes of wrath are filling and growing heavy, growing heavy for the vintage.'

How do John Steinbeck's grapes grow in our 21st century soil? Too well; a double harvest, it turns out, as not only is much of the world starving, amid plenty (for those who can pay) but there is a new 'sorrow in our land that weeping cannot symbolize': pathological 'voluntary' **self-starvation**, again amid plenty, in pursuit of the body-beautiful according to images laid down by media gods. If gastroenterologists had one wish it might not be the ending of all their diseases, but that human-kind stand in a right-relationship with Steinbeck's fertile earth, his straight trees, his sturdy trunks, and his ripe fruit.

Whipple's procedure



Whipple's procedure may be used for removing masses in the head of the pancreas—typically from pancreatic carcinoma, or rarely, a carcinoid tumour.[155]

Carcinoid crisis

When a tumour outgrows its blood supply or is handled too much during surgery, mediators flood out. There is life-threatening vasodilatation, hypotension, tachycardia, bronchoconstriction and hyperglycaemia. It is treated with high-dose ***octreotide***, supportive measures and careful management of fluid balance (ie a central line is needed—see p762 for insertion technique).

Gastrointestinal malabsorption Causes—see BOX

Symptoms

Diarrhoea; ↓weight; lethargy; steatorrhoea (fatty stools, hard to flush away).

Deficiency signs

Anaemia (↓Fe, B_{12}, folate); bleeding disorders (↓vit K); oedema (↓protein); metabolic bone disease (↓vit D); neurological features, eg neuropathy.

Tests

FBC (↓ or ↑MCV); ↓Ca^{2+}; ↓Fe; ↓B_{12} + folate; ↑INR; lipid profile; coeliac serology (below).

Stool:

Sudan stain for fat globules; stool microscopy for infestation.

Barium follow-through:

Diverticula; Crohn's; radiation enteritis.

Breath hydrogen analysis:

for bacterial overgrowth. Take samples of end-expired air; give glucose; take more samples at ½h intervals; ↑exhaled hydrogen = overgrowth.

Endoscopy + small bowel biopsy. ERCP:

(p728) biliary obstruction; chronic pancreatitis.

Tropical malabsorption

Typical causes:

Giardia intestinalis, *Cryptosporidium parvum*, *Isospora belli*, *Cyclospora cayetanensis*, and the microsporidia.

Tropical sprue:

Villous atrophy and malabsorption occurring in the Far and Middle East and Caribbean (it is rarer in Africa[156]) —the cause is unknown. ***Tetracycline*** 250mg/6h PO + ***folic acid*** 15mg/24h PO + optimum nutrition may help. [157]

Coeliac disease

This is a T-cell mediated autoimmune disease of the small bowel in which prolamin (alcohol-soluble proteins in wheat, barley, rye ± oats) intolerance causes villous atrophy and malabsorption.[1]

Associations:

HLA DQ2 in 95%; the rest are DQ8; autoimmune disease; dermatitis herpetiformis.

Prevalence:

1 in 300-1500 (more common in Irish). Occurs at any age (peaks in infancy and 50-60yrs). ♀>♂. There is a 10% prevalence in 1st degree relatives and a 30% relative risk for siblings.

Presentation:

Steatorrhoea; abdominal pain; bloating; nausea + vomiting; aphthous ulcers, angular stomatitis; weight↓; fatigue; weakness; incidental iron-deficiency anaemia; osteomalacia; failure to thrive (children). 1/3 are asymptomatic.

Diagnosis

Antibodies: α-gliadin, transglutaminase & anti-endomysial—an IgA antibody, 95% specific unless the patient is IgA-deficient. Duodenal biopsy done at endoscopy (p248—as good as jejunal biopsy if ≥4 taken): subtotal villous atrophy + crypt hyperplasia, **reversing** on gluten-free diet (along with ↓symptoms & antibodies).

Treatment

Lifelong gluten-free diet (ie no prolamins)—patients become experts. Rice, maize, soya, potatoes, oats (≤50g/d),[158] and sugar are OK. Gluten-free

biscuits, flour, bread, & pasta are prescribable. Verify diet by endomysial antibody tests.

Complications

Anaemia; 2° lactose-intolerance; GI T-cell lymphoma (rare; suspect if refractory symptoms or ↓weight); ↑risk of malignancy (gastric, oesophageal, bladder, breast, brain); myopathies; neuropathies; hyposplenism; osteoporosis.

[1] Infectious aetiological agents have been implicated: eg *Candida albicans* could be one trigger. HWP1 has amino acid sequences identical to coeliac disease-related α-gliadin T-cell epitopes.

Chronic pancreatitis

Epigastric pain 'bores' through to back (eg relieved by sitting forward or hot water bottles on epigastrium/back (look for *erythema ab igne*'s mottled dusky greyness); bloating; steatorrhoea; ↓weight; brittle diabetes. Symptoms relapse and worsen.

Causes:

Alcohol; rarely: familial; cystic fibrosis; haemochromatosis; pancreatic duct obstruction (stones/tumour); ↑PTH; congenital (*pancreas divisum*).

Tests

Ultrasound

(eg pseudocyst) (p259) ± **CT**, **MRCP** + **ERCP** (risks acute attack);

AXR:

speckled pancreatic calcification; ↑glucose; breath tests eg ^{13}C-hiolien.$_{159}$

Treatment:

Drugs:

Give analgesia (± coeliac-plexus block); ***lipase***, eg Creon®; fat-soluble vitamins (eg Multivite®). Insulin requirements may be greater than in idiopathic diabetes and hypoglycaemia is a risk.

Diet:

No alcohol; low fat may help. Medium-chain triglycerides (MCT oil®) may be tried (no lipase needed for absorption, but diarrhoea may be worsened).

Surgery:

For unremitting pain; narcotic abuse (beware of this); weight↓: eg pancreatectomy or pancreaticojejunostomy.

Complications

Pseudocyst; diabetes; biliary obstruction; local arterial aneurysm; splenic vein thrombosis; gastric varices.

Causes of gastrointestinal malabsorption
Commmon in the UK:

- Coeliac disease.
- Chronic pancreatitis.
- Crohn's disease.

Rarer:

- ↓***Bile:*** PBC; ileal resection; biliary obstruction; colestyramine.
- ***Pancreatic insufficiency:*** Pancreatic cancer; cystic fibrosis.
- ***Small bowel mucosa:*** Whipple's diseases (p708); tropical sprue; radiation enteritis; small bowel resection; brush border enzyme deficiencies (eg lactase insufficiency); drugs (metformin, neomycin, alcohol); amyloid (p354).
- ***Bacterial overgrowth:*** Spontaneous (especially in elderly); in jejunal diverticula; post-op blind loops. Try ***metronidazole*** 400mg/8h PO or ***oxytetracycline*** 250mg/6h.
- ***Infection:*** Giardiasis; diphyllobothriasis (B_{12} malabsorption); strongyloidiasis.
- ***Intestinal hurry:*** Post-gastrectomy dumping; post-vagotomy; gastrojejunostomy.

Nutrient	Site of absorption	Deficiency syndrome
Vitamin		
A^F	Small intestine	Xerophthalmia (p270)
B_1 (thiamine)	Small intestine	Beriberi (p270); Wernicke's encephalopathy (p706)
B_2 (riboflavin)	Proximal small intestine	Angular stomatis; cheilitis (p230)
B_6 (pyridoxine)	Small intestine	Polyneuropathy
B_{12}	Terminal ileum	Macrocytic anaemia (p318); neuropathy; glossitis
C	Proximal ileum	Scurvy (p270)
D^F	Jejunum as free vitamin	Rickets (p670); osteomalacia (p670)
E^F	Small intestine	Haemolysis; neurological deficit
K^F	Small intestine	Bleeding disorders (p330)
Folic acid	Jejunum	Macrocytic anaemia (p318)

	Nicotinamide	Jejunum	Pellagra (p270)
Mineral			
	Calcium	Duodenum + jejunum	p670
	Copper	Stomach + Jejunum	Menkes' kinky hair syndrome
	Fluoride	Stomach	Dental caries
	Iodide	Small intestine	Goitre (p622); cretinism
	Iron	Duodenum + jejunum	Microcytic anaemia (p312)
	Magnesium	Small intestine	p672
	Phosphate	Small intestine	Osteoporosis; anorexia; weakness
	Selenium	Small intestine	Cardiomyopathy
	Zinc	Jejunum	Acrodermatitis enteropathica; poor wound healing

[F] = fat-soluble vitamin, thus deficiency is likely if there is fat malabsorption.

Alcoholism

An alcoholic is one whose repeated drinking leads to harm in his work or social life. It is common (~25%), ranging from binge drinking to heavy daily intake,

and is usually tied in with other life or health issues. Other addictions may also be involved. ▸Denial is a leading feature of alcoholism, so be sure to question relatives. Alcohol **c**a**n** do you good in low doses, eg <20U/wk in men, <15U/wk in women (see p228).

CAGE questions

Ever felt you ought to **c**ut down on your drinking? Have people **a**nnoyed you by criticizing your drinking? Ever felt bad or **g**uilty about your drinking? Ever had an **e**ye-opener to steady nerves in the morning? CAGE (yes to ≥2) is quite good at detecting alcohol abuse and dependence (sensitivity 43-94%; specificity 70-97%),[160] but accuracy does change according to background population. There are several other screening methods: eg TWEAK (see BOX); AUDIT.[161]

Organs affected

(▸Don't forget the risk of trauma whilst intoxicated.)[162]

- ***The liver:*** Normal in 50% of alcoholics; γGT↑ or ↑↑, but is non-specific (may be ↑ in any condition that causes liver inflammation, eg AIH (p260), HBV). ***Fatty liver:*** Acute and reversible, but may progress to cirrhosis if drinking continues (also seen in obesity, DM, and with amiodarone). ***Alcoholic hepatitis:*** see BOX. 80% progress to cirrhosis (hepatic failure in 10%). ***Cirrhosis*** (p252): 5yr survival is 48% if drinking continues (if not, 77%). ***Biopsy:*** Mallory bodies ± neutrophil infiltrate.
- **CNS***:* Poor memory/cognition: multiple high-potency vitamins IM may reverse it; cortical atrophy; retrobulbar neuropathy; fits; falls; wide-based gait neuropathy; confabulation; Korsakoff's (p696) ± Wernicke's encephalopathy (p706).
- **GI** ***tract:*** Obesity; diarrhoea; gastric erosions; peptic ulcers; varices (p246); pancreatitis (acute and chronic); carcinoma; oral mucosal lesions.
- ***Blood:*** MCV↑; anaemia from: marrow depression, GI bleeding, alcoholismassociated folate deficiency, haemolysis; sideroblastic anaemia. See p318.
- ***Heart:*** Arrhythmias; BP↑; cardiomyopathy; sudden death in binge drinkers.

Withdrawal

starts 10-72h after last drink.

Signs:

Pulse↑; BP↓; tremor; confusion; fits; hallucinations (*delirium tremens*)—may be visual or tactile, eg animals crawling all over skin. Consider it in any new (≤ 3d) ward patient with acute confusion.

Alcohol contraindications

Driving; hepatitis; cirrhosis; peptic ulcer; drugs (eg antihistamines, metronidazole); carcinoid; pregnancy (fetal alcohol syndrome—IQ↓, short palpebral fissure, absent philtrum, and small eyes).

Management

Alcohol withdrawal:

Admit; do BP + TPR/4h. Beware BP↓. For the 1st 3d give generous ***chlordiazepoxide***, eg 10-50mg/6h PO, weaning over 7-14d (see TABLE); alternative: ***diazepam***; the once-preferred ***clomethiazole*** readily causes addiction. Vitamins may be needed (p706).

Prevention:

(OHCS p513): Alcohol-free beers; low-risk drinking (see below), remembering that there are no absolutes and that risk is a continuum. *1U≈9g ethanol≈1 spirits measure≈1 glass wine≈½ pint beer.*

Treating established alcoholics

may be rewarding, particularly if they really want to change. If so, **group therapy** or **self-help** (eg 'Alcoholics Anonymous') may be useful—especially if self-initiated and determined. Encourage the will to change.

Suggest:

1 Graceful ways of declining a drink, eg 'I'm seeing what it's like to go without for a bit'; **2** not buying him- or herself a drink when it is his/her turn; **3** 'Don't lift your glass to your lips until after the slowest drinker in your group takes a drink'; **4** 'Sip, don't gulp'. Give follow-up and encouragement.

Relapse

50% will relapse soon after starting treatment. ***Acamprosate*** (p443)[163] may help intense anxiety, insomnia, and craving. CI: pregnancy, severe liver failure, creatinine >120μmol/L. SE: D&V, libido ↑ or ↓; dose example: 666mg/8h PO if >60kg and <65yrs old.[164] It should be started as soon as acute withdrawal is complete and continued for ~1yr. ***Disulfiram*** can be used to treat chronic alcohol dependence. It causes acetaldehyde build-up (like metronidazole) with extremely unpleasant effects to **any** alcohol ingestion—eg flushing, throbbing headache, palpitations. Care must be taken to avoid alcohol (eg toiletries, food, medicines) since severe reactions can occur. ▸Confer with experts if drugs are to be used.

TWEAK screening questions[165]

- Have you an increased **t**olerance of alcohol? 2pts
- Do you **w**orry about your drinking? 2pts
- Have you ever had alcohol as an **e**ye-opener in the morning? 1pt
- Do you ever get **a**mnesia after drinking alcohol? 1pt
- Have you ever felt the need to c(**k**)ut down on your drinking? 1pt

A score of ≥2 suggests an alcohol problem. It may be more sensitive than the CAGE questionnaire in some populations (eg pregnant women).[166]

Patterns of lab tests in alcoholic and other liver disease

	AST	ALT	AST : ALT	MCV
Alcoholic liver disease	↑↑	↑	>2	↑↑
Hepatitis C (HCV)	↑ or ↔	↑↑	<1*	↔
Non-alcoholic fatty liver disease	↑	↑↑	<1	↑ or ↔

* ratio may reverse if cirrhosis develops. See p742 for reference intervals.

Managing alcoholic hepatitis

Clinical picture

TPR↑; anorexia; D&V; tender hepatomegaly ± jaundice; bleeding; ascites.

Bloods:

WCC↑; INR↓; AST↑; MCV↑; urea↑. ▸Severe hepatitis is indicated by **jaundice**, **encephalopathy** and **coagulopathy**.

- Stop alcohol consumption: for withdrawal symptoms, if ***chlordiazepoxide*** by the oral route is impossible, try ***lorazepam*** IM.
- High-dose B vitamins IV as ***Pabrinex®***—1 pair of ampoules in 50mL 0.9% saline IVI over ½h; (see Datasheet)—have resuscitation equipment to hand.
- Optimize nutrition (35-40kcal/kg/d non-protein energy) + 1.5g/kg/d of protein (use ideal body weight for calculations eg if malnourished). This prevents encephalopathy, sepsis, and some deaths.
- Daily weight; LFT; U&E; INR. If creatinine↑, get help with this HRS (p251). Na^+↓ is common, but water restriction may make matters worse. See p250.
- Culture ascites fluid and treat for SBP, if suspected (p252).
- Work out the Maddrey Discriminant Factor (DF) = (4.6 × PT-control time) + [bilirubin] (in µmol/L). If >32 (ie severe disease) then start steroid therapy ▸provided sepsis has been excluded: eg ***prednisolone*** 40mg/d for 5d tapered off over 3 weeks. Mortality roughly equivilates to the DF score—see below.

Prognosis:

Mild episodes often resolve with no affect on mortality. Severe hepatitis can have a 30d mortality of 50%, reduced to 5% if only mild. ▸At 1 year after an admission for alcoholic hepatitis, 40% are dead—a sobering thought.

An example of a chlordiazepoxide reducing regime

Day	am	noon	pm	nocte	total/d
1	20mg	20mg	20mg	20mg	80mg
2	20mg	15mg	15mg	20mg	70mg
3	15mg	15mg	15mg	15mg	60mg
4	15mg	10mg	10mg	15mg	50mg
5	10mg	10mg	10mg	10mg	40mg
6	10mg	5mg	5mg	10mg	30mg
7	5mg	5mg	5mg	5mg	20mg

8	5mg	-	-	5mg	10mg
9	-	-	-	5mg	5mg
10	-	-	-	-	discontinue

▸***Caveats:*** doses may need to be higher for the 1st few days for severe withdrawal; there may still be mild withdrawal symptoms at day 3. Have a 5mg dose written for PRN use.

Acknowledgements

We thank Dr Simon Campbell who is our Specialist Reader for this chapter.

Editors: Longmore, Murray; Wilkinson, Ian B; Turmezei, Tom; Cheung, Chee Kay
Title: *Oxford Handbook of Clinical Medicine, 7th Edition*

8

Renal Medicine

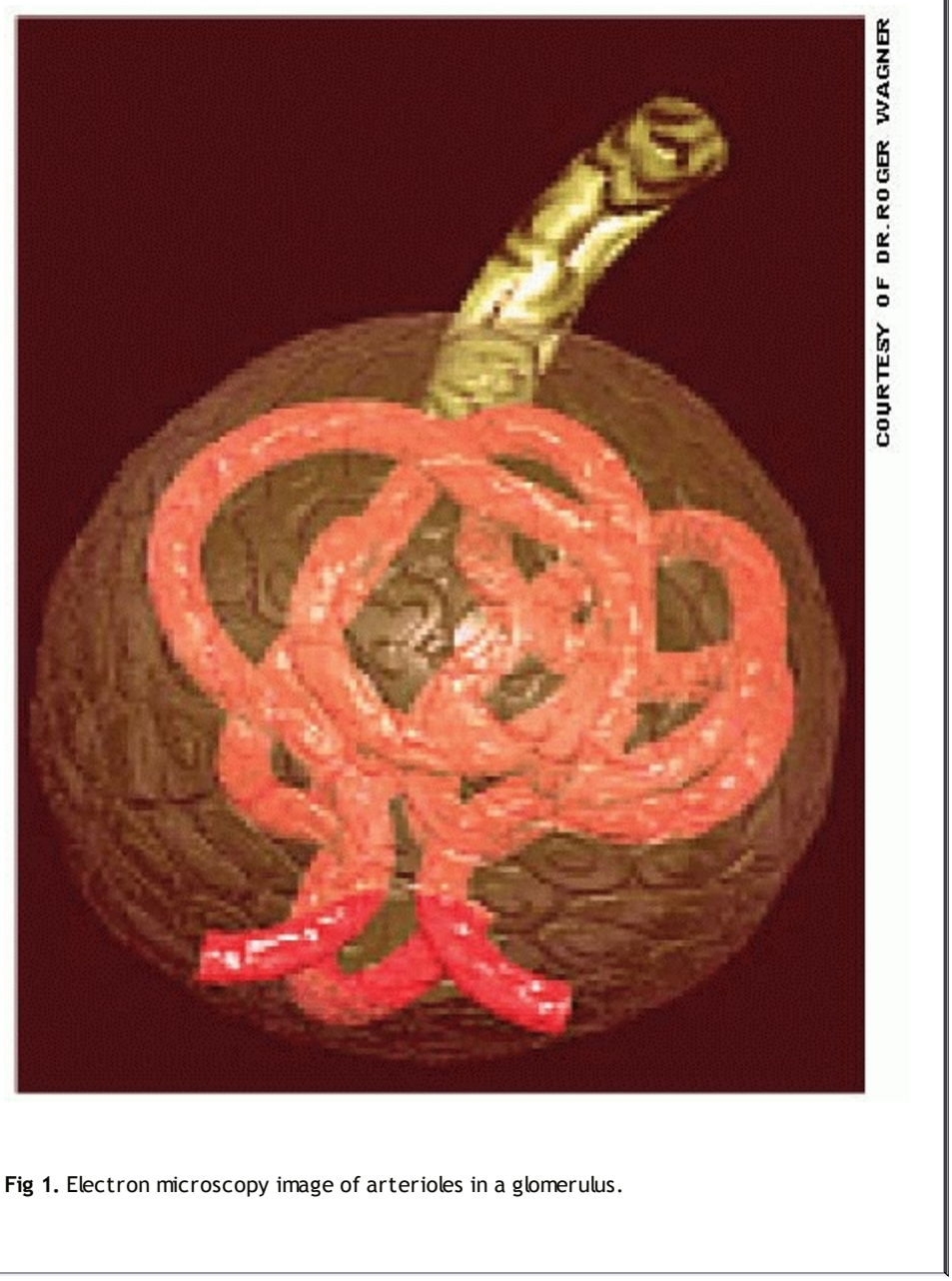


Fig 1. Electron microscopy image of arterioles in a glomerulus.

Renal disease

typically presents with one or more of rather a short list of clinical syndromes—listed from 1 to 7 below. One underlying pathology may have a variety of clinical presentations.

1. ***Proteinuria and nephrotic syndrome:*** Normal protein excretion is <150mg/d. This may rise to ~300mg/d—eg orthostatic proteinuria (related to posture), during fever, or after exercise. *Proteinuria* (excessive protein excretion) is a sign of glomerular or tubular disease. *Nephrotic syndrome* (p290) is the triad of proteinuria (>3g/d), hypoalbuminaemia (albumin <30g/L) and oedema.

2. ***Haematuria and nephritic syndrome:*** Blood in the urine may arise from anywhere in the renal tract. It may be *macroscopic* (visible to the naked eye) or *microscopic* (found on dipstick testing and microscopy). **Haematuria with dysuria** is usually from a UTI. **Painless haematuria** is more ominous, eg bladder or other GU cancer (eg if >40yrs old, esp if a smoker) or glomerulonephritis. **Nephritic syndrome** comprises haematuria and proteinuria—often with hypertension, pulmonary and peripheral oedema, oliguria (urine output <400mL/d), and a rising plasma urea and creatinine. The question of who to refer haematuria patients to (urologist or nephrologist) is answered on p278.

3. ***Renal pain and dysuria:*** **Renal pain** is usually a dull and constant and in the loin. It may be due to renal obstruction (look for swelling ± tenderness), pyelonephritis, acute nephritic syndrome, polycystic kidneys, or renal infarction. **Renal (ureteric) colic** is severe waxing and waning loin pain

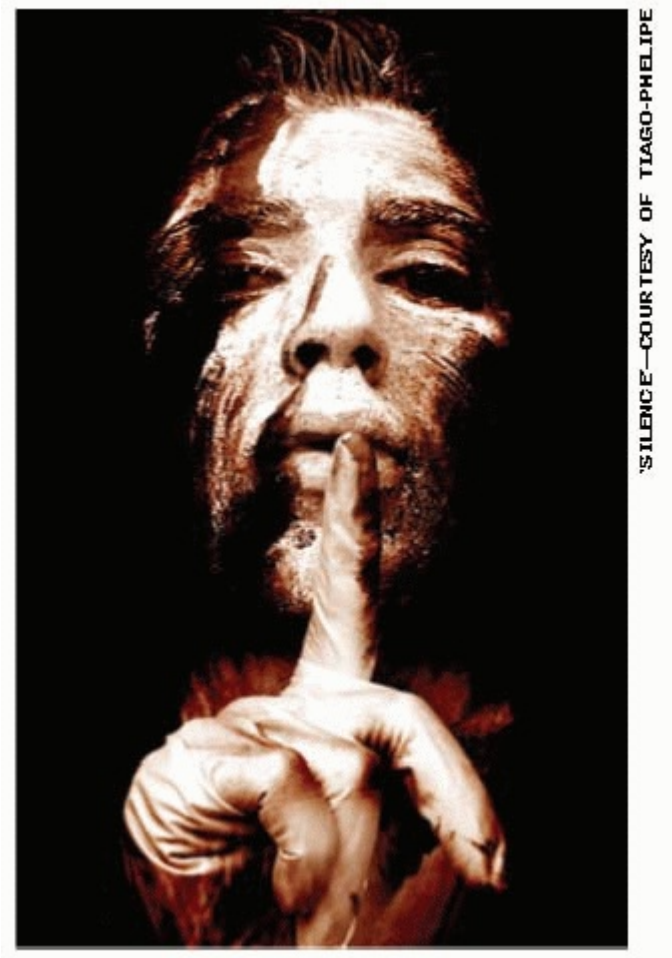
radiating to groin or thigh eg with fever and vomiting. It is caused by a renal stone, clot, or a sloughed papilla. **Urinary frequency** with **dysuria** (pain on voiding) suggests a UTI.

4. ***Oliguria and polyuria:*** **Oliguria** is a urine output of <400mL/d—a normal response to hot climates or fluid restriction. *Pathological causes*: renal perfusion↓, renal parenchymal disease, renal tract obstruction. **Polyuria** is the voiding of abnormally high volumes of urine, usually from high fluid intake—or diabetes mellitus, diabetes insipidus (p224), hypercalcaemia, renal medulla disorders (urine concentration is impaired), and SVT (p112).

5. ***Acute renal failure (*ARF*)*** is significant decline in renal function occurring over hours or days, detected by a rising plasma creatinine (± oliguria). ARF usually occurs secondary to a circulatory dysfunction (hypotension, hypovolaemia, sepsis) or urinary obstruction. Primary renal disease is a less common cause.

6. ***Chronic renal failure (*CRF*)*** or chronic kidney disease (CKD) is defined as irreversible, substantial, and long-standing loss of renal function. It is classified according to glomerular filtration rate (GFR): see p661. There is often a poor correlation between symptoms and severity of CRF. Progression may be so insidious that patients attribute symptoms to age or a minor illnesses**. Current guidelines advise nephrology referral if CKD stage ≥3** (p661),[1] ie GFR <60mL/min, ***if other features are present:*** • GFR is falling progressively • Microscopic haematuria • Urine protein:creatinine ratio (PCR)↑, p301 •Unexplained anaemia, hyperkalaemia, or calcium or phosphate imbalance •Suspected systemic illness (eg SLE) •BP uncontrolled despite taking 3 drugs. Refer ***urgently*** if GFR 15-29 (same-day if <15) even if ***no*** other features present.

7. ***Silence:*** Serious renal failure may cause **no symptoms at all**. This is why we do U&Es before surgery and other major interventions. The silence of renal disease creeps up on us (doctors and patients)—with uncanny stealth which is as alarming as the image opposite—'Silence', by Tiago Phelipe. This picture serves to remind us not to dismiss odd chronic symptoms such as fatigue or 'not being quite with it'—without doing a blood test. ***Microalbuminuria*** is a famously silent harbinger of serious renal and cardiovascular risk. It is described on p306. In one study, 30% of those with type 2 diabetes mellitus died within ~5 years of developing microalbuminuria.



Urine

Examine mid-stream urine (MSU) whenever you suspect renal disease.

Dipstick:

- ***Haematuria:*** *Renal causes:* Neoplasia, glomerulonephritis (often IgA nephropathy, p288), tubulointerstitial nephritis, polycystic kidney, papillary necrosis, infection (pyelonephritis), trauma. *Extrarenal:* Calculi, infection (cystitis, prostatitis, urethritis), neoplasia (bladder, prostate, urethra), trauma (eg from catheter). ***Tests:*** Urine MC&S, FBC, ESR, CRP, U&E, clotting. *Others:* AXR/KUB, p284 (stones), urine cytology, estimation of proteinuria (see below), renal ultrasound ± renal biopsy. ***Management:*** Usually refer first to a urologist, and do ultrasound. Only refer initially to renal physician if the risk of urothelial malignancy is low and risk of glomerulonephritis is not negligible (eg <40yrs old, creatinine↑, BP↑, proteinuria, systemic symptoms, family history of renal disease).[2] Not all women with recurrent UTI + haematuria need cystoscopy, but have a good reason *not* to do cystoscopy (Reynard's rule).[3] ***False +ve dipstick haematuria:*** Haemoglobinuria, myoglobin (eg in rhabdomyolysis), beetroot, porphyria, alkaptonuria, rifampicin, phenindione, phenolphthalein.

- ***Proteinuria:*** Normal protein excretion is <150mg/d, consisting of <30g/d of albumin. *Renal causes of proteinuria:* UTI, orthostatic proteinuria, glomerulonephritis (GN), ↑BP, DM, myeloma, amyloid. *Extrarenal:* Fever, exercise, pregnancy, CCF, vaginal mucus, recent ejaculation. *Tests:* BP, urine MC&S. *Estimation of proteinuria:* 24h urine collection for protein and creatinine quantifies proteinuria *if* collected accurately: spot tests for urine

albumin:creatinine ratio or urine protein:creatinine index are much easier and provide reasonably accurate information; renal ultrasound; autoantibodies eg immunoglobulins, serum electrophoresis, urinary Bence Jones protein (p288); consider a renal biopsy if renal function is deteriorating. ***Microalbuminuria*** is undetectable on dipstick, with albuminuria of 30-300mg/24h on lab tests. ***Causes:*** DM, ↑BP, minimal change GN.

- ***Other substances—Glucose:*** Low renal threshold (eg chronic renal failure), DM, pregnancy, sepsis, renal tubular damage. ***Ketones:*** Starvation, ketoacidosis. ***Leucocytes:*** UTI, vaginal discharge. ***Nitrites:*** UTI, high-protein meal. ***Bilirubin:*** Obstructive jaundice. ***Urobilinogen:*** Pre-hepatic jaundice. ***Specific gravity:*** Normal range: 1.000-1.030 (useful to assess degree of proteinuria or haematuria). ***pH:*** Normal range: 4.5-8 (acid-base balance: p658).

Microscopy

Put a drop of fresh urine (MSU or suprapubic aspirate) on a microscope slide, cover with a coverslip and examine under low (×100) and high (×400) power for leucocytes, red cells, bacteria, casts and crystals. If renal disease is suspected, a centrifuged urine should be examined.

Leucocytes:

>10/mm^3 in an unspun urine specimen is abnormal. Usually due to a UTI, see p283 for causes of sterile pyuria (when no bacteria are found).

Red cells:

>2/mm^3 in unspun urine is abnormal. *Causes:* See haematuria.

Casts

are cylindrical bodies formed in the lumen of distal tubules.

- ***Finely granular*** and ***hyaline casts*** (clear, colourless) are found in normal concentrated urine. They are increased in fever, exercise or loop diuretics.
- ***Densely granular:*** Glomerular or tubular disease eg GN, interstitial nephritis.
- ***Fatty casts:*** Moderate-heavy proteinuria. Don't mistake fat globules for RBCs.
- ***Red cell casts*** are a diagnostic marvel, as they *prove* that haematuria is glomerular, allowing you to start an interesting dialogue with a nephrologist: 'is there vasculitis (p542), glomerulonephritis, or malignant hypertension?'
- ***White cell casts*** occur in pyelonephritis.
- ***Tubular cell casts*** occur in acute tubular necrosis.

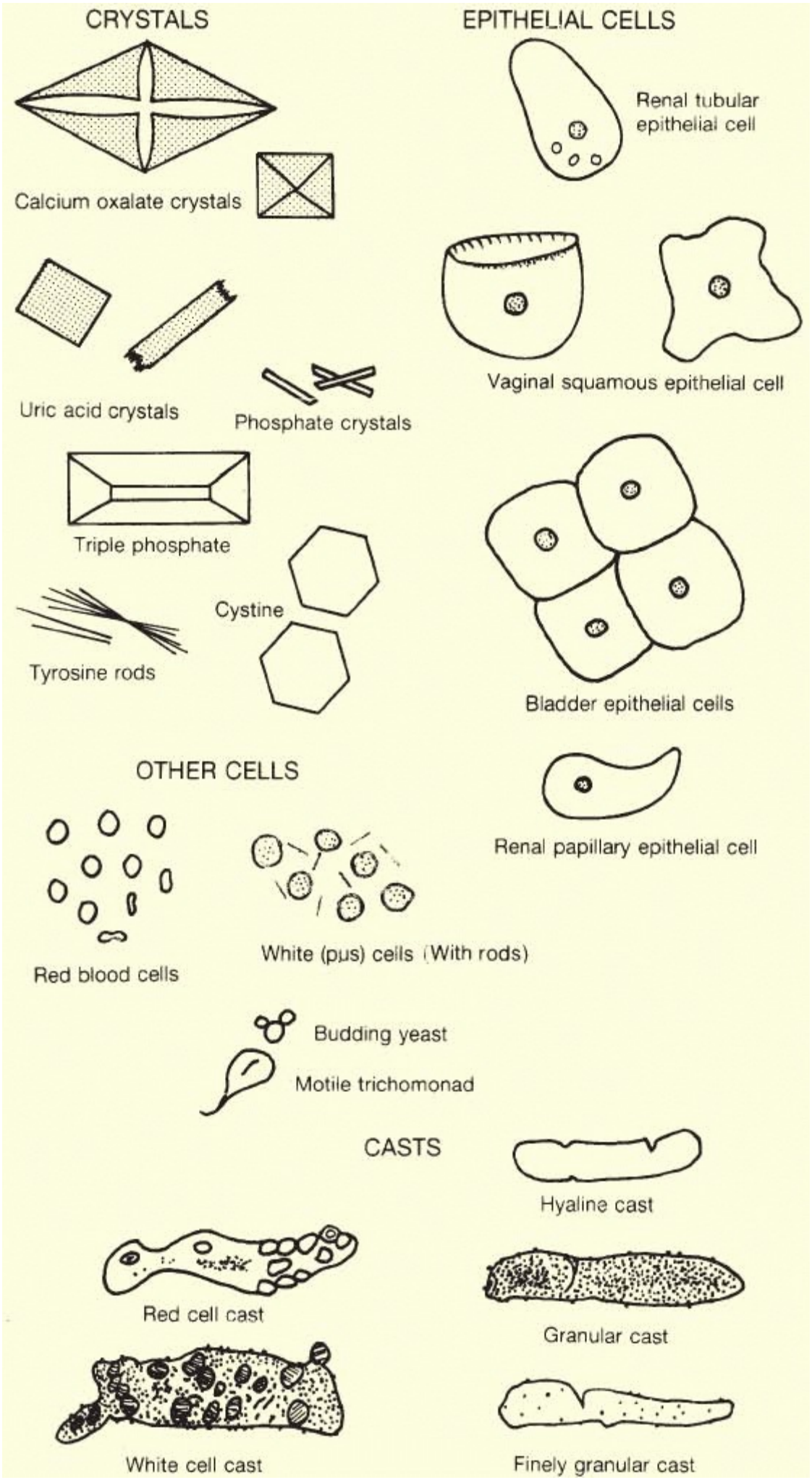
Crystals

are common in old or cold urine and may not signify pathology. They are important in stone formers: cystine crystals are diagnostic of cystinuria, and oxalate crystals in fresh urine may indicate a predisposition to form calculi.

24h urine

for Na^+, K^+, Ca^{2+}, urea, creatinine ± protein excretion. Take blood simultaneously for creatinine to calculate creatinine clearance (p661).

Urine microscopy



Principal source: *Atlas of Bedside Microscopy* ©JM Longmore; RCGP

▸When you find red cells, consider their morphology to understand where in the GU tract they come from. If >10% of RBCs are dysmorphic G1 cells, suspect glomerular bleeding, and look hard for red cell casts. G1 cells have doughnut shapes, target configurations, and membrane protrusions or blebs. **NB:**

identifying dysmorphic red cells is subjective and often difficult.

Acanthocyturia ≈ RBCs with spicules.

G1 cell images

(stained urine cytology): www.uninet.edu/cin2003/conf/nguyen/nguyen.html

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Images of renal histology

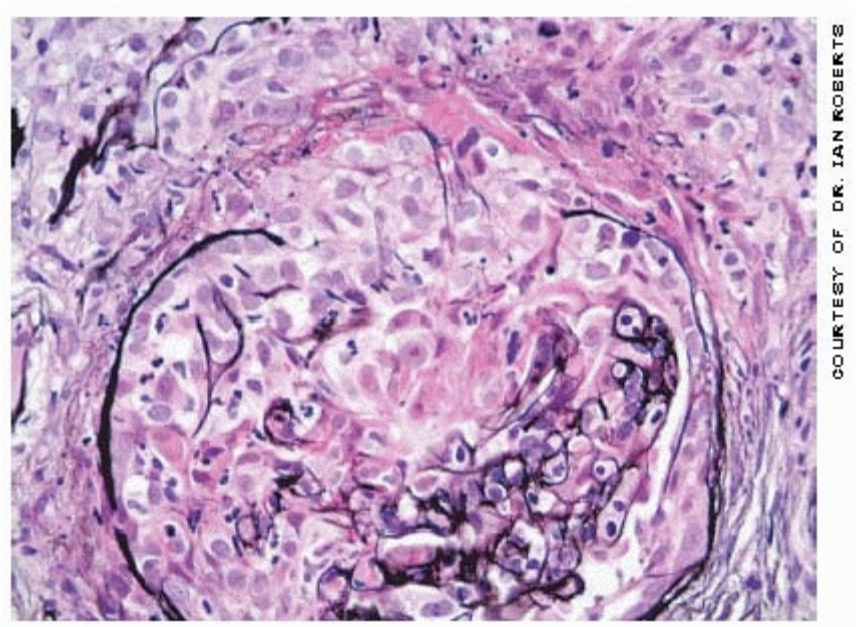

Fig 1. Crescentic glomerulonephritis: a proliferation of epithelial cells and macrophages with rupture of Bowman's capsule, in this patient caused by antiglomerular basement membrane (Goodpasture's) disease, see p692.

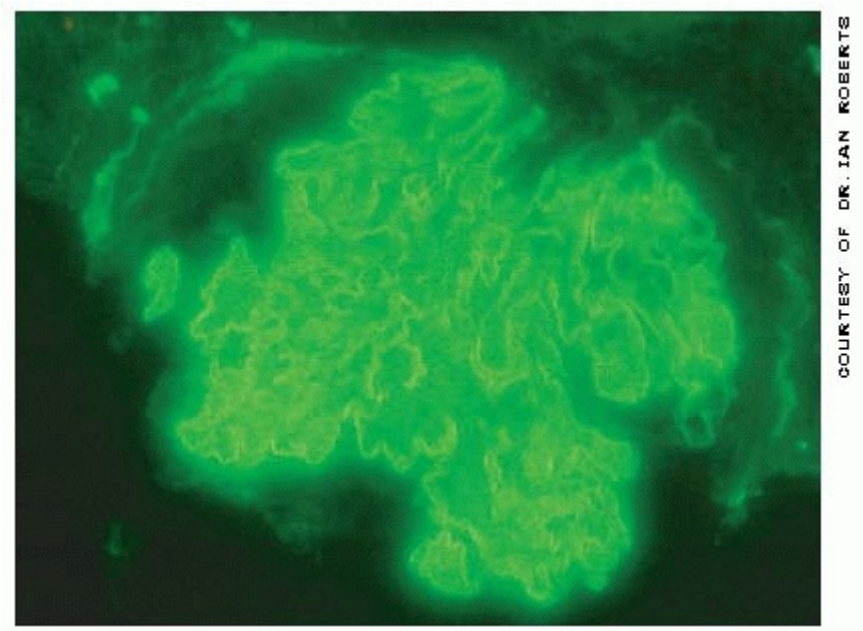

Fig 2. Immunofluorescence for IgG, showing linear staining for glomerular basement, characteristic of anti-glomerular basement membrane (Goodpasture's) disease.

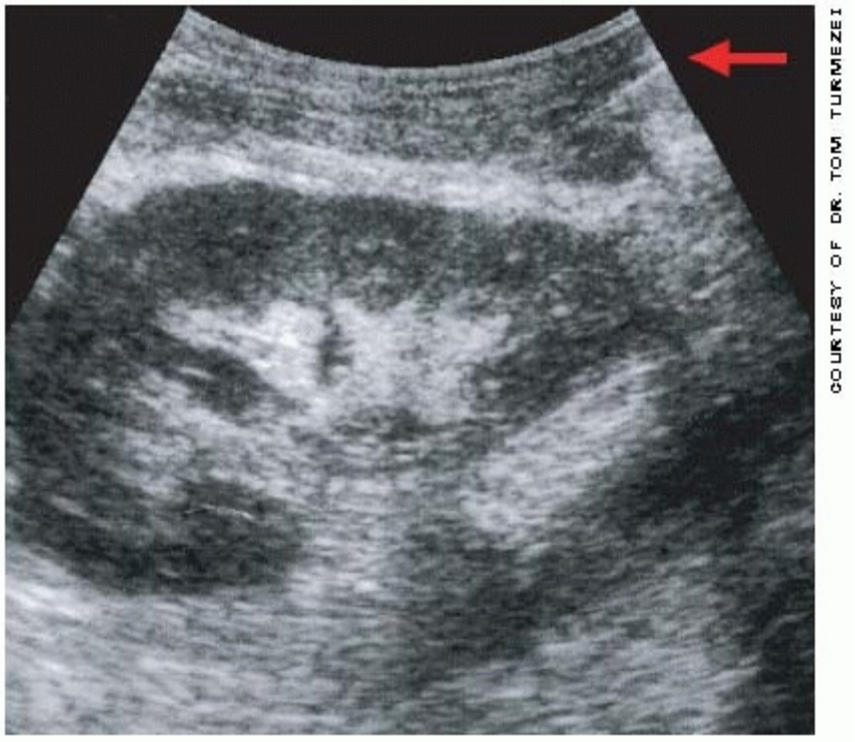

Fig 3. US-guided biopsy of a transplant kidney— this reduces the risk of damaging the renal vessels and pelvis, as well as any nearby bowel (although the graft is usually extra-peritoneal). The red arrow is point of entry of the biopsy needle (hyperechoic and casting an acoustic shadow deeper). The hypoechoic tissue around the needle is from the infiltration of local anaesthetic. 3 separate 'shots' of the biopsy 'gun' are usually enough to get a good sample, though let the patient know what a 'shot' sounds like before starting, so that they don't start off down the ward!

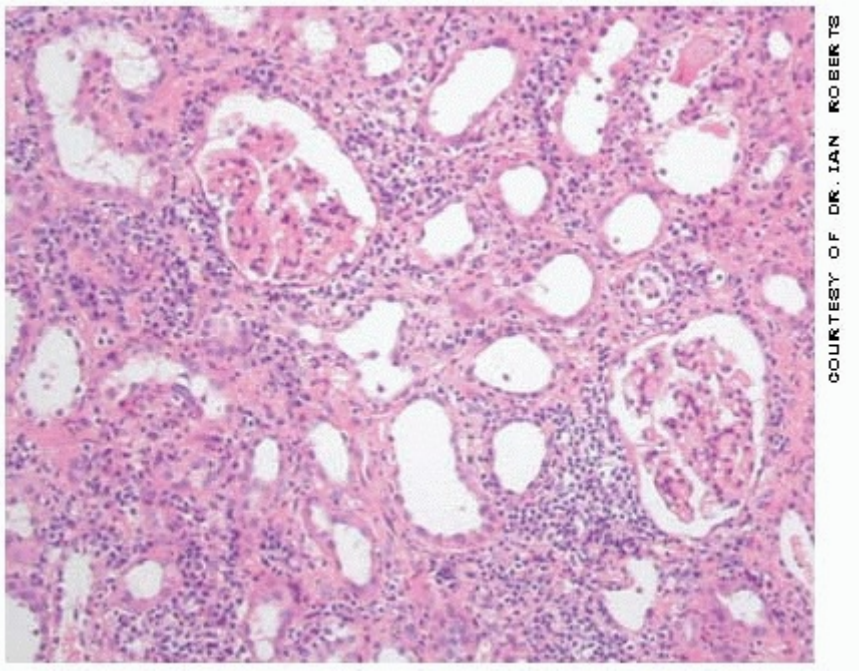

Fig 4. Renal allograft rejection: Cellular rejection, showing a tubulointerstitial infiltrate of lymphocytes—this is usually graded according to the *Banff* criteria. Although 'rejection' may sound fierce, it is usually easily and well-treated by increasing immunosuppression eg with a pulse of methylprednisolone. ▸ Watch for infection (eg CMV).

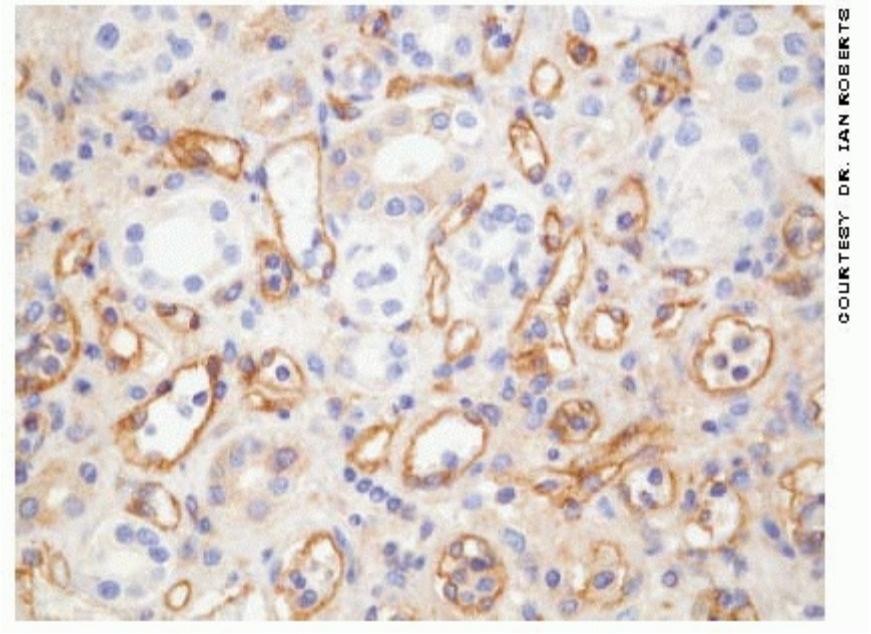

Fig 5. Renal allograft rejection: Antibody-mediated rejection, with diffuse peritubular capillary staining for C4d complement. Humoral (antibody-mediated) rejection is more problematic than cell-mediated rejection (above); it may need immunoglobulin therapy with plasma phoresis in an attempt to clear the system of donor-specific antibodies.

Renal biopsy

Most acute renal failure is due to pre-renal causes or acute tubular necrosis, and recovery of renal function typically occurs over the course of a few weeks. Renal biopsy should be performed only if knowing histology will influence management. Once chronic renal failure is established, the kidneys are small, there is a higher risk of bleeding from biopsy, and the results are usually unhelpful.

Indications for renal biopsy:

- What is the cause of this acute renal failure (p292)?
- Investigating glomerulonephritis, eg is persistent haematuria from IgA nephropathy, thin basement membrane disease, or hereditary nephropathy?
- What is the cause of this heavy proteinuria (eg >1g/d, when you know that diabetes mellitus is not the cause).
- Renal dysfunction post-transplantation (p297): is the cause rejection, acute tubular necrosis, drug toxicity, or recurrence of renal disease?[4]

Pre-procedure:

Check FBC, clotting, group & save. Obtain written informed consent. Ultrasound (if only 1 kidney, risk is magnified). Stop aspirin 1 week and warfarin at least 2 days in advance.

Contraindications:

• Abnormal clotting • Hypertension >160/>90 • Single kidney • Chronic renal failure with small kidneys (<9cm) •Uncooperative patient

Procedure:

Biopsy is done under ultrasound guidance with the patient lying in the prone position and the breath held. Samples should be sent to histology. A clear indication on the request form of why the test has been done, eg exclude amyloidosis, will help in the selection of special stains, immunofluorescence and use of electron microscopy.

Post procedure:

Bed rest for a minimum of 6hrs. Monitor pulse, BP, symptoms, and urine colour. Bleeding is the main complication; most occurs within 8 hrs, although it may be delayed by up to 72hrs. Macroscopic haematuria occurs in ~10%, although blood transfusion is only needed in ~1-2%. Aspirin or warfarin can be restarted the next day if uncomplicated.

Urinary tract infection (UTI) Childhood UTI: *OHCS* p174

Definitions

Bacteriuria: Bacteria in the urine, may be asymptomatic or symptomatic. **UTI:** The presence of a pure growth of $>10^5$ organisms per mL of fresh MSU. UTI sites: urethra (**urethritis**), bladder (**cystitis**), prostate (**prostatitis**), or renal pelvis (**pyelonephritis**). Up to **À** of women with symptoms have bacteriuria; (=**abacterial cystitis** or the **urethral syndrome**).

Classification:

UTIs may be **uncomplicated** (normal renal tract and function) or **complicated** (abnormal renal/GU tract, ↓renal function, impaired host defences, or virulent organism eg *Staph. aureus*). Assume that UTI in men without risk factors (below) is complicated until proved otherwise. A **recurrent** UTI is a further infection with a new organism. A **relapse** is a further infection with the same organism. For urethritis, see p406.

Risk factors

♀, sexual intercourse, exposure to spermicide in ♀ (by diaphragm or condoms), pregnancy, menopause; ↓*host defence*: immunosuppression, DM; *urinary tract*: obstruction (p286), stones, catheter, malformation. **NB:** in pregnancy, UTI is common and often asymptomatic, until serious pyelonephritis, premature delivery (± fetal death) supervenes, so do routine dipstix in pregnancy. Urine in catheterized bladders is almost always infected—it is pointless sending samples or treating unless the patient is ill.

Organisms

E. coli is the main organism (>70% in the community but ¢41% in hospital). Also *Staphylococcus saprophyticus, Proteus mirabilis*. Rarer: *Enterococcus faecalis*, *Klebsiella*, *Enterobacter* and *Acinetobacter* species, *Pseudomonas aeruginosa*, *Serratia marascens, Candida albicans,* and *Staph. aureus*.

Symptoms

Cystitis:

Frequency, dysuria, urgency, strangury, haematuria, suprapubic pain.

Acute pyelonephritis:

High fever, rigors, vomiting, loin pain and tenderness, oliguria (if acute renal failure).

Prostatitis:

Flu-like symptoms, low backache, few urinary symptoms, swollen or tender prostate on PR.

Signs

Fever, abdominal or loin tenderness, foul-smelling urine. Occasionally distended bladder, enlarged prostate. **NB:** see *Vaginal discharge*, p406.

Tests

If symptoms are present, dipstick the urine and treat empirically if nitrites or leucocytes are positive. If they are negative, consider sending an MSU for lab MC&S to confirm this. Send a lab MSU anyway if male, a child (OHCS p174), pregnant, immunosuppressed or ill, or if symptoms don't resolve after one course of empirical treatment. A pure growth of $>10^5$ organisms per mL is diagnostic. If $<10^5$ organisms/mL and pyuria (eg >20 WBCS/mm^3), the result may still be significant. Cultured organisms are tested for sensitivity to a range of antibiotics (p368).

Blood tests:

FBC, U&E, CRP, and blood cultures eg if systemically unwell.

Ultrasound or IVU/cystoscopy:

Consider for UTI in children; men; if failure to respond to treatment; recurrent UTI (>2/year); pyelonephritis; unusual organism; persistent haematuria. In one study on men, ultrasound combined with plain XR of kidneys, ureters and bladder (KUB) was as effective as IVU in detecting urinary tract abnormalities, and avoided exposure to IV contrast.[5]

Treatment

▸ Drink plenty of fluids; urinate often (don't 'hold on'). In pregnancy, get expert help. *Know your local pattern of resistance*. Until the organism is known:

- ***Cystitis:*** Trimethoprim 200mg/12h PO (3d course in ♀, 7d in ♂). Alternative: cefalexin 1g/12h. 2nd line: ciprofloxacin or co-amoxiclav PO (7d course).
- *Acute pyelonephritis:* Cefuroxime 1.5g/8h IV then oral × 7d course.
- *Prostatitis:* Ciprofloxacin 500mg/12h PO for ~ 4wks.

Prevention

Antibiotic prophylaxis, continuously or post-coital, ↓infection rates in women with recurrent UTIs. Self-treatment with a single antibiotic dose as symptoms start is an option. Drinking 200-750ml of cranberry or lingonberry juice a day, or taking cranberry concentrate tablets, reduces the risk of symptomatic recurrent infection in women by 10-20%,[6] may be by inhibiting adherence of bacteria to bladder uroepithelial cells. There is no evidence that postcoital voiding or advice on wiping patterns in females is of benefit.[7]

Causes of sterile pyuria

▸ *Always remember renal* TB (do 3 early morning urines). Other causes:

- Treated UTI <2 weeks prior
- Inadequately treated UTI

- Appendicitis
- Calculi
- Prostatitis
- Bladder tumour
- UTI with fastidious culture requirement
- Papillary necrosis (eg DM or analgesic excess)
- Tubulointerstitial nephritis
- Polycystic kidney
- Chemical cystitis (eg cyclophosphamide).

What is the predictive value of urinary symptoms and dipstick for diagnosing UTI?

This is a controversial area, with a meta-analysis on 70 studies concluding that in the general population, a combination of negative nitrite and leucocyte tests on dipstick was sufficient to rule out UTI.[MET][8]

However, a recent small prospective study (n=59) showed that although a negative dipstick test accurately predicted the absence of UTI according to urine culture, treating these patients with trimethoprim still reduced symptoms of dysuria, suggesting that the cause in these patients may be infection not detected by current urine dipstick or culture techniques.[9]

Renal calculi (nephrolithiasis)

Renal stones (calculi) consist of crystal aggregates. Stones form in collecting ducts and may be deposited anywhere from the renal pelvis to the urethra.

Prevalence

Common: lifetime incidence up to 15%. *Peak age:* 20-40yr. ♂:♀~3:1.

Types of stone

- Calcium oxalate: 75%.
- Magnesium aluminium phosphate (struvite, triple phosphate): 10-20%.
- Others: urate (5%), hydroxyapatite (5%), brushite, cystine (1%), mixed.

The patient

may be asymptomatic or present with a variety of symptoms.

Pain:

Stones in the kidney cause loin pain. Stones in the ureter cause renal (ureteric) colic. This occurs in spasms, classically radiates from the 'loin to the groin', and is associated with nausea and vomiting. Patients often cannot lie still, differentiating this from peritonitis. Bladder or urethral stones cause pain on micturition, strangury or interruption of urine flow.

Infection

can co-exist with renal stones, presenting with cystitis (frequency, dysuria), pyelonephritis (fever, rigors, loin pain, nausea, vomiting), or pyonephrosis (infected hydronephrosis).

Others:

Haematuria, proteinuria, sterile pyuria, anuria.

Tests:

FBC, U&E, Ca^{2+}, PO_4^{3-}, glucose, bicarbonate, urate.

Urine dipstick:

Usually +ve for blood.

MSU:

MC&S.

Further tests for cause:

Urine pH (on dipstick); 24h urine for: calcium, oxalate, urate, citrate, sodium, creatinine; stone biochemistry.

Imaging:

KUB XR (kidneys+ureters+bladder). Look along the ureters for calcification, over the transverse processes of the vertebral bodies: 80% of stones are visible (99% on CT). Ultrasound to look for hydronephrosis or hydroureter. CT is superior to IVU for imaging stones, and helps exclude differential causes of an acute abdomen. ▸A ruptured abdominal aortic aneurysm may present similarly.

Management

Give prompt analgesia, ideally an NSAID: eg diclofenac 75mg IV or IM, or 100mg suppository.[MET]$_{10}$ If contraindicated: morphine 5-10mg IV with metoclopramide 10mg IV. Give IV fluids if unable to tolerate orally; antibiotics (eg cefuroxime 1.5g/8h IV) if infection. After imaging ▸*seek urological help urgently if evidence of obstruction*, delay may lead to infection and permanent loss of renal function. Procedures include extracorporeal shockwave lithotripsy (ESWL) using ultrasonic waves to shatter the stone, percutaneous nephrostomy to relieve obstruction, ureteroscopy ± laser, or percutaneous nephrolithotomy (PCNL), using keyhole techniques to remove stones. Open surgery is rarely done.

Stones not causing obstruction between attacks of renal colic may be managed conservatively. Advise to increase fluid intake and sieve the urine to catch the stone for biochemical analysis. Most pass within 48h, although some take >30d. Stones <5mm in diameter pass spontaneously in ~90% and so are treated conservatively, with their progress monitored on serial abdominal films every 1-2 weeks. The remainder may require intervention to remove the stone. Ureteric stones <1cm are suitable for ESWL, with ureteroscopy preferred if >1cm, (although there is some debate over the preferred approach in distal stones). For renal stones, ESWL is preferred if <2cm; PCNL is reserved for larger stones.$_{11}$

Prevention

General:

Drink plenty of fluid, especially in the summer or warm weather (aim for 2-3L/day of colourless urine). A *normal* calcium intake is now recommended, as low calcium diets increase oxalate excretion.

Specifically:

•*Calcium stones:* if there is hypercalciuria, a thiazide diuretic (eg bendroflumethiazide) is used to ↓calcium excretion •*Oxalate:* ↓oxalate intake (less tea, chocolate, nuts, strawberries, rhubarb, spinach, beans, beetroot); pyridoxine may be used (p304) •*Magnesium aluminium phosphate:* treat infection promptly •*Urate:* allopurinol (100-300mg/24h PO) to ↓uric acid. Urine alkalinization may also be recommended, as urate is more soluble at pH>6 (eg with potassium citrate or sodium bicarbonate) •*Cystine:* vigorous hydration to keep urine output >3L/day and urinary alkalinization (as above). D-penicillamine is used to chelate cystine, given with pyridoxine to prevent Vitamin B6 deficiency.

Questions to address when confronted by a stone

• ***What is its composition?***

Type	Causative factors	Appearance on XR
Calcium oxalate	Metabolic or idiopathic	Spiky, radiopaque
Calcium phosphate	Metabolic or idiopathic	Smooth, may be large, radiopaque
Magnesium aluminium phosphate	UTI	Large, horny, ‘staghorn’ radiopaque
Urate	Hyperuricaemia	Smooth, brown, radiolucent

Cystine	Renal tubular defect	Yellow, crystalline, semi-opaque

• ***Why has he or she got this stone now?***

'*What do you eat?* ' Chocolate, tea, rhubarb and spinach ↑oxalate levels.

'*Is it summer?* ' Seasonal variations in calcium and oxalate levels are thought to be mediated by vitamin D synthesis via sunlight on skin.

'*What's your job?* ' Can he/she drink freely? Is there dehydration?

'*Are there any precipitating drugs?*' These include:

Loop diuretics, antacids, acetazolamide, corticosteroids, theophylline, aspirin, thiazides, allopurinol, vitamin C & D, indinavir.

'*Are there any predisposing factors?* ' eg:

Recurrent UTIS (in magnesium aluminium phosphate calculi).

Metabolic abnormalities:

- Hypercalciuria/hypercalcaemia (p672): hyperparathyroidism, neoplasia, sarcoidosis, hyperthyroidism, Addison's, Cushing's, lithium, vit D excess.
- Hyperuricosuria/↑plasma urate: on its own, or with gout.
- Hyperoxaluria (p304).
- Cystinuria (p304).
- Renal tubular acidosis (p302).

Urinary tract abnormalities: eg pelviureteric junction obstruction, hydronephrosis (renal pelvis or calyces), calyceal diverticulum, horseshoe kidney, ureterocele, vesicoureteric reflux, ureteral stricture, medullary sponge kidney.[1]

• *Is there a family history?* ↑risk of stones × 3-fold. Specific diseases include X-linked nephrolithiasis and Dent's disease: proteinuria, hypercalciuria and nephrocalcinosis.[12]

▸***Is there infection above the stone?*** eg fever, loin tender, pyuria? This needs urgent intervention.

[1] Medullary sponge kidney is a typically asymptomatic developmental anomaly of the kidney mostly seen in adult females, where there is dilatation of the collecting ducts, which if severe leads to a sponge-like appearance of the renal medulla. *Complications/associations:* UTIs, nephrolithiasis, haematuria and hypercalciuria, hyperparathyroidism (if present, look for genetic markers of MEN type 2A, see p207).

Urinary tract obstruction

▸*Urinary tract obstruction is common and should be considered in any patient with impaired renal function.* Damage can be permanent if the obstruction is not treated promptly. It occurs anywhere from the renal calyces to the urethral meatus, and may be *partial* or *complete*, *unilateral* or *bilateral*. Obstructing lesions are *luminal* (stones, blood clot, sloughed papilla, tumour: renal, ureteric, or bladder), *mural* (eg congenital or acquired stricture, neuromuscular dysfunction, schistosomiasis), or *extra-mural* (abdominal or pelvic mass/tumour, retroperitoneal fibrosis). Unilateral obstruction may be clinically silent (normal urine output and U&E), if the other kidney is functioning. ▸Bilateral obstruction or obstruction with infection requires urgent treatment. See emergency box 603.

Clinical features

- ***Acute upper tract obstruction:*** Loin pain radiating to the groin. There may be superimposed infection ± loin tenderness, or an enlarged kidney.
- ***Chronic upper tract obstruction:*** Flank pain, renal failure, superimposed infection. Polyuria may occur owing to impaired urinary concentration.
- ***Acute lower tract obstruction:*** Acute urinary retention typically presents with severe suprapubic pain, often preceded by symptoms of bladder outflow obstruction (as below). Clinically: distended, palpable bladder, dull to percussion.
- ***Chronic lower tract obstruction: Symptoms:*** urinary frequency, hesitancy, poor stream, terminal dribbling, overflow incontinence. *Signs:* distended, palpable bladder ± large prostate on PR. *Complications:* UTI, urinary retention.

Tests

Blood:

U&E, creatinine.

Urine:

MC&S.

Ultrasound

(p730) is the imaging modality of choice. If there is hydronephrosis or hydroureter (distension of the renal pelvis and calyces or ureter), the next test is *antegrade or retrograde ureterograms* (p730): it offers a therapeutic option of drainage. **NB:** In ~5% of cases of obstruction, no distension is seen on ultrasound.

Radionuclide imaging

enables functional assessment of the kidneys. CT & MRI also have a role.

Treatment

Upper tract obstruction:

Nephrostomy or ureteric stent. Pyeloplasty, to widen the PUJ, may be performed if obstruction is at this level.

Lower tract obstruction:

Urethral or suprapubic catheter (p750). Treat the underlying cause if possible. Beware of a large diuresis after relief of obstruction; a temporary salt-losing nephropathy may occur resulting in the loss of several litres of fluid a day. Monitor weight, fluid balance, and U&E closely.

Peri-aortitis (retroperitoneal fibrosis *et al*)

Causes include idiopathic retroperitoneal fibrosis (RPF), inflammatory aneurysms of the abdominal aorta, and perianeurysmal RPF. Idiopathic RPF is an autoimmune disorder, where there is B-cell and CD4(+) T-cell associated vasculitis. This results in fibrinoid necrosis of the vasa vasorum, affecting the aorta and small and medium retroperitoneal vessels. The ureters get embedded in dense, fibrous tissue resulting in progressive bilateral ureteric obstruction. Secondary causes of RPF include malignancy, typically lymphoma.

Associations:

Drugs (eg Ò-blockers, bromocriptine, methysergide, methyldopa), autoimmune disease (eg thyroiditis, SLE, ANCA+ve vasculitis), smoking, asbestos.

Typical patient:

Middle-aged ♂ with vague loin, back or abdominal pain, BP↑.

Tests:

- *Blood:* ↑urea and creatinine; ↑ESR; ↑CRP; anaemia.
- *Ultrasound*/IVU: dilated ureters (hydronephrosis) + medial deviation of ureters.
- CT/MRI: peri-aortic mass (this allows biopsy, to rule out malignancy).

Treatment:

Retrograde stent placement to relieve obstruction ± ureterolysis (dissection of the ureters from the retroperitoneal tissue). Immunosuppression with steroids or other agents is controversial, but some studies show benefit.[13]

Problems of ureteric stenting (depend on site)

Common

Trigonal irritation
Haematuria
Fever
Infection
Tissue inflammation
Encrustation
Biofilm formation

Rare

Obstruction
Kinking
Ureteric rupture
Stent misplacement
Stent migration (especially if made of silicone)
Tissue hyperplasia

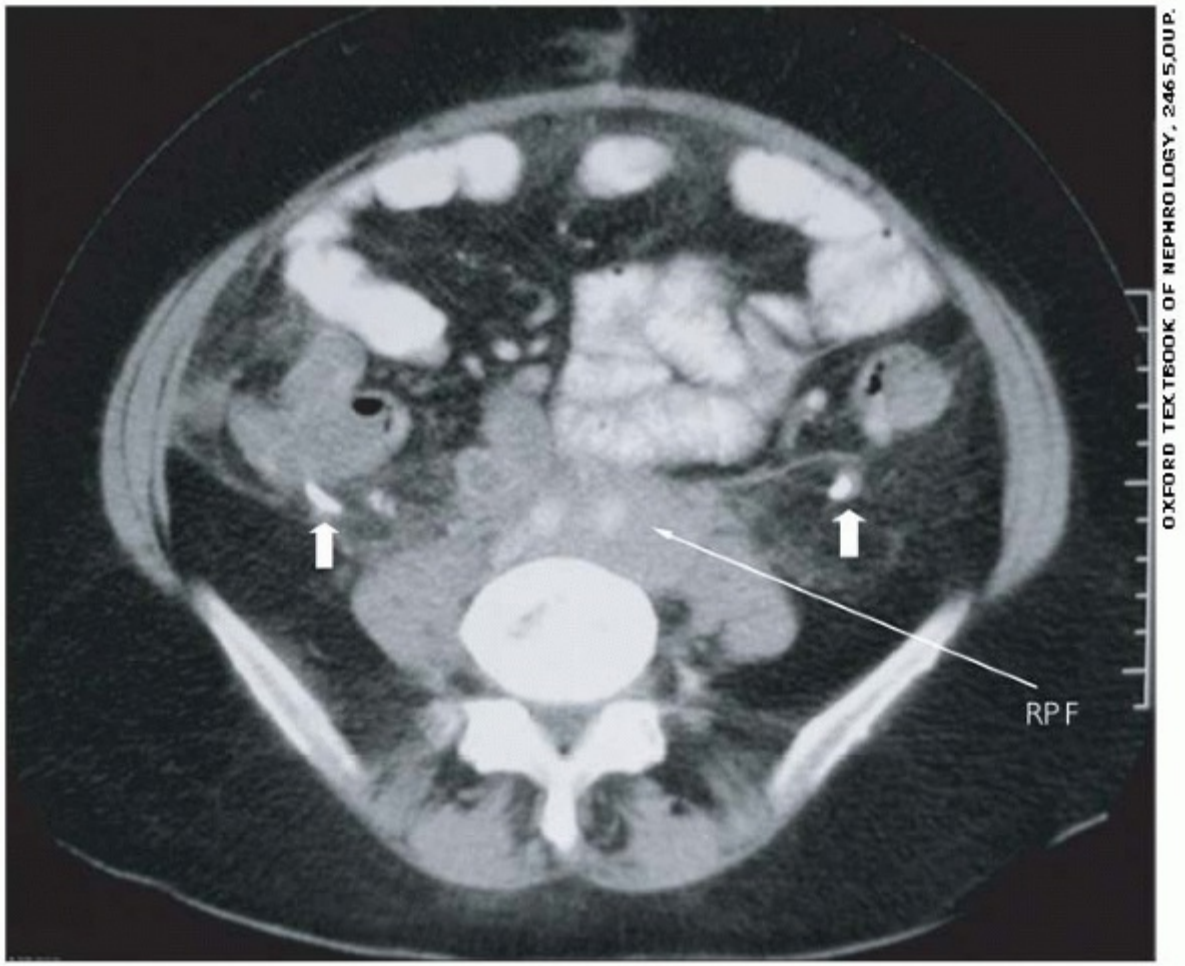

Fig 1. CT scan of retroperitoneal fibrosis (RPF), with subsequent obstruction and dilatation of the ureters (thick arrows).

Glomerulonephritis (GN)

(images: p280)

Features

GN is a common cause of ESRF[1] in adults in the UK, along with diabetes and hypertension. They are a group of disorders where there is damage to the glomerular filtrating apparatus. This causes a leak of protein ± blood into the urine, depending on the disease. Patients may be asymptomatic or present with haematuria (may be microscopic, ± red cell casts, p278), proteinuria, nephrotic syndrome, nephritic syndrome, renal failure, or hypertension.

Tests

Blood:

FBC, U&E, LFT, ESR, CRP; immunoglobulins, electrophoresis, complement (C3, C4); autoantibodies (p539): ANA, ANCA, anti-dsDNA, anti-GBM; blood culture, ASOT, HBsAg, anti-HCV (p394).

Urine:

RBC casts, MC&S, Bence-Jones protein.

24h urine:

protein. **CXR, *renal ultrasound* ± *renal biopsy*** (p280).

General management

▸Refer to a nephrologist. Keep BP ≤130/80, or ≤125/75 if proteinuria >1g/d. Include an ACE-i or A2A; in a recent study, a combination of both was better in preventing progression to renal failure in proteinuria.[14]

Thin basement membrane nephropathy

Genetic cause, autosomal dominant: **persistent microscopic haematuria**, rarely minor proteinuria.

Diagnosis:

Renal biopsy: thin glomerular BM on electron microscopy (EM).

Prognosis:

Usually benign. Small risk of CRF, preceded by ↑BP and proteinuria—monitor 1-2 yearly.

Minimal change glomerulonephritis (MCGN)

Commonest cause of **nephrotic syndrome** in children (76%, and 20% of nephrotic adults), and is thought to be T-lymphocyte mediated. May also present with haematuria or ↑BP.

Associations:

Hodgkin's lymphoma, drugs.

Tests:

Selective proteinuria: only smaller proteins leaked eg albumin.

Renal biopsy:

Normal on light microscopy (hence the name); EM: fusion of podocytes.

[prescription take]:

95% of children and 70% of adults undergo remission with corticosteroids, but are prone to relapse. Cyclophosphamide or ciclosporin are used if frequent relapses or steroid SE/dependence.

Prognosis:

~1% → ESRF.

Membranous nephropathy

Accounts for 20-30% of nephrotic syndrome in adults; 2-5% in children. Unknown cause.

Associations:

Malignancy, drugs (gold, penicillamine, captopril), autoimmune (RA, SLE, thyroid disease), infections (HBV, syphilis, leprosy, filiariasis).

Presentations:

Usually **nephrotic syndrome**. Risk of renal vein thrombosis (p290).

Diagnosis:

Biopsy shows diffuse thickened glomerular BM: IF shows IgG and C3 subepithelial deposits.

[prescription take]:

Corticosteroids with cyclophosphamide or chlorambucil are used if renal function deteriorates.

Prognosis:

If untreated ~40% have spontaneous remission—treatment is based on poor prognostic factors: ie deteriorating renal function, heavy proteinuria.

Focal segmental glomerulosclerosis (FSGS)

may be primary (idiopathic) or secondary (reflux or IgA nephropathy, Alport's syndrome, vasculitis (p542), sickle-cell disease, heroin use). HIV is associated with a subtype.

Presentations:

Usually **nephrotic syndrome** or **proteinuria**. ~50% have impaired renal function.

Renal biopsy:

Some glomeruli have scarring of certain segments (ie *focal sclerosis*). IF (immunofluorescence): IgM and C3 deposits in affected areas.

[prescription take]:

Responds to corticosteroids in ~30%. Cyclophosphamide or ciclosporin are considered if steroidresistant.

Prognosis:

30-50% → ESRF. There is a risk of recurrence post-renal transplant in 20-50%, which may respond to plasma exchange.

IgA nephropathy (Berger's disease)

Commonest GN in the developed world. Most present with **macro-** or **microscopic haematuria**; occasionally nephritic syndrome.

Typical patient:

Young ♂ with episodic macroscopic haematuria, occurring a few days after URTI eg pharyngitis. Recovery is often rapid between attacks. There is overproduction of IgA, possibly due to infection, which forms immune complexes and deposits in mesangial cells.

Renal biopsy:

Mesangial proliferation, IF shows deposits of IgA and C3.

[prescription take]:

General measures. With renal impairment, immunosuppression (eg cyclophosphamide, mycophenolate) may be used, although benefit is unclear.

Prognosis:

Worse if ↑BP, male, proteinuria or renal failure at presentation. 20% of adults develop ESRF over ~20yrs.

Henoch-Schönlein purpura (HSP)

is a systemic variant of IgA nephropathy, causing a small vessel vasculitis.

Features:

Purpuric rash on extensor surfaces (typically on the legs), flitting polyarthritis, abdominal colic and GN.

Diagnosis:

Usually clinical. Confirmed with positive IF for IgA and C3 in skin or renal biopsy (identical to IgA nephropathy).

[prescription take]:

As IgA nephropathy.

Prognosis:

15% nephritic patients ↑ ESRF; if both nephritic & nephrotic syndrome, 50% ↑ESRF.

Proliferative GN

is classified histologically: focal, diffuse, or mesangiocapillary GN. The chief cause is post-streptococcal GN (a diffuse proliferative GN), occurring 1-12 weeks after a sore throat or skin infection. A streptococcal antigen is deposited on the glomerulus, causing a host reaction and immune complex formation.

Presentation:

Usually **nephritic syndrome**.

Renal biopsy:

Inflammatory reaction affecting mesangial and endothelial cells, IF: IgG and C3 deposits.

Serology:

↑ASOT; ↓C3.

[prescription take]:

Supportive: >95% recover renal function.

Mesangiocapillary GN

A rare GN, often presenting with **nephrotic syndrome**, ~30% nephritic syndrome.

Diagnosis:

Biopsy shows large glomeruli: mesangial proliferation and thickened capillary walls ↑ 'tramline' appearance of a double BM. 2 types:

Type I

(subendothelial immune deposits): Idiopathic or seen with HCV, also endocarditis, visceral abscess, infected arteriovenous shunts, HBV. ↓C4 levels (*classical* complement activation);

Type II

(intramembranous deposits): sometimes with partial lipodystropy (gaunt facial appearance). ↓serum C3 and +ve C3 nephritic factor (*alternative* complement activation)

Treatment:

None proven of benefit so far; steroids are used in children, and use of anti-CD20 (Rituximab) therapy has been reported.[15]

Prognosis:

50% develop ESRF.

Rapidly progressive GN (RPGN)

The most aggressive GN, with potential to cause ESRF over days. There are different causes, all have the biopsy finding of crescents affecting most glomeruli (a proliferation of parietal epithelial cells and macrophages in Bowman's capsule).

Causes:

Often microscopic polyangiitis (cANCA +ve), Wegener's granulomatosis (PANCA +ve, p706) or anti-GBM disease (Goodpasture's disease, p692). Also seen with other causes of GN (eg IgA nephropathy), infections (eg endocarditis, shunt nephritis), or with multi-system disease (eg SLE).

Clinically:

Signs of **renal failure**. There may be features of the individual systemic disease (eg fever, malaise, myalgia, weight loss, haemoptysis).

Treatment:

Aggressive immunosuppression with high-dose corticosteroids and cyclophosphamide, with plasma exchange to remove existing antibodies.

Prognosis:

Poor if initial serum creatinine >600μmol/L. Below this, ~80% have some improvement of renal function with treatment.

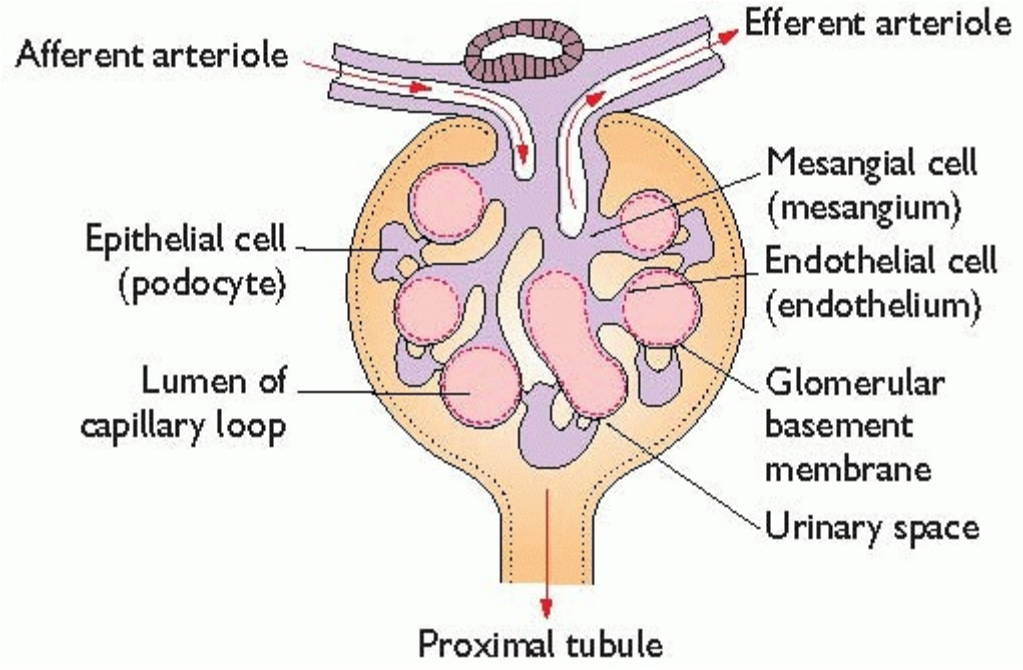

Fig. 1 A normal glomerulus. Blood is filtered from the capillary lumen, through the fenestrated endothelial layer, glomerular basement membrane and the epithelial cell layer.

The nephrotic syndrome

▸*If there is oedema, dipstick an* MSU *for protein to avoid missing this diagnosis.*

Definition

Nephrotic syndrome is a triad of proteinuria (>3g/24h), hypoalbuminaemia (albumin <30g/L), and oedema. It was thought that protein loss caused ↓serum albumin, resulting in ↓plasma oncotic pressure and oedema. However, plasma oncotic pressure remains unchanged in nephrotic syndrome, and oedema is now thought to result from sodium retention in the extracellular compartment and molecular changes in the capillary barrier.

Causes

>80% are due to glomerulonephritis (GN, p288), especially minimal change GN (commonest cause in children), focal segmental glomerulosclerosis, membranous GN (commonest cause in adults), mesangiocapillary GN or proliferative GN. Also seen with DM, amyloidosis, SLE, drugs and allergies.

Clinical features

Ask about acute or chronic infections, drugs, allergies, systemic symptoms (vasculitis, p542; malignancy).

Signs:

Oedema: typically pitting and dependent (↑ with gravity). It occurs periorbitally (tissue resistance is low here), and peripherally in limbs—genital oedema, ascites and anasarca[1] develop later. Hypertension may be present.

Differentials:

Cardiac failure (↑JVP, pulmonary oedema, *mild* proteinuria) or liver disease (↓albumin).

Complications

- ↑*susceptibility to infection*, due in part to loss of immunoglobulin in urine and also to immunosuppressive treatments. Patients are prone to cellulitis, *Streptococcus* infections and spontaneous bacterial peritonitis.
- *Thromboembolism* (up to 40%): eg DVT/PE, renal vein thrombosis. This hypercoagulable state is partly due to ↑clotting factors & platelet abnormalities.
- *Hyperlipidaemia:* ↑cholesterol and triglycerides, thought to be due to hepatic lipoprotein synthesis in response to low oncotic pressure.

Tests

As for GN (p268). Also check cholesterol.

Renal biopsy:

Do in all adults. In children, the majority of cases are due to minimal change GN, so a course of steroids is usually tried initially. Biopsy is reserved for those whose proteinuria has not reduced after 1 month, or if features suggest another cause eg age<1yr, family history, extrarenal disease (eg arthritis, rash, anaemia), renal failure, haematuria.

General measures

▸Monitor U&E, BP, fluid balance and weight regularly. The individual disease should be treated as appropriate (eg GN, see p288).

- Salt intake should be restricted. A normal protein intake is advised.
- In adults, diuretics are often used, eg furosemide 80-250mg/24h PO ± metolazone or spironolactone, with monitoring of U&E. Aim ~1kg/day loss.
- In chronic nephrotic syndrome, ACE-i are proven to ↓proteinuria and slow progression of renal impairment. Some advocate combination with an A2A.[16]
- Treat infections promptly. Pneumococcal vaccinations are recommended.
- Prophylactic heparin if immobile (adjust dose if renal impairment eg enoxaparin 20mg SC daily). Avoid prolonged bed rest.
- Treat hypertension (p126). Proteinuria is an independent risk factor for cardiovascular disease: if >1g/24h, target BP is 125/75.[17] ACE-i or A2A should be used 1st line. Address other risk factors such as smoking, exercise, diet. Persisting hyperlipidaemia should be treated with a statin (p682).

Renal vein thrombosis

The hypercoagulable state in nephrotic syndrome predisposes to renal vein thrombosis, with an increased incidence noted in patients with membranous nephropathy. *Other causes*: Invasion by renal cell carcinoma, thrombophilia.

Clinically:

Often asymptomatic, but may present with loin pain, haematuria, palpable kidney, sudden deterioration in renal function (eg in known GN), or with pulmonary embolism.

Diagnosis:

Doppler ultrasound, CT, MRI or renal angiography (venous phase).

Treatment:

Anticoagulate with warfarin for 3-6 months (or until albumin >25g/L) if no contraindications. Target INR is 2-3.

Acute renal failure (ARF): diagnosis

Definition

A significant deterioration in renal function occurring over hours or days. Clinically, there may be no symptoms or signs, but oliguria (urine volume <400mL/24h) is common. Biochemically, ARF is detected by rising plasma urea and creatinine. ARF may arise as an isolated problem; more commonly it occurs in the setting of circulatory disturbance, eg severe illness, sepsis, trauma, or surgery—or in the context of nephrotoxic drugs.

Causes

NB: Pre-renal failure and ATN accounts for >80%. **1** ***Pre-renal:*** Due to renal hypoperfusion eg hypovolaemia, sepsis (causing systemic vasodilatation), congestive cardiac failure, liver cirrhosis, renal artery stenosis, NSAIDs or ACE-i (these interfere with renal blood flow). **2** ***Intrinsic:*** acute tubular necrosis (ATN): this is damage to the renal tubular cells, caused by *ischaemia* (with causes of renal hypoperfusion as above) or *nephrotoxins* (see p299 for fuller list): often due to drugs (aminoglycosides, amphotericin B, tetracyclines), radiological contrast agents, uric acid crystals, haemoglobinuria (in rhabdomyolysis), or myeloma. Recovery of renal function usually occurs within weeks, although mortality remains ~50%. Others: *Vascular:* vasculitis, malignant hypertension, cholesterol emboli, haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura (p300); glomerulonephritis; interstitial nephritis (p298); hepatorenal syndrome. **3** ***Post-renal:*** Due to urinary tract obstruction.

Assessment

▸Make sure you know about the renal effects of *all* drugs taken.

1. ***Is the renal failure acute or chronic?*** Suspect chronic renal failure if:
   - History of co-morbidity eg diabetes, ↑BP, signs of chronic renal failure.
   - Previously abnormal blood tests (GP records, laboratory results).
   - Small kidneys on ultrasound (<9cm), with increased echogenicity.

   The *presence* of anaemia, Ca^{2+}↓ or PO_4^{3-}↑ may not help to distinguish ARF from CRF, as these can occur within days, but their *absence* suggests ARF.

2. ***Is there urinary tract obstruction?*** Obstruction should always be considered as a cause of ARF because it is reversible and prompt treatment prevents permanent renal damage. Obstruction should be suspected in patients with a single functioning kidney, or in those with history of renal stones, anuria, prostatism, or previous pelvic/retroperitoneal surgery. Examine for a palpable bladder, pelvic or abdominal masses, or an enlarged prostate.
3. ***Is there a rare cause of* ARF?**—eg glomerulonephritis. These are usually associated with haematuria or proteinuria, and warrant urgent renal referral for consideration of a renal biopsy and treatment.

Tests

• ***Blood tests:*** U&E (▸▸beware K^+↑), FBC, LFT, clotting, CK, ESR, CRP. Consider ABG, blood cultures, and also hepatitis serology if dialysis is considered. If the cause is unclear, consider: serum immunoglobulins, electrophoresis, complement levels (C3/C4), autoantibodies (ANA, ANCA, anti-dsDNA, anti-GBM—p288 & p539) and ASOT. • ***Urine: Dipstick*** for leucocytes, nitrite, blood, protein, glucose. *Microscopy* for RBC, WBC, crystals, casts. *Culture* and *sensitivity*. *Chemistry*: it U&E, creatinine, osmolality, Bence-Jones protein. • **CXR***:* Pulmonary oedema? • **ECG***:* Signs of hyperkalaemia? • ***Renal ultrasound:*** Renal size or obstruction?

Distinguishing pre-renal failure and ATN

	Pre-renal	*ATN*
Urine Na (mmol/L)	<20	>40
Urine osmolarity (mosm/L)	>500	<350
Urine/plasma urea	>8	<3
Urine/plasma creatinine	>40	<20
Fractional Na excretion (%)	<1	>2

In pre-renal failure, urine is concentrated and sodium is reabsorbed by working tubular cells. This fails to happen in ATN. NB: Values are influenced by diuretics and pre-existing disease, and they do not predict prognosis.

Acute renal failure (ARF): management

▸*Enlist specialist help.* While awaiting this, make sure that recent U&E and urine microscopy results are to hand. Treat the treatable:

- If shock is the cause (↓intravascular volume, *below*), use protocol on p779.
- Urgent US scan (today); you *must* check for a palpable bladder, but its absence does not rule out obstruction.
- Stop nephrotoxic drugs—eg NSAIDs, ACE-i, gentamicin, vancomycin, amphotericin. Stop metformin if creatinine is >150mmol/L, see p192.
- Signs of vasculitis? Nosebleed, haematuria, rash, ESR/CRP↑? do autoantibodies.
- Find and treat exacerbating factors: eg hypovolaemia, sepsis, BP↑↑.

NB: Assessing signs of ↓intravascular volume can be difficult: look for ↓urine volume, invisible JVP, poor tissue turgor, ↓BP, ↑pulse. When in doubt, insert a CVP line to measure the venous pressure. Signs of fluid overload: gallop rhythm on cardiac auscultation, ↑BP, ↑JVP, lung crepitations, peripheral oedema.

Monitoring

Consider transfer to HDU or ICU. Pulse, BP, CVP, & urine output hourly (insert a urinary catheter). Daily fluid balance + weight chart. Match input to loss (urine, vomit, diarrhoea, drains) + 500mL for insensible loss (more if T°↑).

- Correct volume depletion with intravenous fluid—colloid, saline, or blood (only if hyperkalaemia is not a problem) as appropriate.
- If the patient is septic, take appropriate cultures and treat empirically with antibiotics (p372). Remove any potential sources of sepsis when no longer required, eg IV or urinary catheters.
- Re-check if any nephrotoxic drugs; adjust doses of renally excreted drugs (p295).
- Nutrition is vital: aim for normal calorie intake (more if catabolism↑↑, eg burns, sepsis) and protein ~0.5/kg/d. If oral intake is poor, consider nasogastric nutrition early (parenteral if NGT impossible, p574).

Treat complications

Hyperkalaemia

may cause arrhythmias or cardiac arrest.

ECG changes

(in order): Tall 'tented' T waves; small or absent P wave; increased P-R interval; widened QRS complex; 'sine wave' pattern; asystole. ECG p786.

[prescription take]:

▸▸Intravenous calcium: 10mL of 10% calcium gluconate IV via a big vein over 2min, repeated as necessary until ECG improves. This is cardioprotective.

▸▸Intravenous insulin + glucose: 10U Actrapid® insulin + 50mL 50% glucose IV over 30min. Insulin stimulates intracellular uptake of K^+, lowering serum K^+ by 1-2mmol/L over ~60min. Check capillary glucose ~30 minutes after giving insulin.

▸▸Salbutamol 5mg nebulizer. ▸▸Consider calcium resonium, 15g/8h, p821, PO or PR to bind K^+ in the gut. This works over a longer period. SE: constipation.

▸▸Haemodialysis or haemofiltration is usually required if anuric.

Pulmonary oedema

(p786):

▸▸Sit up and give high-flow oxygen by face mask.

▸▸Venous vasodilator, eg morphine 2.5mg IV (+metoclopramide 10mg IV).

▸▸Furosemide 120-250mg IV over 1 hour (larger doses are needed in renal failure).

▸▸If no response, urgent haemodialysis or haemofiltration is necessary.

▸▸Consider continuous positive airways pressure ventilation (CPAP) therapy.

▸▸Consider venesection (100-200mL) if the patient is *in extremis*.

▸▸Intravenous nitrates also have a role (see p786).

Bleeding:

Impaired haemostasis due to ↑urea may be compounded by the precipitating cause. In patients with ARF who are actively bleeding, give:

- Fresh frozen plasma & platelets as needed—if there are clotting problems.
- Blood transfusion to maintain Hb >10g/dL and haematocrit >30%.
- Desmopressin (p330) to ↑factor VIII activity, normalizing bleeding time.

Indications for acute dialysis

•Refractory pulmonary oedema •Persistent hyperkalaemia (K^+ >7mmol/L) •Severe metabolic acidosis (pH<7.2 or base excess <10) •Uraemic encephalopathy • Uraemic pericarditis (pericardial rub).

Prognosis

Worse if oliguric. Mortality depends on the cause: burns (80%); trauma/surgery (60%); medical illness (30%); obstetric/poisoning (10%).

Chronic renal failure (CRF)

Chronic renal failure (or chronic kidney disease, CKD) is classified into 5 stages (p661). Symptoms usually only occur once stage 4 is reached (GFR <30). Endstage renal failure (ESRF) occurs when dialysis or transplant is required to prolong life.

Causes

Common:

Glomerulonephritis, DM, renovascular disease, BP↑, pyelonephritis, polycystic disease. Also prostatic hypertrophy, interstitial nephritis, analgesic nephropathy, nephrolithiasis.

Rarer:

Myeloma, amyloidosis, SLE, scleroderma, vasculitis (p542), haemolytic uraemic syndrome, nephrocalcinosis, gout, renal tumour, cystinosis, oxalosis, Alport's syndrome, Fabry's disease (p690).

History

Ask about: past UTI, known ↑BP, DM, family history. Take a careful drug history. Any fatigue, weakness, anorexia, vomiting, metallic taste, pruritus, restless legs, bone pain, impotence/infertility? Symptoms are common when urea is>40mmol/L. Dyspnoea, ankle swelling (fluid overload?) Urine output?

Signs:

Pallor, yellow skin pigmentation, brown nails, purpura, bruising, excoriation, BP↑, cardiomegaly, pericardial rub, pleural effusion, pulmonary or peripheral oedema, proximal myopathy (+ cause eg DM: peripheral neuropathy, retinopathy). Later if untreated: arrhythmias, encephalopathy, seizures, and coma.

Tests

•***Blood:*** Hb↓ (normochromic, normocytic), ESR, U&E (↑urea, ↑creatinine), glucose (DM); ↓Ca^{2+}, ↑PO_4^{3-}, ↑alk phos (renal osteodystrophy); ↑PTH (hyperparathyroidism, p206). •***Urine:*** MC&S, dipstick, urine PCI or 24h urinary protein. •***Imaging: Renal ultrasound*** to exclude obstruction and look at renal size (usually small, eg <9cm, but may be normal or large with CRF in DM, polycystic kidney disease, amyloidosis, myeloma, systemic sclerosis, asymmetric renal vascular disease). Consider ***DTPA scan***. **CXR***:* Cardiomegaly, pleural/pericardial effusions or pulmonary oedema. ***Bone X-rays*** may show renal osteodystrophy. •***Renal biopsy*** should be considered if the cause is unclear and there are normal-sized kidneys.

Treatment

▸*Refer early to a nephrologist*. Treat reversible causes: relieve obstruction, stop nephrotoxic drugs, deal with Ca^{2+}↑ and cardiovascular risk: in CKD stages 1 & 2, risk from cardiovascular death is higher than the risk of reaching ESRF.

- ***Hypertension:*** Even a small BP drop may save significant renal function.[18] ACE-i or A2A can ↓rate of loss of function even if BP is normal, if proteinuric, aim for BP of <130/80 (<125/75 if >1g proteinuria/d).[19] ***Hyperlipidaemia:*** Statins (p682).
- ***Oedema:*** This may require high doses of loop diuretics (eg furosemide 250mg-2g/24h ± metolazone 5-10mg/24h PO mane), and restriction on fluid intake.
- ***Anaemia:*** Exclude iron deficiency & chronic infection; consider erythropoietin.[1]
- *Renal bone disease (osteodystrophy):* Treat if ↑PTH. PO_4 rises in CRF, which ↑PTH further, and also precipitates in the kidney and vasculature. Restrict dietary PO_4 (milk, cheese, eggs). Give binders (eg Calcichew®)[2] to bind PO_4^{3-} in the gut to ñ its absorption. Vit. D analogues (eg alfacalcidol=1α-hydroxycholecalciferol)[3] & Ca^{2+} supplements ↓bone disease and hyperparathyroidism (2° & 3°, p206).
- *Diet:* Match dietary and fluid intake with excretion. Na+ restriction: helps control BP and prevent oedema. A moderate protein diet is recommended. K^+ restriction only if hyperkalaemia; HCO_3^- supplements to correct acidosis.
- *Restless legs:* Clonazepam (0.5mg-2mg daily) or gabapentin (p496) may help.
- *Prepare for dialysis/transplantation:* See p296.

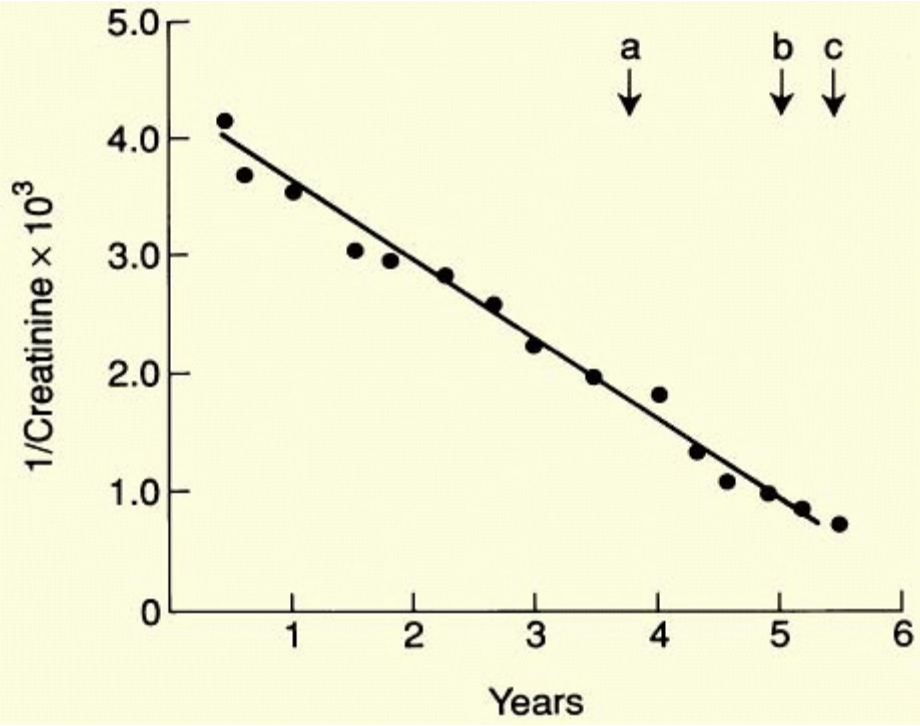

Fig 1. Plot of reciprocal plasma creatinine (μmol/L) against time in a patient with adult polycystic kidney disease. The letters represent life events: (a) work promotion, (b) arterio-venous fistula, and (c) haemodialysis.

Some patients with CRF lose renal function at a constant rate. Creatinine is made at a fairly constant rate and rises on a hyperbolic curve as renal function declines, so the reciprocal creatinine plot is a straight line, parallel to the fall in GFR. This is used to monitor renal function and to predict need for dialysis—but there is much individual variation in progression, so the plot is of limited use.[20] Rapid decline in renal function greater than that expected may be due to: infection, dehydration, uncontrolled ↑BP, metabolic disturbance (eg Ca^{2+}↑), obstruction, nephrotoxins (eg drugs). Intervention at this point may delay ESRF.

Background decline may be retardable by using ACE-i ± A2A (angiotensin-II antagonists). In the COOPERATE randomized prospective trial (over 3yrs) in non-diabetic renal disease, the NNT was ~9 for preventing one case of ESRF (or a doubling of plasma creatinine) by adding losartan (100mg/d) to trandolapril (3mg/d)—ie 11% progressed rather than 23% on ACE-i alone.[21]

[3] Alfacalcidol & calcitriol (=1,25-dihydroxycholecalciferol) help by ↓parathyroid hormone, but greatly ↑ intestinal Ca^{2+} & PO_4^{3-} absorption and bone mineral mobilization, leading to PO_4^{3-} ↑ & Ca^{2+}↑ (risks vascular calcification). New vit. D analogues (eg paricalcitol weekly IV) retain suppressive action on PTH & gland growth, but have less effect on Ca^{2+} & PO_4 absorption, and help cardiovascular status.

Prescribing in renal failure

Relate dose modification to GFR, and the extent to which a drug is renally excreted. This is significant for aminoglycosides (gentamicin, p738), cephalosporins, and a few other antibiotics (p368, p369, p370, p371), heparin, lithium, opiates, and digoxin. ▸Never prescribe in renal failure before checking how its administration should be altered. Loading doses (eg digoxin) should not be changed. If the patient is on dialysis (peritoneal or haemodialysis), dose modification depends on how well it is eliminated by dialysis. Consult the drug's *Data Sheet* or the pharmacist. Dosing should be timed around dialysis.

Nephrotoxic drugs:

Reduce the dose (the dose adjustment factor, DAF, reflects the fraction excreted unchanged in the urine—*F*). DAF = 1/(*F* (kf - 1) + 1), where the kf is the relative kidney function = creatinine clearance/120. The usual dose (but not the loading dose) should be *divided* by the DAF. In only a few drugs is *F* big enough to be important, as below.

Aminoglycosides	0.9	Cephalosporins	1.0
Lithium	1.0	Sulfamethoxazole	0.3-0.5
Digoxin	0.75	Procainamide	0.6

Ethambutol	0.7	Tetracycline	0.4-0.6

Renal replacement therapy

Optimal timing to start dialysis is widely debated; guidelines suggest starting when GFR <15mL/min with symptoms.[22] *Early* psychological preparation is vital. Medical preparation involves Hep B vaccination and creating an arteriovenous fistula (p307) for haemodialysis, or inserting a Tenchkoff catheter for peritoneal dialysis. Choice of haemo- *vs* peritoneal dialysis depends on medical, social,[1] and psychological factors. Mortality was higher in peritoneal *vs* haemodialysis in one study: more are needed.[23] **NB:** Kidney function is only *partly* replaced by dialysis.

Haemodialysis (HD)

Blood flows on one side of a semi-permeable membrane while dialysis fluid flows in the opposite direction on the other side. Solute transfer occurs by diffusion. Ultrafiltration is the removal of excess fluid by creating -ve transmembrane pressure.

Problems:

• Disequilibration syndrome[2] •BP↓/arrhythmias •Time consuming •Access: *fistula:* thrombosis, stenosis, aneurysm, steal syndrome, ischaemia or *temporary line:* infection, blockage.

Haemofiltration

Blood is filtered continuously across a highly permeable synthetic membrane, allowing removal of waste products by a process of convection (not diffusion). The ultrafiltrate is substituted with an equal volume of replacement fluid. It is more expensive and takes longer than HD, but there is less haemodynamic instability and so is used for critically ill patients.

Peritoneal dialysis (PD)

is simple to perform, requires less complex equipment than haemodialysis and is easier at home. It is useful in children, the elderly, and in those with cardiovascular disease. PD fluid is introduced into the peritoneal cavity via a Tenchkoff catheter and uraemic solutes diffuse into it across the peritoneal membrane. Ultrafiltration is achieved by adding osmotic agents, eg glucose to the dialysis fluid.

Problems:

•Peritonitis (60% *Staphylococci*, 20% Gram -ve organisms, <5% fungi) •Exit-site infection •Catheter malfunction •Loss of membrane function. •Obesity (glucose in dialysis fluid) •Hernias •Back pain.

Continuous ambulatory peritoneal dialysis (CAPD)

uses the smallest daily volume of dialysate fluid to prevent uraemia. 2L bags are changed 3-5 times a day to produce, with ultrafiltration, a total dialysate of 10L.

Automated peritoneal dialysis

uses a cycler machine to enhance solute and fluid removal. Techniques include continuous cyclic peritoneal dialysis (CCPD), intermittent peritoneal dialysis (IPD), night intermittent peritoneal dialysis (NIPD), and tidal intermittent peritoneal dialysis (TIPD).

Complications of dialysis

Cardiovascular disease, eg IHD, cardiac failure and stroke are much more common in dialysis patients and are a major cause of mortality. ***Hypertension*** persists in 25-30% of patients on haemodialysis. ***Anaemia*** is common and is treated with erythropoietin (± haematinic supplements). ***Bleeding tendency*** is due to platelet dysfunction. Acute bleeding is treated with desmopressin and transfusion, as necessary. ***Renal bone disease*** is treated with dietary modification, alfacalcidol, Ca2+ supplements, and phosphate binders (p294). ***Infection*** may be due to non-sterility in peritoneal dialysis or intravascular lines in haemodialysis. ***Ò2- microglobulin amyloidosis*** is due to amyloid which accumulates in long-term dialysis patients: it may cause carpal tunnel syndrome, arthralgia, and fractures. ***Acquired renal cysts*** occur years after dialysis and may present with haematuria or malignant transformation. ***Malignancy*** is commoner in dialysis patients; this may be related to the cause, eg urothelial tumours in analgesic nephropathy.

Stopping dialysis

Dialysis exerts a big toll on quality of life, and it may all become too much for patients, eg if very old[24] or there is co-morbidity (eg psychiatric or mobility issues).[1] 8-20% of deaths in dialysis patients are due to its withdrawal.[25]

▸Good palliation allows a good death and mitigates discomfort caused by uraemia:

•Respiratory distress: morphine •Myoclonic jerks: clonazepam •Hallucinations: haloperidol ± midazolam •Secretions: hyoscine. *Doses:* p438. Good communication in the renal team, well-rehearsed protocols, and advance directives (living wills) help the big ethical dilemma.[26]

Renal transplantation

This is the treatment of choice for end stage renal failure (ESRF). Each patient requires careful assessment and consideration of the advantages and disadvantages of dialysis vs transplantation.

Assessment

Note the following: Virology status: CMV, Hepatitis B & C, HIV: these may cause severe disease while immunocompromised. Note if there is existing urine output, and cardiovascular disease. Previous TB may reactivate so isoniazid and pyridoxine prophylaxis is given to proven cases and high risk groups.

- ABO blood group and tissue typing for HLA is required.
- Make sure pre-op potassium is ¢5. If above, dialysis may be needed.

Contraindications

Active infection, Ca, severe heart disease or co-morbidity.

Types of graft

>6000 are waiting in the UK, often in vain, for a transplant.

Cadaveric donor

grafts are obtained from a brainstem dead donor with supported circulation and ventilation.

Non-heart beating donor

grafts are retrieved from patients without an active circulation, and hence rapid retrieval is needed to minimise ischaemia. Success rates from these is approaching that of cadaveric grafts.

Living related donor

(LRD) grafts offer the advantages of an optimally timed surgical procedure, HLA haplotype matching, and improved graft survival.

Live unrelated donation

has become increasingly common, between spouses or friends who satisfy the complex rules of ULTRA.[3] Consent is problematic: p251.

Immunosuppressants

Most regimes involve **1** ciclosporin or tacrolimus, **2** azathioprine or mycophenolate ± **3** prednisolone. Pre-op anti-interleukin 2 receptor antibodies (eg basiliximab) reduce rates of early rejection.[27]

Complications

Post-op:

Bleed, thrombosis, infection, urinary leaks, oliguria.

Acute rejection:

(<6 months) This is characterized by rising serum creatinine ± fever and graft pain. Graft biopsy shows an immune cell infiltrate and tubular damage.

[prescription take]:

High-dose IV methylprednisolone. Resistant cases require antithymocyte globulin (ATG).

Chronic rejection:

(>6 months) Presents with a gradual rise in serum creatinine and proteinuria. Graft biopsy shows vascular changes, fibrosis, and tubular atrophy. It is not responsive to ↑immunosuppression.

Ciclosporin/tacrolimus toxicity:

Acute: afferent arteriole vasoconstriction, causing ↓renal blood flow and ↓GFR. *Chronic:* tubular atrophy and fibrosis.

Infection:

Often community acquired infections or those related to ↓T-cell immunity (Á immunosuppression), eg skin infections (fungi, warts, HSV, zoster) and opportunists (TB, fungi, *Pneumocystis carinii* pneumonia, CMV).

Malignancy:

Immunosuppression causes ↑risk of neoplasia 5-fold and ↑ infection with viruses of malignant potential (EBV, HBV, HHV-8: p694). Typical tumours: skin (basal & squamous) Ca, lymphoma (EBV-related), anogenital Ca.

Atheromatous vascular disease:

This is commoner in transplant patients than in the general population and is a leading cause of death.

Hypertension:

This occurs in >50% of transplant patients and may be due to diseased native kidneys, immunosuppressant drugs or dysfunction in the graft. Management is along standard lines (p126).

Prognosis

1yr graft survival: HLA identical 95%; 1 mismatch 90-95%; complete mismatch 75-80%. Average *half-life* of cadaveric grafts is ~10yrs, 20yrs for HLA-identical living related donor grafts—this is increasing.

Interstitial nephritides and nephrotoxins

Tubulointerstitial nephritis:

Inflammation of the renal interstitium may be acute or chronic.

Acute tubulointerstitial nephritis

is mediated by an immune reaction to medications, infections and other causes. **Drugs:** NSAIDs, *antibiotics:* cephalosporins, penicillins, sulphonamides, rifampicin; *diuretics:* furosemide, thiazides; also allopurinol, cimetidine, amphotericin; **infections:** *Staphylococci*, *Streptococci*, *Brucella*, *Leptospira*, hantaviruses; **immune disorders** eg SLE, glomerulonephritis— or *no* obvious cause. *Features:* May present with renal impairment, hypertension, or acute renal failure. Systemic symptoms eg fever, rash, arthralgia, with eosinophilia, uveitis, and ↑IgE. *Diagnosis:* Renal biopsy: infiltration of the renal interstitium and tubules with T lymphocytes, macrophages, and plasma cells. Urinary eosinophils may be seen. *Treatment:* Stop any cause. ARF: p293. Prednisolone 1mg/kg is used, but has not been studied in a randomised trial. *Prognosis:* Most have full recovery of renal function.

Chronic tubulointerstitial nephritis

results from many disorders, leading to extensive fibrosis and tubular loss on renal biopsy. Patients present with chronic renal failure. *Causes:* chronic pyelonephritis often with reflux nephropathy, sickle cell disease, lead or cadmium intoxication.

Balkan nephropathy

is a form of chronic tubulointerstitial nephritis causing progressive renal impairment to ESRF. It is endemic in areas along the River Danube. Environmental and genetic factors are thought to be important.

Features:

coppery-yellow pigmentation of the palms and soles, Ò2-microglobinuria. There is an ↑ risk of urothelial tumours, reported in up to 40%.[28]

Analgesic nephropathy

is associated with the prolonged, heavy ingestion of compound analgesics, especially those containing caffeine (as it leads to habituation), NSAIDs, paracetamol, and phenacetin (now withdrawn), leading to interstitial nephritis and papillary necrosis. There is often a history of chronic pain.

Signs:

Presents with sterile pyuria, UTI, or symptoms of chronic renal failure, or hypertension. Renal colic and haematuria can result from a sloughed papilla.

Tests:

IVU demonstrates papillary necrosis. CT may also be used. Biopsy shows chronic interstitial nephritis.

Treatment:

Stop analgesics, antibiotics for infection. Sudden flank pain should prompt an ultrasound or IVU to look for obstruction from a sloughed papilla. There is an ↑ risk of urothelial tumours.

Urate nephropathy

Acute crystal nephropathy

occurs when insoluble uric acid crystals deposit causing blockage of the tubules. It is mainly caused by excess uric acid released during cell lysis in chemotherapy eg in myeloid tumours. The renal parenchyma appears bright on ultrasound. Plasma urate is often markedly raised ± urinary birefringent crystals on microscopy (p351, **fig 1**). *Treatment:* p336: keep well hydrated, allopurinol pre-chemotherapy, urinary alkalinization with sodium bicarbonate (as uric acid is more soluble in alkaline urine).

Chronic urate nephropathy:

Whether chronic hyperuricaemia (eg with gout) leads to renal failure is debated. This does, however, occur in Lesch-Nyhan syndrome[1]. *Treatment:* allopurinol (↓dose in renal impairment).

Uric acid calculi,

see p284.

Hypercalcaemia

is associated with the following renal diseases: nephrogenic diabetes insipidus (p224), renal calculi (p284) and nephrocalcinosis: diffuse renal parenchymal calcification, often asymptomatic, causing progressive renal impairment. Nephrocalcinosis is seen in hypercalcaemia (eg malignancy, hyperparathyroidism, myeloma, sarcoidosis, vitamin D intoxication) or type 1 renal tubular acidosis.

Tests:

AXR for renal calculi/nephrocalcinosis.

[prescription take]:

Treat cause.

Radiation nephritis

is renal impairment following radiotherapy and occurs acutely (<1 year) or chronic (years later). *Signs:* Hypertension, proteinuria, progression to chronic renal failure. Biopsy shows interstitial fibrosis.

[prescription take]:

Strict BP control, nil specific. *Prevention:* Exclusion of renal areas during radiotherapy.

Nephrotoxins

Many agents may be toxic to the kidneys and cause acute renal failure (ARF), usually by direct acute tubular necrosis, or by causing interstitial nephritis.

Exogenous nephrotoxins

include:

- Analgesics (NSAIDs).
- Antimicrobials (gentamicin, sulphonamides, tetracycline, vancomycin, amphotericin, aciclovir).
- Radio-contrast media (see below).
- Anaesthetic agents (methoxyflurane, enflurane).
- Chemotherapeutic agents (cisplatin).
- ACE-i and A2As (angiotensin II receptor antagonists).
- Immunosuppressants (ciclosporin, methotrexate).
- Heavy metal poisoning (mercury, lead, cadmium, arsenic, bismuth).
- Organic solvents (ethylene glycol, carbon tetrachloride).
- Insecticides, herbicides, *Amanita* mushrooms, snake venom.

Endogenous nephrotoxins

include:

- Pigments: eg *haemoglobinuria* in haemolysis: p322, *myoglobin*—see below.
- Crystals: eg urate.
- Proteins: eg immunoglobulin light chains in myeloma.

Aminoglycosides

(gentamicin, amikacin, kanamycin and streptomycin) are well-recognized nephrotoxins. The typical picture is of mild non-oliguric renal failure, 1-2wks into therapy. Risk is increased by old age, renal hypoperfusion, pre-existing renal impairment, high dosage or prolonged treatment, and coadministration of other nephrotoxic drugs. Recovery may be delayed or incomplete. Single bolus doses of aminoglycosides can be as effective as multiple doses in treating infection and less nephrotoxic.

Radiocontrast nephropathy

is a very common cause of iatrogenic ARF with IV contrast radiological studies. Risk factors are diabetes mellitus, high doses of contrast medium, hypovolaemia, other nephrotoxic agents, and pre-existing renal impairment. Prevention is key: stop nephrotoxic agents peri-procedure, and pre-hydrate with IV 0.9% sodium chloride in patients with risk factors. Acetylcysteine or IV sodium bicarbonate may be used ▸follow local protocols, and inform radiology, who may use less nephrotoxic contrast.

Rhabdomyolysis

This results from skeletal muscle breakdown, with release of its contents into the circulation, including myoglobin, potassium, phosphate, urate and creatinine kinase (CK). Complications include hyperkalaemia and ARF: myoglobin is filtered by the glomeruli and precipitates, obstructing renal tubules.

Causes:

Many, including *trauma:* prolonged immobilisation (eg after falling), burns, crush injury, excessive exercise, uncontrolled seizures; *drugs and toxins:* statins, fibrates, alcohol, ecstasy, heroin, snake bite, carbon monoxide, neuroleptic malignant syndrome (p827); *infections:* coxsackie, EBV, influenza; *metabolic:* K^+↓, PO_4^{3-} ↓, myositis, malignant hyperpyrexia (p558); *inherited muscle disorders:* McArdle's disease (p696), Duchenne's muscular dystrophy (p502).

Clinical features:

Often of the cause, with muscle pain, swelling, tenderness, and red-brown urine.

Tests:

Blood tests show a raised CK >1000iU/L (often >10000iU/L). Dark urine is +ve for blood on dipstick but *without* RBCs on microscopy. Confirmed by +ve urinary myoglobin. Others: K^{+}↑, PO_4 3-↑↑, Ca^{2+}↓ (enters muscle), urate↑. ARF occurs 12-24 hours later, and disseminated intravascular coagulation is associated (p336). Compartment syndrome can result from muscle injury.

Treatment:

Urgent treatment for hyperkalaemia (p821). IV fluid rehydration is a priority to prevent ARF: maintain urine output at 300mL/h until myoglobinuria has ceased, initially up to 1.5L fluid/h may be needed. If oliguric, CVP monitoring is useful to prevent fluid overload. IV sodium bicarbonate is used to alkalinize urine to pH >6.5, to stabilise a less toxic form of myoglobin. Dialysis may be needed, but full renal recovery is likely.

Renal vascular disease

Hypertension

may be a cause or consequence of renal disease.

Essential hypertension

(p124) The extent to which renal impairment develops in mild-moderate hypertension is debated.

Accelerated (malignant) hypertension

is characterized by a severe increase in BP, grade III or IV hypertensive retinopathy (p544) and renal failure. Â: p124.

Pre-eclampsia:

OHCS p48. ↑BP + proteinuria + oedema in 2^{nd}/3^{rd} trimester. Proteinuria is due to glomerular endothelial cell swelling. ARF may result.

Renal diseases causing hypertension

are the commonest cause of secondary hypertension. Most renal diseases are associated with ↑BP; commonly: diabetic nephropathy, glomerulonephritis, chronic interstitial nephritis, polycystic kidneys or renovascular disease.

Renovascular disease

This is stenosis of the renal artery or one of its branches.

Causes:

Atherosclerosis (in 80%: >50yrs, arteriopaths: often co-existent IHD, stroke or PVD), fibromuscular dysplasia (10%, younger ý). Rarer: Takayasu's arteritis, antiphospholipid syndrome, post-renal transplant, thromboembolism, external mass compression.

Clinically:

↑BP resistant to treatment; worsening renal function after ACE-i/A2A; ‘flash’ pulmonary oedema: sudden onset, without LV impairment on cardiac echo. Abdominal ± carotid or femoral bruits, and weak leg pulses may be found.

Tests:

Ultrasound: renal size asymmetry (affected side is smaller), disturbance in renal blood flow on Doppler ultrasound. CT/MR angiography are more sensitive. Renal angiography is ‘gold standard’, but done after CT/MR as it is invasive. See p731.

[prescription take]:

Percutaneous renal angioplasty ± stent, or revascularisation surgery. Long-term benefits of each are under study.

Haemolytic uraemic syndrome (HUS)

is characterised by microangiopathic haemolytic anaemia (MAHA): intravascular haemolysis + red cell fragmentation. Endothelial damage triggers thrombosis, platelet consumption and fibrin strand deposition, mainly in the renal microvasculature. The strands cause mechanical destruction of passing red blood cells. Thrombocytopenia and ARF result.

Causes:

90% due to *E. coli* 0157: produces a verotoxin which attacks endothelial cells. This affects young children most, often occurring in outbreaks due to consumption of undercooked contaminated meat, with abdominal pain, bloody diarrhoea and ARF. Rarely sporadic.

Tests:

Blood film: fragmented RBC (schistocytes, p322). ↓platelets, ↓Hb. Clotting tests are normal. There may be haematuria/proteinuria.

[prescription take]:

Seek expert advice. Often resolves spontaneously. Dialysis for ARF may be needed. Plasma exchange is used in severe persistent disease.

Prognosis:

Worse in non-*E. Coli* cases. Mortality 3-5%.

Thrombotic thrombocytopenic purpura (TTP)

is a pentad of: **1** Fever **2** Fluctuating CNS signs (eg fits, hemiparesis, ↓consciousness, ↓vision) **3** MAHA (severe, often with jaundice) **4** Thrombocytopenia (severe, often mucosal bleeding) **5** Renal failure. Also: haematuria or proteinuria. Adult ♀ are chiefly affected, mortality is higher than HUS. There is a genetic or acquired deficiency of a protease which normally cleaves multimers of von Willebrand factor (vWf). Large vWf multimers form, causing platelet aggregation and fibrin deposition in small vessels, leading to microthrombi.

Causes:

Often unknown: drugs (eg clopidogrel, ciclosporin), pregnancy, HIV, SLE. ▸*It is a haematological emergency: get expert help.*

Tests:

As HUS.

[prescription take]:

Urgent plasma exchange may be life-saving. Steroids,[29] IV vincristine[30] and splenectomy have roles in non-responders.[31]

Cholesterol emboli

may be released from atheromatous plaques (often aorta) which lodge in the distal microcirculation (eg renal vessels, peripheral circulation, GIT) to cause ischaemia. An inflammatory response leads to fever, myalgia and ↑eosinophils.

Risks:

Atheroma, ↑cholesterol, aortic aneurysm, thrombolysis, arterial catheterisation eg during interventional radiological procedures.

Signs:

Livedo reticularis (p542), gangrene, GI bleeds, renal failure.

[prescription take]:

Statins are tried (p682); avoid anticoagulants and instrumentation.

Prognosis:

Often progressive and fatal; some regain renal function after dialysis.

Diabetes mellitus (type 2) and the kidney

Diabetes is best viewed as a vascular disease—with the kidney as one of its chief targets for end-organ damage. The single most important intervention in the long-term care of DM is the control of BP, to protect the heart, the brain, and the kidney. Renal damage may be preventable. ▸Everyone with type 2 DM should be tested regularly (6-monthly) for microalbuminuria (30-300mg albumin excreted per day). A convenient way to do this test is to look for an early-morning urine (EMU) albumin:creatinine ratio of >3 (using EMUs improves consistency).

Microalbuminuria gives early warning of impending renal problems and is also a strong independent risk factor for cardiovascular disease. Those who are positive should be started on an ACE-i (p123) or angiotensin-2 receptor antagonists (A2A), *irrespective* of blood pressure.

Examples of A2A doses:

irbesartan 150-300mg/24h PO or losartan 50mg/d PO; increase after 1 month to 100mg daily.

SE:

U&E↑ (monitor K^+ & creatinine periodically, stop if there is a rise in creatinine of >20%), flushing, myalgia, headaches, dyspepsia, cough (although commoner with ACE-i). Usually, ACE-i are first-line and ARAs for ACE-i intolerant individuals. Increasingly they may be combined.[32]

▸Example of target BP in DM ***if no proteinuria:*** 140/80 (negotiate with patient; ensure he/she is well informed); ***if microalbuminuria/proteinuria*** is present, aim: 125/75mmHg.

Do targets work?

Target-driven, long-term, intense therapy (including prophylactic aspirin) revolving around microalbuminuria and other risk factors can halve risk of macro- and microvascular events (MI etc.).[33] Steno-2 N=180; 2003

Is microalbuminuria reversible?

Answer: sometimes—and more likely if: •Recent onset •Hb_{A1c} <8% •Systolic <115mmHg •Cholesterol <5mmol/L.[1]

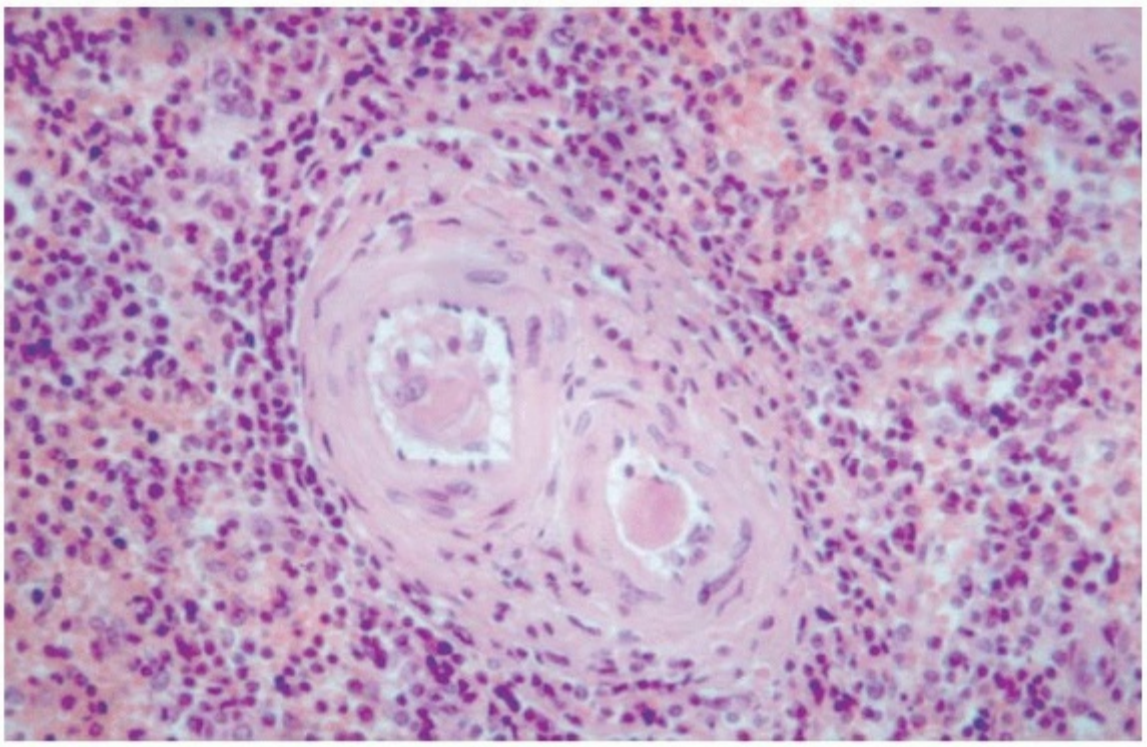

Fig 1. Thrombi in small arterioles due to fibrin and platelet deposition, characteristic of TTP.[34]

Renal tubular disease

Renal tubular acidosis (RTA)

is a metabolic acidosis, due to impaired acid secretion by the kidney. There is a hyperchloraemic metabolic acidosis with normal anion gap (p658). Type 3 RTA is a rare combination of Types 1 & 2.

- **Type 1 (distal) RTA** is due to an inability to excrete H+ and generate acidic urine in the *distal* tubule, even in states of metabolic acidosis. It may complicate many renal disorders. ***Features*** include rickets (+ growth failure) or osteomalacia, due to buffering of H^+ with calcium in bone. Nephrocalcinosis with renal calculi, leading to recurrent UTIs, is due to a combination of hypercalciuria (from bone), ↓urinary citrate (reabsorbed as a buffer for H^+) and alkaline urine: all favour calcium phosphate stone formation. ***Diagnosis:*** Acid load: oral ammonium chloride load is given—there is failure to lower urine pH <5.5. ***Treatment:*** Oral sodium bicarbonate or citrate. Complications are from renal calculi—end-stage renal failure may result from unrecognised obstruction.
- **Type 2 (proximal) RTA** is due to a 'bicarbonate leak': a defect in HCO_3 reabsorption in the *proximal* tubule resulting in excess HCO_3 in the urine. The tubules are able to reabsorb some HCO_3, so urine can acidify during systemic acidosis. Type 2 RTA is often associated with a more generalised tubular defect (Fanconi syndrome, below), and is rarer than Type 1. Hypokalaemia is common, due to the osmotic diuretic effect of ↓HCO_3 reabsorption, causing ↑flow rate to distal tubule ∴ ↑K^+ excretion. *Diagnosis:* IV sodium bicarbonate load: there is a high fractional excretion of HCO_3 (>15%). ***Treatment:*** High doses of bicarbonate (≥10mmol/kg/d) are required (this is often intolerable).
- **Type 4 (hyperkalaemic) RTA** is due to "hyporeninaemic hypoaldosteronism". Hypoaldosteronism causes hyperkalaemia and acidosis (↓K^+ and H^+ excretion). ***Causes:*** Mild renal impairment (eg with tubulointerstitial disease or DM), hypoadrenalism or drugs (K^+ sparing diuretics, NSAIDs, ACE-i/A2A). ***Treatment:*** Remove any cause. Fludrocortisone 0.1mg PO, furosemide or calcium resonium are used to control hyperkalaemia.

Fanconi syndrome

The proximal tubule is responsible for reabsorption of many solutes, including 50% of filtered sodium, most bicarbonate and all filtered glucose and amino acids. Fanconi syndrome is a disturbance of proximal tubule function, with defective reabsorption of amino acids, K^+, phosphate (leading to hypophosphataemic rickets and osteomalacia), glucose (glycosuria) and bicarbonate (Type 2 RTA: above). Also, there is polyuria (due to osmotic diuresis), and hypokalaemia (↑Na delivery to distal tubules leads to ↑exchange).

Causes:

Idiopathic Fanconi syndrome:

No identifiable cause. Mostly sporadic, some inherited. *Features*: dehydration, failure to thrive. Vitamin D resistant rickets is typical. There may be progressive renal failure in early adulthood.

Inherited:

Errors of metabolism eg cystinosis (below), fructose intolerance, galactosaemia, glycogen storage disease, Wilson's disease (p257), Lowe's syndrome,[1] tyrosinaemia.

Acquired:

Tubule damage eg heavy metals (lead, mercury, cadmium, platinum, uranium), drugs (outof-date tetracycline, iphosphamide), light chains (myeloma, amyloidosis), immunological (interstitial nephritis, transplant rejection).

[prescription take]:

Remove any cause and replace losses. K^+, sodium bicarbonate, PO_4^{3-} and vitamin D supplements are used.

Cystinosis

There is accumulation of cystine in lysosomes due to an autosomal recessive defect. Cystine deposits cause Fanconi syndrome, visual impairment and hypothyroidism, with progression to ESRF <10yrs.

[prescription take]:

As Fanconi syndrome. Oral cysteamine ↓intralysosomal cystine and delays ESRF, but is poorly tolerated. Renal cystinosis does not recur after transplant; extra-renal disease progresses.

Hereditary hypokalaemic tubulopathies

Bartter's syndrome:

p212;

Gitelman syndrome:

↓Na^+Cl reabsorption at the distal tubule due to an autosomal recessive mutation, causing ↑solute loss, and ↑K^+ loss due to 2° hyperaldosteronism. Also hypocalciuria and hypomagnesaemia.

Nephrogenic diabetes insipidus

p224.

Causes of renal tubular acidosis
Type 1 (distal)

- Idiopathic.
- Genetic (eg Marfan's, Ehlers-Danlos syndrome).
- Autoimmune disease (eg SLE, Sjögren's, autoimmune hepatitis).
- Nephrocalcinosis (eg hypercalcaemia, medullary sponge kidney).
- Tubulointerstitial disease (eg chronic pyelonephritis, chronic interstitial nephritis, obstructive uropathy, renal transplant rejection).
- Drugs (eg lithium, amphotericin).

Type 2 (proximal)

- Idiopathic.
- Fanconi syndrome.
- Tubulointerstitial disease (eg myeloma, interstitial nephritis).
- Drugs (eg lead or other heavy metals, acetazolamide, out of date tetracycline).

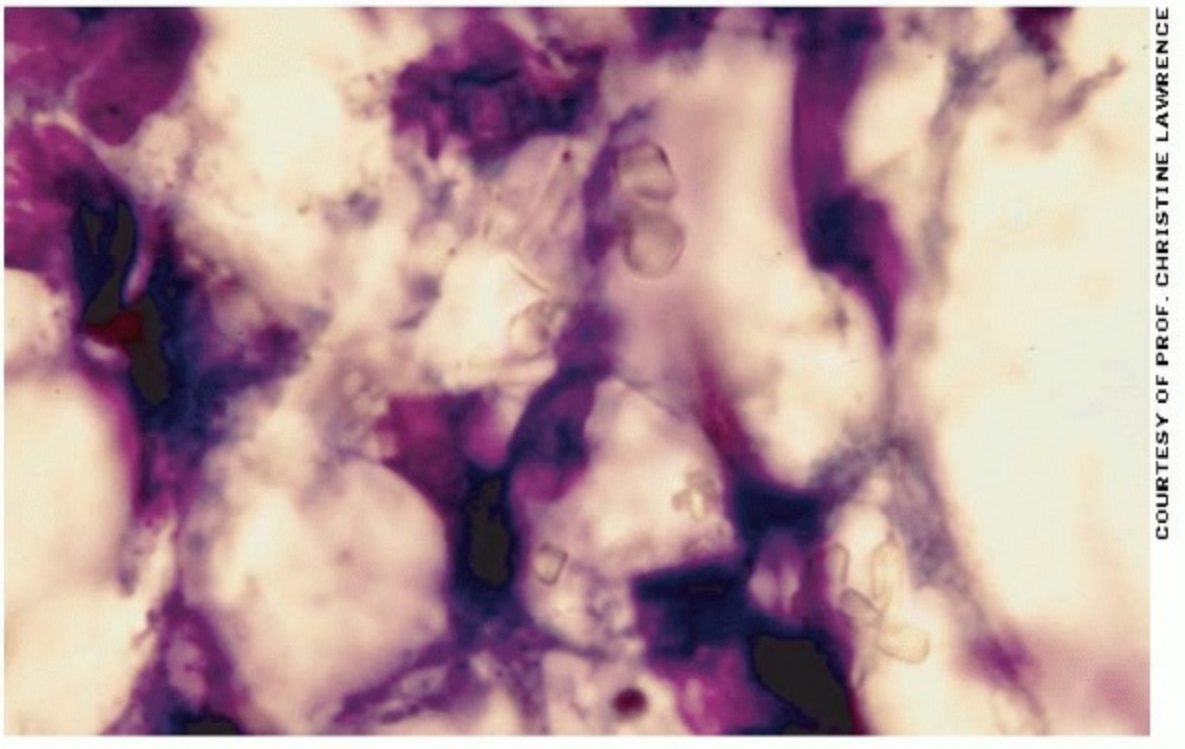

Fig 1. Cystine crystals in the bone marrow, found in cystinosis. Crystals accumulate in most tissues, especially the kidneys.[35]

Inherited kidney diseases

Autosomal dominant polycystic kidney disease (ADPKD)

Prevalence:

1:1000. Genes on chromosomes 16 (PKD1) and 4 (PKD2).

Signs:

Renal enlargement with cysts, abdominal pain ± haematuria (haemorrhage into a cyst), cyst infection, renal calculi, BP↑, progressive renal failure. *Extrarenal*: liver cysts, intracranial aneurysm→subarachnoid haemorrhage (SAH), mitral valve prolapse.

Treatment:

Monitor U&E. Treating ↑BP is important to prevent cardiovascular complications and SAH. Treat infections, dialysis or transplantation for ESRF, genetic counselling. Pain may be helped by laparoscopic cyst removal or nephrectomy.

Screening for SAH

with magnetic resonance angiography may be done in 1st-degree relatives of those with SAH + ADPKD. Some screen with no family history.

Autosomal recessive polycystic kidney disease

OHCS p132. Prevalence 1:40,000, chromosome 6. *Signs*: Infancy: renal cysts, congenital hepatic fibrosis.

Medullary cystic disease

Inherited disorder with tubular loss and medullary cyst formation. The juvenile (autosomal recessive) form accounts for 10-20% of ESRF in children. The adult form (autosomal dominant; restricted to the kidney) is rare.

Signs:

Polyuria, polydipsia, enuresis (↓urine concentrating ability), failure to thrive, renal impairment → ESRF. *Extrarenal:* include retinal degeneration, retinitis pigmentosa, skeletal changes, cerebellar ataxia, liver fibrosis.

Renal phakomatoses

(neuroectodermal syndromes).

Tuberous sclerosis:

OHCS p638. A complex autosomal dominant disorder with hamartoma formation in skin, brain, eye, kidney, and heart caused by genes on chromosomes 9 (TSC1) & 16 (TSC2). *Signs* are variable: •Skin: adenoma sebaceum, angiofibromas, 'ash leaf' hypomelanic macules, shagreen patches (sacral plaques of shark-like skin), periungual fibroma •IQ↓ •Epilepsy.

Von Hippel-Lindau syndrome

(p704) is the chief cause of inherited renal cancers.

Cause:

Germline mutations of the VHL tumour-suppressor gene (also inactivated in most sporadic renal cell cancers).[36]

Alport's syndrome

OHCS p638.

Prevalence:

1:5000. Variable inheritance (mainly expressed in ♂: 85% are X-linked). The affected genes code for type IV collagen molecules.[37]

Pathology:

Thickened GBM with 'splitting'. The Goodpasture's antigen is missing (hence risk of anti-GBM glomerulonephritis post-renal transplant).

Signs:

Haematuric nephritis, sensorineural deafness, and progressive renal failure. Some have lenticonus: bulging of lens capsule seen on slit-lamp examination.

[prescription take]:

None specific, as for renal failure.

Fabry's disease

See p690.

Hyperoxaluria

Primary hyperoxaluria

is an autosomal recessive inherited error of metabolism due to an enzyme defect.

Secondary hyperoxaluria

is due to •↑intake eg rhubarb, spinach, tea •↑intestinal reabsorption due to ileal disease (Crohn's, ileal bypass), short bowel syndrome, low Ca^{2+} intake.

Signs:

Oxalate renal stones (p284), nephrocalcinosis, progressive renal failure, cardiac conduction defects, arterial disease (oxalate crystallisation), osteodystrophy.

Treatment:

High fluid intake to prevent calculi (keep urine output ~3L/day), ↓dietary oxalate, calcium supplements (binds oxalate in the gut so ↓absorption). If these do not work, pyridoxine (vitamin B_6) is used to ↓endogenous oxalate production (SE: peripheral neuropathy in high doses). Magnesium or cholestyramine are also used to ↓oxalate absorption. Hepatic transplantation may be curative in primary hyperoxaluria, and may be combined with renal transplant.

Cystinuria

The commonest aminoaciduria, causing ↓tubular reabsorption of the dibasic amino acids **COAL** **C**ystine, **O**rnithine, **A**rginine and **L**ysine, due to an autosomal recessive defect.

Features:

Manifests with cystine renal stones (p284).

Treatment:

↑Fluid intake to keep urine output ~3L/day; urine alkalinization with potassium citrate (↑solubility of cystine). Penicillamine is used, which binds cystine in soluble complexes. **NB:** Do not confuse this condition with cystinosis where there are no stones (p302).

Genetics: triumphs and disasters

As soon as genetics solves one problem, others appear. You might think that the application of science to medicine is an undisputed boon. Petty has provided a compelling counter-example.[38] A man with adult polycystic kidney disease due to a PKD1 mutation is in end-stage renal failure. A transplant from a matched, living, related, unaffected donor is highly desired. There are problems in his family, but he persuades his adult children to have genetic testing to see if there are eligible donors. Each is apparently happy to donate a kidney to his/her father.

A can of worms is opened when one son realizes that he is the only child who can offer a good match—and that his brother is carrying the same mutation as his estranged father (there is a 50:50 chance of passing on the PKD gene). The eligible son would rather save his kidney to help his brother than his father. Old animosities resurface, and the family is in turmoil. How will you feel if the father dies of a complication of dialysis, and both his sons feel guilty forever? We should not be too surprised at all this: often in medicine bad comes out of our good intentions. How can we make good come out of bad? By remembering this example, and not doing tests lightly, and by making genetic counselling as professional as possible, so complications can be foreseen and disasters pre-empted. Furthermore, do not have unreasonable expectations about what genetic counselling can do. The number of diseases being found to have a significant genetic component is increasing faster than geneticists can formulate rational guidelines for screening.[1]

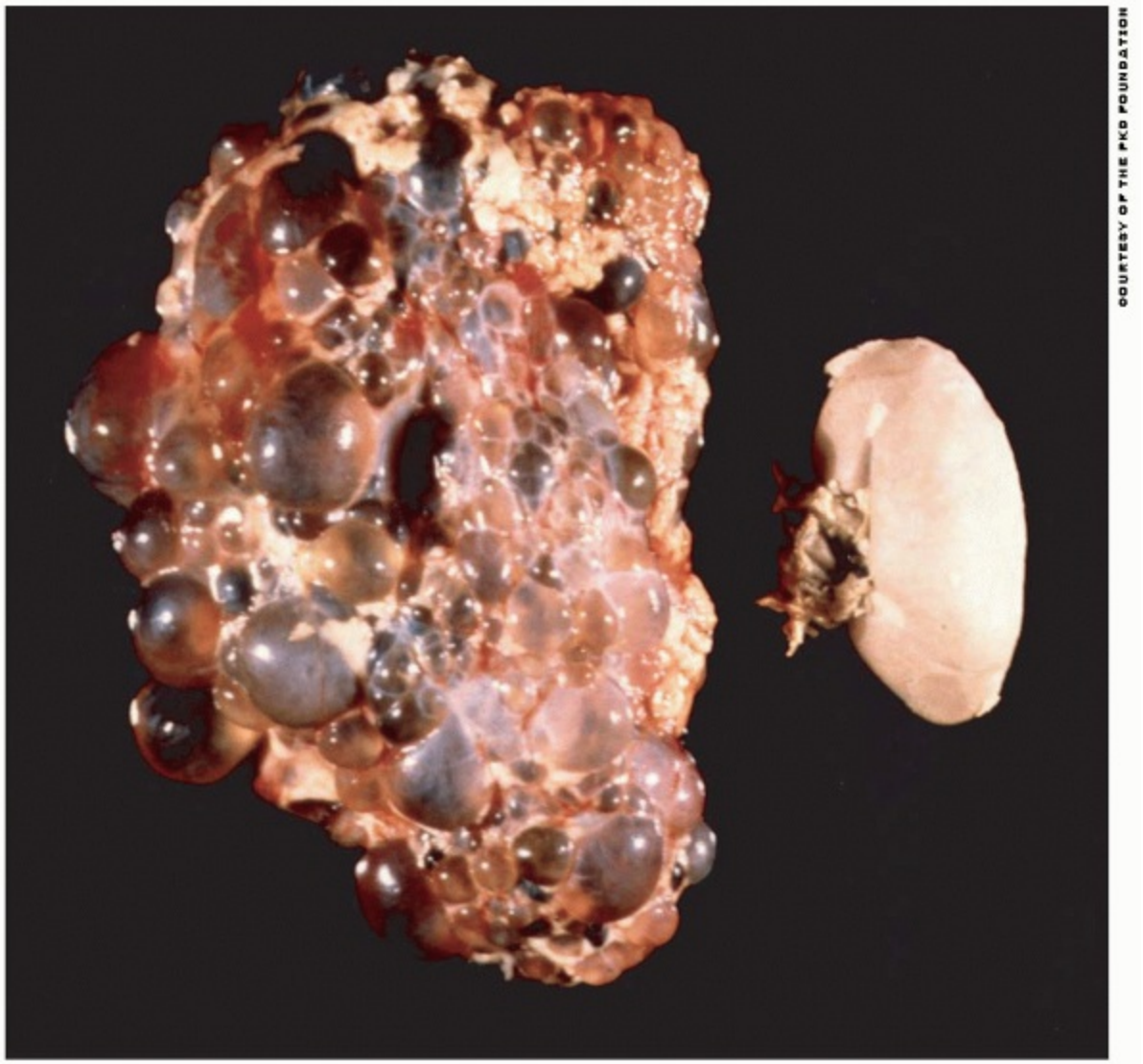

Fig 1. A polycystic kidney (left) compared to a normal sized kidney (right). The progressive increase in size often leads to abdominal discomfort, and there may be haemorrhage into a cyst causing haematuria, or infection.[39]

Renal manifestations of systemic disease

Amyloidosis

(p354) can cause proteinuria, nephrotic syndrome or progressive renal failure.

Diagnosis:

US: large kidneys; biopsy: see p354.

Treatment

p354.

Diabetes

This is one of the commonest causes of ESRF in the UK, accounting for ~18%.

Pathology:

Hyperglycaemia causes renal hyperperfusion, increasing GFR. This causes hypertrophy and ↑renal size. Mesangial hypertrophy and focal glomerulosclerosis (Kimmelstiel-Wilson lesion) occur later due to ↑glomerular pressure. This initially causes ***microalbuminuria*** (detectable on laboratory tests but not on dipstick: albuminuria 30-300mg/d), a sign of early diabetic nephropathy and a strong independent predictor of cardiovascular mortality. This progresses to proteinuria (albuminuria >300mg/d): ESRF usually occurs within 5-10 years. Diabetic retinopathy usually co-exists, and hypertension is common. It occurs in ~30%, partly due to genetic predisposition.

- ***Type 1*** **DM *nephropathy*** occurs typically 20-40yrs post-diagnosis.
- ***Type 2*** **DM *('maturity onset') nephropathy:*** ▸See p301 (BOX). >10-30% have nephropathy at diagnosis, and prevalence increases linearly with time.

Treatment:

Good glycaemic control delays onset and progression of nephropathy. If microalbuminuria is present, additional important interventions to slow progression of renal disease are •BP target <125/<75 •Use of ACE-i or A2A, even if normotensive (these ↓intraglomerular pressure, p301) •Smoking cessation. Once ESRF has been reached, combined pancreas and renal transplant is possible in *selected* patients.

Infection

associated nephropathies are common causes of renal disease.

Glomerulonephritis

occurs with many bacterial, viral and parasitic infections, including post-streptococcal, hepatitis B or C, HIV, SBE/IE, shunt nephritis, visceral abscess, syphilis, malaria, schistosomiasis and filiariasis.

Vasculitis

(p542) may occur with hepatitis B or C, post-streptococcal or staphylococcal septicaemia.

Interstitial nephritis:

Seen with bacterial pyelonephritis, viral (CMV, HIV, hepatitis B, hantavirus), fungal and parasitic (leishmaniasis, toxoplasmosis) infections.

Malignancy

Direct effects:

Renal infiltration (leukaemia, lymphoma), obstruction (pelvic tumours), metastases.

Indirect:

Hypercalcaemia, nephrotic syndrome, acute renal failure, amyloidosis, glomerulonephritis.

Treatment associated:

Nephrotoxic drugs, tumour lysis syndrome, radiation nephritis.

Myeloma

(p352) is characterized by excess production of monoclonal antibody ± light chains, which are excreted and detected in 2/3 of cases as Bence-Jones proteinuria. Myeloma kidney is due to blockage of tubules by casts, consisting of light chains. The light chains have a direct toxic effects on tubular cells, causing ATN.

Features:

ARF, CRF, amyloidosis (may cause proteinuria and nephrotic syndrome), hypercalcaemic nephropathy.

Treatment:

Ensure fluid intake of 3L/day to prevent further impairment. Dialysis may be required in ARF.

Rheumatological diseases

Rheumatoid arthritis (RA)

NSAIDs may cause interstitial nephritis. Penicillamine and gold can cause membranous nephropathy. AA amyloidosis (p354) occurs in ~15% of RA (often asymptomatic).

SLE

involves the glomerulus in 40-60% of adults, causing acute or chronic disease. Proteinuria and ↑BP are common. Histological patterns range from minimal change to crescentic GN. Consider a renal biopsy if nephritic syndrome or deteriorating renal function.

[prescription take]:

ACE-i if proteinuria. Corticosteroids and immunosuppressants (cyclophosphamide or mycophenolate) are used if biopsy shows aggressive GN (p540).

Systemic sclerosis

(p538) may affect the kidney, especially in diffuse disease. 'Renal crisis' presents with ARF + accelerated hypertension.

[prescription take]:

ACE-i if ↑BP or in renal crisis. Dialysis or transplant may be required.

Hyperparathyroidism

Clinical features are from hypercalcaemia: p298.

Sarcoidosis

may involve the kidney, often by abnormal calcium metabolism (p178). Interstitial nephritis and rarely glomerulonephritis are also associated.

Epilogue: the man in a red canoe who saved a million lives

Mostly we commute to work each day driven by motives we would rather not look at too deeply. But one renal physician used a red canoe to commute each day from his houseboat to the hospital. He could have been a very rich man but instead Belding Scribner gave his invention away, and continued his modest existence. He invented the Scribner shunt—a **U** of teflon connecting an artery to a vein, so allowing haemodialysis to be something which could be repeated as often as needed. Before Scribner, glass tubes had to be painfully inserted into blood vessels, which would be damaged by the procedure and haemodialysis could only be done for a few cycles. Clyde Shields was his first patient with chronic renal failure to receive the shunt—on 9 March 1960, and said that his first treatment 'took so much of the waste I'd stored up out of me that it was just like turning on the light from darkness'.[40] Scribner took something that was 100% fatal and overnight turned it into a condition with a 90% survival. In so doing he founded a branch of bioethics because not everyone could have the treatment immediately. This is the branch of ethics that is to do with who gets what—ie distributive justice. In Scribner's day, this was decided by the famous 'Life and Death Committee' which had the unenviable job of choosing who would survive by placing people in order precedence.

Scribner has said that his inventions sprang from his empathy for patients, including himself. 'I was a sickly child' he said, and at various times he needed a heart-lung machine, a new hip, and donated corneas. He was the sort of man whose patients would inspire him to worry away at their problems during the day—and then to awake at night with a brilliant solution.

On 19 June 2003, his canoe was found afloat but empty—and like those ancient Indian burial canoes found at Wiskam which have been polished to an unimaginable lustre by the action of the shifting sands around the Island of the Dead, so we polish and cherish the image of this man who gave everything away.

Acknowledgements

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9

Haematology

Fig 1. The **old** methodology: a naked haematologist works alone hammering a red cell into shape. “Every space larger than a red globule of man's blood is visionary, and it is created by the Hammer of Los.” Image from the *Song of Los*, William Blake.

Fig 2. The **new** methodology: teamwork in action, as haematologist, geneticist, and lab staff deal with a troublesome spherocyte.[2] (×3000)

On the taking of blood and of holidays

This is not one of those pages about how you should be kind to the patient, explain in full what you are going to do, talk him or her through venepuncture, label the bottles carefully, and make a plan for communicating the results. Be all this as it may, there is something else which needs communicating about the *act* of taking blood. It is partly to do with the fact that as blood is life, and, because, as Ruskin taught us, 'there is no wealth but life', we are led to the conclusion that what is special about taking blood is that for once *we* are being given something valuable by the patient. What is this wealth? The answer is *time*. For while the blood is flowing into our tube we cannot be disturbed. We are excused from answering our bleeps, and from making polite conversation (a few grunts in reply to patients' enquires about the colour of their blood is quite sufficient)— and we can indulge in that almost unimaginable luxury, at least as far as life on the wards is concerned, of *being alone with our own thoughts*. Thinking of this sacred time as a sort of hypnotic holiday is excellent. For however many nights we have been awoken, and through however many wards we have traipsed to this bedside, this little holiday will be worth an hour's sleep—if our mind is furnished and ready to empty itself of all objectivity. The best sight in haematological practice is, during venepuncture, to watch for those occasions when, owing to some chance characteristic of flow, the jet of blood streaming into our tube breaks up into countless globules, and before coalescing again, these globules jostle together like the overcrowded chain of events which led us to this bedside. During this time, allow your own thoughts to coalesce into a more peaceful order if you can, and let William Blake help you in the task of furnishing your mind to banish objectivity, for he knew some truths about haematology unknown to strictly rational practitioners of this art:

The Microscope knows not of this nor the Telescope: they alter

The ratio of the Spectators Organs but leave Objects untouch'd

For every space larger than a red globule of Mans blood

Is visionary, and it is created by the Hammer of Los:[1]

And every space smaller than a Globule of Mans blood opens

Into eternity of which this vegetable Earth is but a shadow.

The red Globule is the unwearied Sun by Los created

To measure Time and Space to mortal Men …

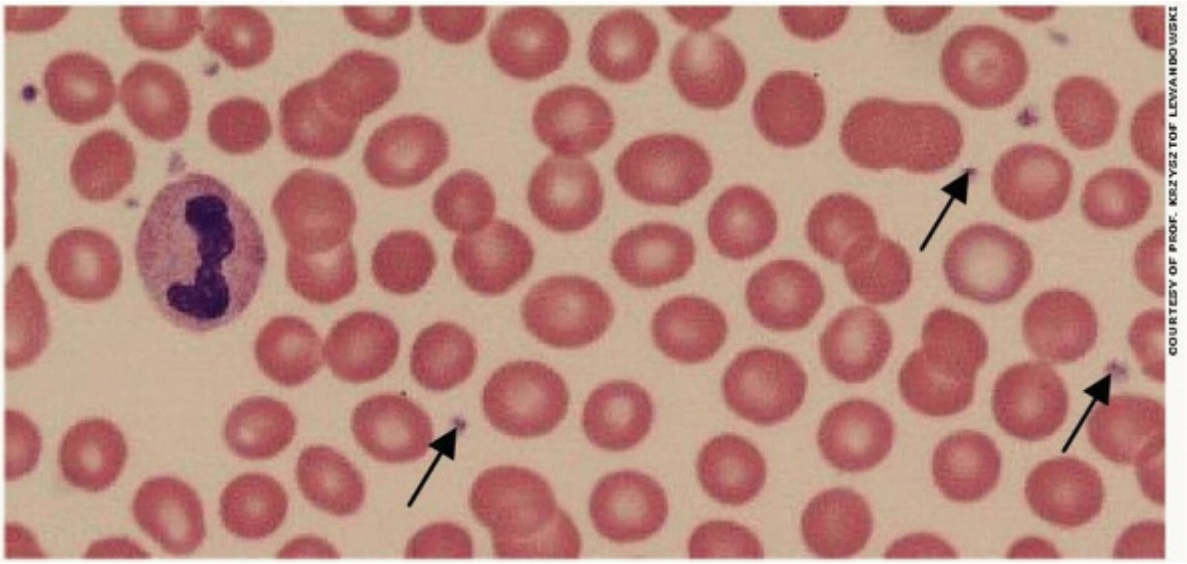


Fig 1. A normal blood film, with a neutrophil, normal red cells, and platelets (arrows).[3]

Anaemia

Anaemia is defined as a low haemoglobin (Hb) concentration, and may be either due to a low red cell mass, or increased plasma volume (eg in pregnancy). A low Hb (at sea level) is <13.5g/dL for men and <11.5g/dL for women. Anaemia may be due to reduced production or increased loss of RBC and has many causes. These will often be distinguishable by history, examination, and inspection of the blood film.

Symptoms

Due to the underlying cause or to the anaemia itself: fatigue, dyspnoea, faintness, palpitations, headache, tinnitus, anorexia—and angina if there is pre-existing coronary artery disease.

Signs

May be absent even in severe anaemia. There may be pallor (eg conjunctivae, although this is not a reliable sign). In severe anaemia (Hb <8g/dL), there may be signs of a hyperdynamic circulation, eg tachycardia, flow murmurs (ejection-systolic loudest over apex), and cardiac enlargement; or retinal haemorrhages (rarely). Later, heart failure may occur: here, rapid blood transfusion may be fatal.

Types of anaemia

The first step in diagnosis is to look at the mean cell volume (MCV, *normal* MCV is 76-96 femtolitres, 10^{15} fL = 1L).

Low MCV (microcytic anaemia)

- Iron-deficiency anaemia (IDA, most common cause): p312.
- Thalassaemia (suspect if the MCV is 'too low' for the level of anaemia and the red cell count is raised): p328.
- Sideroblastic anaemia (very rare): p312.

NB: The last two are conditions where there is an accumulation of iron, and so tests will show serum iron↑, ferritin↑, and a low total iron-binding capacity (TIBC).

Normal MCV (normocytic anaemia)

- Acute blood loss
- Anaemia of chronic disease (or ↓MCV)
- Bone marrow failure
- Renal failure
- Hypothyroidism (or ↑MCV)
- Haemolysis (or ↑MCV)
- Pregnancy

If wcc↓ or platelet↓, suspect marrow failure: see p348.

High MCV (macrocytic anaemia)

- B_{12} or folate deficiency
- Alcohol excess—or liver disease
- Reticulocytosis (eg with haemolysis)
- Cytotoxics, eg hydroxycarbamide
- Myelodysplastic syndromes
- Marrow infiltration
- Hypothyroidism
- Antifolate drugs (eg phenytoin)

Haemolytic anaemias:

(p322). These disorders do not fall elegantly into the above classification as the anaemia may be normocytic, or, if there are many young (hence larger) RBCs and reticulocytes, macrocytic. Suspect if there is a reticulocytosis (>2% of RBCs; or reticulocyte count >100×10^9/L), mild macrocytosis, haptoglobin↓, bilirubin↑ & urobilinogen↑. Often mild jaundice (but no bilirubin in urine as haemolysis causes pre-hepatic jaundice).

Blood transfusion

The decision on whether to transfuse depends on a number of factors: the onset (acute or chronic), the severity of anaemia (one review suggests that transfusion is not essential for *most* patients unless Hb <7g/dL)[4], if there is co-morbidity (have a lower threshold to transfuse in ischaemic heart disease) and whether the patient is symptomatic. If there is an acute cause (eg haemorrhage with active peptic ulcer), transfuse up to 8g/dL. Chronic anaemia is better tolerated, and it is important to ascertain the cause eg in iron deficiency anaemia, iron supplements will raise the haemoglobin in a safer and less costly way. In severe anaemia with heart failure, transfusion is vital to restore Hb to safe level, eg 6-8g/dL, but must be done with great care. Give packed cells *slowly* with 10-40mg furosemide IV/PO with alternate units (dose depends on previous exposure to diuretics; do not mix with blood). Check for rising JVP and basal crackles. If CCF gets worse, stop and treat. If immediate transfusion is essential, a 2-3 unit exchange transfusion can be tried, removing blood at same rate as it is transfused.

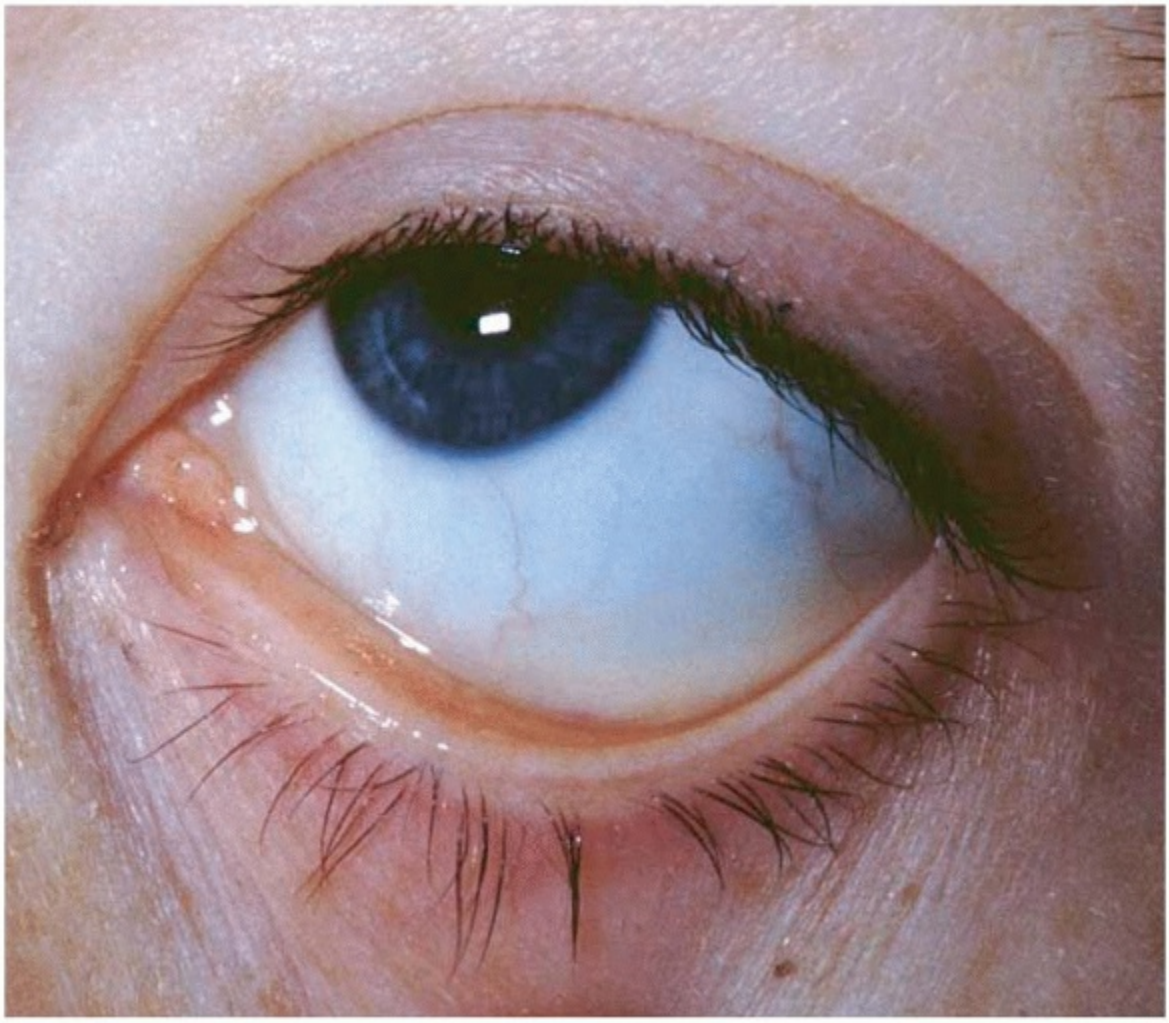


Fig 1. 'Conjunctival pallor', *the* classic sign of anaemia, is a confusing term as the conjunctiva is translucent, transmitting the colour of the structures under it. The 'pallor' in fact refers to the vasculature on the inner surface of the lid which lacks haemoglobin.

It is this colour  , whereas it should be more like this:  .

Iron-deficiency anaemia (IDA)

This is common (seen in up to 14% of menstruating women).

Causes:

- Blood loss eg menorrhagia or GI bleeding (upper p244; lower p70).
- Poor diet may cause IDA in babies or children (but rarely in adults), those on special diets, or wherever there is poverty.
- Malabsorption (eg coeliac disease) is a cause of refractory IDA.
- In the Tropics, hookworm (GI blood loss) is the most common cause.

Signs:

Chronic IDA (signs now rare): koilonychia (**fig 1** and p27), atrophic glossitis, angular cheilosis (**fig 2**), and rarely, post-cricoid webs (Plummer-Vinson syndrome).

Tests:

Microcytic, hypochromic anaemia with anisocytosis and poikilocytosis (**fig 3** and **4**). ↓MCV, ↓MCH & ↓MCHC. Confirmed by ferritin↓ (also serum iron↓ with ↑total iron binding capacity—TIBC, but these are less reliable). ↑red cell protoporphyrin. **NB:** Ferritin is an acute phase protein and ↑ with inflammation eg infection, malignancy. Serum transferrin receptors are also ↑ in IDA but are less affected by inflammation. If MCV↓, and good history of menorrhagia, oral iron may be started without further tests. Otherwise investigate for GI blood loss: gastroscopy, sigmoidoscopy, barium enema or colonoscopy, stool microscopy for ova if foreign travel. Faecal occult blood is not recommended as sensitivity is poor. ▸*Iron deficiency without an obvious source of bleeding mandates a careful* GI *workup.*[1]

[1] In one study, 11% presenting to their GP with IDA had GI carcinoma. Consider both upper and lower GI investigation as in another study, 29% (n=89) had abnormalities on both.

Treatment:

Treat the cause. Oral iron eg ferrous sulfate 200mg/8h PO. SE: nausea, abdominal discomfort, diarrhoea or constipation, black stools. Hb should rise by 1g/dL/week, with a modest reticulocytosis (ie young RBC, p314). Continue until Hb is normal and for at least 3 months, to replenish stores. Intravenous iron is almost never needed, but may be indicated if the oral route is impossible or ineffective, eg functional iron deficiency in chronic renal failure, where there is inadequate mobilization of iron stores in response to the acute demands of erythropoietin therapy.

The usual reason that IDA fails to respond to iron replacement is that the patient has rejected the pills. Negotiate on concordance issues (p3). Is the reason for the problem GI disturbance? Altering the dose of elemental iron with a different preparation may help. There may be continued blood loss, malabsorption, anaemia of chronic disease; or there is misdiagnosis, eg when thalassaemia is to blame.

The anaemia of chronic disease

This is associated with many diseases, including chronic infection (eg TB, osteomyelitis), vasculitis, rheumatoid arthritis, malignancy, renal failure. There is cytokine driven inhibition of red cell production.

Investigations:

Mild normocytic anaemia (eg Hb >8g/dL), ferritin normal or ↑.

Treatment:

Treat the underlying disease. The anaemia of renal failure is partly due to erythropoietin deficiency and recombinant erythropoietin is effective in raising the haemoglobin level (SE: 'flu-like symptoms, hypertension, mild rise in the platelet count). It is also effective in raising Hb and improving quality of life in those with malignant disease.[5]

Sideroblastic anaemia

Characterized by ineffective erythropoiesis, leading to ↑iron absorption, iron loading (bone marrow) and occasionally haemosiderosis (endocrine, liver and

cardiac damage due to iron deposition). It may be congenital (rare, X-linked) or acquired—usually idiopathic as one of the myelodysplastic disorders, but can follow chemotherapy, irradiation, alcohol or lead excess, anti-TB drugs or myeloproliferative disease. Hypochromic RBCs are seen on the blood film with ring sideroblasts in the marrow (erythroid precursors with iron deposited in mitochondria in a ring around the nucleus).

Treatment:

Remove the cause if possible. Pyridoxine may be of benefit. Repeated blood transfusion may be needed in severe anaemia.

Interpretation of plasma iron studies

	Iron	TIBC	Ferritin
Iron deficiency	↓	↑	↓
Anaemia of chronic disease	↓	↓	↑
Chronic haemolysis	↑	↓	↑
Haemochromatosis	↑	↓ (or ↔)	↑
Pregnancy	↑	↑	↔
Sideroblastic anaemia	↑	↔	↑

TIBC: total iron binding capacity.

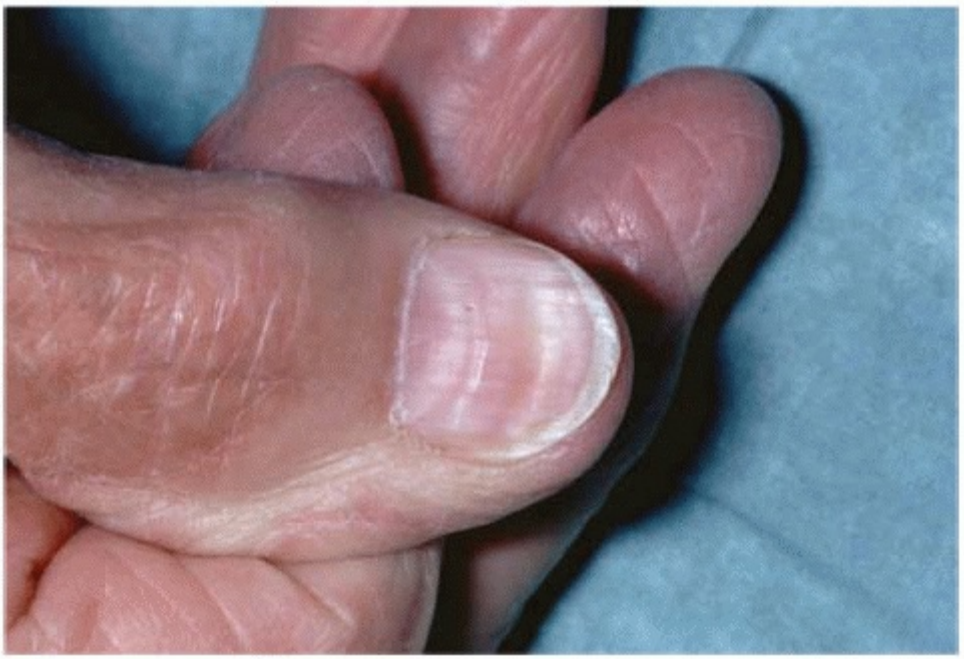


Fig 1. Koilonychia. Spoon-shaped nails, found in iron deficiency anaemia.

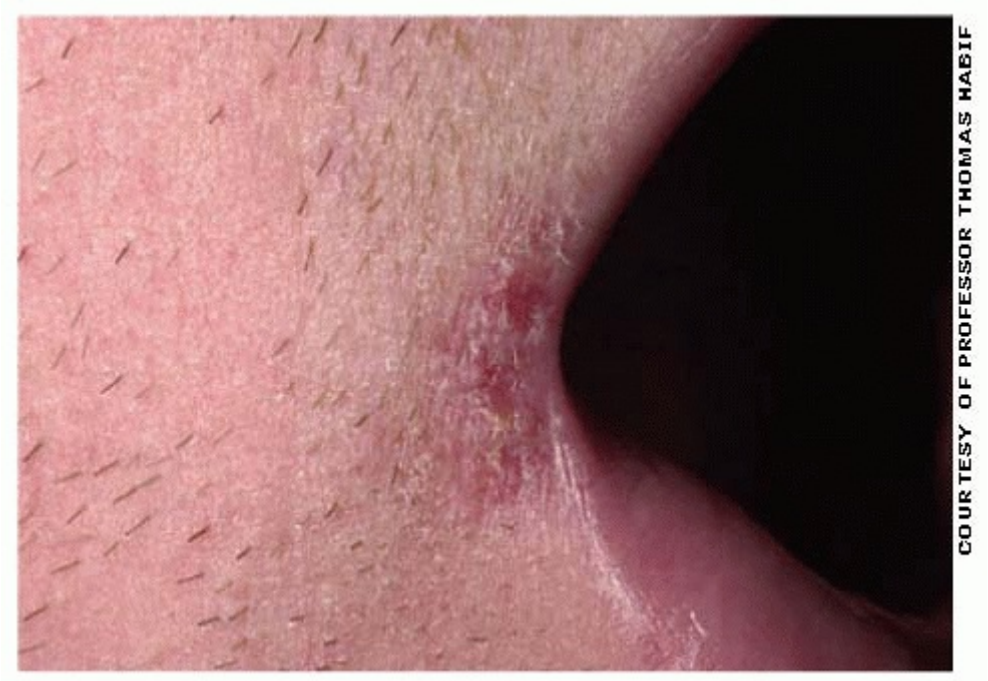


Fig 2. Angular cheilosis, ulceration at the side of the mouth, in iron deficiency anaemia. Also a feature of Vitamin B_{12} and B_2 (riboflavin) deficiency. [6]

COURTESY OF PROFESSOR THOMAS HABIF

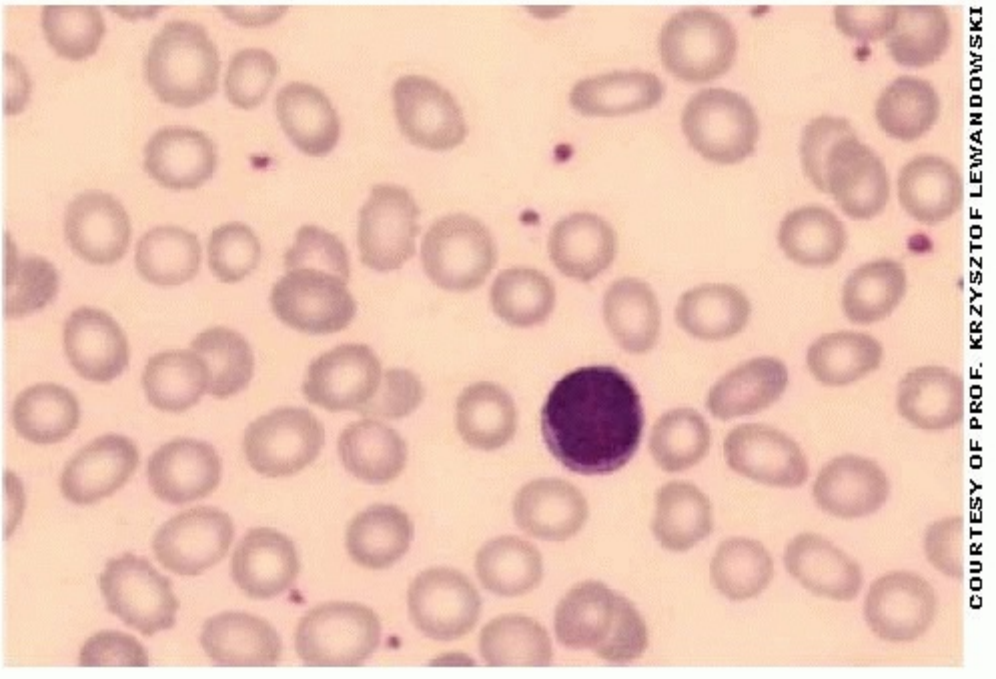


Fig 3. Microcytic hypochromic cells in iron deficiency anaemia.[7]

COURTESY OF PROF KRZYSZTOF LEWANDOWSKI

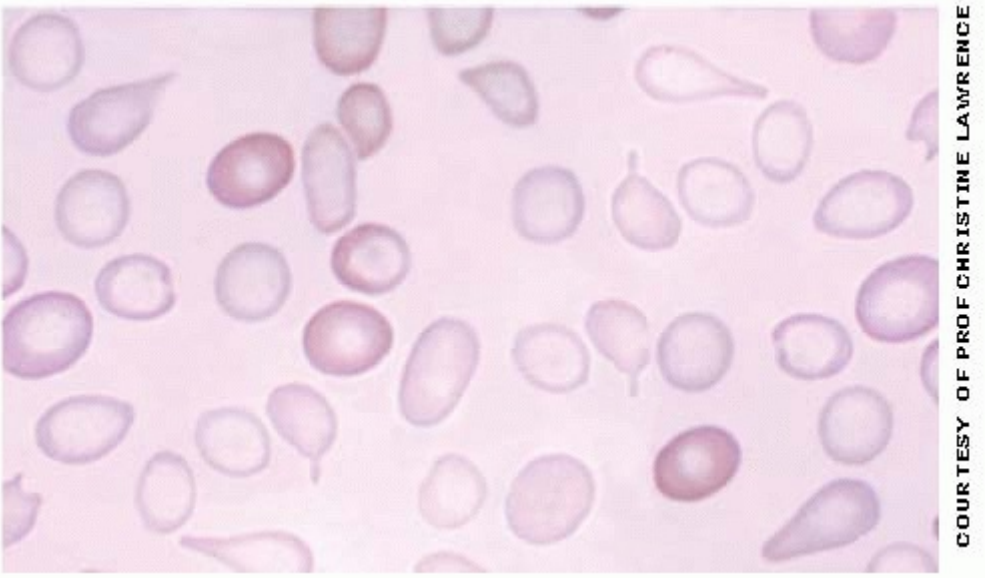


Fig 4. Poikilocytosis and anisocytosis seen in iron deficiency anaemia.[8]

COURTESY OF PROF CHRISTINE LAWRENCE

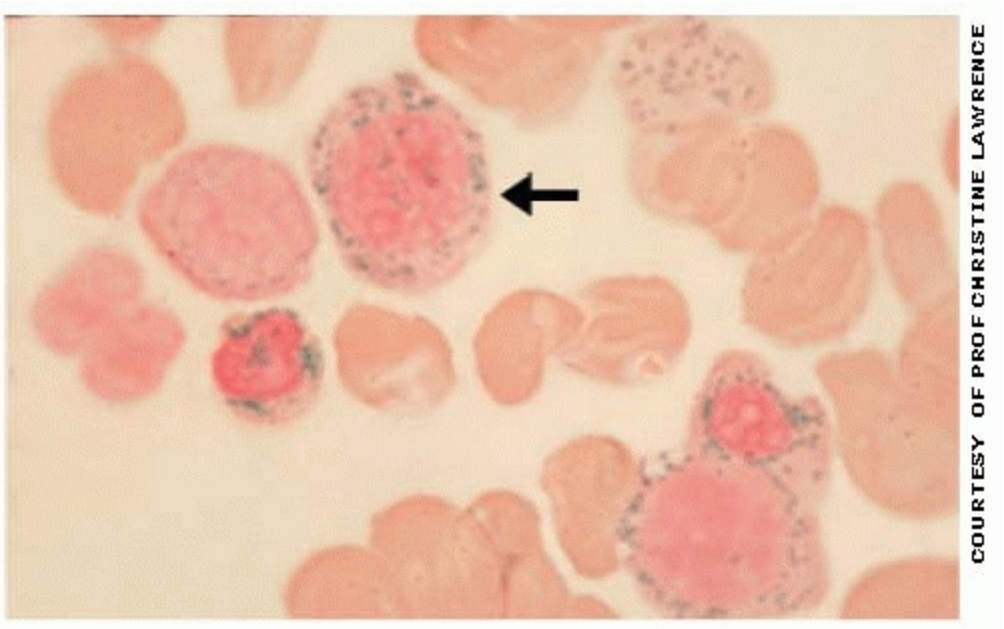


Fig 5. Pathological ring sideroblasts in the bone marrow, with a perinuclear ring of iron granules, found in sideroblastic anaemia.[9]

The peripheral blood film

▸Many haematological (and other) diagnoses are made by careful examination of the peripheral blood film. It is also necessary for interpretation of the FBC indices.

Anisocytosis

is variation in RBC size, eg megaloblastic anaemia, thalassaemia, IDA.

Acanthocytes:

(**fig 1**) RBCs show many spicules due to an unstable red cell membrane lipid structure (eg in abetalipoproteinaemia).

Basophilic RBC stippling:

(**fig 2**) Denatured RNA found in RBCs, indicating accelerated erythropoiesis or defective Hb synthesis. Seen in lead poisoning, megaloblastic anaemia, myelodysplasia, liver disease, haemoglobinopathy eg thalassaemia.

Blasts:

Nucleated precursor cells. They are not normally in peripheral blood, but are seen in myelofibrosis, leukaemia or malignant infiltration by carcinoma.

Burr cells:

Irregularly shaped cells occurring in uraemia.

Dimorphic picture:

Two populations of red cells. Seen after treatment of Fe, B_{12} or folate deficiency, in mixed deficiency (↓Fe with ↓B_{12} or folate), post-transfusion, or with primary sideroblastic anaemia, where a clone of abnormal erythroblasts produce abnormal red cells, alongside normal red cell production.

Howell-Jolly bodies:

DNA nuclear remnants in RBCs, which are normally removed by the spleen (**fig 8**). Seen post-splenectomy and in hyposplenism (eg sickle cell disease, coeliac disease, congenital, UC/Crohn's, myeloproliferative disease, amyloid). Also in dyserythopoietic states: myelodysplasia, megaloblastic anaemia.

Hypochromia:

(p312). Less dense staining of RBCs due to ↓Hb synthesis, seen in IDA, thalassaemia, and sideroblastic anaemia (iron stores unusable).

Left shift:

Immature neutrophils are sent out of the marrow, eg in infection.

Leucoerythroblastic anaemia:

Immature cells (myelocytes, promyelocytes, metamyelocytes, normoblasts) seen in film. Due to marrow infiltration (eg malignancy) when these cells are displaced; also seen in anorexia, sepsis, severe haemolysis.

Leukaemoid reaction:

A marked leucocytosis (WCC>50×10^9/L). Seen in severe illness eg with infection or burns, and also in leukaemia.

Pappenheimer bodies:

(**fig 5**) Granules of siderocytes containing iron. Seen in lead poisoning, carcinomatosis, and post-splenectomy.

Poikilocytosis

is variation in RBC shape, eg in IDA, myelofibrosis, thalassaemia.

Polychromasia:

RBCs of different ages stain unevenly (young are bluer). This is a response to bleeding, haematinic replacement (ferrous sulfate, B_{12}, folate), haemolysis, or marrow infiltration. Reticulocyte count is raised.

Reticulocytes:

(normal range: 0.8-2%; or <85×10^9/L) **fig 6**. Young, larger RBCs (contain RNA) signifying active erythropoiesis. Increased in haemolysis, haemorrhage, and if B_{12}, iron or folate is given to marrow that lack these.

Right shift:

Hypermature white cells: hypersegmented polymorphs (>5 lobes to nucleus) seen in megaloblastic anaemia, uraemia, and liver disease. See p318, **fig 1**.

Rouleaux formation:

(**fig 7**) Red cells stack on each other (it causes a raised ESR; p356). Seen with chronic inflammation, paraproteinaemia and myeloma.

Spherocytes:

Spherical cells found in hereditary spherocytosis and autoimmune haemolytic anaemia. See p324.

Schistocytes:

Fragmented RBCs sliced by fibrin bands, in intravascular haemolysis. (p324, **fig 4**) Look for microangiopathic anaemia, eg DIC (p336), haemolytic uraemic syndrome, thrombotic thrombocytopenic purpura (TTP: p300), or pre-eclampsia.

Target cells:

(also known as Mexican hat cells, **fig 8**). These are RBCs with central staining, a ring of pallor, and an outer rim of staining seen in liver disease, hyposplenism, thalassaemia—and, in small numbers, in iron-deficiency anaemia.

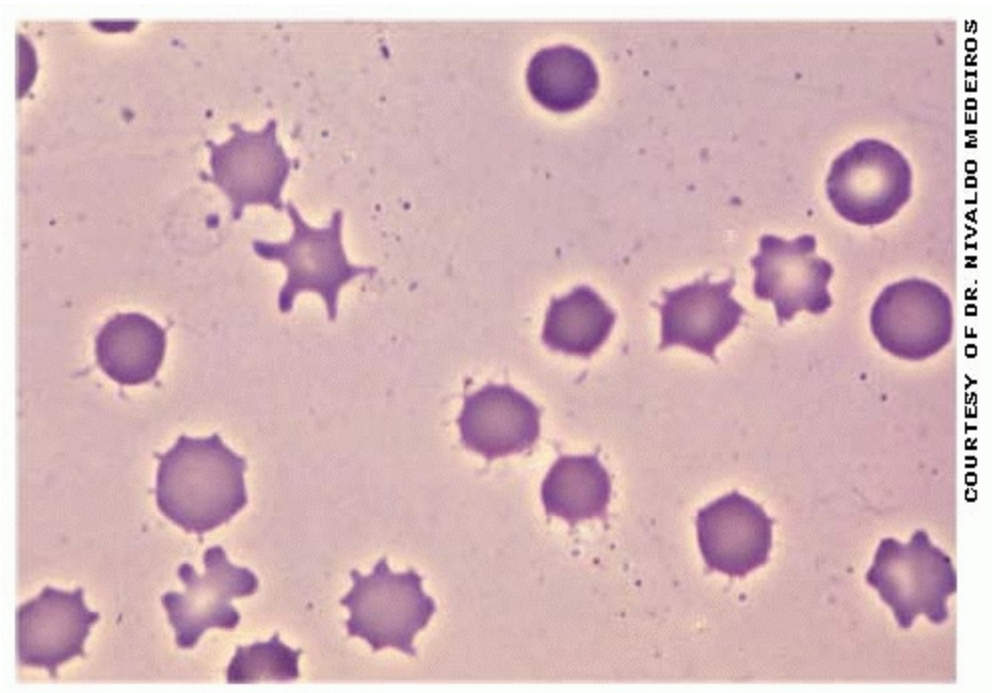


Fig 1. Acanthocytosis.[10]

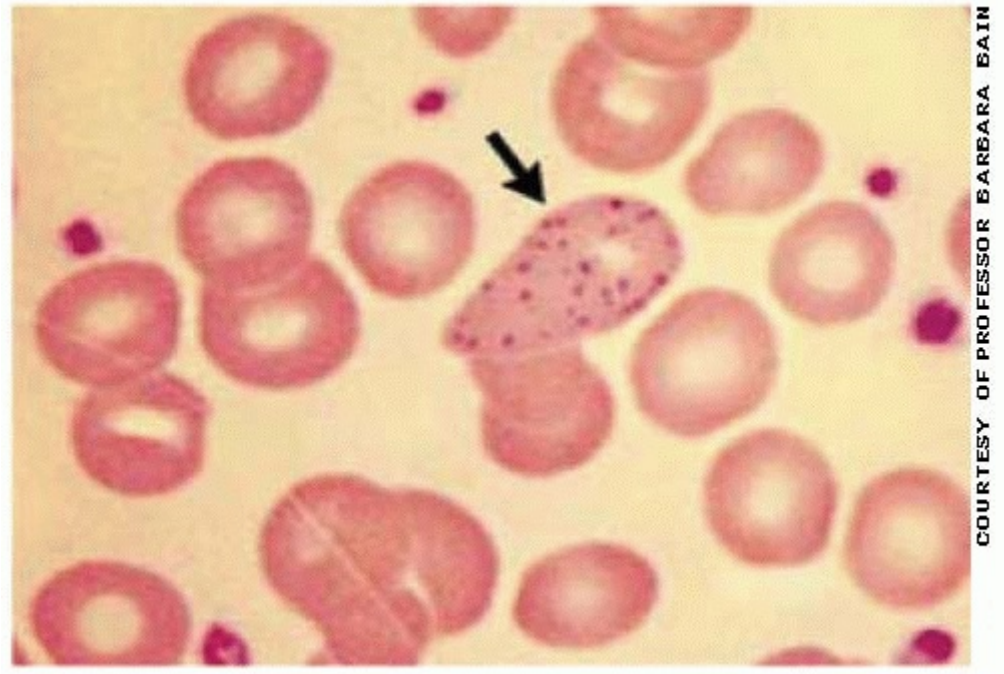


Fig 2. Basophilic stippling.[11]

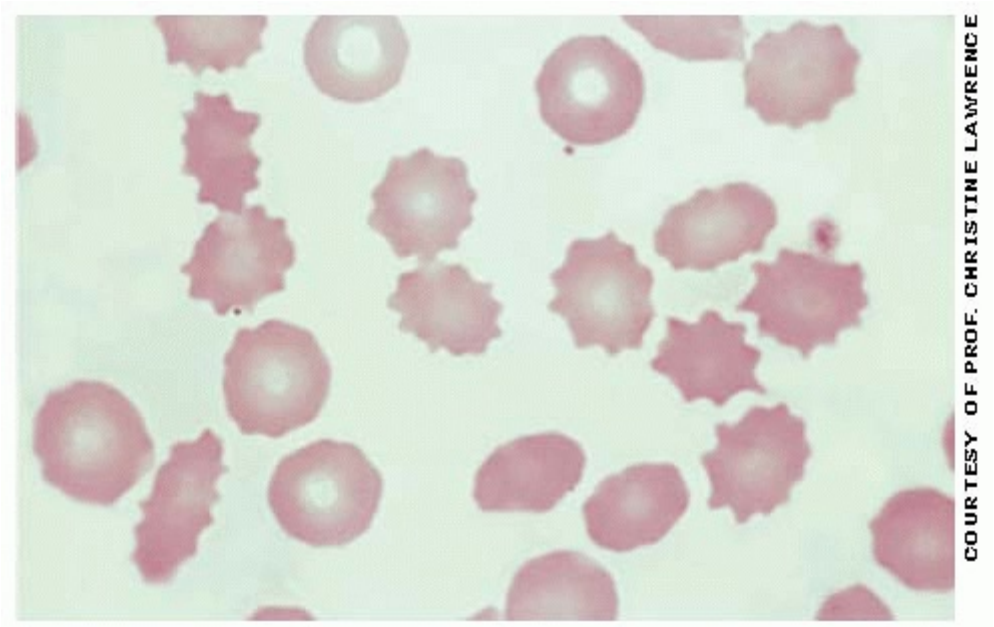


Fig 3. Burr cells.[12]

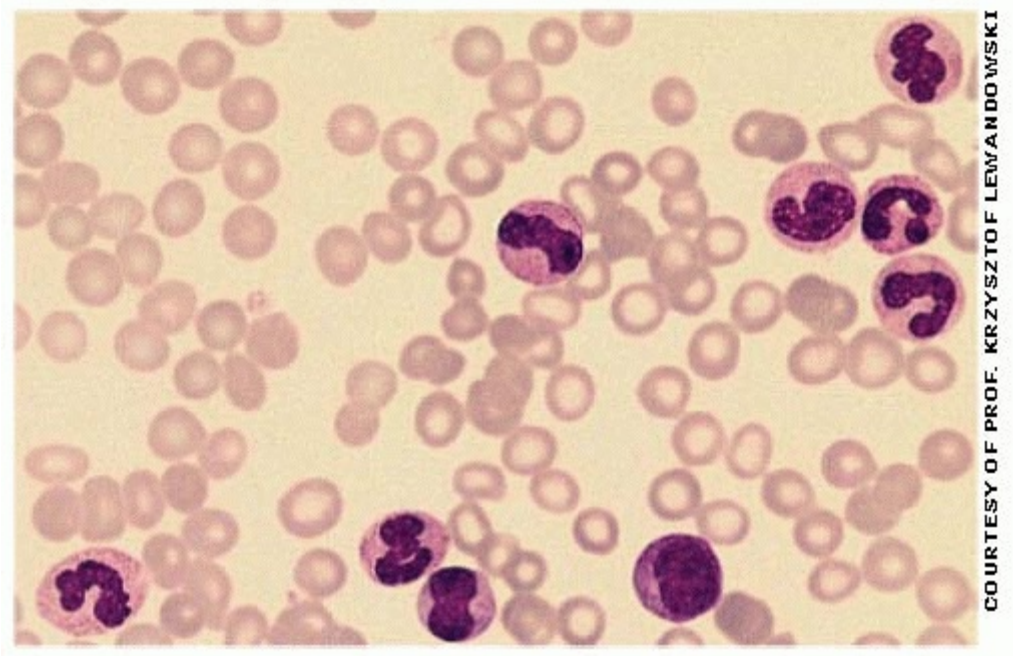


Fig 4. Left-shift: presence of immature neutrophils in the blood.[16]

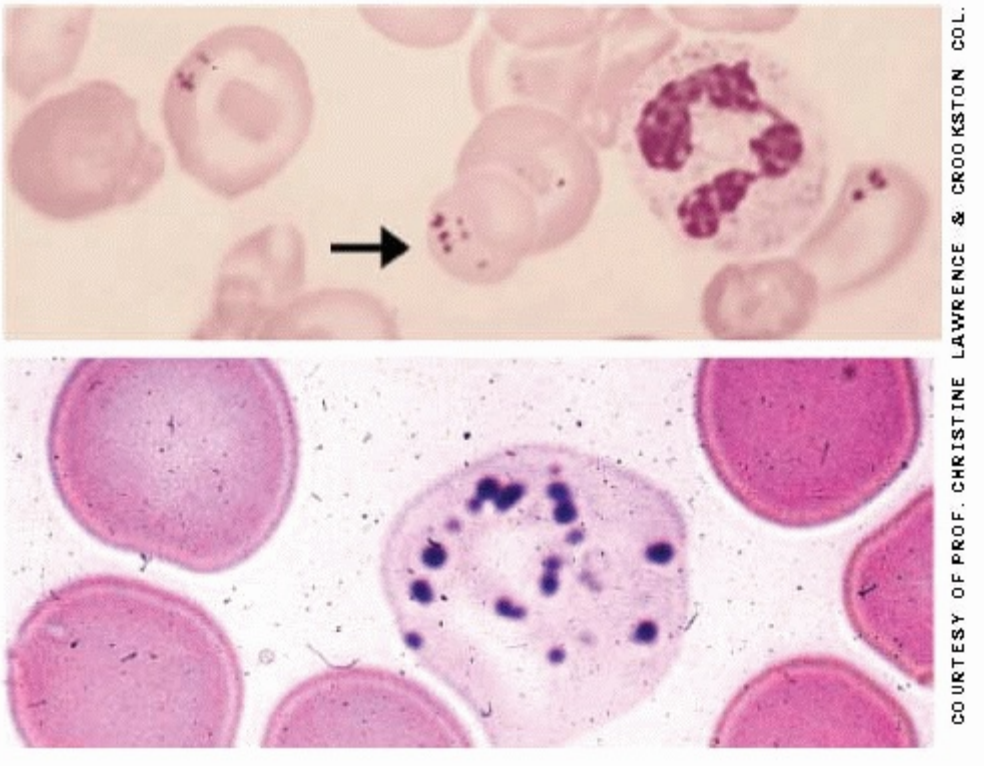


Fig 5. Pappenheimer bodies.[14] [15]

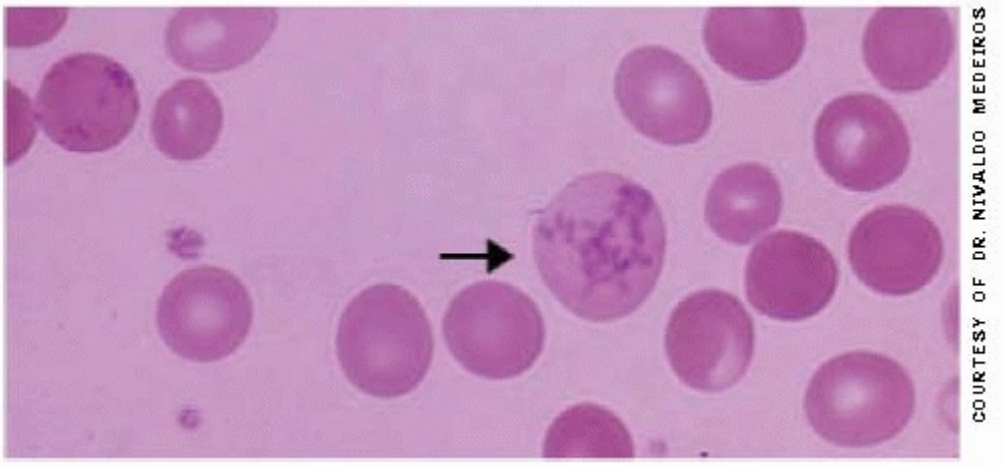


Fig 6. Reticulocytes. RNA in RBCs; supravital staining (azure B; cresyl blue) is needed.[13]

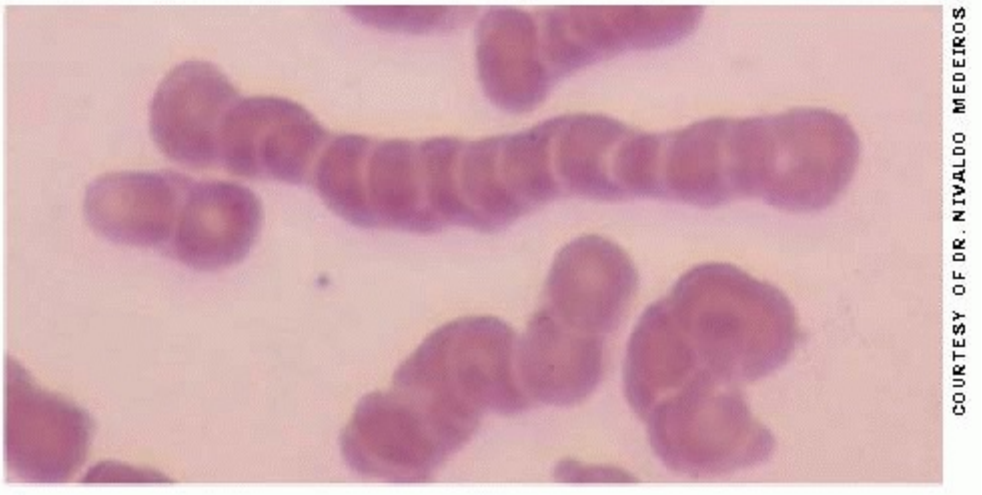


Fig 7. Rouleaux formation.[17]

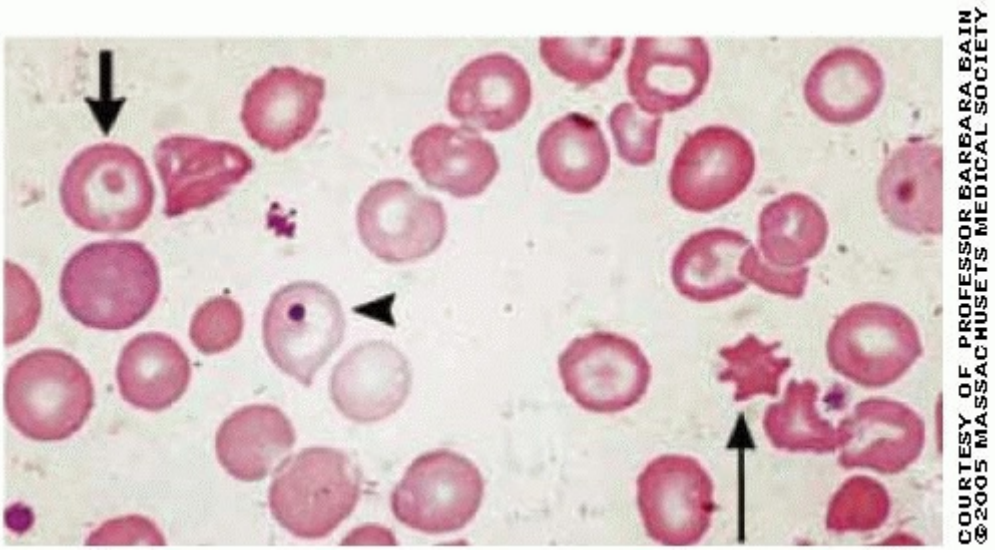


Fig 8. Film in hyposplenism: target cell (short arrow), acanthocyte (long arrow) and a Howell-Jolly body (arrow head).[18]

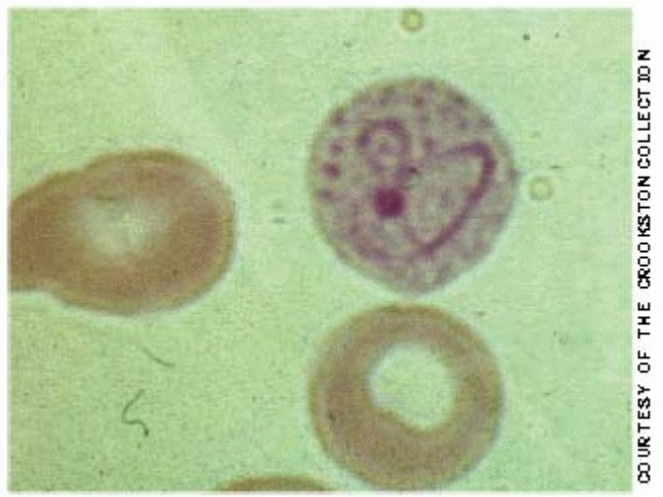


Fig 9. A Cabot ring; these red/purple-staining filamentous figure-of-8 rings are often seen in RBCs with basophilic stippling.[19] They may be microtubules from mitotic spindles or nuclear remnants. They occur in severe or megaloblastic anaemia, leukaemia, and lead poisoning. It is easy to

confuse them with malaria parasites, p385 (especially if stippling gives a 'chromatin dot' artefact, as here).[20]

The differential white cell count

Neutrophils

2-7.5 × 10^9/L (40-75% of white blood cells: but absolute values are more meaningful than percentages).

Increased in:

- Bacterial infections.
- Inflammation eg myocardial infarction, polyarteritis nodosa.
- Myeloproliferative disorders.
- Drugs (steroids).
- Disseminated malignancy.
- Stress eg trauma, surgery, burns, haemorrhage, seizure.

Decreased in:

(see p336)

- Viral infections.
- Drugs eg post-chemotherapy, cytotoxic agents, carbimazole, sulfonamides.
- Severe sepsis.
- Neutrophil antibodies (SLE, haemolytic anaemia)—↑ destruction.
- Hypersplenism eg Felty's syndrome (p357).
- Bone marrow failure—↓ production (p348).

Lymphocytes

1.5-4.5 × 10^9/L (20-45%).

Increased in:

- Acute viral infections.
- Chronic infections eg TB, Brucella, hepatitis, syphilis.
- Leukaemias and lymphomas, especially chronic lymphocytic leukaemia.

Large numbers of abnormal ('atypical') lymphocytes are characteristically seen with EBV infection: these are T-cells reacting against EBV-infected B-cells. They have a large amount of clearish cytoplasm with a blue rim that flows around neighbouring RBCs. Other causes of 'atypical' lymphocytes: see p389.

Decreased in:

- Steroid therapy; SLE; uraemia; Legionnaire's disease; HIV infection; marrow infiltration; post chemotherapy or radiotherapy.

T-lymphocyte subset reference values: CD4 count: 537-1571/mm3 (low in HIV infection). CD8 count: 235-753/mm3; CD4/CD8 ratio: 1.2-3.8.

Eosinophils

0.04-0.4 × 10^9/L (1-6%).[21]

Increased in:

- Drug reactions eg with erythema multiforme, p546.

- Allergies: asthma, atopy.
- Parasitic infections (especially invasive helminths).
- Skin disease: especially pemphigus, eczema, psoriasis, dermatitis herpetiformis.

Also seen in malignant disease (including lymphomas and eosinophilic leukaemia), PAN, adrenal insufficiency,[22] irradiation, Löffler's syndrome (p696), and during the convalescent phase of any infection.

The hypereosinophilic syndrome[1]

is a disease of unknown cause, with a sustained eosinophil count >1.5 × 10^9/L for more than 6wks, leading to end-organ damage (endomyocardial fibrosis causing restrictive cardiomyopathy, skin lesions, thromboembolic disease, pulmonary disease, neuropathy, and hepatosplenomegaly).

[1] Many previously diagnosed with this have been recently found to have monoclonal genetic abnormalities consistent with chronic eosinophilic leukaemia, with improved molecular techniques.

Monocytes

0.2-0.8 × 10^9/L (2-10%).

Increased in:

Post chemo- or radiotherapy, chronic infections (eg malaria, TB, brucellosis, protozoa), malignant disease (including M4 and M5 acute myeloid leukaemia—(p340), and Hodgkin's disease), myelodysplasia.

Basophils

0-0.1 × 10^9/L (0-1%).

Increased in:

Myeloproliferative disease, viral infections, IgE mediated hypersensitivity reactions (eg urticaria, hypothyroidism), and inflammatory disorders (eg UC, rheumatoid arthritis).

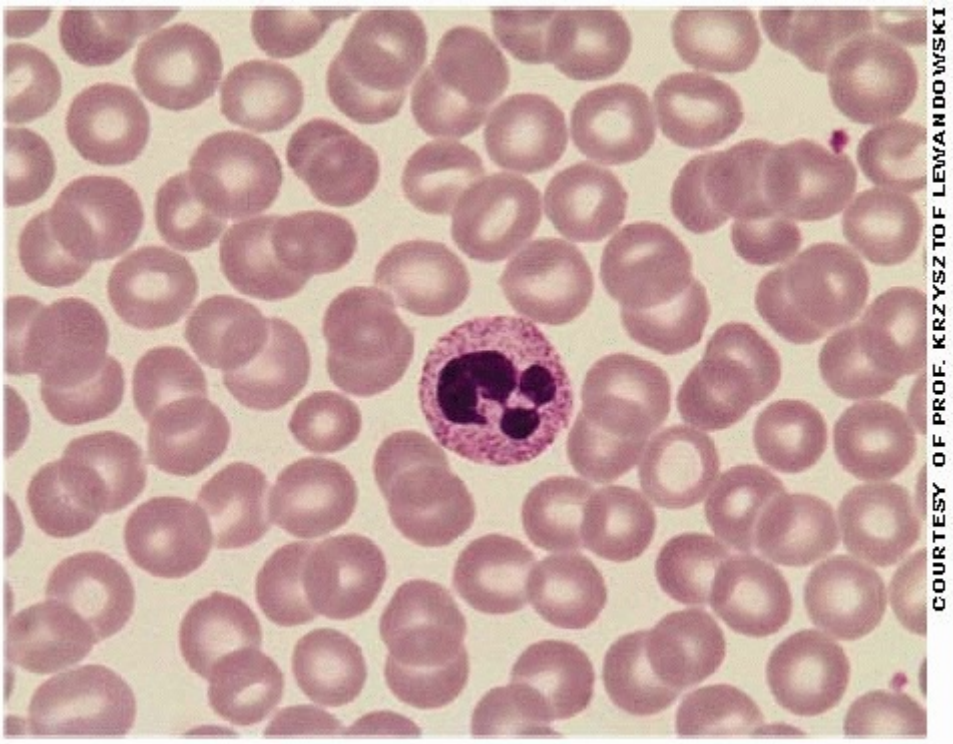


Fig 1. Neutrophil. These ingest and kill bacteria, fungi and damaged cells.[23]

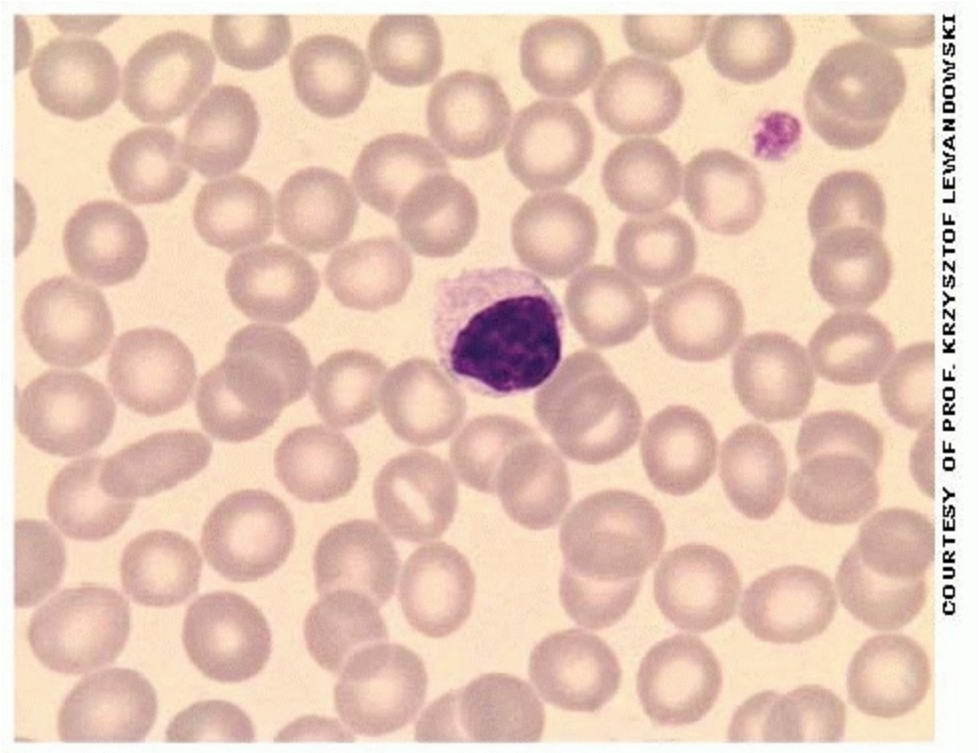


Fig 2. Lymphocyte: divided into T & B types, which have important roles in cell mediated immunity & antibody production.[24]

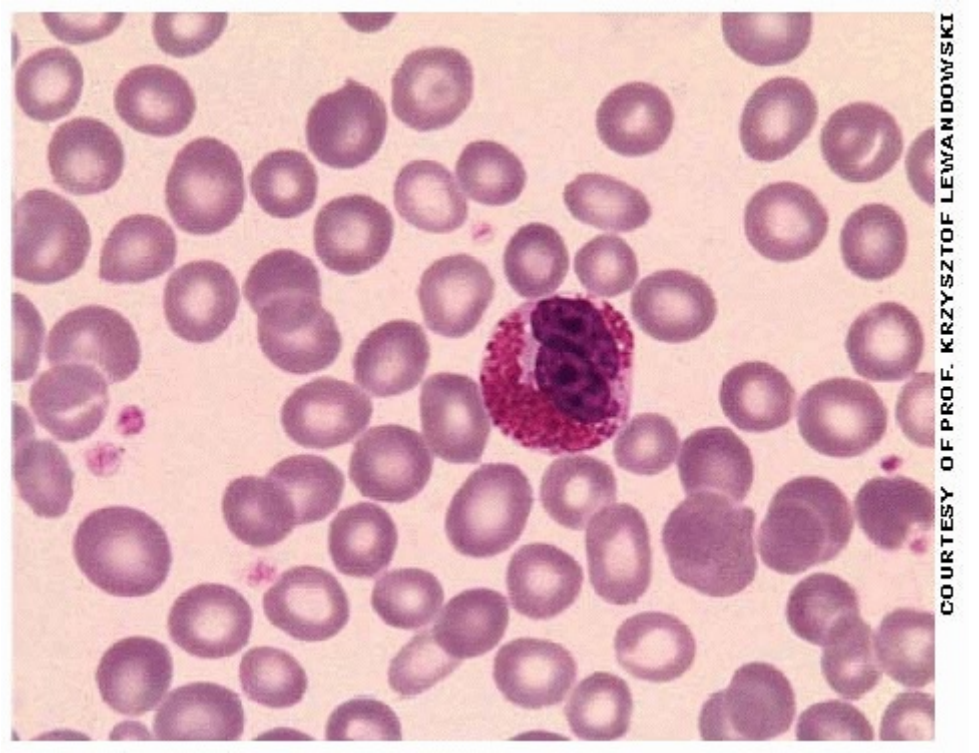


Fig 3. Eosinophil: these play a role in allergic reactions, and in defence against parasitic infections.[25]

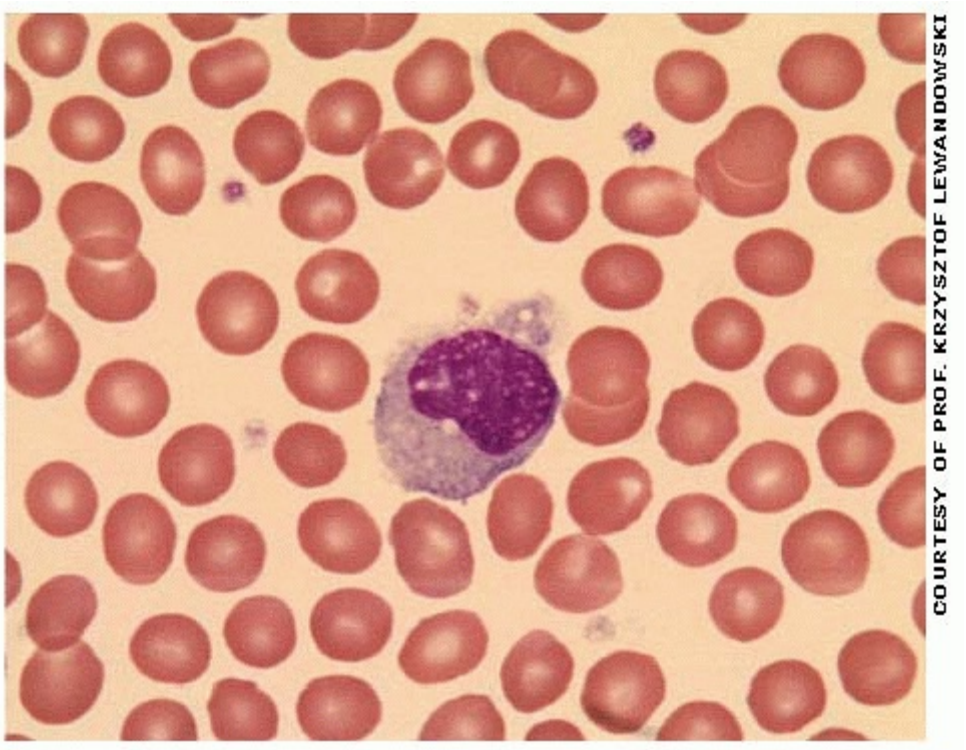


Fig 4. Monocyte: precursors of tissue macrophages.[26]

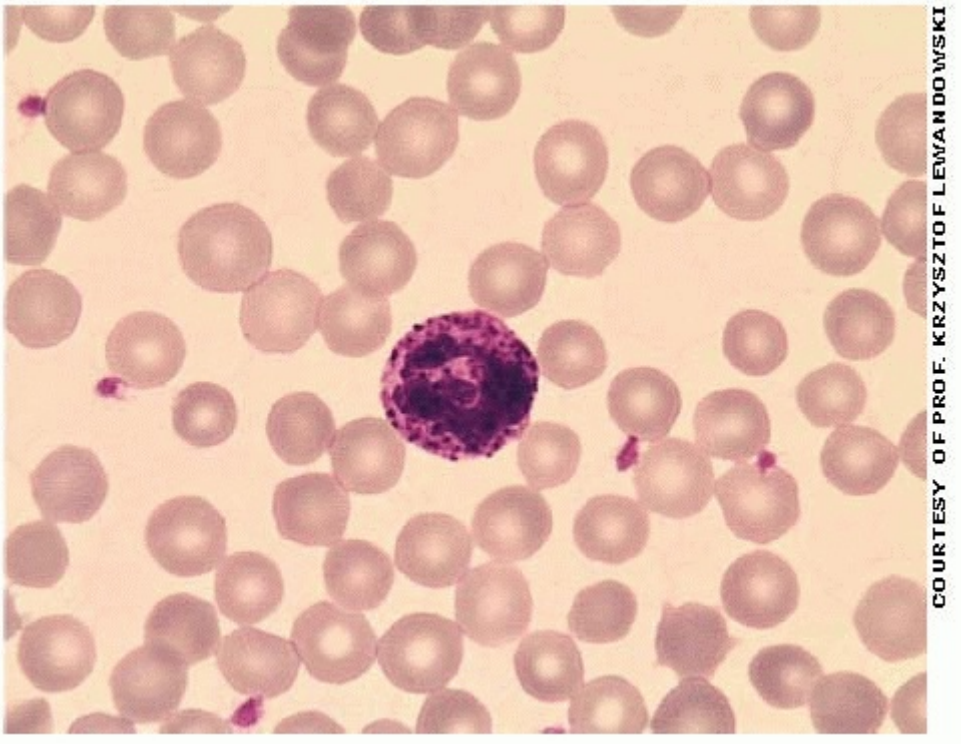


Fig 5. Basophil. The cytoplasm is filled with dark staining granules, containing histamine, myeloperoxidase and other enzymes. On binding IgE, histamine is released from the basophil.[27]

Macrocytic anaemia

Macrocytosis (MCV >96fL) is common, often due to alcohol excess without any accompanying anaemia. Although only ~5% are due to B_{12} deficiency, pernicious anaemia is the most common cause of a macrocytic anaemia in Western countries. B_{12} and folate deficiency are megaloblastic anaemias. A megaloblast is a cell in which nuclear maturation is delayed compared to the cytoplasm. This occurs with B_{12} and folate deficiency, as they are both required for DNA synthesis.

Causes of macrocytosis

- ***Megaloblastic:*** B_{12} deficiency, folate deficiency, cytotoxic drugs.
- ***Non-megaloblastic:*** Alcohol, reticulocytosis (eg in haemolysis), liver disease, hypothyroidism, pregnancy.
- ***Other haematological disease:*** Myelodysplasia, myeloma, myeloproliferative disorders, aplastic anaemia.

Tests:

B_{12} and folate deficiency result in similar blood film and bone marrow biopsy appearances.

Blood film:

Hypersegmented polymorphs in B_{12} and folate deficiency, (target cells if liver disease).

Other tests:

LFT (include γGT), TFT, serum B_{12} and serum folate (or red cell folate—a more reliable indicator of folate status, as serum folate only reflects *recent* intake).

Bone marrow biopsy

is indicated if the cause is not revealed by the above tests. It is likely to show one of the following four states:

1. Megaloblastic.
2. Normoblastic marrow (eg in liver disease, hypothyroidism).
3. Abnormal erythropoiesis (eg sideroblastic anaemia, leukaemia, aplasia).
4. Increased erythropoiesis (eg haemolysis).

Folate

is found in green vegetables, nuts, yeast & liver; it is synthesized by gut bacteria. Body stores can last for 3-4 months. Maternal folate deficiency may cause neural tube defects in the fetus. It is absorbed by duodenum and proximal jejunum.

Causes of deficiency

- Poor diet: eg poverty, alcoholics, elderly.
- Increased demand: eg pregnancy or ↑cell turnover (seen in haemolysis, malignancy, inflammatory disease and renal dialysis).
- Malabsorption: eg coeliac disease, tropical sprue.
- Drugs: eg alcohol, antiepileptics (phenytoin, sodium valproate), methotrexate, trimethoprim.

Treatment:

Assess for an underlying cause eg poor diet, malabsorption. Treat with folic acid 5mg/day PO for 4 months, ▸never without B_{12} unless the patient is known to have a normal B_{12} level, as in low B_{12} states, it may precipitate, or worsen, subacute combined degeneration of the spinal cord (p320). In pregnancy prophylactic doses of folate (400μg/day) are given from conception until at least 12 wks; this helps prevent spina bifida, as well as anaemia.

NB: In ill patients with megaloblastic anaemia (eg with CCF), it may be necessary to treat before the results of serum B_{12} and folate are at hand. Do tests then treat with large doses, eg hydroxocobalamin 1mg/24h IM, with folic acid 5mg/24h PO. Blood transfusions are very rarely needed, but see p310.

Folate and ischaemic heart disease

Previous observational studies have indicated that higher homocysteine concentrations are associated with a greater risk of coronary heart disease. It has been suggested that folic acid supplementation may have a role in prevention of cardiac disease by lowering homocysteine levels. However, trial results have so far been disappointing (further studies awaited).[28] One meta-analysis also showed no causal relationship between high homocysteine concentrations and coronary heart disease risk in Western populations.[29]

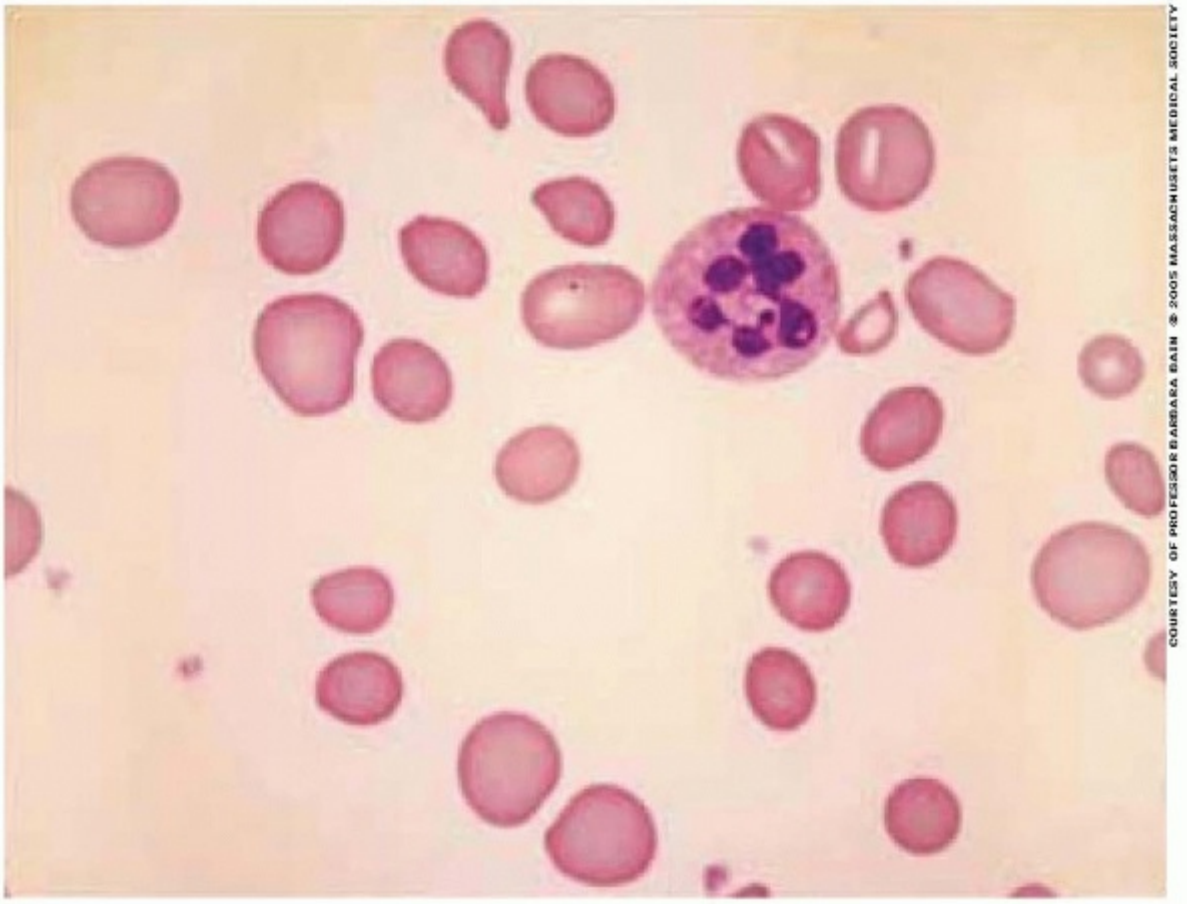


Fig 1. Megaloblastic anaemia: peripheral blood film showing many macrocytes and one hypersegmented neutrophil (normally there should be ≤5 segments).[30]

B_{12} deficiency and pernicious anaemia

Vitamin B_{12} is found in meat and dairy products, but not in plants. Body stores are sufficient for 4yrs. It is protein bound and released during digestion. B_{12} then binds to intrinsic factor in the stomach, and this complex is absorbed in the terminal ileum. In B_{12} deficiency, synthesis of thymidine, and hence DNA, is impaired, so red cell production is reduced.

Causes of deficiency:

• Dietary (eg vegans) • Malabsorption: *Stomach* (lack of intrinsic factor): pernicious anaemia, post gastrectomy; *Terminal ileum:* ileal resection, Crohn's disease, bacterial overgrowth, tropical sprue, tapeworms (*Dyphyllobothrium*) • Congenital abnormalities in metabolism.

Features:

General:

Symptoms of anaemia (p310), 'lemon tinge' to skin due to combination of pallor (anaemia) and mild jaundice (due to haemolysis), glossitis (beefy-red sore tongue), angular cheilosis (also known as stomatitis, p312).

Neuropsychiatric:

Irritability, depression, psychosis, dementia.

Neurological:

Paraesthesiae, peripheral neuropathy. Also:

Subacute combined degeneration of the spinal cord:

Onset is insidious (*subacute*) with peripheral neuropathy due to $\downarrow B_{12}$. There is a *combination* of symmetrical posterior (dorsal) column loss, causing sensory and LMN signs, and symmetrical corticospinal tract loss, causing motor and UMN signs (p438). Joint-position and vibration sense are often affected first leading to ataxia, followed by stiffness and weakness if untreated. The classical triad is: • Extensor plantars (UMN) • Absent knee jerks (LMN) • Absent ankle jerks (LMN). It may present with falls at night-time, due to a combination of ataxia and reduced vision, which is also seen with $\downarrow B_{12}$. Pain and temperature sensation may remain intact even in severe cases, as the spinothalamic tracts are preserved.

▸Neurological signs with B_{12} deficiency can occur without anaemia.

Pernicious anaemia (PA)

This is caused by an autoimmune atrophic gastritis, leading to achlorhydria and lack of gastric intrinsic factor secretion.

Incidence

1 : 1000; ♀:♂≈1.6:1; usually >40yrs; higher incidence if blood group A.

Associations

Other autoimmune diseases (p539): thyroid disease (~25%), vitiligo, Addison's disease, hypoparathyroidism. Carcinoma of stomach is ~3-fold more common in pernicious anaemia, so have a low threshold for upper GI endoscopy.

Tests

• Hb↓ (3-11g/dL) • MCV↑ •WCC & platelets ↓ in severe cases • Serum B_{12} ↓[1] • Reticulocytes ↓ or normal as production impaired • Hypersegmented polymorphs (p318) • Megaloblasts in the marrow • Specific tests for PA: **1** Parietal cell antibodies: found in 90% with PA, but also in 3-10% without. **2** Intrinsic factor (IF) antibodies: specific for pernicious anaemia, but lower sensitivity. These target B_{12} binding sites (in 50%) or ileal binding sites (in 35%). **3** Schilling test (BOX).

Treatment

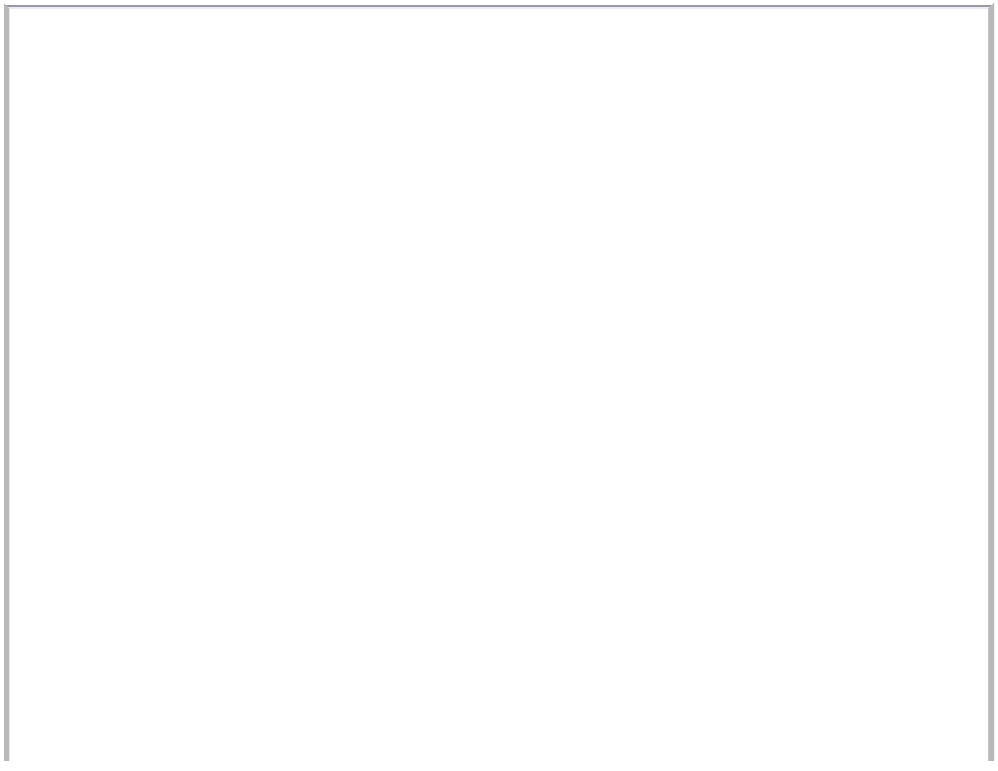
Treat the cause if possible. Most cases are due to malabsorption so injections are required. Replenish stores with hydroxocobalamin (B_{12}) 1mg IM alternate days eg for 2wks (or, if CNS signs, until improvement stops). Maintenance: 1mg IM every 3 months for life (child's dose: as for adult). If the cause is dietary, then oral B_{12} can be given after the initial acute course. Initial improvement is heralded by a transient marked reticulocytosis and hence ↑MCV, after 4-5 days.

Practical hints

- Beware of diagnosing PA in those under 40 yrs old: look for GI malabsorption (small bowel biopsy, p272).
- Watch for hypokalaemia as treatment becomes established.
- Transfusion is best avoided, but PA with high output CCF may require exchange transfusion (p310), after doing tests for FBC, folate, B_{12}, and marrow sampling.
- As haemopoiesis accelerates on treatment, additional iron may be needed.
- Hb rises ~1g/dL per week, WCC and platelet count should normalize in 1wk.

Prognosis

Supplementation usually improves peripheral neuropathy within the first 3-6 months, but has little effect on cord signs. Patients do best if treated as soon as possible after the onset of symptoms: don't delay!



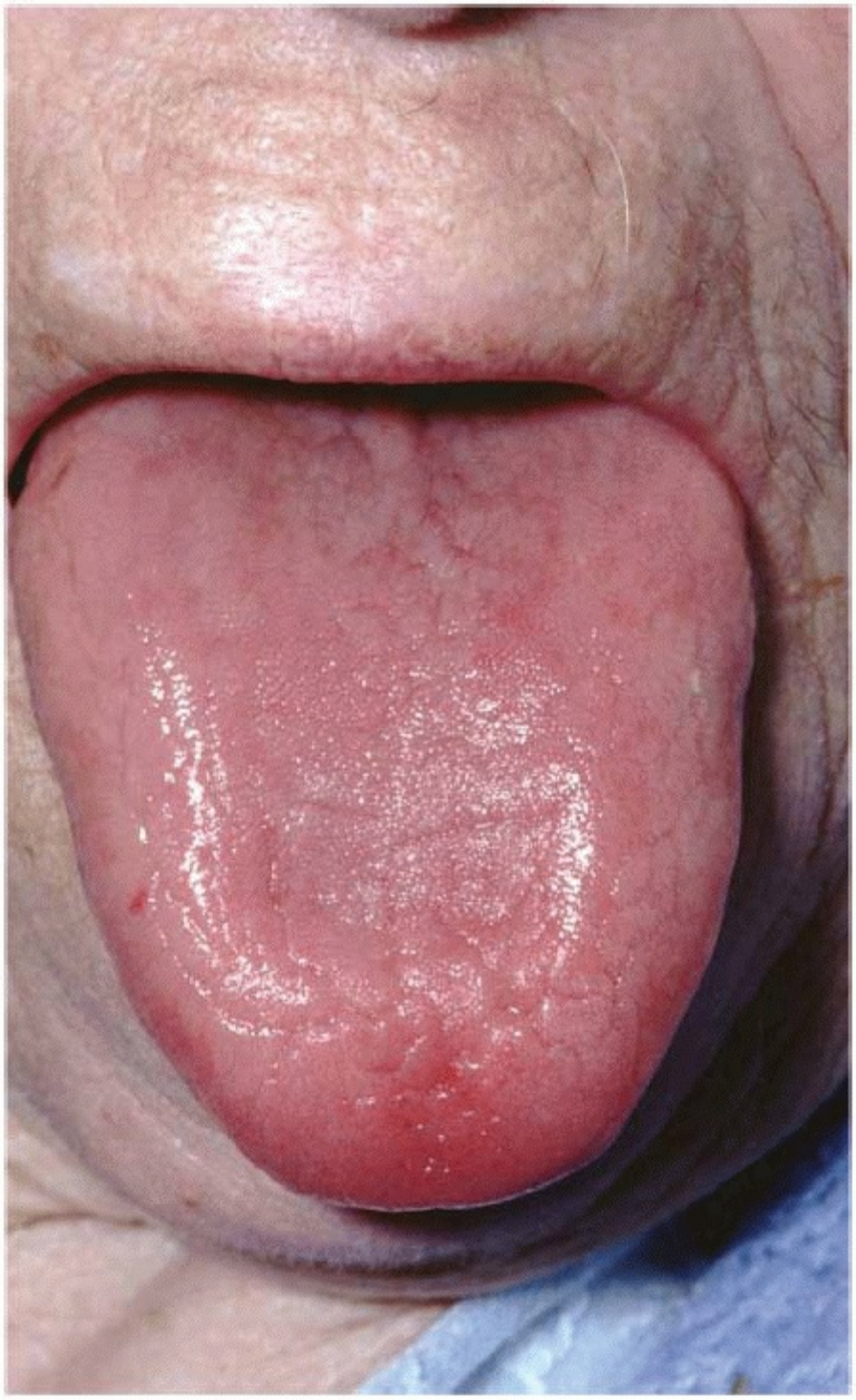


Fig 1. Glossitis in B_{12} deficiency.

Schilling test [31]

If there is B_{12} deficiency, and the parietal cell and intrinsic factor antibodies do not give the answer, consider a Schilling test to help to identify the cause. This determines whether a low B_{12} is due to malabsorption from the terminal ileum or due to a lack of intrinsic factor—by comparing the proportion of an oral dose (1µg) of radioactive B_{12} absorbed and hence excreted in urine, with and without the concurrent administration of intrinsic factor (the blood must be saturated by giving an IM dose of 1000µg of B_{12} first). If intrinsic factor enhances absorption leading to increased urine B_{12}, then lack of intrinsic factor, ie pernicious anaemia, is likely to be the cause. Note that the Schilling test is rather cumbersome, and some labs have stopped offering this test, hoping to rely on serology testing for parietal cell and intrinsic factor antibodies, and the plasma response to oral or IM B_{12}.

An approach to haemolytic anaemia[1]

Haemolysis is the premature breakdown of RBCs, before their normal life span of ~120d. It occurs in the circulation (*intravascular*) or in the reticuloendothelial system ie macrophages of liver, spleen and bone marrow (*extravascular*). In sickle-cell anaemia, lifespan may be as short as 5d. Haemolysis may be asymptomatic, but if the bone marrow does not compensate sufficiently, a haemolytic anaemia results.

An approach is to first confirm haemolysis and then find the cause—try to answer these 4 questions:

1. ***Is there increased red cell breakdown?***

   - Anaemia with normal or ↑MCV.
   - ↑Bilirubin: unconjugated, from haem breakdown (prehepatic jaundice).
   - ↑Urinary urobilinogen (no urinary conjugated bilirubin).
   - ↑Serum lactic dehydrogenase (LDH), as released from the RBC.

2. *Is there increased red cell production?*

   - ↑Reticulocytes, causing ↑MCV (reticulocytes are large immature RBCs) and polychromasia.

3. *Is the haemolysis mainly extra- or intravascular?*

   Extravascular haemolysis may lead to splenic hypertrophy and splenomegaly. Features of intravascular haemolysis are:

   - ↑Free plasma haemoglobin: released from RBCs.
   - Methaemalbuminaemia: some free Hb is broken down in the circulation to produce haem and globin; haem combines with albumin to make methaemalbumin.
   - ↓Plasma haptoglobin: mops up free plasma Hb, then removed by the liver.
   - Haemoglobinuria: causes red-brown urine, in absence of red blood cells.
   - Haemosiderinuria: occurs when haptoglobin binding capacity is exceeded, causing free Hb to be filtered by the renal glomeruli, absorption of free Hb via the renal tubules and storage in the tubular cells as haemosiderin. This is detected in the urine in sloughed tubular cells by Prussian blue staining ~1 week after onset (implying a *chronic* intravascular haemolysis)

4. *Why is there haemolysis?* Causes are on p324.

History

Family history, race, jaundice, dark urine, drugs, previous anaemia, travel.

Examination

Jaundice, hepatosplenomegaly, gallstones (pigmented, due to ↑bilirubin from haemolysis), leg ulcers (due to poor blood flow).

Investigation

FBC, reticulocytes, bilirubin, LDH, haptoglobin, urinary urobilinogen. Thick and thin films for malaria screen if history of travel. The blood film may show polychromasia and macrocytosis due to reticulocytes, or point to the diagnosis:

- Hypochromic microcytic anaemia (thalassaemia).
- Sickle cells (sickle cell anaemia).
- Schistocytes (microangiopathic haemolytic anaemia).
- Abnormal cells in haematological malignancy.
- Spherocytes (hereditary spherocytosis or autoimmune haemolytic anaemia).
- Elliptocytes (hereditary elliptocytosis).
- Heinz bodies, "bite" cells[2], (glucose-6-phosphate dehydrogenase deficiency).

Further tests:

- *Direct antiglobulin (Coombs') test* (DAT) identifies red cells coated with antibody or complement. A positive result indicates an immune cause of the haemolysis.
- RBC lifespan may be determined by *chromium labelling* and the major site of RBC breakdown may also be identified. This test is rarely done now.

The cause may now be obvious, but further tests may be needed. Membrane abnormalities are identified on the film and can be confirmed by *osmotic fragility* testing. Hb *electrophoresis* will detect haemoglobinopathies. *Enzyme assays* are reserved for situations when other causes have been excluded.

Causes of haemolytic anaemia

Acquired—these are divided into immune and non-immune causes.

- **Immune mediated** (=direct antiglobulin test +ve).

- ***Drug-induced*** Causing formation of RBC autoantibodies from binding to the RBC membrane (eg penicillin) or production of immune complexes (eg quinine).
- ***Autoimmune haemolytic anaemia (AHA)*** Mediated by autoantibodies causing mainly extravascular haemolysis and spherocytosis. They are divided by their optimal binding temperature to RBCS. ***Warm AHA:*** IgG-mediated, bind at body 37°C. ***Treatment:*** Steroids/immunosuppressants (± splenectomy). ***Cold AHA:*** IgM-mediated, bind at lower temperature (<4°C), activating cell surface complement. Causes a chronic anaemia made worse by cold, often with Raynaud's or acrocyanosis. ***Treatment:*** Keep warm. Chlorambucil may help. ***Causes:*** Most are idiopathic; secondary causes of warm AHA include lymphoproliferative disease (eg CLL, lymphoma), drugs, autoimmune disease eg SLE. Cold AHA may follow infections eg ***Mycoplasma pneumoniae***, EBV.
- ***Paroxysmal cold haemoglobinuria*** is seen with viruses/syphilis. It is caused by the Donath-Landsteiner antibodies, which stick to RBCs in cold, and cause complement-mediated haemolysis on rewarming. Haemolysis is self-limiting.

- Isoimmune Acute transfusion reaction (p571); haemolytic disease of newborn.
- Microangiopathic haemolytic anaemia (MAHA) A mechanical disruption of RBCs in circulation, causing intravascular haemolysis and schistocytes. Causes include haemolytic-uraemic syndrome (HUS), TTP (p300), DIC, pre-eclampsia, eclampsia. Treat the underlying disease; transfusion or plasma exchange may be needed. Also caused by intravascular devices eg prosthetic heart valves.
- Infection eg malaria (p382): RBC lysis and 'blackwater fever' (haemoglobinuria).
- Paroxysmal nocturnal haemoglobinuria RBCs (also platelets, neutrophils) are sensitive to complement-mediated lysis due to an inherited loss of surface glucosylphosphatidylinositol (GPI). There is chronic intravascular haemolysis (especially at night→haemoglobinuria), pancytopenia, and ↑thrombosis (eg Budd- Chiari syndrome, p688). ***Diagnosis:*** Urinary haemosiderin +ve. Cellular immunophenotype shows altered GPI. Ham's test +ve (***in vitro*** acid-induced lysis, but rarely done now). ***Â:*** Anticoagulation. Stem cell transplant may be curative.

Hereditary

Is there a defect in RBC enzymes, membrane, or Hb?

Enzyme defects:

- *Glucose-6-phosphate dehydrogenase (*G6PD*) deficiency* is the commonest RBC enzyme defect. Inheritance is X-linked, affecting 100 million mainly û in Africa, Mediterranean and Middle/Far East. Most are asymptomatic, but are susceptible to oxidative crises due to ↓glutathione production, precipitated by many drugs (eg primaquine, sulfonamides, aspirin), exposure to the broad bean *Vicia fava* (favism) or illness. During an attack, there is rapid anaemia and jaundice, with bite cells and blister cells on the film. *Diagnosis:* Enzyme assay. Don't do until ~2- 3 months after a crisis: young RBCs may have sufficient enzyme so results may appear normal. *Â:* Avoid precipitants; transfuse if severe.
- *Pyruvate kinase deficiency* Autosomal recessive, ↓ATP production causing shortened red cell survival. Homozygotes have neonatal jaundice; later, chronic haemolysis with splenomegaly and jaundice. *Diagnosis:* Enzyme assay. *Â:* Often the condition is well tolerated. No specific therapy—splenectomy may help.

Membrane defect—Hereditary spherocytosis

Autosomal dominant RBC membrane defect.[32] Less deformable spherical RBCs, so trapped in spleen → extravascular haemolysis.

Signs:

Splenomegaly, jaundice. *δ:* Mild anaemia. Film (p314): many spherocytes. Osmotic fragility tests: RBCs show ↑fragility in hypotonic solutions.

- ***Hereditary elliptocytosis*** Autosomal dominant, most are asymptomatic.

  Treatment: Folate, splenectomy is curative but reserved for severe cases.
- ***Haemoglobinopathy: Sickle-cell disease*** p326.
- ***Thalassaemia*** p328.

Factors exacerbating haemolysis

Infection leads to ↑haemolysis. The anaemia may be exacerbated by parvoviruses (OHCS p142), producing a cessation of marrow erythropoiesis, ie aplastic anaemia, with no reticulocyte formation (p348).

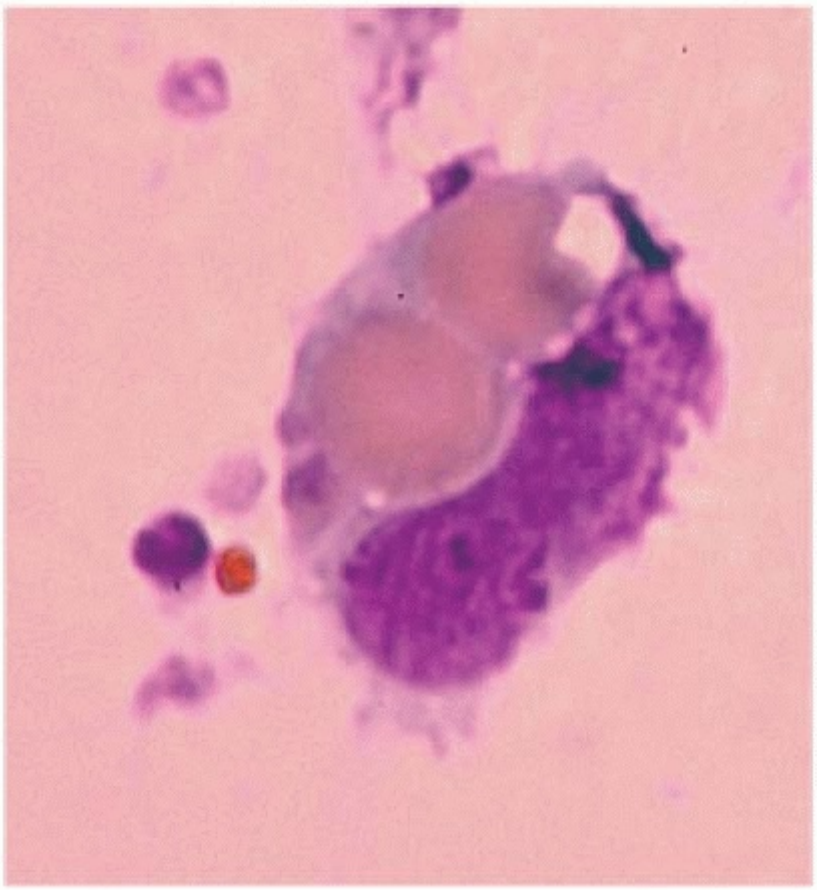


Fig 1. Autoimmune haemolytic anaemia: antibody coated red cells undergoing phagocytosis by monocytes.[33]

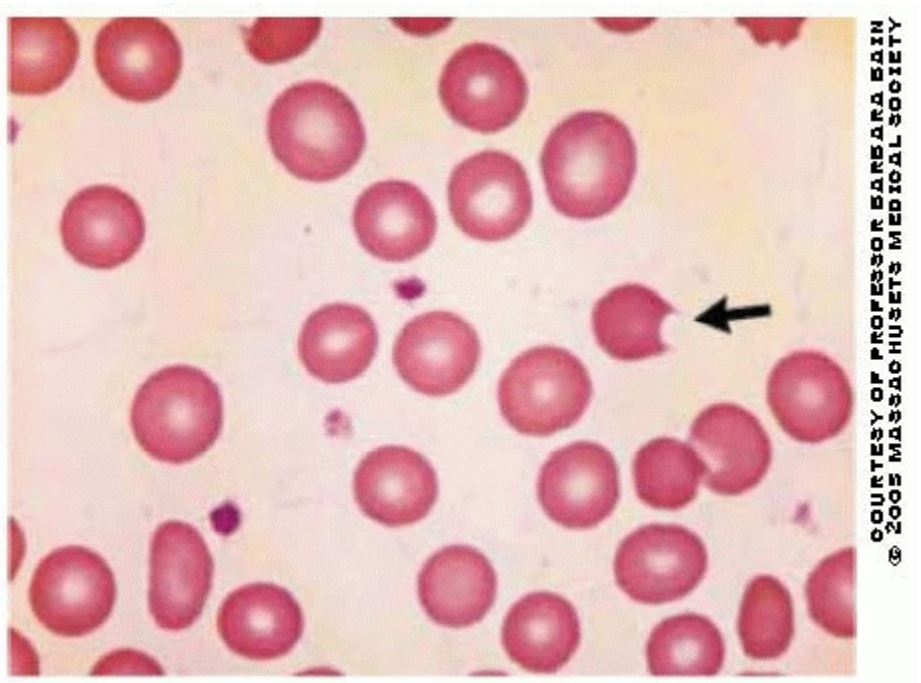


Fig 2. A 'bite' cell in G6PD, following removal of Heinz bodies by the spleen. Heinz bodies are formed from oxidized, denatured Hb during oxidative crises.[34]

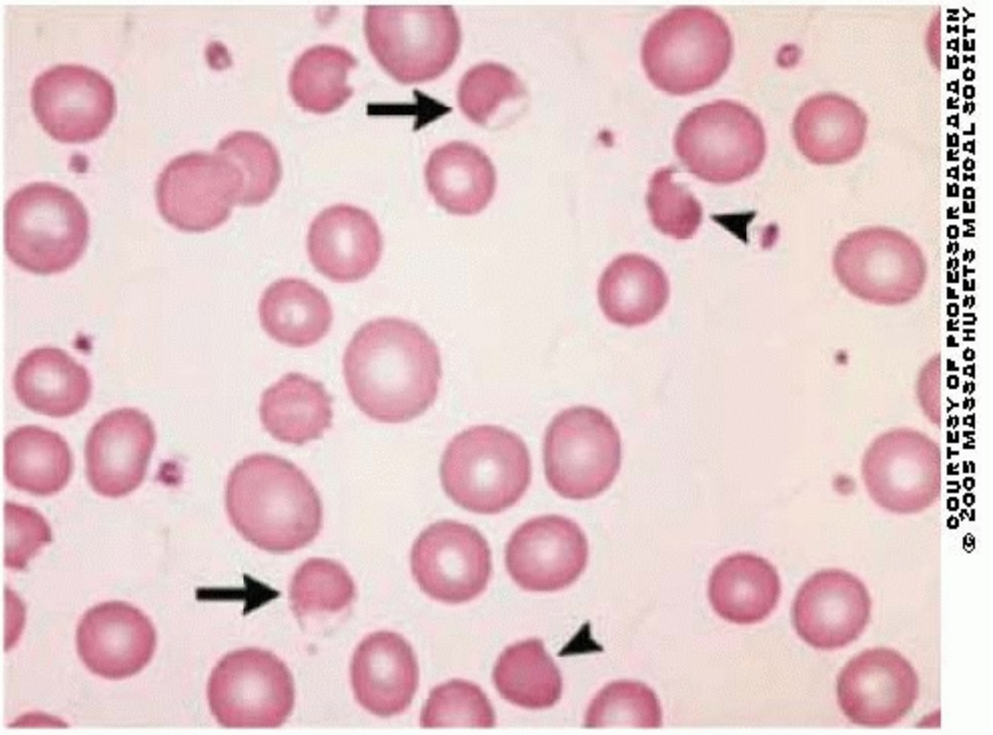


Fig 3. 'Blister' cells (arrows) in G6PD, following removal of Heinz bodies. Also contracted red cells (arrowheads).[35]

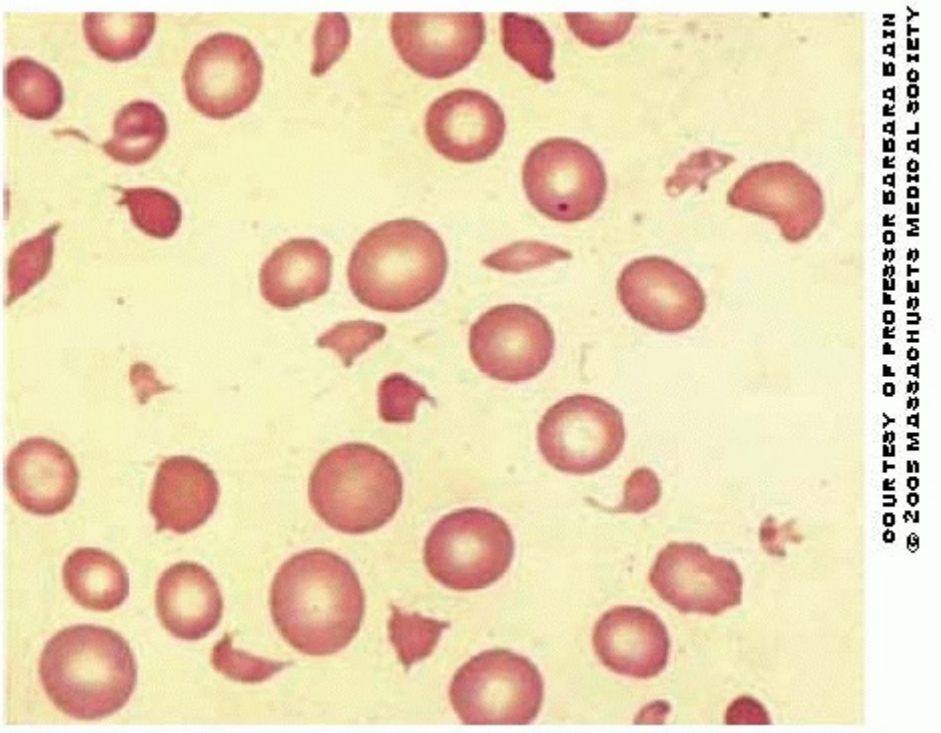


Fig 4. Microangiopathic anaemia eg from DIC: numerous cell fragments (schistocytes) are present.[36]

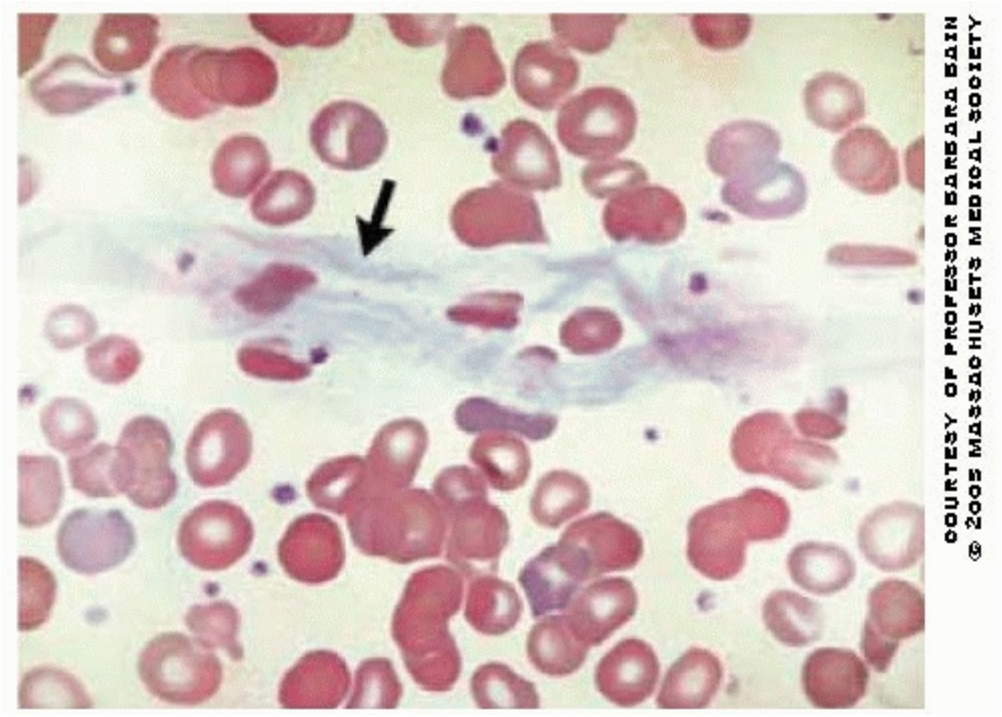


Fig 5. Fibrin strands, deposited in HUS & TTP (p300), slice up passing red cells (microangiopathic anaemia).[37]

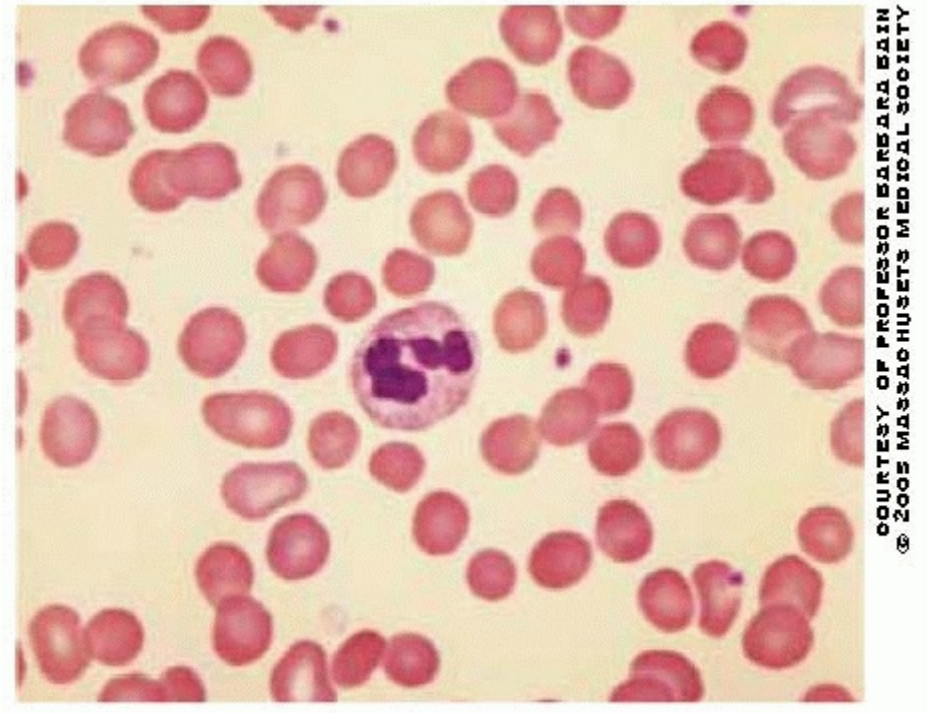


Fig 6. Hereditary spherocytosis.[38]

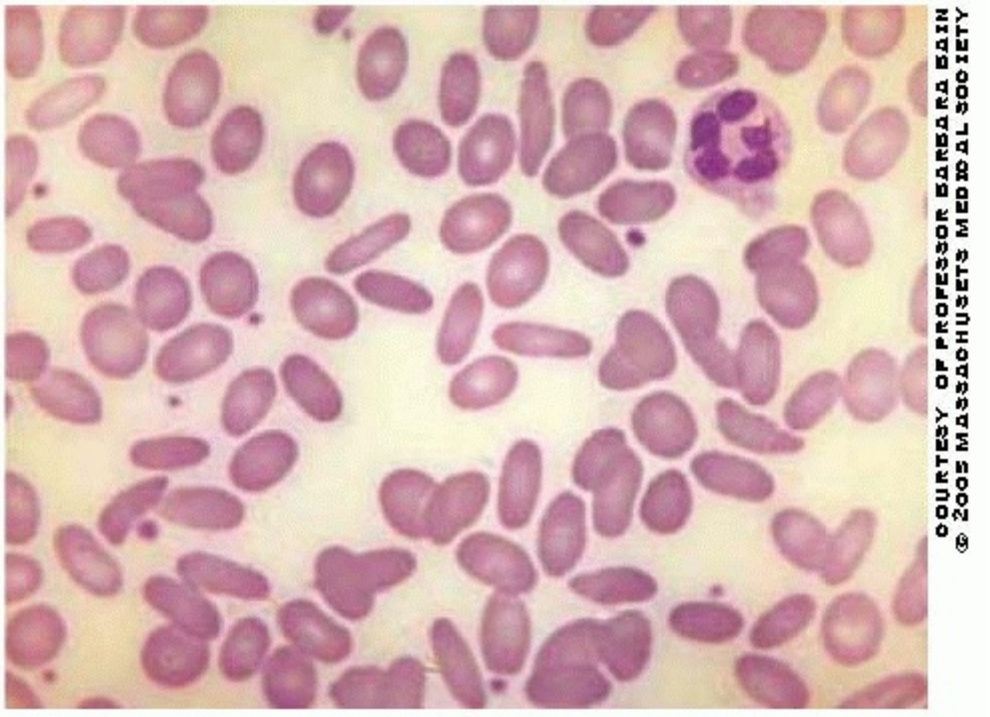


Fig 7. Hereditary elliptocytosis.[39]

Sickle-cell anaemia

Sickle-cell anaemia is an autosomal recessive disorder causing production of abnormal ß globin chains. An amino acid substitution in the gene coding for the ß chain (Glu ↑ Val at position 6), results in the production of HbS rather than HbA. HbA2 and HbF are still produced. It is common in people of African origin. The homozygote (SS) has sickle-cell *anaemia* (HbSS), and heterozygotes (HbAS) have sickle-cell *trait*, which causes no disability (and protects from *falciparum* malaria) except in hypoxia, eg in unpressurized aircraft or anaesthesia, when vaso-occlusive events may occur, so all those of African descent need a sickle cell test pre-op. Symptomatic sickling also occurs in heterozygotes with genes coding other Hb variants (eg HbC leading to HbSC, or ß-thalassaemia trait leading to HbS/ßthal).

Pathogenesis

HbS polymerizes when deoxygenated, causing RBCs to deform. This produces sickle cells, which are fragile and haemolyse, and also block small vessels.

Tests

Haemolysis is variable. Hb ≈ 6-9g/dL, ↑reticulocytes 10-20%, ↑bilirubin. *Film:* sickle cells and target cells. *Sickle solubility test:* +ve, but does not distinguish between HbSS and HbAS. Hb *electrophoresis:* Confirms the diagnosis and distinguishes SS, AS states, and other Hb variants. Aim for diagnosis *at birth* (cord blood) to aid prompt pneumococcal prophylaxis (vaccine, p152, or penicillin V).

Signs and symptoms

are highly variable. There is a chronic haemolytic anaemia, usually well tolerated unless there is a supervening crisis (below and see BOX).

Vaso-occlusive 'painful' crises:

Common, due to micro-vascular occlusion. Often affects the bone marrow, causing severe pain. Precipitated by cold, dehydration, infection or hypoxia. Hands and feet are affected in children <3yrs leading to dactylitis. Occlusion may also cause mesenteric ischaemia, mimicking an acute abdomen. Cerebral infarction occurs in ~10% of children, leading to stroke, seizures or cognitive defects. Transcranial Doppler ultrasonography indicates risk of impending stroke, and blood transfusions can be used to prevent this, by reducing HbS.[40] Priapism may occur; if >12h, arrange prompt cavernosus-spongiosum shunting—prevents future erectile dysfunction (also occurs in CML, p342).

Aplastic crises:

This is due to Parvovirus B19, with sudden reduction in marrow production, especially RBCs. Usually self-limiting <2wks, transfusion may be needed.

Sequestration crises:

Mainly affects children as the spleen has not yet undergone atrophy. There is pooling of blood in the spleen ± liver, with organomegaly, severe anaemia and shock. Urgent transfusion is needed.

Complications

•Splenic infarction occurs before 2yrs old, due to repeated microvascular occlusion, leading to ↑susceptibility to infection (p357) •Growth impairment •Bone necrosis due to ↓blood supply, especially the femoral head •Chronic renal failure •Chronic leg ulcers •Gallstones •Retinal disease and visual impairment •Multiple blood transfusions may lead to iron overload or blood-borne infection •Long-term lung damage—hypoxia, fibrosis and pulmonary hypertension, partly preventable by incentive spirometry—10 maximal inspirations/2h.[41]

Management of chronic disease

- Consider hydroxycarbamide (hydroxyurea) if frequent crises.[1]
- Splenic infarction leads to hyposplenism. Prophylaxis, in terms of antibiotics and immunization should be given (p357).
- Febrile children risk septicaemia: repeated admission may be avoided by outpatient ceftriaxone (eg 2 doses, 50mg/kg IV on day 0 and 1). Admission may still be needed, eg if Hb <5g/dL, WCC <5 or >30 × 10^9/L, T° >40°C, severe pain, dehydration, lung infiltration. Seek expert advice.
- Bone marrow transplant can be curative, but remains controversial.

[1] Long-term hydroxycarbamide causes ↑production of fetal haemoglobin (HbF) and decreased Hb polymerization, causing reduction in painful crises, acute chest syndrome, admissions, blood transfusions and mortality.[] This may result from fewer episodes of bone marrow ischaemia and embolization.

Prevention

Genetic counselling; prenatal tests (OHCS p152-3). Parental education can help prevent 90% of deaths from sequestration crises.[42]

Management of sickle-cell crisis[1] ▸Seek expert help early.

- Give *prompt*, generous analgesia, eg IV opiates (see p560).
- Crossmatch blood. FBC, reticulocytes, blood cultures, MSU ± CXR if fever or chest symptoms.
- Rehydrate with IVI and keep warm.
- Give O_2 by mask if P_aO_2↓ or O_2 sats <95%.
- 'Blind' antibiotics (eg cephalosporin, p372) if fever T° >38°, unwell, or chest symptoms, after sending infection screen.
- Measure PCV, reticulocytes, liver, and spleen size twice daily.
- Give blood transfusion if Hb or reticulocytes fall sharply. Match blood for the blood group antigens Rh(C, D, E) and Kell, to prevent formation of antibodies. Red cell transfusion improves oxygenation, and is as good as exchange transfusion, which is reserved for those who are rapidly deteriorating.[43] ***Exchange transfusion*** is a process where blood is removed and donor blood is given in stages. Indications: severe chest crisis, suspected CNS event or multiorgan failure—when the proportion of HbS should be reduced to <30%.

The acute chest syndrome:

Entails pulmonary infiltrates involving complete lung segments, causing pain, fever, tachypnoea, wheeze, and cough. It is a serious condition. Incidence: ~0.1 episodes/patient/yr. 13% in the landmark Vichinsky study needed ventilation, 11% had CNS symptoms, and 9% of those over 20 years old died. Prodromal painful crisis occur ~2.5 days before any abnormalities on CXR in 50% of patients. The chief causes of the infiltrates are fat embolism from bone marrow or infection with *Chlamydia*, *Mycoplasma*, or viruses.[44] *Â:* Oxygen, analgesia, empirical antibiotics (cephalosporin + macrolide) until culture results known. Bronchodilators (eg salbutamol, p167) have proved to be very effective in those with wheezing or obstructive pulmonary function at presentation. Blood transfusion (exchange if severe). *Take to* ITU if PaO_2 cannot be kept above 9.2kPa (70mmHg) when breathing air.

Patient-controlled analgesia (PCA):

An example with paediatric doses. First try warmth, hydration, and oral analgesia: ibuprofen 5mg/kg/6h PO (codeine phosphate 1mg/kg/4-8h PO up to 3mg/kg/d may also be tried, but is relatively ineffective). If this fails, see on the ward and offer prompt morphine by IVI—eg 0.1mg/kg. Start PCA with morphine 1mg/kg in 50mL 5% dextrose, and try a rate of 1mL/h, allowing the patient to deliver extra boluses of 1mL when needed. Do respiration and sedation score every 1/4h + pulse oximetry if chest/abdominal pain.[45] For further advice, liaise with the local pain service.

[1] Brit. Committee for Standards in Haem. Management of the acute painful crisis in sickle cell disease.[]

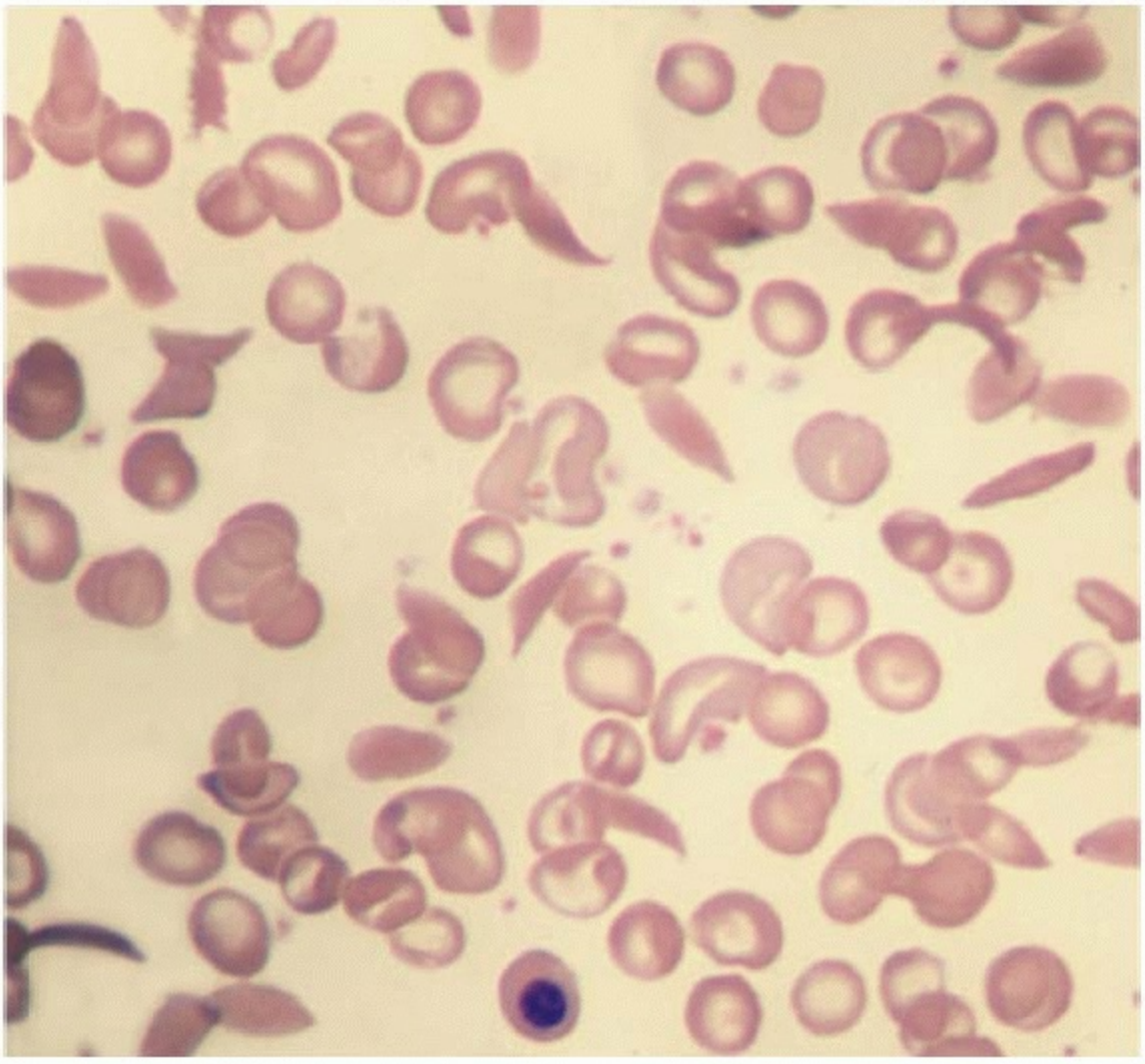


Fig 1. Blood film in sickle-cell anaemia: there are sickle cells, target cells, and a nucleated red cell.[46]

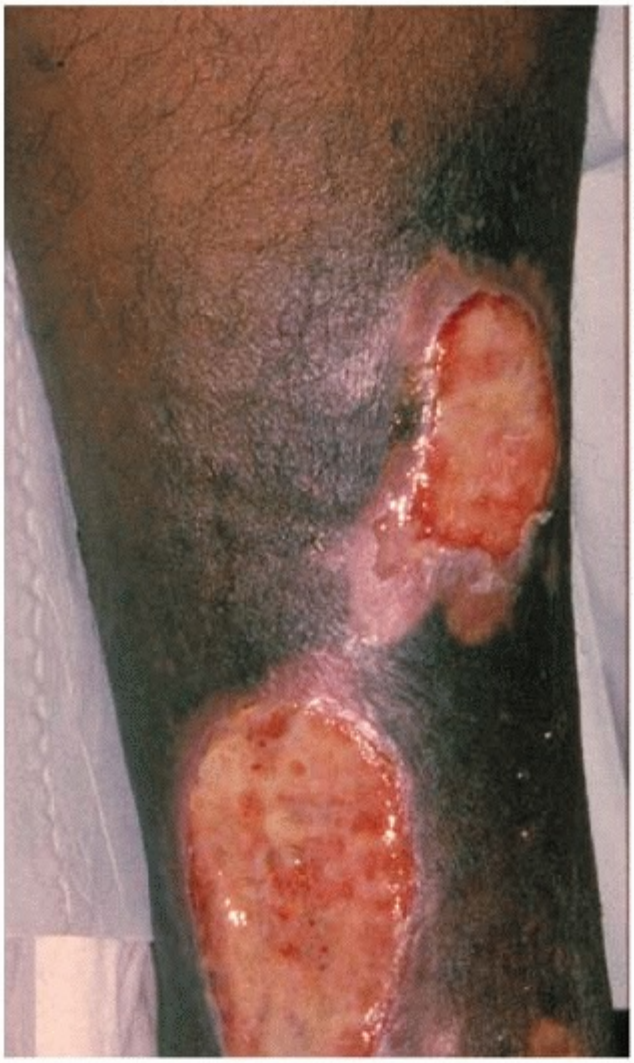


Fig 2. Leg ulcers in sickle cell disease.[47]

Thalassaemia

The thalassaemias are genetic diseases of unbalanced Hb synthesis, as there is underproduction (or no production) of one globin chain (BOX). Unmatched globins precipitate, damaging RBC membranes, causing their haemolysis while still in the marrow. They are common in areas from the Mediterranean to the Far East.

The β thalassaemias

are usually caused by point mutations in β-globin genes on chromosome 11, leading to ↓β chain production (β+) or its absence (β0). Various combinations of mutations are possible (eg β0/β0, β+/β+, or β+/β0).

Tests

FBC, MCV, film, iron, HbA_2, HbF, Hb electrophoresis.

β thalassaemia minor or trait (eg β/β+; heterozygous state):

This is a carrier state, and is usually asymptomatic. Mild, well-tolerated anaemia (Hb >9g/dL) which may worsen in pregnancy. MCV <75fL, HbA_2 >3.5%, slight ↑HbF. Often confused with iron deficiency anaemia.

β thalassaemia intermedia

describes an intermediate state with moderate anaemia but not requiring transfusions. There may be splenomegaly. There are a variety of causes including mild homozygous β thalassaemia mutations eg β+/β+, or co-inheritance of β thalassaemia trait with another haemoglobinopathy eg HbC thalassaemia (1 parent has the HbC trait, and the other has β+). Sickle-cell β+ thalassaemia produces a picture similar to sickle-cell anaemia.

β thalassaemia major (Cooley's anaemia)

describes abnormalities in both β-globin genes, and presents within the 1st year, with severe anaemia and failure to thrive. Extramedullary haematopoiesis (production of RBCs outside the bone marrow) occurs in response to the anaemia, causing characteristic facial deformities eg skull bossing (**fig 1**) and

hepatosplenomegaly (also due to haemolysis). Skull x-ray shows a 'hair on end' appearance due to increased marrow activity. Life-long blood transfusions are needed, with resulting iron overload and deposition occurring after ~10yrs as endocrine failure (pituitary, thyroid, pancreas↑diabetes mellitus), liver disease, and cardiac toxicity. Long-term infusion of desferrioxamine helps to prevent iron loading. The film shows very hypochromic, microcytic cells with target cells and nucleated RBCs. HbF↑↑, HbA_2 variable, HbA absent.

Treatment [48]

- Folate supplements.
- Regular (~2-4 weekly) life-long transfusions to keep Hb >9g/dL, to suppress the ineffective extramedullary haematopoiesis and to allow normal growth.
- Iron-chelators to prevent iron deposition, eg desferrioxamine infusions given SC for 8-12 hours per day. SE: pain, hearing loss, cataracts, retinal damage, ↑risk of *Yersinia* infection. Compliance can be a problem. The role of newer oral iron-chelators, eg deferiprone, are under study (neutropenia may be a problem).
- Large doses of ascorbic acid also increase urinary excretion of iron.
- Splenectomy if hypersplenism persists with increasing transfusion requirements (p357)—this is best avoided until >5 yrs old due to risk of infections.
- Hormonal replacement or treatment for endocrine complications eg diabetes mellitus, hypothyroidism. Growth hormone treatment has had variable success.[49]
- A histocompatible marrow transplant can offer the chance of a cure.[50]

Prevention

Approaches include genetic counselling or antenatal diagnosis using fetal blood or DNA, then 'therapeutic' abortion.

The a thalassaemias

There are two separate α-globin genes on each chromosome 16 ∴ there are four genes (termed αα/αα). The α thalassaemias are mainly caused by gene deletions. If all 4 α genes are deleted (—/—), death is *in utero (Bart's hydrops)*. Here, HbBarts (γ_4) is present, which is physiologically useless. HbH disease occurs if 3 genes are deleted (—/-α), there may be moderate anaemia and features of haemolysis: hepatosplenomegaly, leg ulcers and jaundice. In the blood film, there is formation of β_4 tetramers (=HbH) due to excess β chains, HbBarts, HbA and HbA_2. If 2 genes are deleted (—/αα or -α/-α), there is an asymptomatic carrier state, with ↓MCV. With one gene deleted, the clinical state is normal.

Structure of haemoglobin

The three main types of Hb in adult blood are:

Type	Peptide chains	% in adult blood	% in fetal blood
HbA	$\alpha_2\ \beta_2$	97	10-50
HbA_2	$\alpha_2\ \delta_2$	2.5	Trace
HbF	$\alpha_2\ \gamma_2$	0.5	50-90

Adult haemoglobin (HbA) is a tetramer of 2 α- and 2 β-globin chains each containing a haem group. In the first year of life, adult haemoglobin replaces fetal haemoglobin (HbF).

It might be thought that because the molecular details of the thalassaemias are so well worked out they represent a perfect example of the reductionist principle at work: find out *exactly* what is happening *within* molecules, and you will be able to explain all the manifestations of a disease. But this is not so. We have to recognize that two people with the identical mutation at their β loci may have quite different diseases. Co-inheritance of other genes and conditions (eg α thalassaemia) is part of the explanation, as is the efficiency of production of fetal haemoglobin. The reasons lie beyond simple co-segregation of genes promoting the formation of fetal Hb. The rate of proteolysis of excess α-globin chains may also be important—as may mechanisms that have little to do with genetic or molecular events. So the lesson the thalassaemias teach is more subtle than the reductionist one: it is that if you want to understand the *whole* picture, you must look at *every* level: genetic, molecular, physiological, social, and cultural. Each level influences the other, without necessarily determining them.

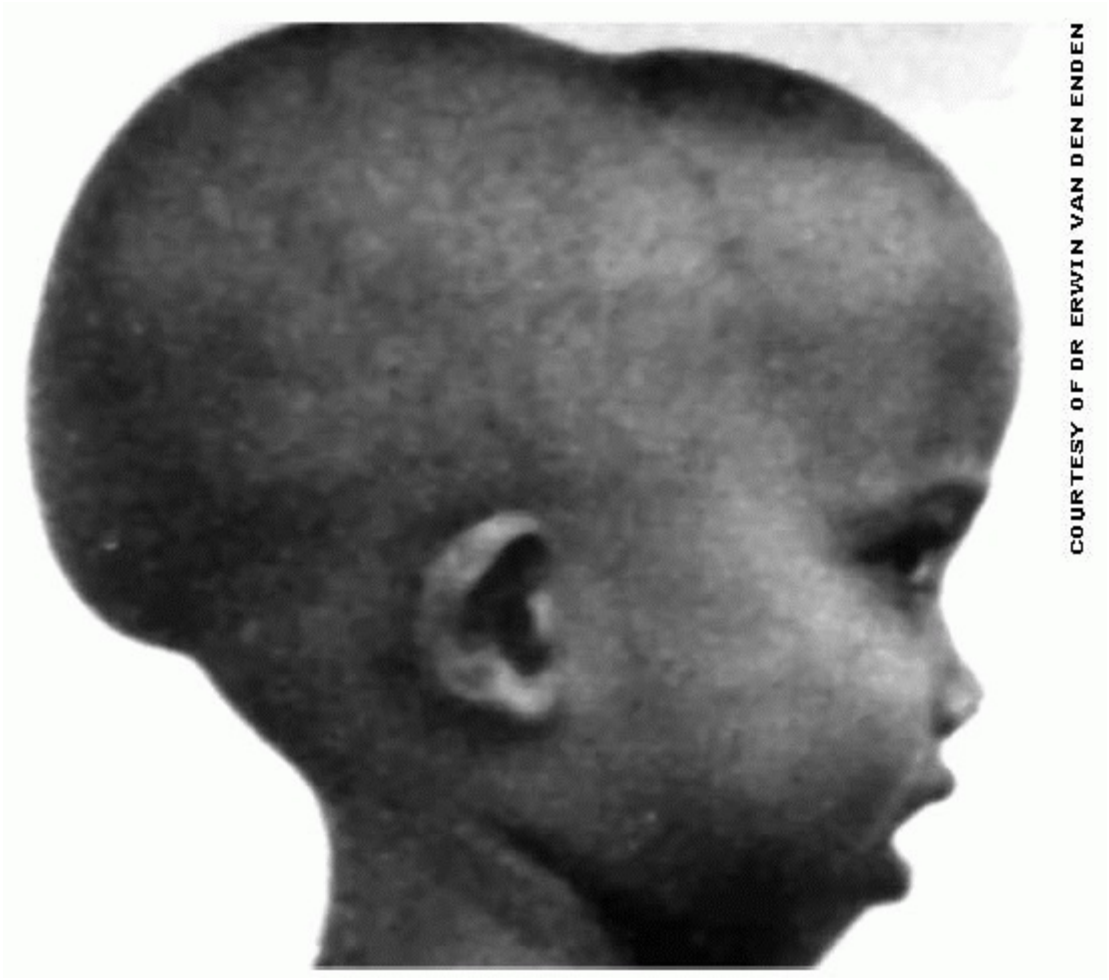


Fig 1. ß thalassaemia major: bossing due to extra-medullary haematopoiesis.[51]

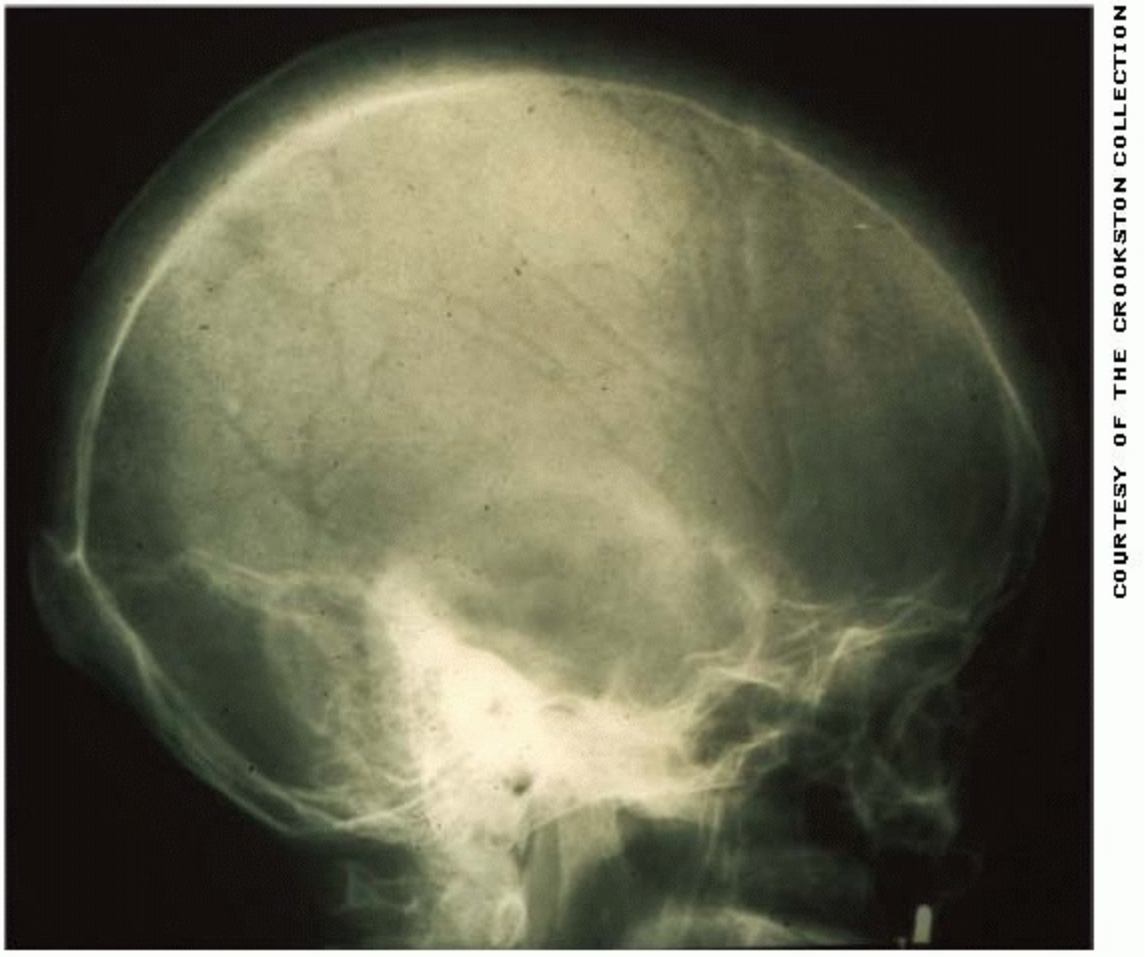


Fig 2. Thalassaemia major: skull X-ray.[52]

Further Reading: Drew Provan and John G Gribben 2004 *Molecular Hematology 2e*, Blackwell Publishing.

Bleeding disorders

After injury, 3 processes halt bleeding: vasoconstriction, gap-plugging by platelets, and the coagulation cascade. Disorders of haemostasis fall into these 3 groups. The pattern of bleeding is important—vascular and platelet disorders lead to prolonged bleeding from cuts, bleeding into the skin (eg easy bruising and purpura), and bleeding from mucous membranes (eg epistaxis, bleeding from gums, menorrhagia). Coagulation disorders cause delayed bleeding into joints and muscle.

1 Vascular defects ***Congenital:*** Osler-Weber-Rendu syndrome (p700), connective tissue disease (eg Ehlers-Danlos syndrome OHCS p642, pseudoxanthoma elasticum).

Acquired: Senile purpura, infection (eg meningococcal, measles, dengue fever), steroids, scurvy (perifollicular haemorrhages), Henoch-Schönlein purpura (p694), painful bruising syndrome—women who develop tingling under the skin followed by bruising over limbs/trunk, resolving without treatment.

2 Thrombocytopenia ↓ ***marrow production:*** Aplastic anaemia (p348), megaloblastic anaemia, marrow infiltration (eg leukaemia, myeloma), marrow suppression (cytotoxic drugs, radiotherapy). ***Excess destruction: Immune:*** Immune thrombocytopenic purpura (ITP), other autoimmune causes eg SLE, CLL, drugs eg heparin, viruses; *Non-immune:* DIC p336, thrombotic thrombocytopenic purpura (**TTP**) or HUS (p300), sequestration (in hypersplenism). ITP is caused by antiplatelet autoantibodies leading to phagocytic destruction. It is acute (usually in children, 2wks after infection with sudden self-limiting purpura: OHCS p197) or chronic (seen mainly in adult women). Chronic ITP runs an indefinite fluctuating course of bleeding, purpura (especially dependent pressure areas), epistaxis and menorrhagia. There is no splenomegaly.

Tests: ↑megakaryocytes in marrow, antiplatelet autoantibodies may be present although not always. ***Â:*** Mild disease may not need treatment. If symptomatic or platelets <20 × 10^9/L, prednisolone 1mg/kg/d, and reduce after remission; aim to keep platelets >30 × 10^9/L—takes a few days to work. If relapse, splenectomy cures ≤80%. If this fails: immunosuppression, eg azathioprine or cyclophosphamide. Platelet transfusions are not used (except during splenectomy or life-threatening haemorrhage) as these are destroyed quickly by the autoantibodies. IV immunoglobulin may temporarily raise the platelet count eg for surgery, pregnancy.

Causes of ↓platelet function Myeloproliferative disease, NSAIDs, urea↑.

3 Coagulation disorders ***Congenital:*** Haemophilia, von Willebrand's disease (p704). ***Acquired:*** Anticoagulants, liver disease, DIC (p336), vitamin K deficiency.

- Haemophilia A: Factor VIII deficiency; inherited in an X-linked recessive pattern in 1:10,000 male births—usually due to a 'flip tip' inversion in the Factor VIII gene in the X chromosome. There is a high rate of new mutations (30% have no family history). ***Presentation*** depends on severity and is often early in life or after surgery/trauma—with bleeds into joints leading to crippling arthropathy, and into muscles causing haematomas, which may lead to nerve palsies and compartment syndrome due to pressure. ***Diagnose*** by ↑APTT and ↓factor VIII assay. ***Management:*** Seek expert advice. ***Avoid* NSAIDs *and* IM *injections***. Minor bleeding: pressure and elevation of the part. Desmopressin (0.3µg/kg/12h IVI over 20min) raises factor VIII levels, and may be sufficient. Major bleeds (eg haemarthrosis) require factor VIII levels to be ↑ to 50% of normal and life-threatening bleeds (eg

obstructing airway) need levels of 100%, eg with recombinant factor VIII. ***Genetic counselling:*** **OHCS** p154.

- **Haemophilia B (Christmas disease):** Factor IX deficiency (inherited, X-linked recessive); behaves clinically like haemophilia A.
- **Liver disease** produces a complicated bleeding disorder with ↓synthesis of clotting factors, ↓absorption of vitamin K, and abnormalities of platelet function.
- **Malabsorption** leads to less uptake of vitamin K (needed for synthesis of factors II, VII, IX, and X). Treatment is IV vitamin K (10mg) or FFP for acute haemorrhage.

The intrinsic and extrinsic pathways of blood coagulation

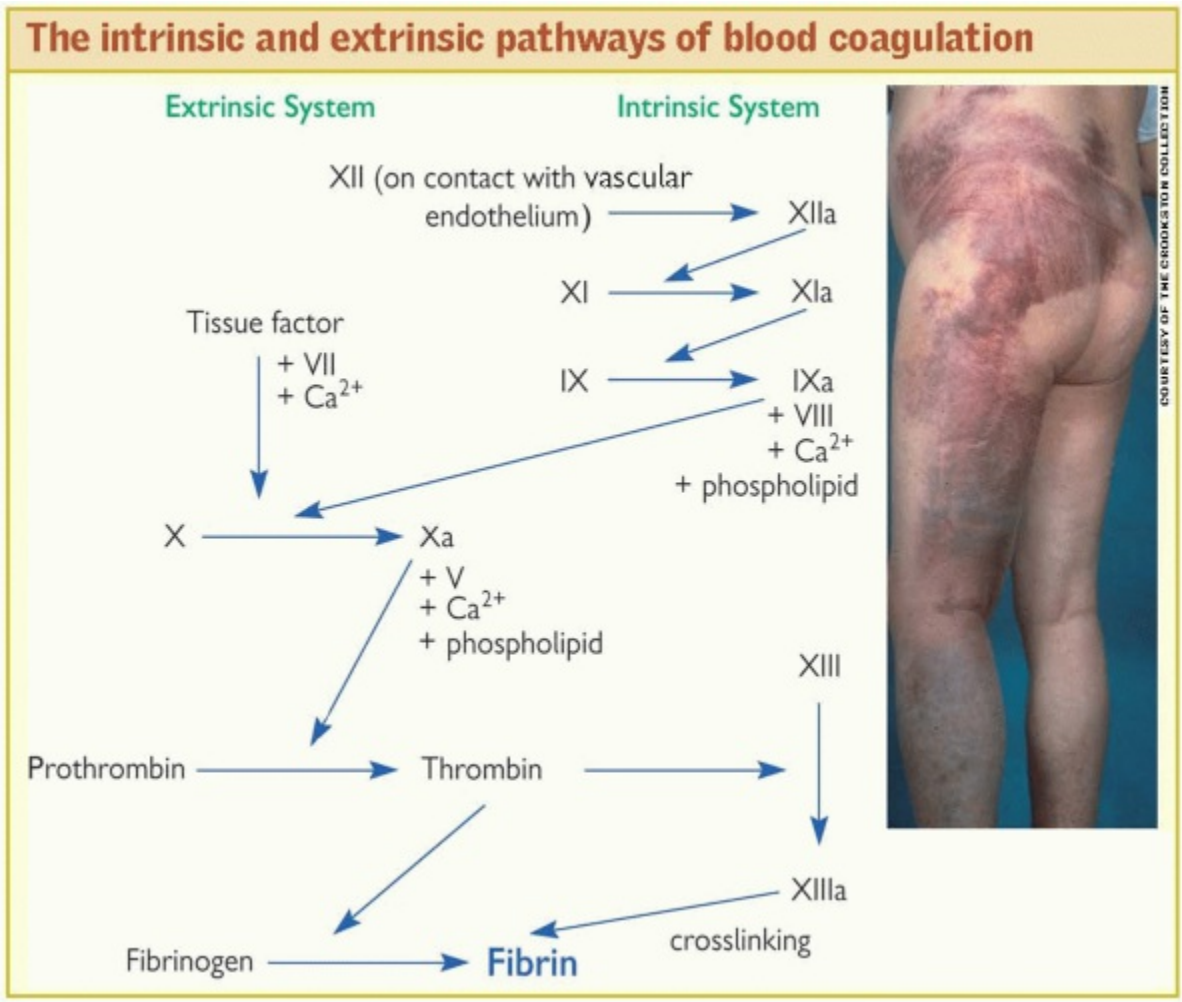


Fig 1. Mild haemophilia after an IM injection [53]. Give vaccines etc SC.

Fibrinolysis

The fibrinolytic system

causes fibrin dissolution and acts via the generation of plasmin. The process starts with the release of tissue plasminogen activator (t-PA) from endothelial cells, a process stimulated by fibrin formation. t-PA converts inactive plasminogen to plasmin which can then cleave fibrin, as well as several other factors. t-PA and plasminogen both bind fibrin thus localizing fibrinolysis to the area of the clot.

Mechanism of fibrinolytic agents

Alteplase (=rt-PA=Actilyse®; from recombinant DNA) is a fibrinolytic enzyme imitating t-PA, as above. Plasma $t_{½}$ ≈ 5min.

Streptokinase is a streptococcal exotoxin and forms a complex in plasma with plasminogen to form an activator complex, which forms plasmin from unbound plasminogen. Initially there is rapid plasmin formation which can cause uncontrolled fibrinolysis. However, plasminogen is rapidly consumed in the complex and then plasmin is only produced as more plasminogen is synthesized. The activator complex binds to fibrin, so producing some localization of fibrinolysis.

An approach to bleeding

There are 3 sets of questions to be answered:

Is there an emergency?

—needing immediate resuscitation or senior help?

- Is the patient about to exsanguinate (shock, coma, p774-9)?
- Is there hypovolaemia (postural hypotension, oliguria)?
- Is there CNS bleeding (meningism, CNS, and retinal signs)?

Why is the patient bleeding?

Is bleeding normal, given the circumstances (eg surgery, trauma, parturition), or does the patient have a bleeding disorder?

- Is there a secondary cause eg drugs (warfarin), alcohol, liver disease, sepsis?
- Is there unexplained bleeding, bruising, or purpura?
- Past or family history of excess bleeding eg during trauma, dentistry, surgery?
- Is the pattern of bleeding indicative of vascular, platelet, or coagulation problems (p330)? Are venepuncture or old cannula sites bleeding (DIC, p336)? Look for associated conditions (eg with DIC).
- Is a clotting screen abnormal? Check FBC, platelets, PT, APTT and thrombin time. Consider D-dimers, bleeding time, and a factor VIII assay.

In the case of a bleeding disorder, what is the mechanism?

Coagulation tests

(Sodium citrate tube; false results if under-filled)

- ***Prothrombin time (PT):*** Thromboplastin is added to test the *extrinsic system*. PT is expressed as a ratio compared to control [International Normalized Ratio (INR), normal range = 0.9-1.2]. It tests for abnormalities in factors I, II, V, VII, X. Prolonged by: warfarin, vitamin K deficiency, liver disease, DIC.
- *Activated partial thromboplastin time (*APTT*):* Kaolin is added to test the *intrinsic system*. Tests for abnormalities in Factor I, II, V, VIII, IX, X, XI, XII. Normal range 35-45s. Prolonged by: heparin treatment, haemophilia, DIC, liver disease.
- *Thrombin time:* Thrombin is added to plasma to convert fibrinogen to fibrin. Normal range: 10-15s. Prolonged by: heparin treatment, DIC, dysfibrinogenaemia.

D-dimers:

These are a fibrin degradation product, released from cross-linked fibrin during fibrinolysis (p331). This occurs during DIC, or in the presence of venous thromboembolism—deep vein thrombosis (DVT) or pulmonary embolism (PE). D-dimers may also be raised in inflammatory states eg with infection or malignancy.

Bleeding time:

This is a test of haemostasis, carried out by making two small incisions into the skin of the forearm. Normal time <7 minutes. **NB:** This test is seldom performed now, as results are very operator dependent.

Interpretation

- ***Platelets:*** If low, do FBC, film, clotting.
- ***PT:*** If long, look for liver disease or anticoagulant use.
- **APTT***:* If long, consider liver disease, haemophilia (factor VIII or IX deficiency), or heparin.
- ***Bleeding time:*** Raised in von Willebrand's disease (p704), or platelet disorders. Aspirin also prolongs the bleeding time.
- If both PT & APTT are very raised, with low platelets, and ↑D-dimers, consider DIC.

Management

depends on the degree of bleeding. If shocked, resuscitate (p778). If bleeding continues, in the presence of a clotting disorder, or a massive transfusion, discuss the need for FFP and platelets with a haematologist. In ITP (p330), steroids ± IV immunoglobulin may be used. Especially in pregnancy (OHCS p88), consult an expert. Is there overdose with anticoagulants (p826)? In haemophiliac bleeds, *consult early* for coagulation factor replacement. *Never* give IM injections.

Disorder[1]	INR	APTT	Thrombin time	Platelet count	Bleeding time	Notes
Heparin	↑	↑↑	↑↑	↔	↔	
DIC	↑↑	↑↑	↑↑	↓	↑	↑D-d, p336
Liver disease	↑	↑	↔/↑	↔/↓	↔/↑	AST↑
Platelet defect	↔	↔	↔	↔	↑(↑)	
Vit K deficiency	↑↑	↑	↔	↔	↔	
Haemophilia	↔	↑↑	↔	↔	↔	see p330
von Willebrand's	↔	↑↑	↔	↔	↑(↑)	see p704
Special tests may be available (factor assays: ▸consult a haematologist).						

[1] After *OTS*, p215. D-d = D-dimer.

Anticoagulants

Main indications

- ***Therapeutic:*** Venous thromboembolic disease: DVT and PE.
- ***Prophylactic:*** Prevention of DVT/PE in high-risk patients (p359), eg post-op. Prevention of stroke, eg in chronic AF or prosthetic heart valve.

Heparin

1 Low molecular weight heparin (LMWH) Given SC. Molecular weight ~5000 Daltons (Da), eg dalteparin, enoxaparin, tinzaparin. Inactivates factor Xa (but not thrombin). T½ is 2-4-fold longer than standard heparin, and response is more predictable, and so only needs to be given once or twice daily, and no laboratory monitoring is usually required. It has replaced unfractionated heparin (UFH) as the preferred option in the prevention and treatment of venous thromboembolism and in acute coronary syndrome. See BNF for doses. It accumulates in renal failure: lower doses are used for prophylaxis, or UFH for therapeutic doses. *2 Unfractionated heparin (UFH)* IV or SC. ~13,000Da. A glycosaminoglycan, which binds antithrombin (an endogenous inhibitor of coagulation), increasing its ability to inhibit thrombin, factor Xa, and IXa. Rapid onset and has a short T½. Monitor and adjust dose with APTT (p332).

SE for both:

↑Bleeding (eg at operative site, gastrointestinal, intracranial), heparininduced thrombocytopenia (HIT), osteoporosis with long-term use. HIT and osteoporosis are less common with LMWH than UFH. Beware hyperkalaemia.

CI:

Bleeding disorders, platelets $<60\times10^9$/l, previous HIT, peptic ulcer, cerebral haemorrhage, severe hypertension, neurosurgery.

Warfarin

is used orally once daily as long-term anticoagulation. The therapeutic range is narrow, varying with the condition being treated (see BOX)—and is measured as a ratio compared with the standard INR. Warfarin inhibits the reductase enzyme responsible for regenerating the active form of vitamin K, producing a state analogous to vit K deficiency.

CI:

Peptic ulcer, bleeding disorders, severe hypertension, pregnancy (teratogenic, see OHCS p640). Use with caution in the elderly and those with past GI bleeds. In the UK, warfarin tablets are 0.5mg (white), 1mg (brown), 3mg (blue), or 5mg (pink). ▸Interactions: p740.

Others:

Fondaparinux is a pentasaccharide Xa inhibitor and may be used in place of LMWH for prophylaxis in certain situations.[54] Ximelagatran, a direct thrombin inhibitor, may provide an alternative to warfarin that does not require monitoring.

Beginning therapeutic anticoagulation

(follow local guidelines, and see BNF). For treatment of venous thromboembolism, LMWH or UFH are used initially, and warfarin is given in combination usually from day 1. Heparin should be continued until INR has reached target therapeutic range (see BOX) *and* until day 5, as warfarin has an initial prothrombotic effect.

LMWH

Dose according to weight (see BNF).

UFH

IV infusion:

- Give heparin 5000iu IV bolus over 30min. (10000iu in severe PE).
- Prepare syringe pump: Add 25,000iu to 50mL 0.9% saline (=500iu/mL).
- Start infusion at 1000-2000iu/h IVI (2.8mL/h=1400iu/h). Check APTT at 6h, aim for APTT ratio 1.5-2.5 (see BOX). Measure APTT daily or 10h after dose change.

Warfarin

is given daily; start with 10mg stat at 18.00. Do INR 16h later.

- If INR <1.8 (as is likely) the 2nd dose of warfarin is 5 or 10mg at 18.00 (24h after first dose). Give the lower dose if >60yrs, liver disease, or cardiac failure. But if INR >1.8 (warfarin sensitivity; rare) give just 0.5mg.
- Do INR daily for 5d and adjust dose (see BOX—use 5mg, not 10mg dose 3 if over 60, or liver disease, or cardiac failure).
- Stop heparin after 5d and when INR >2 for 2d. Tell lab when stopped.
- Measure INR on alternate days until stable, then weekly or less often.

Antidotes

If UFH overdose: stop infusion. If there is bleeding, protamine sulphate counteracts UFH: discuss with a haematologist. Warfarin: see Box 2.

Warfarin guidelines and target levels for INR[1]

- Pulmonary embolism and DVT. Aim for INR of 2-3; 3.5 if recurrent.
- Atrial fibrillation[2]: for stroke prevention (p116). Target INR 2-3. An alternative is aspirin (but less effective), if the risk of bleeding with warfarin is high (eg falls with risk of intracranial bleed, or difficulty with monitoring).
- Prosthetic metallic heart valves: for stroke prevention. Target INR 3-4.

Duration of anticoagulation in DVT/PE

- If the cause will go away (eg post-op immobility):
  - At least 6 weeks for below knee DVT.
  - At least 3 months for above knee DVT or PE.
- At least 6 months if no cause found.
- Indefinitely for identified, enduring causes, eg thrombophilia (p358).

Warfarin dosage and excessive anticoagulation[55]

Below is a guide to warfarin dosing, for target INR of 2-3:

INR	<2	2	2.5	2.9	3.3	3.6	4.1
3rd dose	10mg	5mg	4mg	3mg	2mg	0.5mg	0mg
Maintenance	≥6mg	5.5mg	4.5mg	4mg	3.5mg	3mg	*

* Miss a dose; give 1-2mg the next day (if INR >4.5, miss 2 doses). Lower doses are given in certain groups of patients (see TEXT).

In cases of raised INR (see BNF):

INR 4.5-6	Reduce warfarin dose or omit. Restart when INR <5.
6-8	Stop warfarin. Restart when INR <5.
>8, no bleed or minor bleed	If no bleeding: stop warfarin. 0.5-2.5mg vitamin K (oral) if risk factors for bleeding. Check INR daily.
Major bleed, (including intracranial haemorrhage)	Stop warfarin. Give prothrombin complex concentrate (50units/kg; discuss with a haematologist). If unavailable, give FFP (15mL/kg ≈ 1L for a 70kg man). Also give 5-10mg vitamin K IV.

Minor bleeding includes epistaxis.

Vitamin K may take several hours to work, and can cause prolonged resistance when restarting warfarin, so should be avoided if possible when long-term anticoagulation is needed. Prothrombin complex concentrate contains a concentrate of Factor IX, and provides a more complete and rapid reversal of warfarin than FFP.

IV heparin dosing

APTT ratio	>5	4-5	3-4	2.5-3	**1.5-2.5**	1.2-1.4	<1.2
Change rate (iu/h) by	Stop* - 500	- 300	- 100	-50	**0**	+200	+400

* Stop for 1 hour then recheck APTT. Reduce dose by 500iu/h and restart if <5. [56]

Leukaemia and the house officer

Leukaemic patients often fall ill suddenly and deteriorate quickly. Prompt appropriate treatment is essential. Major concerns are infection, bleeding and hyperviscosity (p356). Take non-specific confusion/drowsiness seriously: do blood cultures, exclude hypoglycaemia, measure renal function, LFT, and Ca^{2+}. Check clotting screen. Consider CNS bleeding—CT/MRI of brain if any doubt. Correct any haemostatic defect urgently with platelets/FFP. (See p476 for delirium.)

Neutropenic regimen

(for patients with a neutrophil count ¢1.0 × 10^9/L).

▸Close liaison with a microbiologist and haematologist is essential.

- Full barrier nursing if possible, but simple hand-washing is probably most important. Use a side room.
- Avoid IM injections (danger of an infected haematoma).
- Look for infection (mouth, axilla, perineum, IVI site). Take swabs.
- Check: FBC, platelets, INR, U&E, LFT. Take cultures (blood×3—peripherally ± Hickman line; urine, sputum, stool if diarrhoea) and request a CXR.
- Wash perineum after defecation. Swab moist skin with chlorhexidine. Avoid unnecessary rectal examinations. Oral hygiene (eg hydrogen peroxide mouth washes/2h) and *Candida* prophylaxis are important (p230).
- TPR 4-hrly. High-calorie diet; avoid foods with high risk of microbial contamination. Vases containing cut flowers pose a *Pseudomonas* risk.

Use of antibiotics in neutropenia

▸Treat any known infection promptly.

- If T° >38°C or T° >37.5°C on separate occasions, 1-2h apart, or the patient is toxic, assume septicaemia and start blind broad spectrum antibiotics, eg antipseudomonal penicillin/cephalosporin and aminoglycoside. Vancomycin (p371) may be added if suspected Hickman line sepsis. Check local preferences.
- Continue antibiotics until afebrile for 72 hours or 5d course, and until neutrophils recover (>0.5×10^9/L). If fever persists despite antibiotics, consider CMV or fungal infection (eg *Candida* or *Aspergillus*, p428).
- May need to consider treatment for *Pneumocystis* (see p399 eg co-trimoxazole =trimethoprim 20mg/kg with sulfamethoxazole 100mg/kg per day PO/IV in 2-4 divided doses). Also remember TB.

- Genetically engineered recombinant human granulocyte-colony stimulating factor (G-CSF) may be used to stimulate neutrophil production. Follow local guidelines, and seek expert advice.

Other dangers

• ***Tumour lysis syndrome:*** Caused by a massive destruction of cells leading to K^+↑, urate↑ and renal impairment. Prevent by giving a high fluid intake + allopurinol pre-cytotoxics. For patients at high risk of cell lysis, eg children with high count ALL, recombinant uricase (rasburicase) may be given. Seek advice.

• ***Hyperviscosity:*** (p356). If WCC is >100 × 10^9/L WBC thrombi may form in brain, lung, and heart (leucostasis). Avoid transfusing before lowering WCC, eg with hydroxycarbamide or leucopheresis, as viscosity rises (risk of leucostasis ↑).

• ***Disseminated intravascular coagulation (*DIC*):*** This is pathological widespread activation of coagulation, due to release of procoagulant agents into the circulation. Clotting factors and platelets are consumed, with ↑risk of bleeding. Fibrin strands fill small vessels, haemolysing passing RBCs, and fibrinolysis is also activated.

Causes:

Malignancy, sepsis, trauma, obstetric: OHCS p88.

Signs:

Extensive bruising, bleeding anywhere eg recent venepuncture sites, renal failure.

Tests:

Platelets↓; PT↑; APTT↑; fibrinogen↓ (correlates best with severity); fibrin degradation products (D-dimers) ↑↑. Film: broken RBCs (schistocytes).

[prescription take]:

Treat the cause. Give replacement therapy: platelets if <50×10^9/L, cryoprecipitate to replace fibrinogen, FFP to replace coagulation factors. Heparin is controversial. Activated protein C reduces mortality in DIC with severe sepsis or multi-organ failure.[57] The use of alltransretinoic acid (ATRA) has significantly reduced the risk of DIC in acute promyelocytic leukaemia (the commonest leukaemia associated with DIC).

Leukaemias

These are divided into 4 main types depending on the cell line involved and the speed of disease progression:

	Lymphoid	Myeloid
Acute	Acute lymphoblastic leukaemia (ALL)	Acute myeloid leukaemia (AML)
Chronic	Chronic lymphocytic leukaemia (CLL)	Chronic myeloid leukaemia (CML)

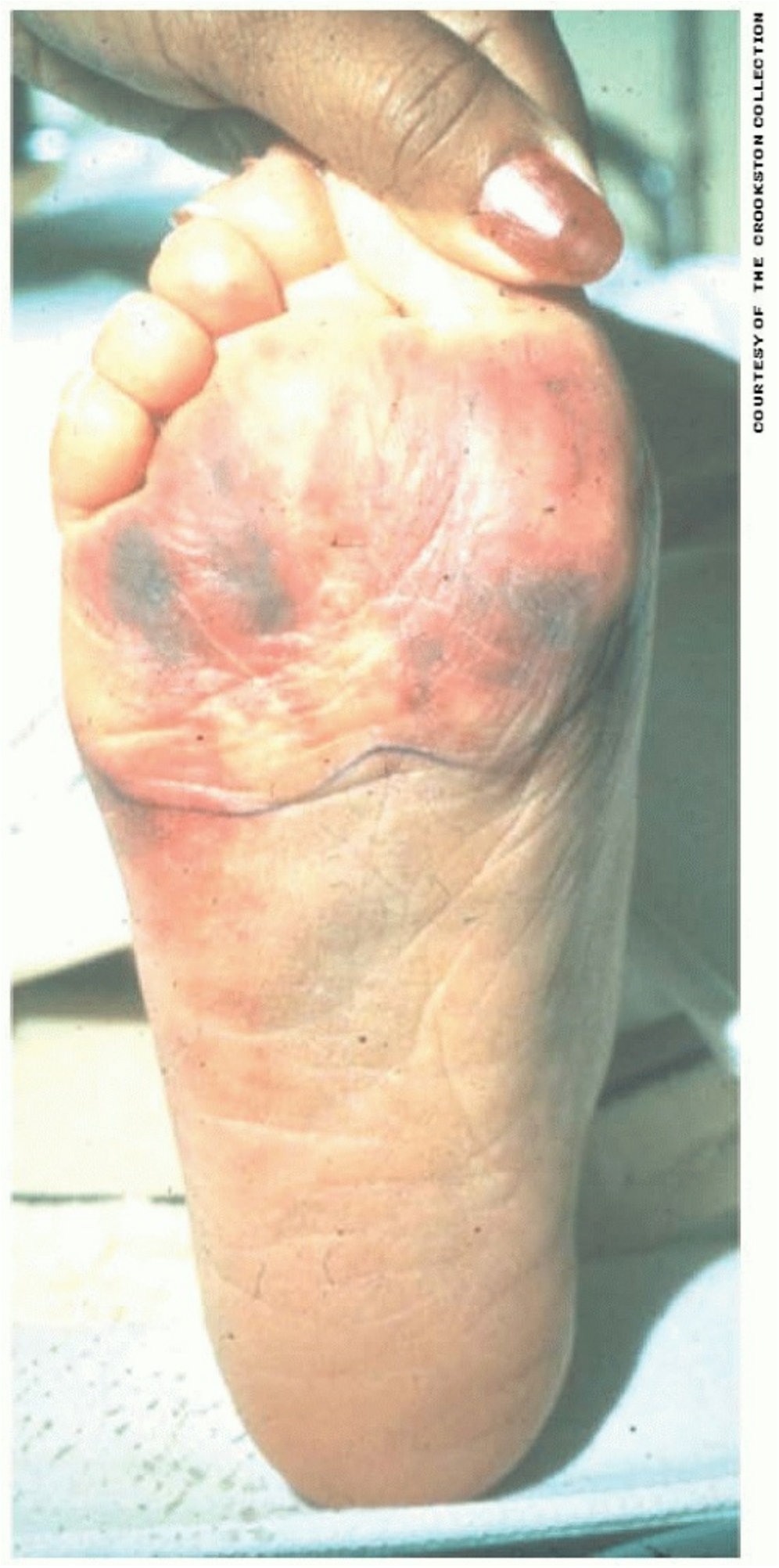


Fig 1. The appearance of DIC on the sole.[58]

Acute lymphoblastic leukaemia (ALL)

This is a malignancy of lymphoid cells, affecting either B or T lymphocyte cell lines, arresting maturation and promoting uncontrolled proliferation of immature blast cells, with bone marrow failure and tissue infiltration. It is thought to develop from a combination of an environmental trigger in the presence of genetic susceptibility. In most cases these are unknown, but predisposing factors include ionizing radiation (eg X-rays) during pregnancy, and syndromes including Down's.[59] It is the commonest cancer of childhood, and is rare in adults. CNS involvement is common.

Classification

is based on 3 systems:

1. ***Morphological*** The FAB[1] system divides ALL into 3 types (L1, L2, L3) by microscopic appearance. Provides limited information.
2. ***Immunological*** Surface markers are used to classify ALL into:
   - Precursor B-cell ALL
   - T-cell ALL
   - B-cell ALL.
3. ***Cytogenetic*** Chromosomal analysis. Abnormalities are detected in up to 85%, which are often translocations . Useful for predicting prognosis eg poor with Philadelphia chromosome (see below), and for detecting disease recurrence.

Signs and symptoms

are due to:

- Marrow failure: Anaemia (↓Hb), infection (↓WCC), and bleeding (↓platelets).
- Infiltration: Hepato- and splenomegaly, lymphadenopathy—superficial or mediastinal, orchidomegaly, CNS involvement—eg cranial nerve palsies, meningism.

Common infections:

Especially chest, mouth, perianal and skin. Bacterial septicaemia, Zoster, CMV, measles, candidiasis, *Pneumocystis* pneumonia (p398).

Tests

- Characteristic blast cells on blood film and bone marrow. WCC usually high.
- CXR and CT scan to look for mediastinal and abdominal lymphadenopathy.
- Lumbar puncture should be performed to look for CNS involvement.

Treatment

- ***Supportive care:*** Blood and platelet transfusions, IV fluids and allopurinol to prevent tumour lysis. Insert a Hickman line for venous access.
- ***Infections:*** These are dangerous, due to neutropenia caused by the disease and treatment. Immediate IV antibiotics for infection. Start the neutropenic regimen (p336): prophylactic antivirals, antifungals and antibiotics (eg co-trimoxazole to prevent *Pneumocystis* pneumonia (p336), but beware: can worsen neutropenia).
- ***Chemotherapy:*** Patients are entered into national trials. A typical programme is:
  - ***Remission induction:*** This may be achieved with vincristine, prednisolone, L-asparaginase, and daunorubicin.
  - ***Consolidation:*** High/medium-dose therapy in 'blocks' over several weeks.
  - **CNS *prophylaxis:*** Intrathecal (or high-dose IV) methotrexate ± CNS irradiation.
  - ***Maintenance:*** Prolonged chemotherapy, eg mercaptopurine (daily), methotrexate (weekly), and vincristine + prednisolone (monthly) for 2yrs. Relapse is common in blood, CNS, or testis (so examine these sites at follow-up). More details: OHCS p194.
- ***Marrow transplant:*** (p340) Consider if poor prognosis or relapse. This is the only way to cure those with Philadelphia chromosome—see below.[60]

Haematological remission

means no evidence of leukaemia in the blood, a normal or recovering blood count, and < 5% blasts in a normal regenerating marrow.

Prognosis:

Cure rates for children are 70-90%; for adults only 35% (<5% if >65yrs old, where there is a 2nd peak in incidence). Poor prognosis if adult, male, Philadelphia chromosome (p342): BCR-ABL gene fusion due to translocation of chromosomes 9 & 22, presentation with CNS signs, WCC $>100\times10^9$/L or B-cell ALL. PCR is used to detect minimal residual disease, undetectable by standard means. Prognosis is poor if seen in high amounts at presentation or during remission.

The future

may lie in tailoring therapy to the exact gene defect, and according to the individual's metabolism. Monoclonal antibodies, gene-targeted retinoids, cytokines, vaccines, and T-cell infusions are all being studied.[61]

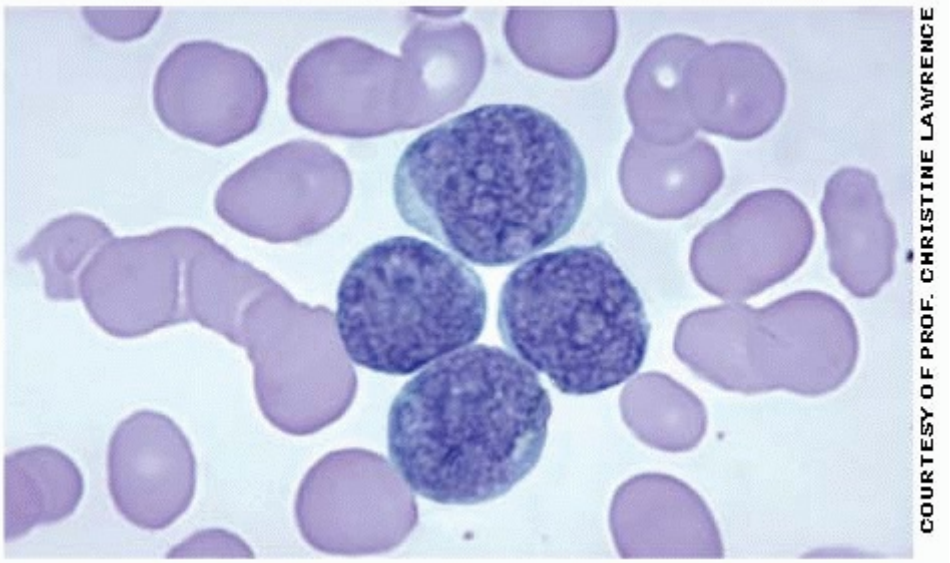


Fig 1. Blood film in ALL, L1 subtype. Small blasts with scanty cytoplasm.[62]

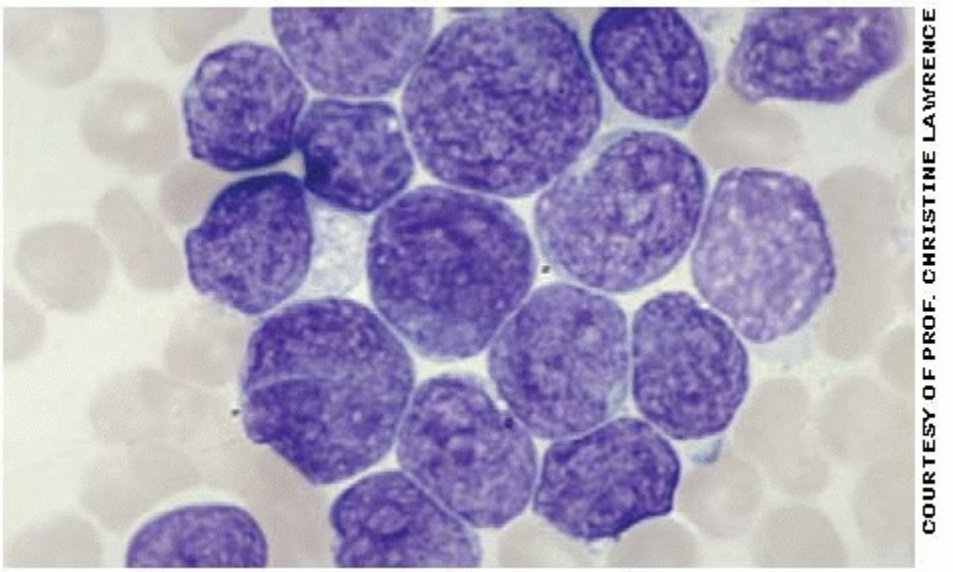


Fig 2. Bone marrow in ALL, L1 subtype.[63]

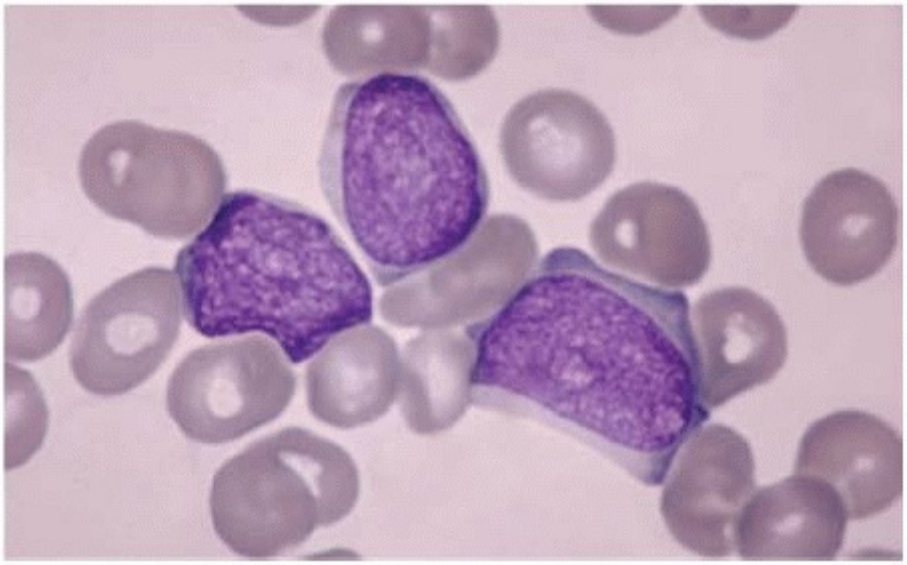


Fig 3. Blood film in ALL, L2 subtype. Larger blast cells with greater morphological variation, and more abundant cytoplasm.[64]

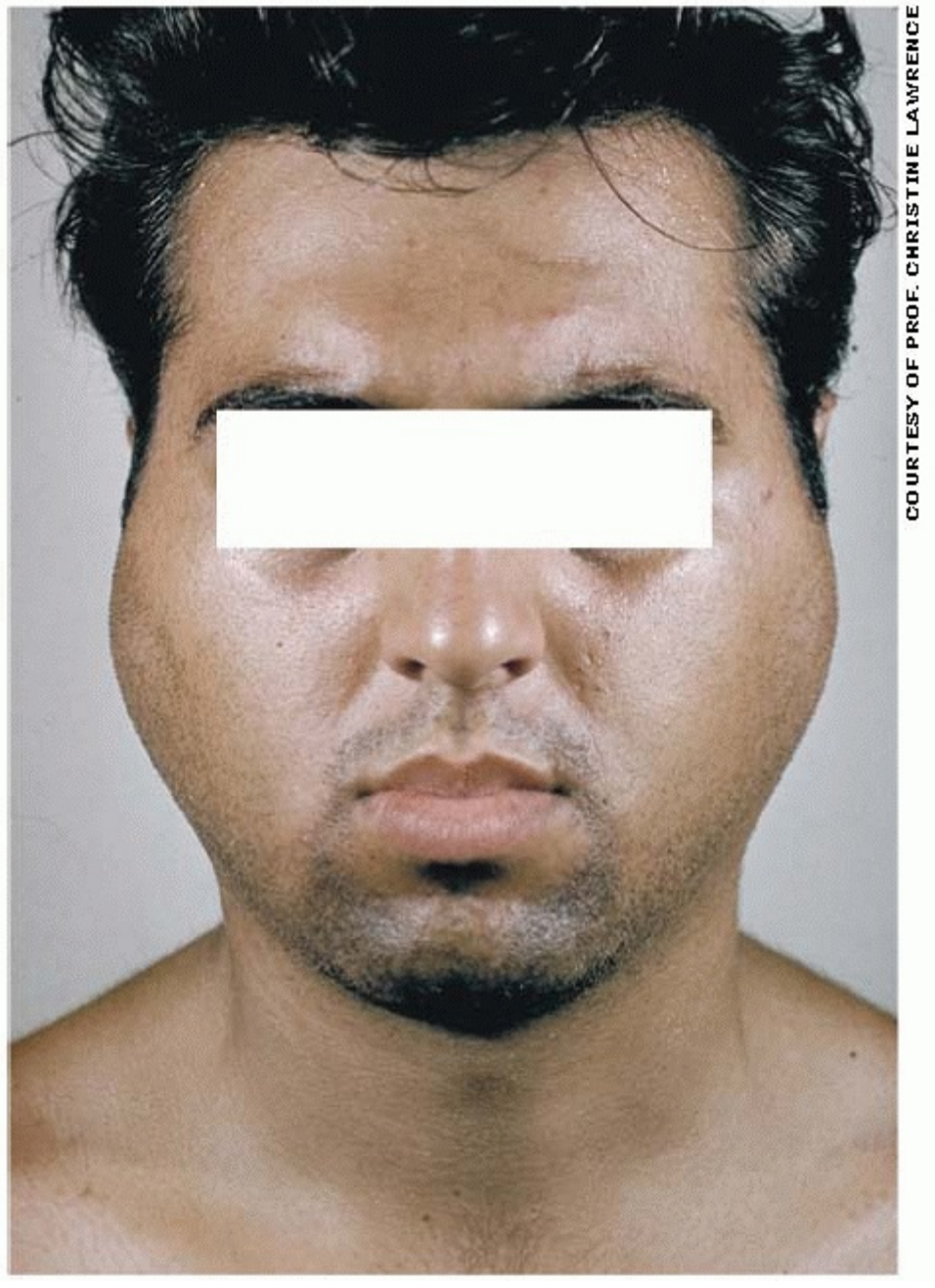


Fig 4. Bilateral parotid infiltration in ALL.[65] (Enlarged parotid glands are also seen in mumps and sarcoidosis.)

Acute myeloid leukaemia (AML)

This neoplastic proliferation of blast cells is derived from marrow myeloid elements. It is a very rapidly progressive malignancy (death in ~2 months if untreated; ~20% 3-yr survival after chemotherapy).

Incidence

1/10,000/yr. Increases with age, and is the commonest acute leukaemia of adults. Seen increasingly as a long-term complication of chemotherapy, eg for lymphoma. Also associated with myelodysplastic syndromes (see BOX), ionising radiation and syndromes eg Down's.

Morphological classification

now based on WHO histological classification, which is complex and requires specialist interpretation. It recognizes the important prognostic information from cytogenetics and molecular genetics. 5 main types:

- AML with recurrent genetic abnormalities.
- AML, other.
- AML multi-lineage dysplasia (usually 2° to preexisting myelodysplastic syndrome).
- AML, therapy related.
- Acute leukaemias of ambiguous lineage (both myeloid and lymphoid phenotype).

Symptoms

- ***Marrow failure:*** Patients usually present with symptoms of anaemia, infection or bleeding. DIC occurs in acute promyelocytic leukaemia, a subtype of AML, where there is release of thromboplastin. Use of all-transretinoic acid with chemotherapy reduces the risk of DIC (see p336).
- ***Infiltration:*** Hepato- and splenomegaly, gum hypertrophy, skin involvement. CNS involvement at presentation is rare in AML.

Diagnosis

WCC is often ↑, but can be normal or even low. Blast cells may be few in the peripheral blood, so diagnosis depends on bone marrow biopsy. Differentiation from ALL may be by microscopy (Auer rods are diagnostic of AML), but is now based on immunophenotyping and molecular methods. Cytogenetic analysis (eg type of mutation) affects treatment recommendations, and guides prognosis.

Complications

- Infection is the major problem, related to both the disease and during treatment. Be alert to septicaemia (p336). Infections may be bacterial, fungal or viral, and prophylaxis is given for each during treatment. ***Pitfalls:*** AML itself causes fever, common organisms present oddly, few antibodies are made, rare organisms—particularly fungi (especially *Candida* or *Aspergillus*).
- Chemotherapy causes ↑plasma urate levels (from tumour lysis)—so give allopurinol with chemotherapy, and keep well hydrated with IV fluids.
- Leucostasis (p336) may occur if WCC ↑↑.

Treatment

- ***Supportive care*** As for ALL.
- ***Chemotherapy*** is very intensive, resulting in long periods of marrow suppression with neutropenia + platelets↓. The main drugs used include daunorubicin, and cytosine arabinoside, with ~5 cycles given in 1 week blocks to achieve remission.
- ***Bone marrow transplant (BMT)*** Pluripotent haematopoietic stem cells are collected from the bone marrow. *Allogeneic* transplants from HLA-matched siblings or from matched unrelated donors (accessed via international databases) is indicated during first remission in disease with poor prognosis. The idea is to destroy leukaemic cells and the immune system by cyclophosphamide + total body irradiation, and then repopulate the marrow by transplantation from a matched donor infused IV. BMT allows the most intensive chemotherapy regimens because marrow suppression is not an issue. Ciclosporin ± methotrexate may be used to reduce the effect of the new marrow attacking the patient's body (graft vs host disease). ***Complications:*** Graft *vs* host disease (may help explain the curative effect of BMT); opportunistic infections; relapse of leukaemia; infertility. ***Prognosis:*** Lower relapse rates ~60% long-term survivors, but significant mortality of ~10%. *Autologous BMT* where stem cells are taken from the patient themselves, is used in intermediate prognosis disease, although some studies suggest better survival rates with intensive chemotherapy regimes.
- Supportive care, or lower dose chemotherapy for disease control, may be more appropriate in elderly patients, where intensive therapies have poorer outcomes.

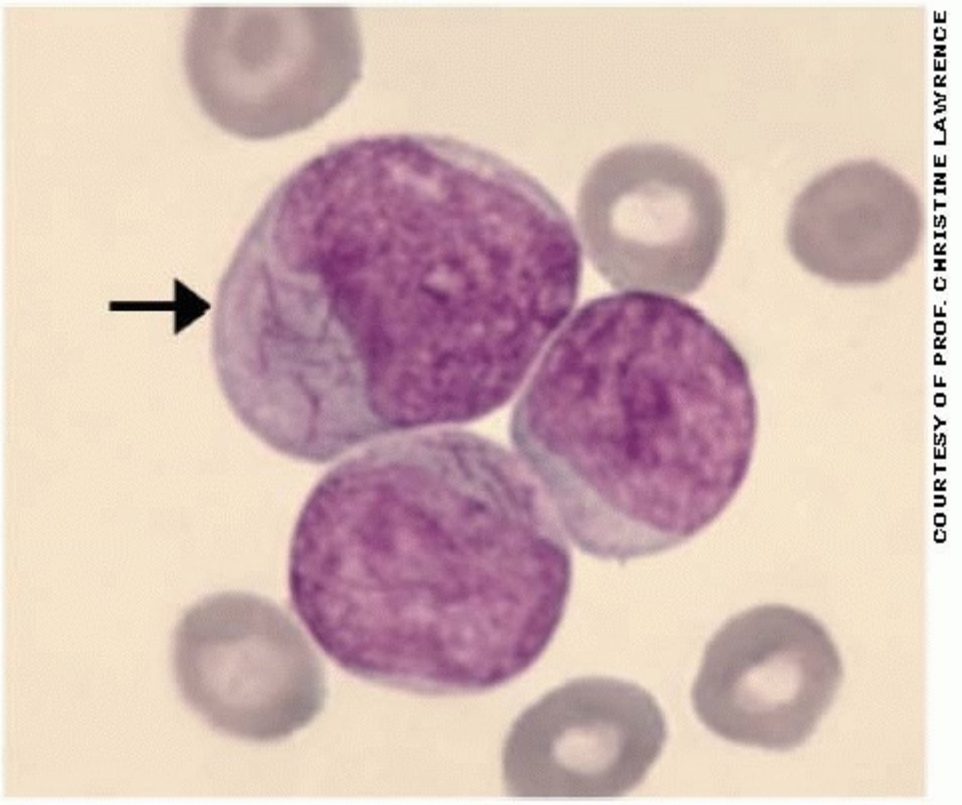


Fig 1. Auer rods found in AML myeloblast cells, representing crystals of coalesced granules.[66]

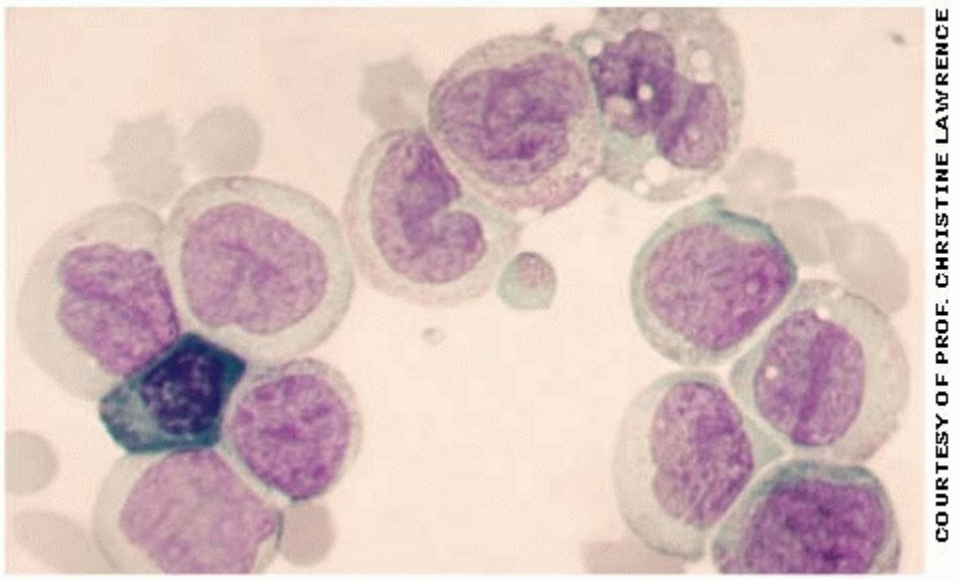


Fig 2. AML with monoblasts and myeloblasts on the peripheral blood film.[67]

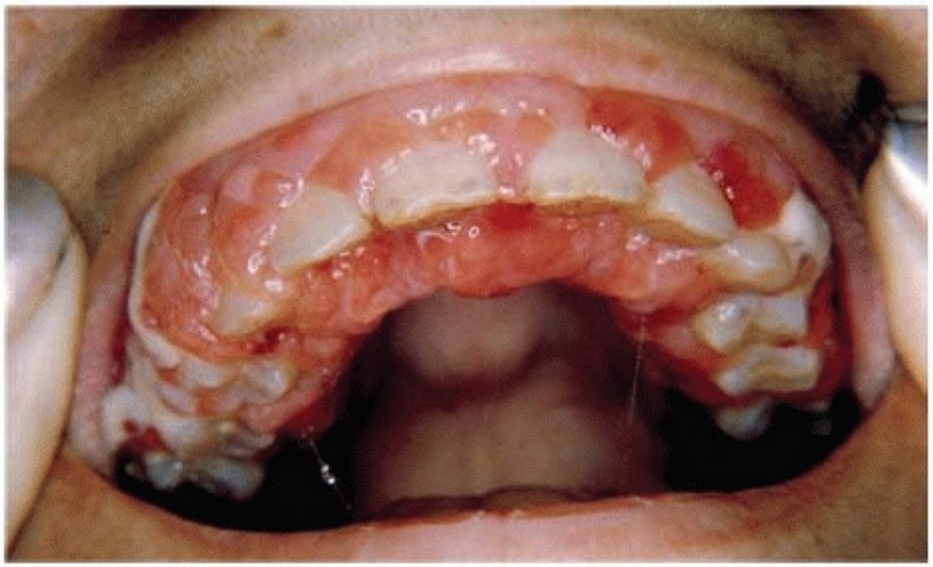


Fig 3. Gum hypertrophy, in AML.[68]

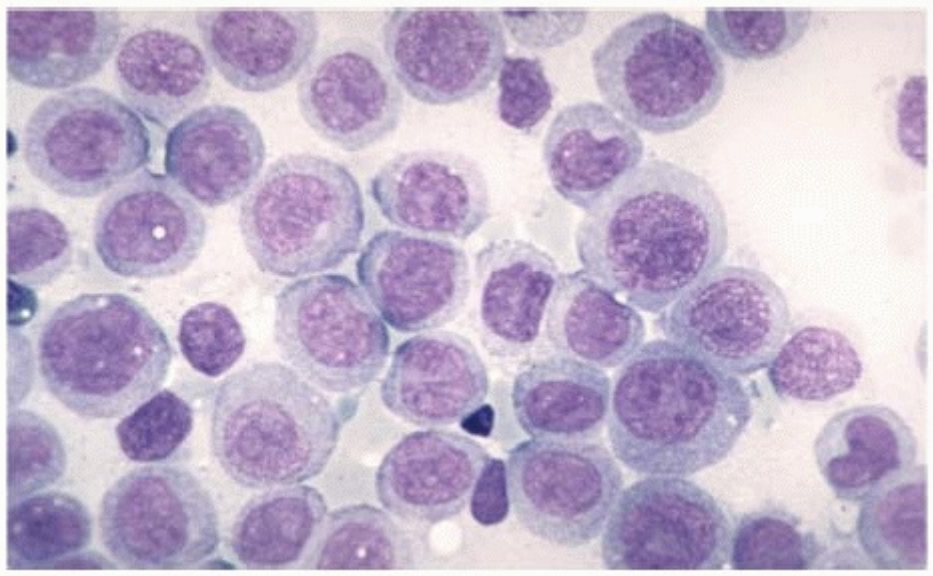


Fig 4. Bone marrow in AML: multiple monoblasts.[69]

Myelodysplastic syndromes (myelodysplasia)

These are a group of diseases where there is a neoplastic clonal disorder of multipotent haematopoietic stem cells, leading to progressive bone marrow failure and ineffective haematopoiesis. This produces functional abnormalities of myeloid cells and peripheral cytopenias, with reduced numbers of red blood cells, neutrophils, and platelets. A proportion of patients later undergo transformation to AML. In most cases, these are primary disorders, but they may also develop secondary to chemotherapy or radiotherapy, given for other malignancies.

Clinically,

around half present >70 years old. There may be no symptoms with detection on blood tests, or they may present with anaemia, infections (neutropenia), or easy bruising and bleeding (↓platelets). Tests show a pancytopenia (p348), with a reduced reticulocyte count. Bone marrow cellularity is usually increased due to the ineffective haematopoiesis. Ring sideroblasts may also be seen in the marrow. There are different subtypes, grouped according to WHO classification.

Treatment

differs according to disease prognosis, and the individual. Allogeneic stem cell transplantation offers a cure, but is associated with a risk of mortality, and is thus reserved for younger patients (<55yrs) with poor prognosis disease. Alternatively, intensive combination chemotherapy may be used. In those where there is a better prognosis, or in older patients where intensive treatment is associated with poorer outcomes, single agent chemotherapy may be used to try to obtain disease control. Multiple transfusions of red cells or platelets are often required. Erythropoietin ± human granulocyte colony stimulating factor (G-CSF) may be used to lower the transfusion requirement. Immunosuppressive agents may also be used, eg ciclosporin or antithymocyte globulins.

Prognosis

Median survival: from 6 months to 6 years according to disease type.

Chronic myeloid leukaemia (CML)

CML is characterized by an uncontrolled clonal proliferation of myeloid cells. It accounts for 15% of leukaemias. It is a myeloproliferative disorder (p350) having features in common with these diseases eg splenomegaly. It occurs most often between 40-60yrs, with a slight male predominance, and is rare in childhood.

Philadelphia chromosome

(Ph) Present in >80% of those with CML. It is a hybrid chromosome comprising reciprocal translocation between the long arm of chromosome 9 and the long arm of chromosome 22—t(9;22) forming a fusion gene BCR/ABL on chromosome 22, which has tyrosine kinase activity. Those without Ph have a worse prognosis. Some patients have a masked translocation—cytogenetics do not show the Ph, but the rearrangement is detectable by molecular techniques.

Symptoms

Mostly chronic and insidious: weight↓, tiredness, fever, sweats. There may be features of gout (due to purine breakdown), bleeding (platelet dysfunction), and abdominal discomfort (splenic enlargement). ~30% are detected by chance.

Signs

Splenomegaly (>75%)—often massive. Hepatomegaly, anaemia, bruising.

Tests

WBC ↑↑ (often >100 × 10^9/L) with whole spectrum of myeloid cells ie ↑neutrophils, myelocytes, basophils, eosinophils. Hb↓ or normal, platelets variable. Urate↑, B12↑. Neutrophil alk phos score↓ (seldom performed now). Bone marrow is hypercellular. Ph found on cytogenetic analysis of blood or bone marrow.

Natural history

Variable, median survival 5-6yrs. There are three phases: *chronic*, lasting months or years of few, if any, symptoms → *accelerated phase*, with increasing symptoms, spleen size, and difficulty in controlling counts → *blast transformation*, with features of acute leukaemia ± death. Treatment See BOX.

Chronic lymphocytic leukaemia (CLL)

This is a monoclonal proliferation of non-functional mature B lymphocytes (T cell CLL occurs rarely). CLL constitutes 25% of all leukaemias. ♂:♀ 2:1. It is a disease of the elderly, median age at diagnosis is ~65 years. Staging correlates with survival:

Stage 0	**Lymphocytosis alone.**	**Median Survival >13yrs**
I	Lymphocytosis + lymphadenopathy.	8yrs
II	Lymphocytosis + spleno- or hepatomegaly.	5yrs
III	Lymphocytosis + anaemia (Hb <11g/dL).	2yrs
IV	Lymphocytosis + platelets <100 × 10^9/L.	1yr

Symptoms

(none in 25%) Infection, anaemia. If severe: weight↓, sweats, anorexia.

Signs

Enlarged, rubbery, non-tender nodes. Splenomegaly, hepatomegaly.

Tests

↑Lymphocytes—may be marked. Later: autoimmune haemolysis (p324), marrow infiltration: ↓Hb, ↓neutrophils, ↓platelets.

Complications

1. **1** Autoimmune haemolysis.
2. **2** ↑Infection due to hypogammaglobulinaemia (=↓IgG), bacterial, viral especially herpes zoster.
3. **3** Marrow failure.

Natural history

Some remain in *status quo* for years, or even regress. Usually nodes slowly enlarge (± lymphatic obstruction). Death is often due to infection (commonly pneumococcus, haemophilus, meningococcus, *Candida* or aspergillosis), or transformation to aggressive lymphoma (Richter's syndrome).

Treatment

If asymptomatic, the patient can be monitored. Chlorambucil is used to ↓lymphocyte count, improve marrow function, and reduce node size. Dose: eg 0.1-0.2mg/kg daily PO. The purine analogue fludarabine is an alternative. Steroids are used in autoimmune haemolysis.

Radiotherapy:

For relief of lymphadenopathy or splenomegaly.

Supportive care:

Transfusions, IV human immunoglobulin if recurrent infections. Bone marrow transplant is currently experimental.

Prognosis

Current treatments are mainly non-curative at present. Prognosis is often good: depends on stage and molecular/immunological factors.

Treatment of CML

Chemotherapy

- Imatinib (Glivec®), a specific BCR/ABL tyrosine kinase inhibitor, has revolutionized CML therapy. It is more effective than the previous gold standard of ×- interferon—± cytarabine in chronic phase patients, in terms of preventing disease progression. It is likely that this will be translated into a survival advantage; long term data are awaited. The drug may also be effective in accelerated phase and blast crises. Imatinib gives high haematological response rates (>90%). Cytogenetic remissions are also common, but complete eradication of the Philadelphia clone, as detected by the most sensitive molecular methods, is unusual (<5% patients). SE: usually mild: nausea, cramps, oedema, skin rash, headache, arthralgia. May cause myelosuppression.
- Hydroxycarbamide may still be used in patients intolerant of imatinib, or where imatinib has proved ineffective. Busulfan is very rarely used now.
- The use of ×-interferon in CML has declined dramatically with the introduction of imatinib, but ×-interferon may still have a role in combination therapy.
- Treatment of CML blast crisis is problematic. Patients not previously treated with imatinib may respond temporarily to this. Those with lymphoblastic transformation may benefit from treatment as for ALL. Treatment of myeloblastic transformation with chemotherapy rarely achieves lasting remission and allogeneic transplantation offers the only hope of long-term survival.

Stem cell transplantation

- Allogeneic transplantation from a HLA matched sibling or unrelated donor is the only curative treatment but carries significant morbidity and mortality. Guidelines suggest that this approach should be used 1st line only in young patients where mortality rates are lower. Other patients should be offered imatinib. Patients are then reviewed annually to decide whether to continue imatinib, or to offer combination therapy or stem cell transplantation.
- The role of autologous transplantation, if any, in CML, remains to be defined.

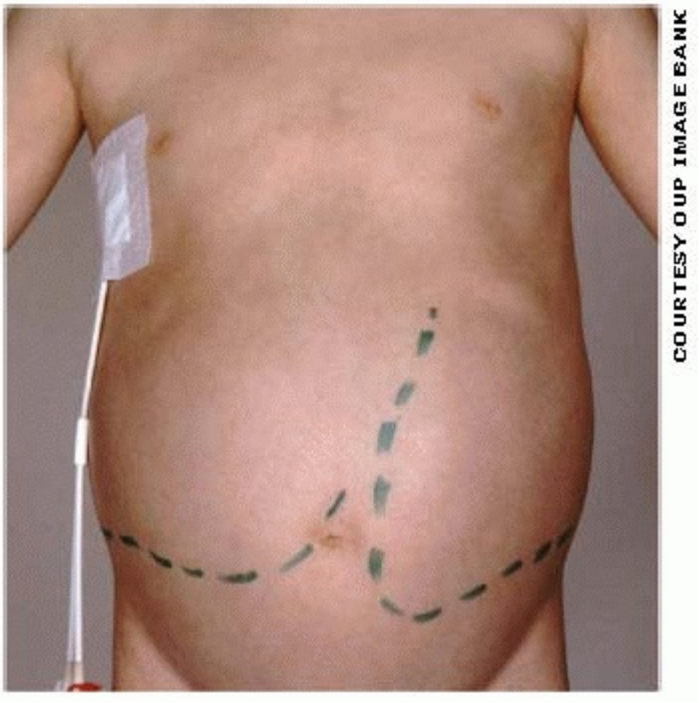


Fig 1. Hepatosplenomegaly in CML.

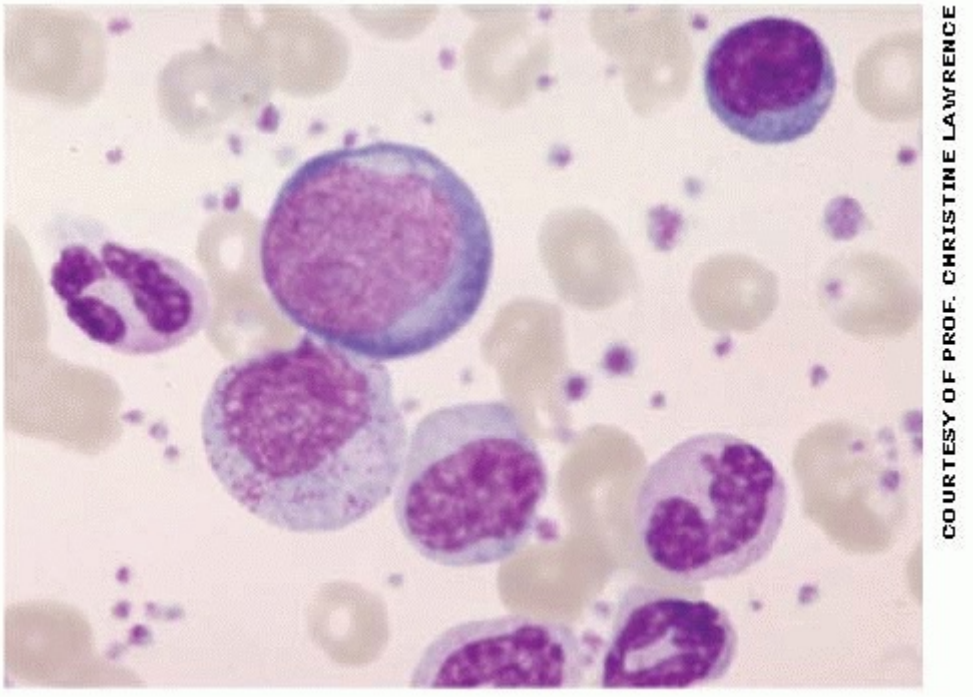


Fig 2. CML: Numerous granulocytic cells at different stages of differentiation.[70]

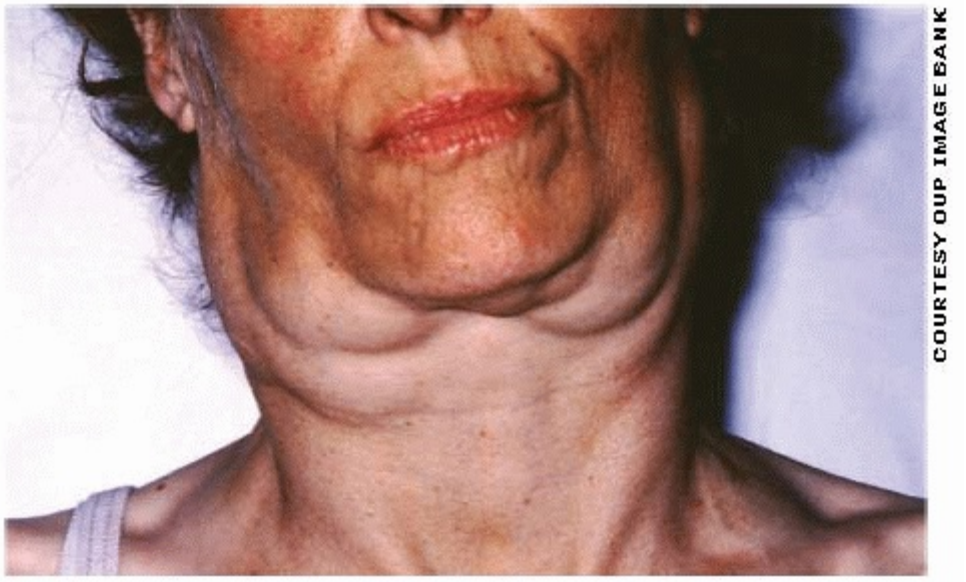


Fig 3. Bilateral cervical lymphadenopathy in CLL.

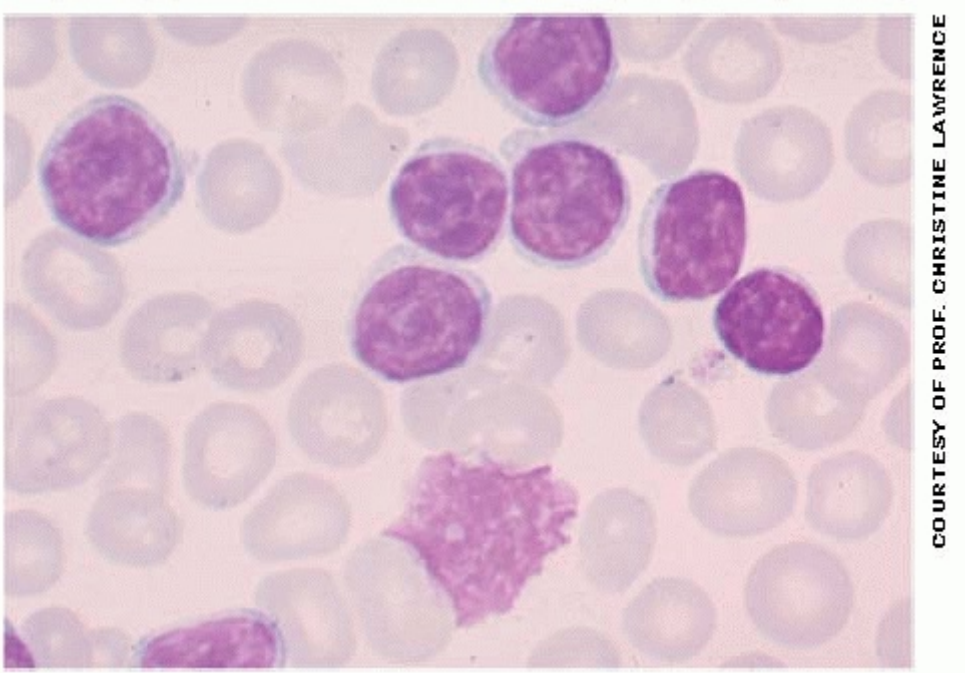


Fig 4. CLL: Numerous lymphocytes and a typical 'smear' cell: a fragile cell damaged in preparation.[71]

Hodgkin's lymphoma [Thomas Hodgkin, Guy's,UK 1798-1866]

Lymphomas are disorders caused by malignant proliferations of lymphocytes. These accumulate in the lymph nodes causing lymphadenopathy, but may also be found in peripheral blood or infiltrate organs. Lymphomas are histologically divided into Hodgkin's and non-Hodgkin's types. In Hodgkin's lymphoma, characteristic cells with mirror-image nuclei are found, called Reed-Sternberg cells.

Hodgkin's lymphoma:

2 peaks of incidence: young adults and elderly. ♂:♀≈2:1;

Symptoms

Often presents with enlarged, painless, non-tender, 'rubbery' superficial lymph nodes, typically cervical (60-70%), also axillary or inguinal nodes. The size of the nodes may increase and decrease spontaneously, and nodes can become matted. 25% have constitutional upset, eg fever, weight loss, night sweats, pruritus, and lethargy. There may be alcohol-induced lymph node pain. Mediastinal lymph node involvement can cause features due to mass effect eg

bronchial or SVC obstruction (p514), or direct extension eg causing pleural effusions. *Pel-Ebstein fever* implies a cyclical fever with long periods (15-28 days) of normal or low temperature: it is, at best, rare—and some have called it mythical.[1]

[1] Pel-Ebstein fever is dismissed by Richard Asher (*Talking Sense*), as existing only thanks to its having been exotically named (the 1885 patients of Dr P Pel had no histology, and fevers in Hodgkin's are *usually* non-specific). Another unfair reason for consigning it to myth is that the paper proving its existence and its relation to cyclical changes in node size doesn't come up in literature searches as Wilhelm *Ebstein* was spelled *Epstein* throughout.

Signs

Lymph node enlargement. Also, cachexia, anaemia, spleno- or hepatomegaly.

Tests

Tissue diagnosis

Lymph node excision biopsy if possible. Image guided needle biopsy, laparotomy or mediastinoscopy may be needed to obtain a sample.

Bloods

FBC, film, ESR, LFT, LDH, urate, Ca^{2+}. ↑ESR or ↓Hb indicate a worse prognosis. LDH is raised as it is released during cell turnover.

Staging

(Ann Arbor system) Influences treatment and prognosis. Done by CXR, CT of thorax, abdo, pelvis ± bone marrow biopsy if B symptoms, or stage III-IV disease.

I	Confined to single lymph node region.
II	Involvement of two or more nodal areas on the same side of the diaphragm.
III	Involvement of nodes on both sides of the diaphragm.
IV	Spread beyond the lymph nodes eg liver or bone marrow.

Each stage is subdivided into **'A'**—no systemic symptoms other than pruritus; or **'B'**—presence of B symptoms: weight loss >10% in the last 6 months, unexplained fever >38°C, or drenching night sweats (requiring change of clothes). **'B'** indicates more extensive disease. Localized extra-nodal extension does not advance the stage, but is indicated by subscripted **'E'**, eg **I-A_E** .

Treatment

This is with chemotherapy, radiotherapy or both. Radiotherapy ± short courses of chemotherapy for stages I-A and II-A (eg with ¢3 areas involved). Longer courses of chemotherapy for II-A with >3 areas involved through to IV-B. The standard regime is **'ABVD'**: **A**driamycin, **B**leomycin, **V**inblastine, and **D**acarbazine. More intensive regimens are used if poor prognosis or advanced disease. In relapsed disease, where disease recurs after treatment, high dose chemotherapy with peripheral stem-cell transplantation may be used, involving autologous (or occasionally allogeneic) transplantation of peripheral blood progenitor cells to restore marrow function after therapy.[72]

Complications of treatment

See p516-9: Radiotherapy may ↑ risk of second malignancies—solid tumours (especially lung and breast, also melanoma, sarcoma, stomach and thyroid cancers), ischaemic heart disease, hypothyroidism and lung fibrosis due to the radiation field. Chemotherapy SE include myelosuppression, nausea, alopecia, infection. AML (p340), non-Hodgkin's lymphoma and infertility may be due to both chemo- or radiotherapy—see page 519.

5-year survival

Depends on stage and grade: >95% in I-A lymphocyte-predominant disease; <40% with IV-B lymphocyte-depleted.

Emergency presentations

Infection; SVC obstruction—JVP↑, sensation of fullness in the head, dyspnoea, blackouts, facial oedema (seek expert help; see p514).

Classification (In order of incidence)		Prognosis
Classical Hodgkin's lymphoma		
	Nodular sclerosing	Good
	Mixed cellularity*	Good
	Lymphocyte rich	Good
	Lymphocyte-depleted*	Poor

NB: nodular lymphocyte predominant Hodgkin's is recognized as a separate entity, behaving as an indolent B-cell lymphoma.

* *Higher incidence and worse prognosis if HIV +ve.* [73]

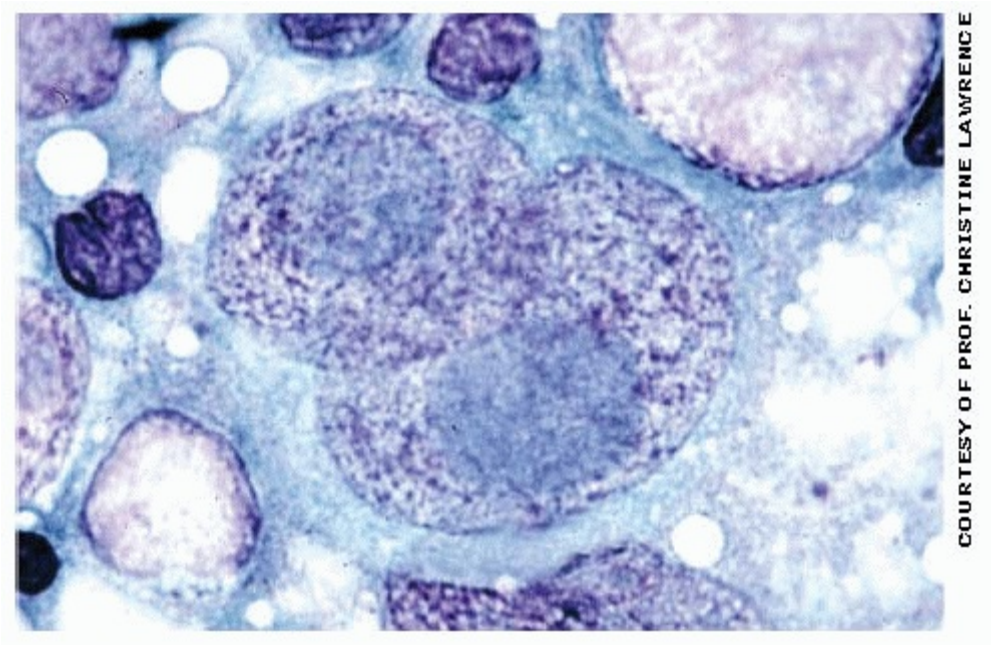


Fig 1. A Reed-Sternberg cell, which contains 2 nuclei, characteristic of Hodgkin's lymphoma.[74]

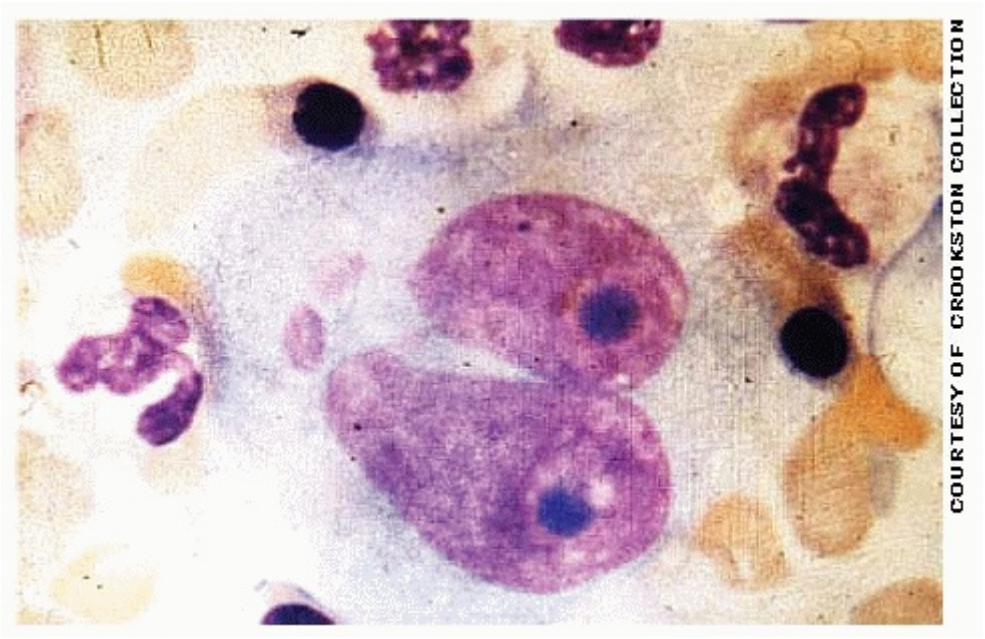


Fig 2. Another Reed-Sternberg cell.[75]

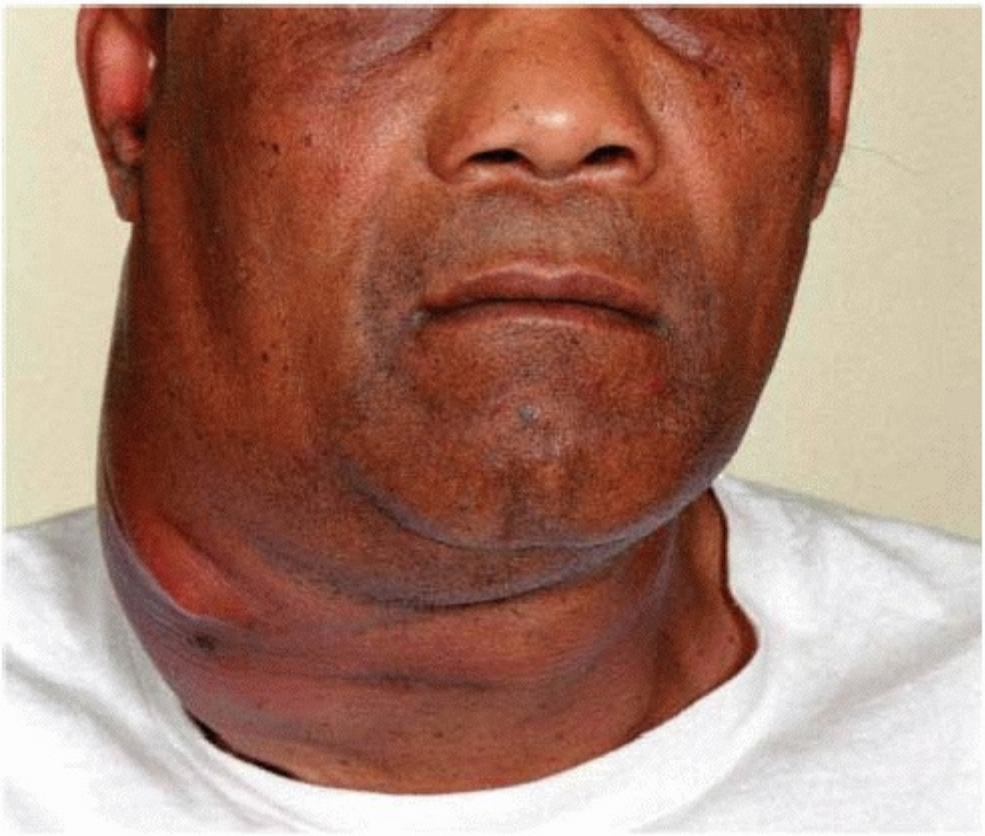


Fig 3. Cervical lymphadenopathy in Hodgkin's disease.

Non-Hodgkin's lymphoma

This includes all lymphomas without Reed-Sternberg cells, and is a very diverse group of diseases. Most are derived from B-lymphocyte cell lines. Not all are centred on lymph nodes (extranodal tissues generating lymphoma include mucosaassociated lymphoid tissue—MALT. Gastric MALT is associated with *H. pylori*, and may regress when this is eradicated). The overall incidence of lymphoma has doubled since 1970 (to 1 : 10,000). *Causes:* congenital immunodeficiency, acquired immunodeficiency eg drugs, HIV infection (usually high grade lymphoma), infection (eg HTLV-1 p336, EBV, *H. pylori*) or environmental toxins.

Signs and symptoms

- Nodal disease (75% at presentation): superficial lymphadenopathy
- Extranodal disease (25%) involving the oropharynx, skin (especially T cell lymphomas—p548), bone, gut, CNS, or lung. Disease of the oropharyngeal lymphoid tissue (Waldeyer's ring) causes sore throat and obstructed breathing.
- Systemic symptoms—fever, night sweats, weight loss (less common than in Hodgkin's lymphoma, and indicates disseminated disease)
- Pancytopenia due to marrow involvement—anaemia, neutropenia (infection) and ↓platelets (bleeding).

Tests

As for Hodgkin's disease with the Ann Arbor system (p344).

Diagnosis

Lymph node biopsy.

Bloods

FBC, U&E, LFT, LDH. ↑LDH indicates worse prognosis as it is released with cell turnover.

Stage

with CT or MRI of chest, abdomen, pelvis, and bone marrow aspiration. Send cytology of any effusion; lumbar puncture for CSF cytology if any CNS signs.

Histology

This is something of a quagmire as classification systems are complex and changing. The current classification is based on the WHO classification of lymphoid neoplasms. Discuss diagnosis and management as a multidisciplinary team, bringing together information available from clinical evaluation, histology, immunology, molecular genetics, and imaging. *Generally:*

- Low-grade lymphomas are indolent, and are often incurable and widely disseminated at presentation. Include: follicular lymphoma, marginal zone lymphoma (includes MALT lymphomas), lymphocytic lymphoma (closely related to CLL and treated similarly), lymphoplasmacytoid lymphoma (associated with production of IgM = Waldenström's macroglobulinaemia, p354).
- High-grade lymphomas are more aggressive, but long-term cure may be achievable. There is often a short history of rapidly enlarging lymphadenopathy with systemic symptoms. Include: Burkitt's lymphoma (childhood disease with characteristic jaw lymphadenopathy), lymphoblastic lymphomas (shares features with ALL), diffuse large B-cell lymphoma.

Treatment

Depends on disease subtype.

Low grade:

If symptomless, none may be needed. Radiotherapy may be curative in localized disease. Chlorambucil is used in diffuse disease. Remission may be maintained by using ×-interferon or rituximab (see below).

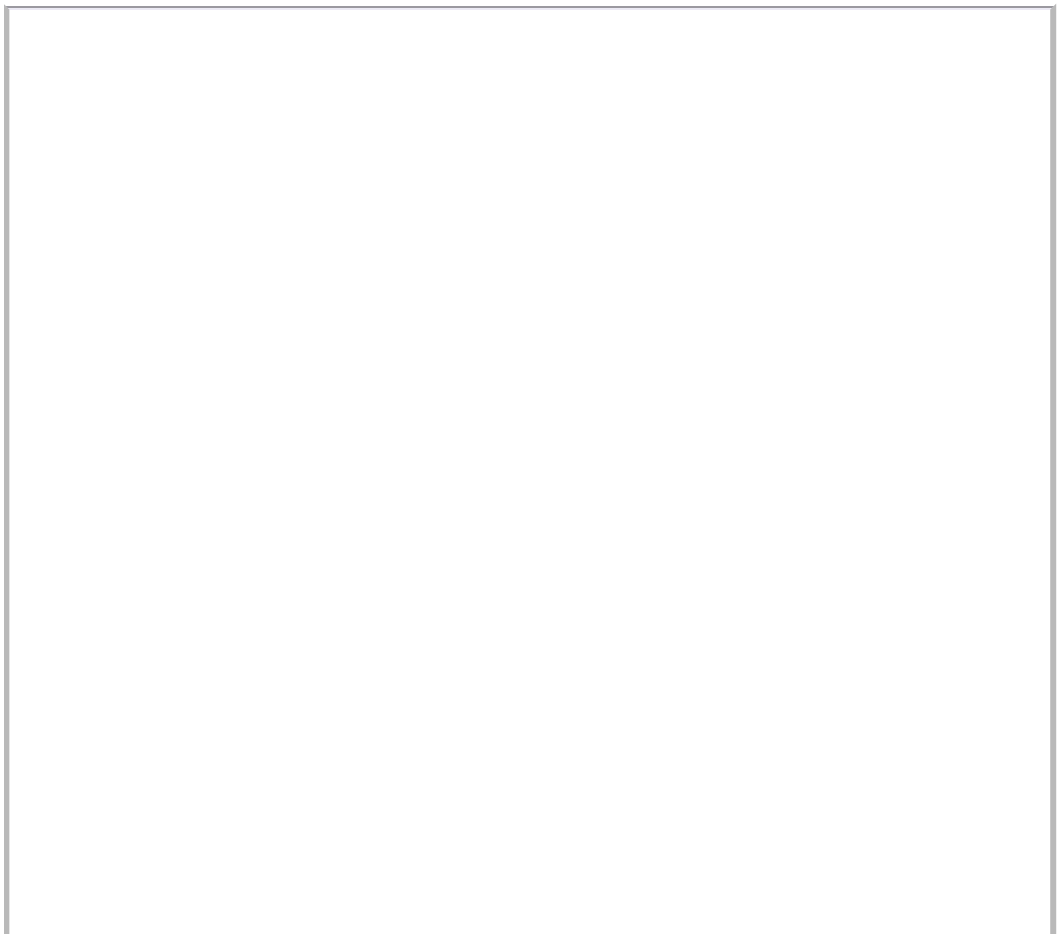
High grade:

For diffuse large B-cell lymphoma (DLBCL), the **'CHOP'** regime**: C**yclophosphamide, **H**ydroxydaunorubicin, vincristine (**O**ncovin®) and **P**rednisolone plus rituximab may be used.[1] The addition of rituximab, an anti-CD20 monoclonal antibody, to this regimen has produced the first major advance in the treatment of this disorder for 30yrs.

Survival

Histology is important. Prognosis is worse if at presentation:

- Age >60yrs
- Systemic symptoms
- Bulky disease (abdominal mass >10cm)
- ↑LDH
- Disseminated disease. Typical 5-yr survival for treated patients: ~30% for high-grade and >50% for low-grade lymphomas, but the picture is very variable.



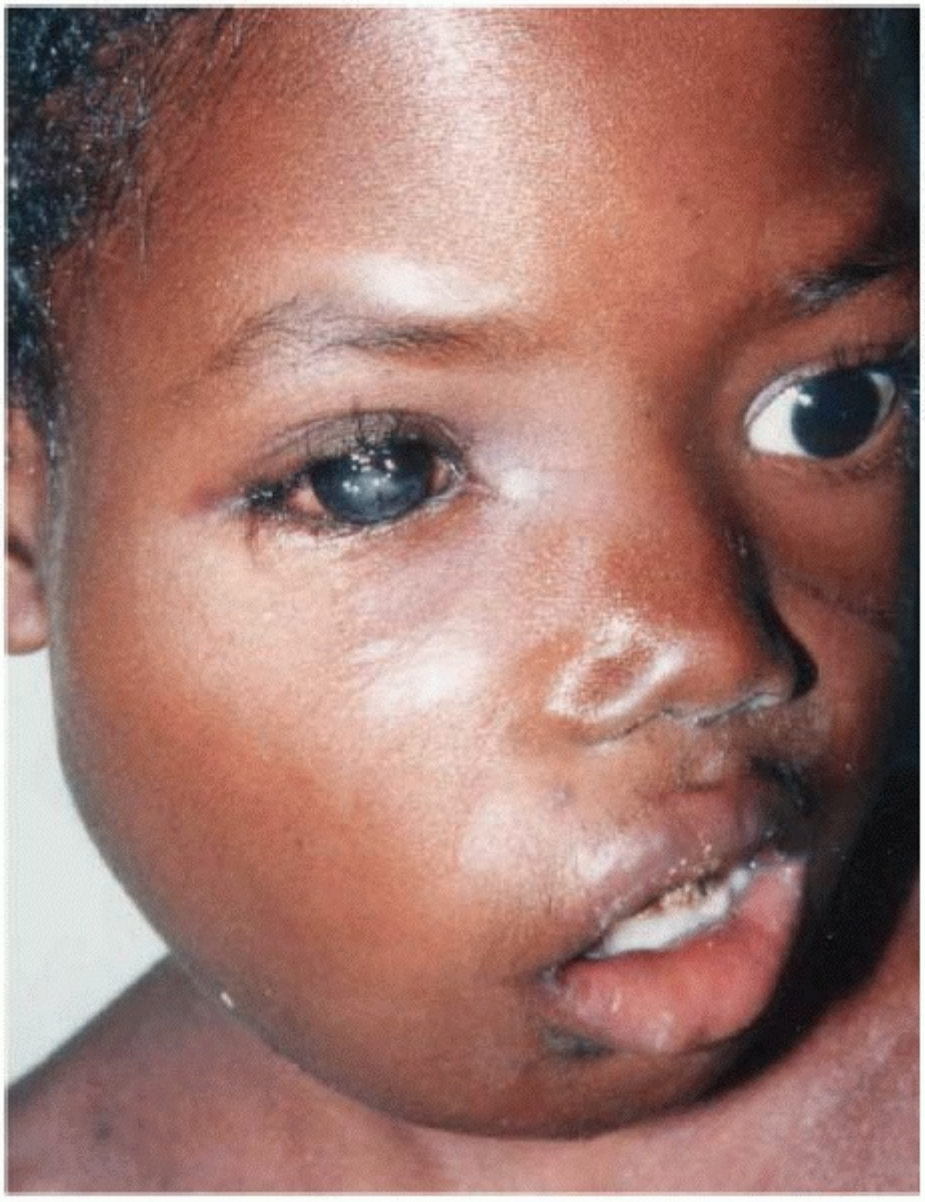


Fig 1. Burkitt's lymphoma, with characteristic jaw lymphadenopathy.[76]

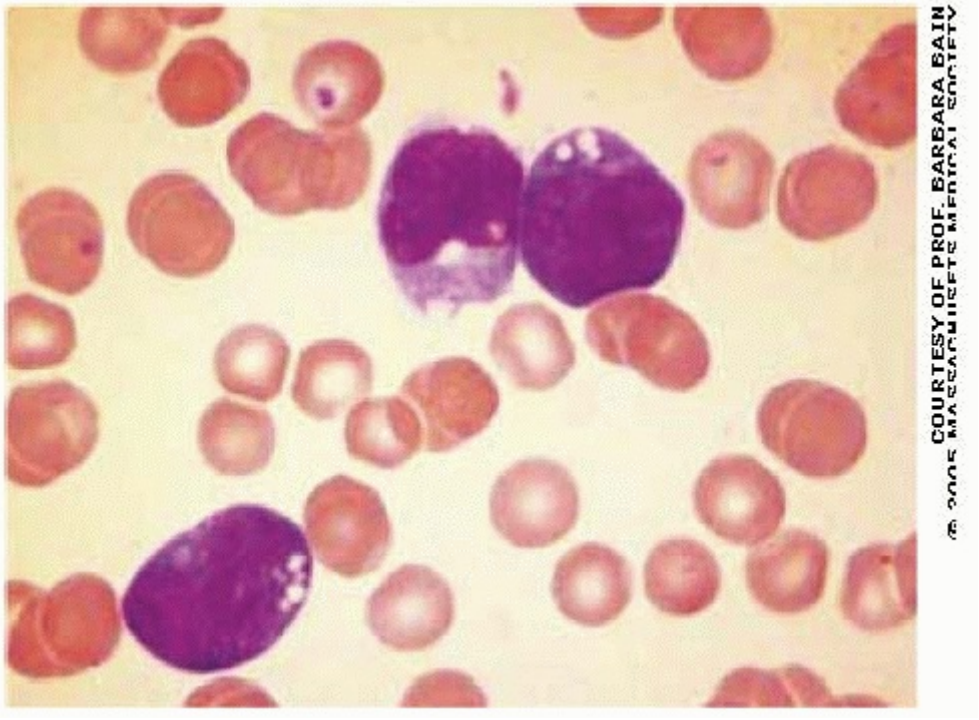


Fig 2. Burkitt's lymphoma, with 3 basophilic vacuolated lymphoma cells.[77]

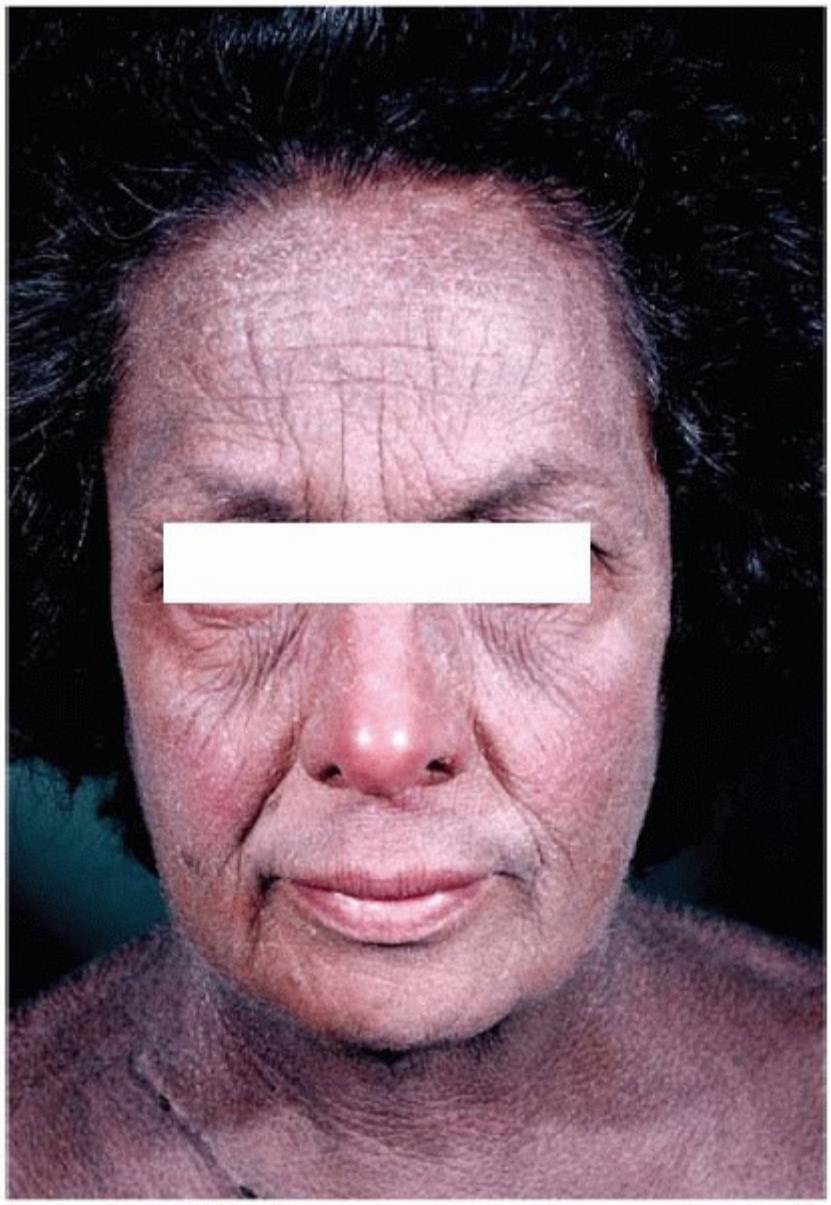


Fig 3. Cutaneous T cell lymphoma, which has caused severe erythroderma (Sézary syndrome) in a Caucasian woman.[78]

Pancytopenia, and bone marrow failure

The bone marrow is responsible for haemopoiesis. In adults, this normally takes place in the central skeleton (vertebrae, sternum, ribs, skull) and proximal long bones. In some anaemias (eg thalassaemia), increased demand produces haematopoiesis outside the bone marrow (extramedullary haematopoiesis), in the liver and spleen causing organomegaly. All blood cells arise from an early pluripotent stem cell, which divides in an asymmetrical way to produce another stem cell and a progenitor cell committed to a specific cell line. Committed progenitors undergo further differentiation under myeloid or lymphocyte lineage, before their release into the blood as mature cells.

Pancytopenia

is reduction in all the major cell lines: red cells, white cells and platelets. Causes are due to

1. ↓*marrow production:* aplastic anaemia, infiltration (eg acute leukaemia, myelodysplasia, myeloma, lymphoma, solid tumours, TB), megaloblastic anaemia, paroxysmal nocturnal haemoglobinuria (p324), myelofibrosis (p350), SLE.
2. ↑*peripheral destruction:* hypersplenism.

Aplastic anaemia

is a rare stem cell disorder leading to pancytopenia and a hypoplastic bone marrow (the marrow stops making cells). Presents with features of anaemia (↓Hb), infection (↓WCC) or bleeding (↓platelets).

Incidence:

~5 cases per million/year.

Causes:

Most cases are autoimmune, triggered by drugs, (viruses eg Parvovirus, hepatitis) or irradiation. May also be inherited eg Fanconi anaemia (p690).

Tests:

A bone marrow examination is required for the diagnosis.

Treatment:

Support the blood count (below). Asymptomatic patients do not require specific treatment, but supportive treatment (eg neutropenic regimen) may be required. The treatment of choice in young patients who are severely affected is an allogeneic marrow transplantation from an HLA matched sibling, which can be curative. Otherwise, immunosuppression with ciclosporin and antithymocyte globulin may be effective, although is not curative in most.

Marrow support

Red cells survive for ~120d, platelets for ~8d, and neutrophils for 1-2d, so early problems are mainly from neutropenia and thrombocytopenia.

Red cell transfusion:

Transfusing 1U should raise Hb by ~1-1.5g/dL (p570). Transfusion may drop the platelet count (you may need to give platelets before or after).

Platelets:

Traumatic bleeds, purpura and easy bruising occur if platelets $<50\times10^9$/L. Spontaneous bleeding may occur if platelets $<20\times10^9$/L, with intracranial haemorrhage rarely. Platelets are stored at room temperature (22°C; not in the fridge). In marrow transplant or if severely immunosuppressed, platelets may need irradiation before use, to prevent transfusion-associated graft-versus-host disease (GVHD). Platelets should be ABO compatible. They are not used in ITP (p330). Indications:

- Platelets $<10\times10^9$/L
- Haemorrhage, including DIC (p336)
- Before invasive procedures (eg biopsy, lumbar puncture) to increase count to $>50\times10^9$/L. 4U of fresh platelets should raise the count to $>40\times10^9$/L in adults; check dose needed with lab.

Neutrophils:

Use a 'neutropenic regimen' if the count $<0.5\times10^9$/L. See p336.

Bone marrow biopsy

may provide diagnostic information where there are abnormalities in the peripheral blood, and is also an important staging test in the lymphoproliferative disorders. Ideally an aspirate *and* trephine should be taken, usually from the posterior iliac crest (aspirates can also be taken from the anterior iliac crest or sternum). The aspirate provides a film which is examined by microscope. The trephine is a core of bone which allows assessment of bone marrow cellularity, architecture and the presence of infiltrative disease. Coagulation disorders may need to be corrected pre-biopsy. Apply pressure afterwards (lie on that side for 1-2h if platelets are low).

The myeloproliferative disorders

These form a group of disorders caused by proliferation of a clone of haematopoietic myeloid stem cells in the marrow. While the cells proliferate, they also retain the ability to differentiate into RBCs, WBCs or platelets.

Classification

is by the cell type which is proliferating

RBC	→	Polycythaemia rubra vera (PRV).

WBC	→	Chronic myeloid leukaemia (CML, p342).
Platelets	→	Essential thrombocythaemia.
Fibroblasts	→	Myelofibrosis.

Polycythaemia

may be relative (↓plasma volume, normal RBC mass) or absolute (↑RBC mass). *Relative polycythaemia* may be acute and due to dehydration (eg alcohol or diuretics). A more chronic form exists which is associated with obesity, hypertension, and a high alcohol and tobacco intake. *Absolute polycythaemia* is distinguished by red cell mass estimation, using radioactive chromium (51Cr) labelled RBCs. Causes are primary (***polycythaemia rubra vera***) or secondary due to hypoxia (eg high altitudes, chronic lung disease, cyanotic congenital heart disease, heavy smoking) or inappropriately ↑erythropoietin secretion (eg in renal carcinoma, hepatocellular carcinoma).

Polycythaemia rubra vera

This is a malignant proliferation of a clone derived from one pluripotent marrow stem cell. The erythroid progenitor offspring are unusual in not needing erythropoietin to avoid apoptosis (p499). There is excess proliferation of RBCs, WBCS, and platelets, leading to thrombotic complications due to hyperviscosity. Usually affects older patients >60yrs.

Signs

May be asymptomatic and detected on FBC, or present with vague signs due to hyperviscosity (p356): headaches, dizziness, tinnitus, visual disturbance. Itch after a hot bath, and erythromelalgia, a burning sensation in fingers and toes, are characteristic. Examination may show facial plethora and splenomegaly (in 60%). Gout may occur due to ↑urate from RBC turnover. Features of arterial (cardiac, cerebral, peripheral) or venous (DVT, cerebral, hepatic) thrombosis may be present.

Investigations

- FBC: ↑RCC, ↑Hb, ↑HCT, ↑PCV, often also ↑WBC and ↑platelets
- B_{12}↑
- Marrow shows hypercellularity with erythroid hyperplasia
- Neutrophil alkaline phosphatase (NAP) score is ↑ (↓ in CML)
- ↓serum erythropoietin
- Raised red cell mass on 51Cr studies and splenomegaly, in the setting of a normal P_aO_2, is diagnostic.

Treatment:

Aim to keep HCT <0.45 to ↓risk of thrombosis. In younger patients at low risk, this is done by venesection. If higher risk (age >60yrs, previous thrombosis), hydroxycarbamide (=hydroxyurea) is used. ×-interferon is preferred in women of childbearing age. Low dose aspirin 75mg daily PO is also given.

Prognosis:

Variable, many remain well for years. Thrombosis and haemorrhage (due to defective platelets) are the main complications. Transition to myelofibrosis occurs in ~30% or acute leukaemia in ~5%. Monitor FBC every 3 months.

Essential thrombocythaemia

A clonal proliferation of megakaryocytes leads to persistently ↑platelets, often >1000 × 10^9/L, with abnormal function, causing bleeding or arterial and venous thrombosis, and microvascular occlusion— headache, atypical chest pain, light-headedness, erythromelalgia. Exclude other causes of thrombocytosis (see BOX).

Treatment:

Low dose aspirin 75mg daily. Hydroxycarbamide is given to ↓platelets if >60yrs old or if previous thrombosis.

Myelofibrosis

There is hyperplasia of megakaryocytes which produce platelet derived growth factor, leading to intense marrow fibrosis and myeloid metaplasia (haemopoiesis in the spleen and liver)→massive hepatosplenomegaly.

Presentation:

Hypermetabolic symptoms: night sweats, fever, weight loss; abdominal discomfort due to splenomegaly; or bone marrow failure (↓Hb, infections, bleeding).

Film:

Leucoerythroblastic cells (nucleated red cells, p314); characteristic teardrop RBCs (see **fig 2**). Hb↓. Bone marrow trephine for diagnosis.

Treatment:

Marrow support (see p662). Allogeneic stem cell transplant may be curative in young people but carries a high risk of mortality.

Prognosis:

Median survival 4-5 years.

Causes of thrombocytosis

↑Platelets >450 × 10^9/L may be a reactive phenomenon, seen with many conditions including:

- Bleeding
- Infection
- Chronic inflammation, eg collagen disorders
- Malignancy
- Trauma
- Post-surgery
- Iron deficiency

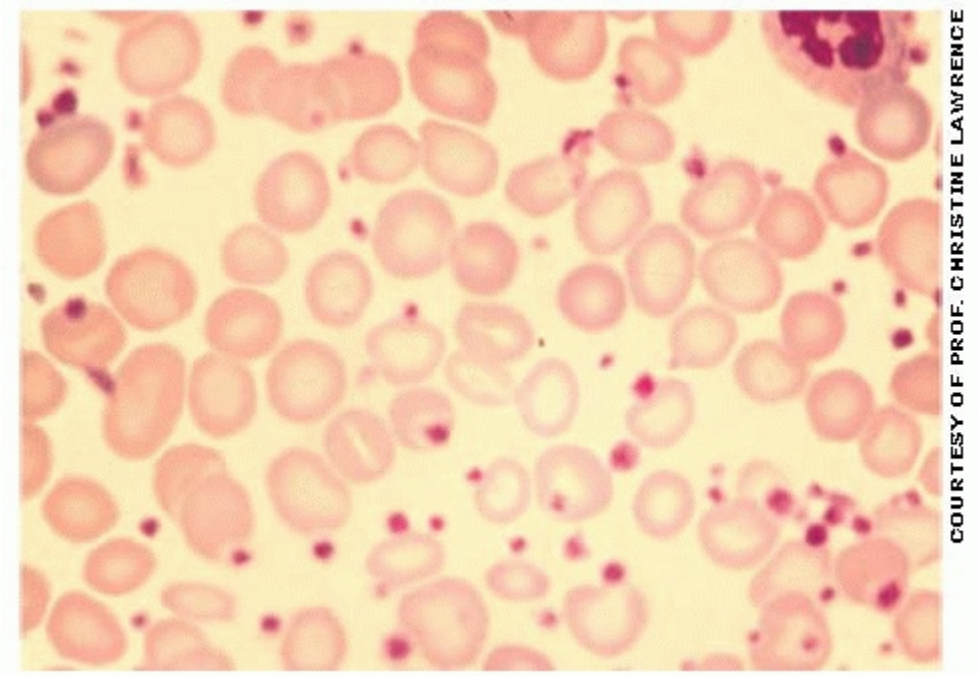


Fig 1. Essential thrombocythaemia: numerous platelets seen.[79]

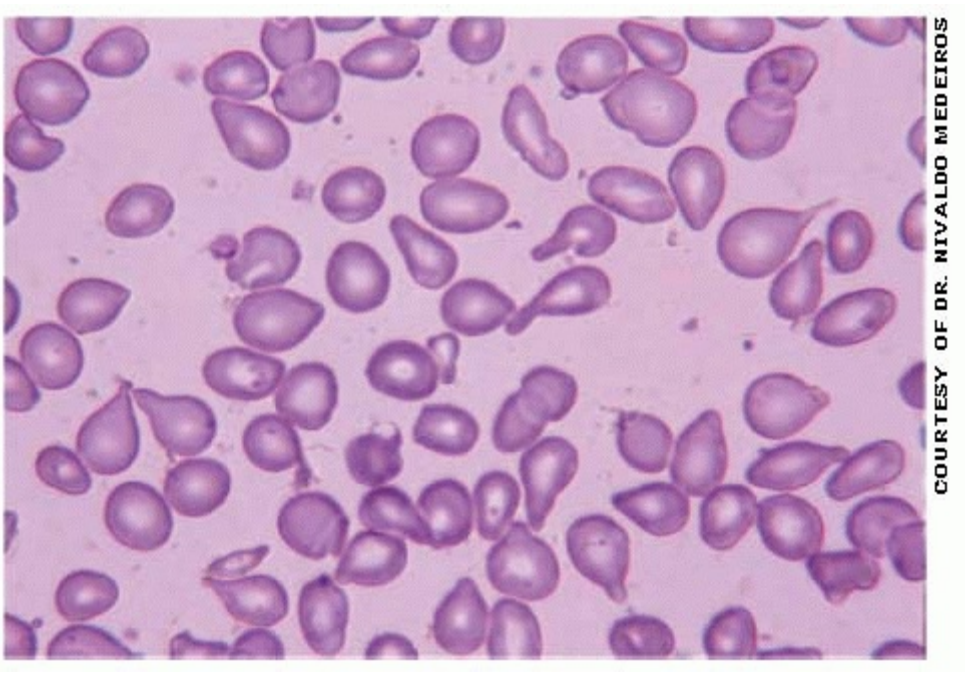


Fig 2. Tear drop cells, seen in myelofibrosis.[80]

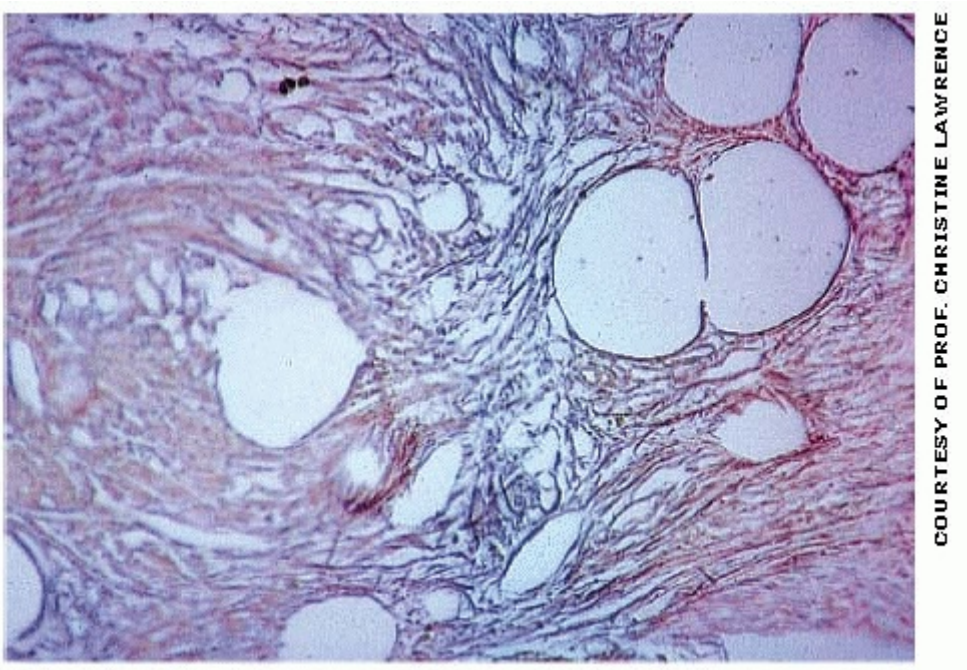


Fig 3. Bone marrow trephine in myelofibrosis: the streaming effect is caused by intense fibrosis. Other causes of marrow fibrosis include any myeloproliferative disorder, lymphoma, secondary carcinoma, TB, leukaemia, and irradiation.[81]

Myeloma

Myeloma is a malignant clonal proliferation of B-lymphocyte derived plasma cells (fig 1). Normally many different plasma cells produce different immunoglobulins (Igs) which are polyclonal. In myeloma, a single clone of plasma cells produce identical Igs. This can be detected as a monoclonal band, or paraprotein, on serum and/or urine electrophoresis (see p678). *Classification* is based on the Ig product, which is IgG in ~2/3 and IgA in ~1/3. The small remainder are IgM or IgD. The other Ig levels are low. This is termed immunoparesis, causing increased susceptibility to infection. In ~2/3 of cases, the urine contains Bence-Jones protein, which are free Ig light chains of either kappa (κ) or lambda (λ) type, filtered by the kidney.

Incidence

5/100,000. Peak age: 70yrs.♂:♀≈1. Afro-Caribbeans:Caucasians≈2:1.

Symptoms

- ***Osteolytic bone lesions*** causing unexplained backache, pathological fractures eg long bones or ribs, and vertebral collapse. ***Hypercalcaemia*** may result with symptoms (p672). Lesions are due to ↑ osteoclast activation, from signalling by myeloma cells.
- ***Anaemia, neutropenia, or thrombocytopenia*** **may result from marrow infiltration** by proliferating plasma cells, leading to symptoms of anaemia, infection and bleeding.
- ***Recurrent bacterial infections*** due to immunoparesis, and also because of neutropenia due to the disease and from chemotherapy.
- ***Renal impairment*** due to light chain deposition (p306 & p354).
- ***Systemic AL amyloidosis*** occurs in 15% (p354).

Tests

FBC—normocytic normochromic anaemia, film—rouleaux formation (p314), persistently ↑ESR or PV (p356), ↑urea and creatinine, ↑Ca^{2+} (in ~40%), alk phos usually normal (unless healing fracture).

Screening test:

Serum & urine electrophoresis. Ò2-microglobulin (as a prognostic test).

Imaging

X-rays show lytic 'punched-out' lesions, eg pepper-pot skull, vertebral collapse, fractures or osteoporosis. CT or MRI may be useful to detect lesions not seen on XR.

Diagnosis:

see BOX.

Treatment

Supportive:

- Bone pain should be treated with analgesia (avoid NSAIDs due to risk of renal impairment). Give all patients a bisphosphonate (clodronate, zolendronate or pamidronate), as they reduce fracture rates and bone pain. Local radiotherapy can help rapidly in focal disease. Orthopaedic procedures (vertebroplasty or kyphoplasty) may be helpful in vertebral collapse.
- Anaemia should be corrected with transfusion, and erythropoietin may be used.
- Renal failure: Rehydrate, and ensure adequate fluid intake of 3L/day to prevent further renal impairment by light chains. Dialysis may be needed in acute renal failure
- Infections: Treat rapidly with broad spectrum antibiotics until culture results are known. Regular IV immunoglobulin infusions may be needed if recurrent.

Chemotherapy:

In elderly patients, either melphalan or cyclophosphamide are used with prednisolone. This is usually effective in controlling disease for about 1 year, reducing paraprotein levels and bone lesions. The disease may then become uncontrollable and often resistant to treatment. One randomized trial (2006) found the addition of thalidomide (a teratogenic immunomodulator) markedly improved event-free survival in the elderly.RCT_{82} Its use is non-standard. SE: birth defects; drowsiness; neuropathy; neutropenia; sepsis; thromboembolism (anticoagulation is probably wise); orthostatic hypotension. In younger or fitter people, a more aggressive approach is used (high-dose therapy and stem-cell rescue, HDT) with a **VAD** type regime: **V**incristine, **A**driamycin and **D**examethasone. Autologous stem cell transplant may then be done, which improves survival but is not curative. Allogeneic transplantation can be curative in younger patients, but carries ↑risk of mortality (~30%). Thalidomide or bortezomib may be tried in relapsed disease.

Prognosis

Median survival is 3-4 years. A raised Ò2-microglobulin is associated with a worse prognosis. Death is commonly due to infection or renal failure.

Diagnostic criteria $_{83}$

1. Monoclonal protein band in serum or urine electrophoresis
2. Increased plasma cells found on bone marrow biopsy
3. Evidence of end organ damage from myeloma
   - Hypercalcaemia
   - Renal insufficiency
   - Anaemia

- Bone lesions: a skeletal survey is performed after diagnosis to detect bone disease, consisting of X-rays of chest; cervical, thoracic, and lumbar spine; skull and pelvis.

Complications of myeloma

- ***Hypercalcaemia*** (p672). Occurs with active disease ie at presentation or relapse. Rehydrate vigorously with IV saline 0.9% 4-6L/d (careful fluid balance). IV bisphosphonates, eg zolendronate or pamidronate are useful for treating hypercalcaemia acutely.
- ***Spinal cord compression*** (p458 & p515). Occurs in 5% of patients with myeloma. Urgent MRI if suspected. Treatment is with dexamethasone 8-16mg/24h PO and local radiotherapy.
- ***Hyperviscosity*** (p356), causes reduced cognition, disturbed vision, and bleeding. It is treated with plasmapheresis, to remove light chains.
- ***Acute renal failure*** is treated with rehydration. Patients may require urgent dialysis.

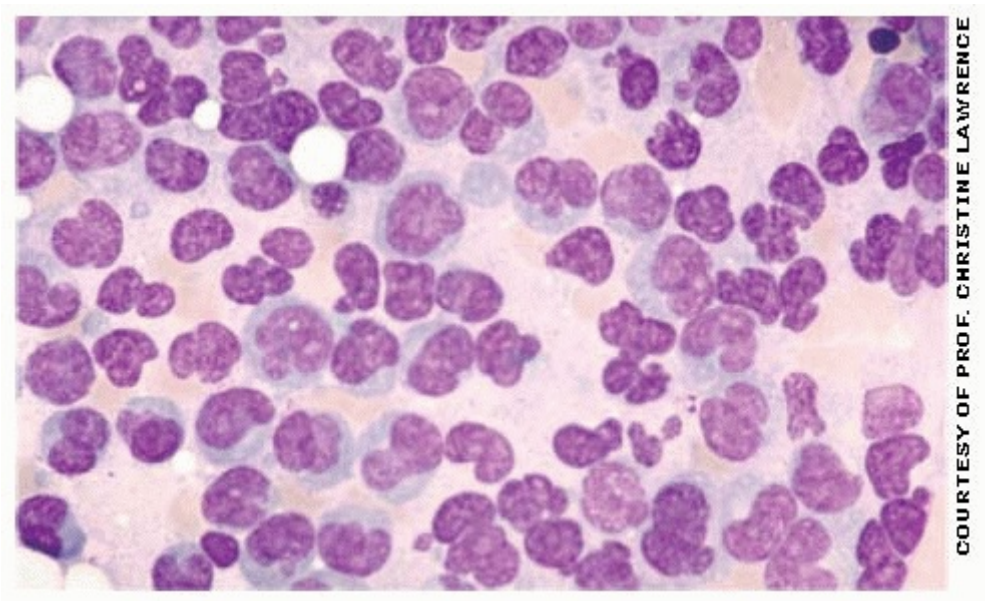


Fig 1. The bone marrow in myeloma: large number of plasma cells with abnormal forms.[84]

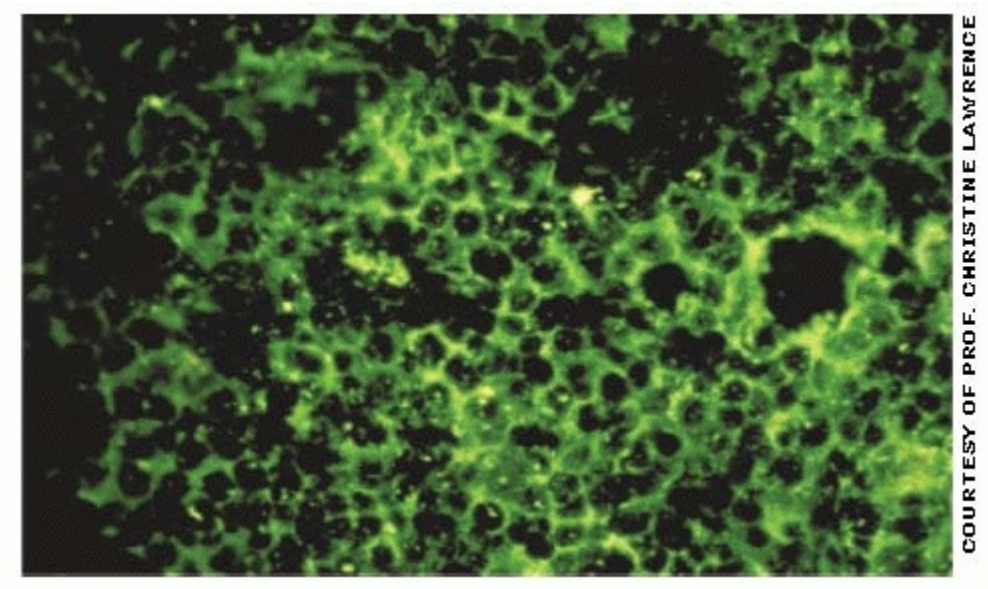


Fig 2. A bone marrow section in myeloma, stained with IgG kappa monoclonal antibody.[85]

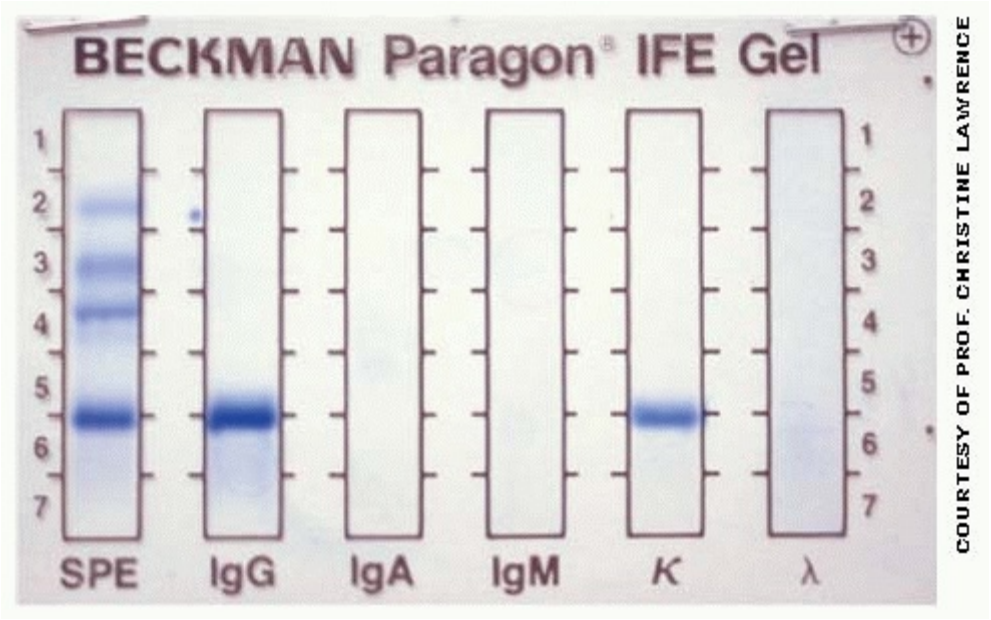


Fig 3. An IgG kappa paraprotein monoclonal band on electrophoresis (a control sample has run on the left).[86]

Paraproteinaemia

Paraproteinaemia denotes presence in the circulation of immunoglobulins produced by a single clone of plasma cells. The paraprotein is recognized as a monoclonal band (M band) on serum electrophoresis.[1] There are 6 major categories:

1. ***Multiple myeloma:*** See p352.
2. ***Waldenström's macroglobulinaemia:*** This is a lymphoplasmacytoid lymphoma producing a monoclonal IgM paraprotein. Hyperviscosity is common (p356), with CNS and ocular symptoms. Lymphadenopathy and splenomegaly are also seen. ↑ESR, with IgM paraprotein on serum electrophoresis. **[prescription take]:** None if asymptomatic. Chlorambucil, fludarabine or combination chemotherapy may be used. Plasmapheresis1 for hyperviscosity (p356).
3. ***Primary amyloidosis:*** See below.
4. ***Monoclonal gammopathy of uncertain significance*** (MGUS) is common (3% >70yrs). There is a paraprotein in the serum but no myeloma, macroglobulinaemia or lymphoma, with no bone lesions, no Bence-Jones protein and a low concentration of paraprotein, with <10% plasma cells in the marrow. A proportion of these patients develop myeloma or lymphoma in the future.
5. ***Paraproteinaemia in lymphoma or leukaemia:*** Eg seen in 5% of CLL.
6. ***Heavy chain disease:*** This is where neoplastic cells produce free Ig heavy chains. × chain disease is the most important, causing malabsorption from infiltration of small bowel wall. It may progress to lymphoma.

Amyloidosis [87]

This is a group of disorders characterized by extracellular deposits of a protein in abnormal fibrillar form, resistant to degradation. The following are the systemic forms of amyloidosis. Amyloid deposition is also a feature of Alzheimer's disease, Type 2 diabetes mellitus and haemodialysis-related amyloidosis.

AL amyloid (primary amyloidosis):

Due to clonal proliferation of plasma cells, with production of amyloidogenic monoclonal immunoglobulins. In most cases, it occurs on its own as a primary amyloidosis, with occult plasma cell proliferation. It is also seen in 15% of patients with myeloma, and smaller proportions with Waldenströms, MGUS, or lymphoma. Deposition may occur in

- Kidneys: Glomerular lesions—proteinuria and nephrotic syndrome
- Heart: Restrictive cardiomyopathy ('sparkling' appearance on Echo), arrhythmias, angina
- Nerves: Peripheral and autonomic neuropathy, carpal tunnel syndrome
- Gut: Macroglossia (big tongue), malabsorption, perforation, haemorrhage, obstruction, and hepatomegaly.
- Vascular: Purpura, especially periorbital—a characteristic feature.

AA amyloid (secondary amyloidosis):

The amyloid here is derived from serum amyloid A, an acute phase protein. It occurs with chronic inflammation in rheumatoid arthritis, inflammatory bowel disease, familial Mediterranean fever, and chronic infections—TB, bronchiectasis, osteomyelitis. It affects the kidneys, liver, and spleen, and commonly presents with proteinuria, nephrotic syndrome or hepatosplenomegaly. Macroglossia is not seen, and cardiac involvement is rare.

Familial amyloidosis

is a group of autosomal dominant disorder, most commonly caused by mutations in transthyretin, a transport protein produced by the liver. Usually causes a sensory or autonomic neuropathy ± renal or cardiac involvement.

Diagnosis

is made with biopsy of affected tissue, and positive Congo Red staining with red-green birefringence under polarized light microscopy. The rectum or subcutaneous fat are relatively non-invasive sites for biopsy and are +ve in 80%.

[prescription take]:

AA amyloidosis may improve if the primary disease is treated. AL may respond to therapy as for myeloma. Liver transplant can be curative in familial amyloidosis.

Prognosis

Median survival is 1-2 years. Patients with myeloma and amyloidosis have a shorter survival than those with myeloma alone.

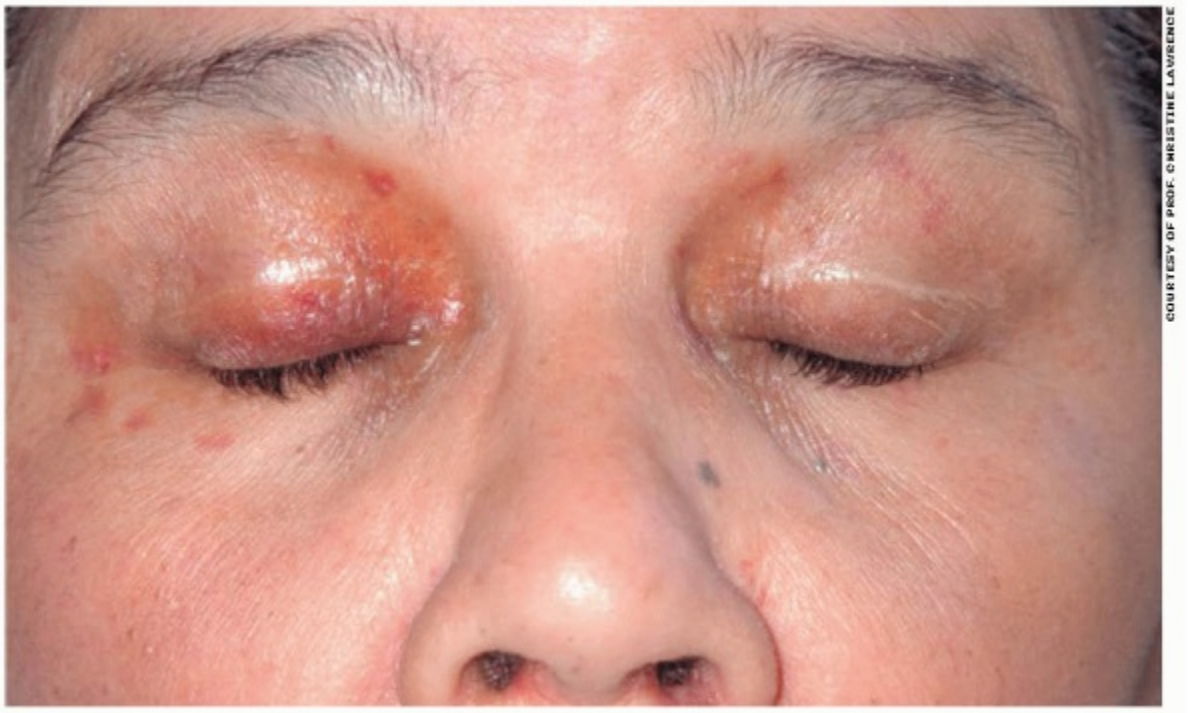


Fig 1. Periorbital purpura in amyloidosis.[88]

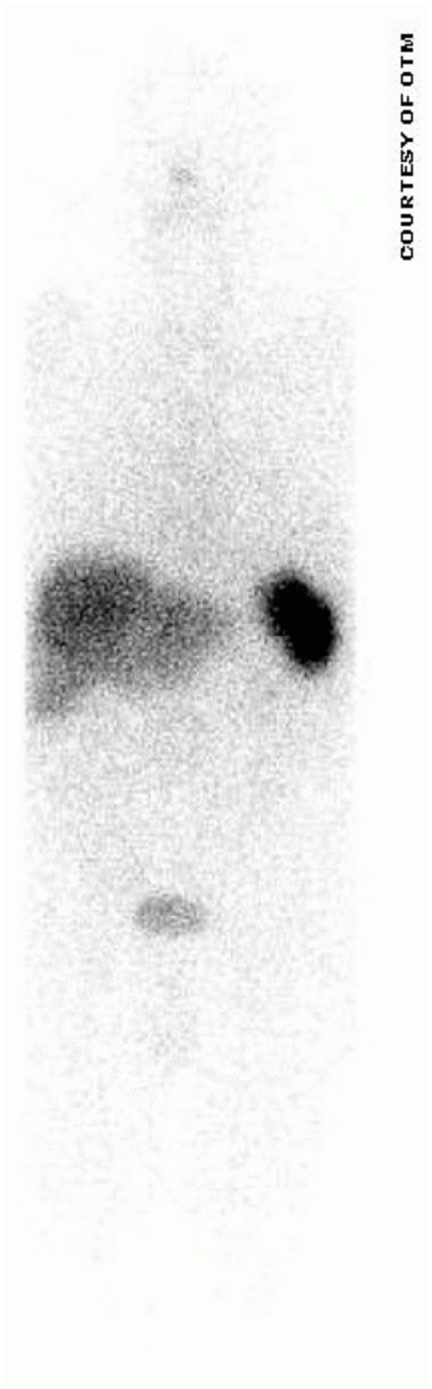


Fig 2. Isotope scan in amyloidosis showing areas of amyloid deposition in the liver and spleen.

Erythrocyte sedimentation rate (ESR)

Normal range:

<20mm/h.

The ESR is a sensitive but non-specific indicator of the presence of disease. It measures how fast RBCs fall through a column of anticoagulated blood over 1h. If certain proteins cover red cells, these cause RBCs to stick to each other in columns so they fall faster (the same phenomenon as rouleaux on the blood film, p314). The main causes of a raised ESR are any inflammation eg infection, rheumatoid arthritis, malignancy, myocardial infarction; or anaemia.

In those with a slightly raised ESR, the best plan is probably to wait a month and repeat it. There is a group of patients whose vague symptoms would have prompted nothing more than reassurance—were it not for a markedly raised ESR— and in whom there are no pointers to specific disease. The same advice does not hold true for those with a very high ESR (>100mm/h), where there is a 90% predictive value for disease. In practice, most have signs pointing to the cause. In one survey, serious underlying disease later found in such patients included myeloma, giant cell arteritis, abdominal aneurysm, metastatic prostatic carcinoma, leukaemia, and lymphoma. Therefore, it would be wise (after history and examination) to consider these tests: FBC, plasma electrophoresis, U&E, PSA, chest and abdominal X-rays, ± biopsy of bone marrow or temporal artery.

ESR also rises with age. A simple, reliable[89] way to allow for this is to calculate the upper limit of normal, using the Westergren method, to be (for men) age in years ÷ 2. For women, the formula is (years+10) ÷ 2.

Some conditions *lower* the ESR, eg polycythaemia (due to ↑red cell concentration), and sickle-cell anaemia. Even a slightly raised ESR in these patients should prompt one to ask: *What else is the matter?*

Plasma viscosity (PV)

Normal range:

1.50-1.72mPa/s.

In many laboratories, this has replaced the ESR, as it is less affected by anaemia and results can be produced in 15min. The PV is affected by the concentration of large plasma proteins and is raised in the same conditions as the ESR. The PV and ESR are both raised in chronic inflammation and are less affected by acute changes under 24h in duration. The CRP is more sensitive in acute change (see p678).

Hyperviscosity syndrome

This occurs if the viscosity of blood rises enough to impair the microcirculation. It affects patients with a very high red cell count (haematocrit >50), white cell count (>100×10^9/L), or plasma components (usually immunoglobulins).

Causes:

Polycythaemia rubra vera (↑red cells), acute or chronic leukaemia (↑peripheral blast cells), myeloma (p352), Waldenström's macroglobulinaemia (p354, as IgM is larger and so ↑ viscosity more than the same amount of IgG).

Presentation:

Features include lethargy, confusion, spontaneous bleeding: GU or GI, CNS disturbance, visual disturbance, and retinopathy: engorged retinal veins, haemorrhages, exudates, and a blurred disc. The visual symptoms ('slow-flow retinopathy') may be described as 'looking through a watery car windscreen'. (Other causes of slow-flow retinopathy are carotid occlusive disease and Takayasu's disease: p704).

Treatment:

Urgent treatment is needed which depends on the cause. Venesection is done in polycythaemia. Leucopheresis in leukaemias to remove white cells. Plasmapheresis in myeloma and Waldenström's: blood is withdrawn via a plasma exchange machine, the supernatant plasma from this is discarded, and the RBCs returned to the patient after being re-suspended in a suitable medium.

The spleen and splenectomy

The spleen was a mysterious organ for many years; we now know that it plays a vital immunological role by acting as a reservoir for lymphocytes, and in dealing with bacteraemias. Splenomegaly is a commonish problem and its causes are divided into *massive* (into the RIF) and *moderate*.

Causes of massive splenomegaly

CML, myelofibrosis, malaria (hyperreactive malarial splenomegaly), leishmaniasis, 'tropical splenomegaly' (idiopathic—Africa, SE Asia), and Gaucher's syndrome.

Moderate splenomegaly:

See p624.

- Infection (eg EBV, endocarditis, TB, malaria, leishmaniasis, schistosomiasis)
- Portal hypertension (liver cirrhosis),
- Haematological (haemolytic anaemia, leukaemia especially CML, lymphoma)
- Connective tissue disease (RA, SLE)
- Others: sarcoidosis, primary antibody deficiency (OHCS p198), idiopathic.

Splenomegaly can be uncomfortable and may lead to *hypersplenism:* pancytopenia as cells become trapped in the spleen's reticuloendothelial system, with symptoms of anaemia, infection, or bleeding. Splenectomy may be required if severe.

When faced with a mass in the left upper quadrant, it is vital to recognize the spleen:

- Dull to percussion
- It enlarges towards the RIF
- It moves down on inspiration
- You may feel a medial notch
- 'You can't get above it' (ie the top margin disappears under the ribs). The last three features differentiate the spleen from an enlarged left kidney. Abdominal USS or CT are used to image the spleen. When hunting the cause for enlargement look for lymphadenopathy and liver disease, eg: FBC, ESR, LFT ± liver, marrow, or lymph node biopsy.

Splenectomy

Main indications: splenic trauma, hypersplenism, autoimmune haemolysis: in ITP (p330) or warm autoimmune haemolytic anaemia (p324), congenital haemolytic anaemias. Splenectomy was historically performed for staging in Hodgkin's disease, but CT and MRI have replaced this role. Mobilise early post-splenectomy as transient ↑platelets predisposes to thrombi. A characteristic blood film is seen following splenectomy, with Howell-Jolly bodies, Pappenheimer bodies and target cells (see p314).

▸*The main problem post-splenectomy is lifelong increased risk from infection.* The spleen contains macrophages which filter and phagocytose bacteria. Post-splenectomy infection is caused most commonly by encapsulated organisms: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*. Reduce this risk by giving:[1]

- Immunizations:

- Pneumococcal vaccine (p152), at least 2 weeks pre-op to ensure good response, or as soon as possible after emergency splenectomy eg after trauma. Re-immunize every 5-10yrs. Avoid in pregnancy.
- *Haemophilus influenzae* type b vaccine (p381).
- Meningococcal C vaccine.
- Annual influenza vaccine (p390).

- Lifelong prophylactic oral antibiotics (phenoxymethylpenicillin). Erythromycin if penicillin allergic.
- Patient-held cards alerting health professionals to the infection risk.
- Pendants or bracelets to alert medical staff.
- Advice to seek medical attention if any signs of infection.
- Urgent hospital admission if infection develops, for treatment with broad spectrum antibiotics.
- If travelling abroad, warn of risk of severe malaria and advise meticulous prophylaxis, with nets, repellent, and medication.

The above advice also applies to hyposplenic patients, eg in sickle-cell anaemia or coeliac disease.

Thrombophilia 90

Thrombophilia is an inherited or acquired coagulopathy predisposing to thrombosis, usually venous: DVT or PE (venous thromboembolism: VTE). Special precautions are needed in *surgery*, *pregnancy*, and *enforced inactivity*. Risk is further increased by obesity, immobility, trauma (accidents or surgery), pregnancy, and malignancy. **NB:** Thrombocytosis and polycythaemia may also cause thrombosis (p350). Note only ~50% of patients with thrombosis and a +ve family history have an identifiable thrombophilia: others may have abnormalities that are as yet unidentified.

Inherited

• ***Activated Protein c (APC) resistance/Factor V Leiden:*** Commonest cause of inherited thrombophilia. Present in ~5% population, although most will not develop thrombosis. Usually associated with a single point mutation in factor V (Factor V Leiden), so that this clotting factor is not broken down by APC. Risk of venous thromboembolism (DVT or PE) is increased 5-fold in patients who are heterozygous for the mutation, and 50-fold in homozygotes. Thrombotic risk is increased in pregnancy and those on oestrogens (OHCS p257 & p302).

• ***Prothrombin gene mutation:*** Leads to high prothrombin levels and increased thrombosis due to down-regulation of fibrinolysis, by thrombin-activated fibrinolysis inhibitor.

• ***Protein C and Protein S deficiency:*** These vitamin K-dependent factors act together to cleave and thus neutralize Factors V and VIII. Heterozygotes deficient for either protein risk thrombosis. Skin necrosis also occurs, especially if on warfarin. Homozygous deficiency for either protein causes neonatal purpura fulminans—fatal, if untreated.

• ***Antithrombin deficiency:*** Antithrombin is a co-factor of heparin, and inhibits thrombin. Less common, affects 1 : 500. Heterozygotes' thrombotic risk is greater than Protein C or S deficiency by ~4-fold. Homozygosity is incompatible with life.

Acquired

Causes: newer '3rd generation' progesterones in the oral contraceptive pill and the *antiphospholipid syndrome* (APL: p540) when serum antiphospholipid antibodies are found (lupus anticoagulant ± anticardiolipin antibody)—predisposing to venous *and* arterial thrombosis, thrombocytopenia, and recurrent fetal loss in pregnant women. In most it is a primary disease, but it is also seen with SLE.

Who to investigate?

Consider special tests if:

- Arterial thrombosis <50yrs (for APL)
- Venous thrombosis <40y with no risk factors
- Unexplained recurrent VTE
- Unusual site, eg mesenteric/portal vein thrombosis
- Familial VTE or with oral contraceptives/pregnancy
- Recurrent fetal loss (≥3)
- Neonatal thrombosis

Liaise with a haematologist. Do FBC, film, clotting tests: PT, thrombin time, APTT, and fibrinogen concentration. Further tests: APC resistance test, lupus anticoagulant and anticardiolipin antibodies, and assays for antithrombin and proteins C and S deficiency. Haematologists may advise DNA analysis by PCR for the Factor V Leiden mutation if the APC resistance test is +ve, and for prothrombin gene mutation. Ideally investigate while well, not pregnant, and not anticoagulated for 1 month.

Treatment

Treat acute thrombosis as standard—heparin, then warfarin to target INR of 2-3 (p335). If recurrence occurs with no other risk factors, lifelong warfarin should be considered. Recurrence whilst on warfarin should be treated by increasing target INR to 3-4. In antithrombin deficiency, high doses of heparin may be needed so liaise with a haematologist. In protein C or S deficiency, monitor treatment closely as skin necrosis may occur with warfarin.

Prevention

Life-long anticoagulation is not needed in asymptomatic patients. Patients should be advised of increased risk of VTE with the Pill or HRT, and counselled as regards to the best form of contraception. Patients should also be warned of other risk factors for VTE. Prophylaxis may be needed in pregnancy, eg in antiphospholipid syndrome. Get expert help: aspirin and prophylactic heparin are used, as warfarin is teratogenic. Prophylactic SC heparin may also be indicated in high risk situations, eg pre-surgery.

Other risk factors for thrombosis

Arterial

- Smoking
- Hypertension
- Hyperlipidaemia
- Diabetes mellitus

Venous

- Surgery
- Trauma
- Immobility
- Pregnancy, oral contraceptive pill, HRT
- Age
- Obesity
- Varicose veins
- Other conditions: heart failure, malignancy, inflammatory bowel disease, nephrotic syndrome, paroxysmal nocturnal haemoglobinuria (p324).

For thrombophilia in pregnancy, see OHCS p33; for anticoagulant use in pregnancy and thromboprophylaxis, see OHCS p16.

Immunosuppressive drugs

As well as being used in leukaemias and cancers, these are used in organ and marrow transplants, rheumatoid arthritis, psoriasis, chronic hepatitis, asthma, SLE, vasculitis (eg Wegener's, giant cell arteritis, polymyalgia, PAN), inflammatory bowel and other diseases (so this page could figure in almost any chapter).

Prednisolone

Steroids can be life-saving, but a number of points should be taken into consideration before initiating treatment.

- Certain conditions may be made worse by steroids, eg TB, hypertension, osteoporosis, diabetes: here careful monitoring is needed.
- Growth retardation may occur in young patients, and the elderly frequently get more side effects from treatment.
- Interactions: [Prednisolone]↓ by antiepileptics (below) and rifampicin.
- Avoid pregnancy (may cause fetal growth retardation). If breast-feeding and prednisolone >40mg/day, see BNF.

Minimize side effects by using the lowest dose possible for the shortest period of time. Give doses in the morning, and alternate days if possible, to minimize adrenal suppression. Before starting long-term treatment (>3 weeks, or repeated courses) observe these guidelines:

- Explain about not stopping steroids suddenly. Collapse may result, as endogenous production takes time to restart. ÕSee p818.
- Inform about the need to consult a doctor if unwell, and increase the dose of steroid at times of illness/stress (eg flu or pre-op).
- Encourage to carry a steroid card saying dose taken, and the reason.
- You *must* warn patients about the listed side effects if they are receiving long-term treatment (over 6 weeks worth): see BOX.
- Avoid over-the-counter drugs, eg NSAIDs: aspirin and ibuprofen (↑risk of DU).
- Prevent osteoporosis if long-term use (p674): exercise, bisphosphonates, calcium and vitamin D supplements, smoking cessation advice.

Do not stop long-term steroids abruptly as adrenal insufficiency may occur. Once a daily dose of 7.5mg of prednisolone is reached, withdrawal should be gradual. Patients on short-term treatment (<3 weeks) can be stopped immediately, unless they have had repeated courses of steroids, a history of adrenal suppression, greater than 40mg daily, or doses at night, where withdrawal should be gradual.

Azathioprine

- SE: p533.

- *Interactions:* mercaptopurine and azathioprine (which is metabolized to mercaptopurine) are metabolized by xanthine oxidase (XO). So azathioprine toxicity results if XO inhibitors are co-administered (eg allopurinol).

Ciclosporin

This is a calcineurin inhibitor, as is tacrolimus which works in a similar way. It has an important role in reducing rejection in organ and marrow transplant. The main SE is dose-related nephrotoxicity. Doses are monitored by blood levels.

- Other SE: Gum hyperplasia, tremor, BP↑ (stop if ↑↑), oedema, paraesthesiae, confusion, seizures, hepatotoxicity, lymphoma, skin cancer—avoid sunbathing.
- Monitor U&E and creatinine every 2 weeks for the first 3 months, then monthly if dose >2.5mg/kg/d (every 2 months if less than this). ▸Reduce the dose if creatinine rises by >30% on 2 measurements *even if the creatinine is still in normal range*. Stop if the abnormality persists. Also monitor LFT.
- Interactions are legion: [Ciclosporin]↑ by: ketoconazole, diltiazem, verapamil, the Pill, erythromycin, grapefruit juice. [Ciclosporin]↓ by: barbiturates, carbamazepine, phenytoin, rifampicin. Avoid concurrent nephrotoxics: eg gentamicin. Concurrent NSAIDs augment hepatotoxicity—monitor LFT.

Methotrexate

An antimetabolite. Inhibits dihydrofolate reductase, which is involved in the synthesis of purines and pyrimidines. See p533.

Cyclophosphamide

An alkylating agent.

- SE: marrow suppression (monitor FBC), nausea, infertility, teratogenic, haemorrhagic cystitis due to an irritative urinary metabolite. There is a slight ↑risk of later developing bladder cancer or leukaemia.

Side effects of steroid use

System:	Adverse reactions:
Gastrointestinal	Pancreatitis
	Candidiasis
	Oesophageal ulceration
	Peptic ulceration
Musculoskeletal	Myopathy
	Osteoporosis

	Fractures
	Growth suppression
Endocrine	Adrenal suppression
	Cushing's syndrome
CNS	Aggravated epilepsy
	Depression; psychosis
Eye	Cataracts; glaucoma
	Papilloedema
Immune	Increased susceptibility to, and severity of infections, especially chicken pox.

Steroids can also cause fever and leucocytosis; steroids only rarely cause leucopenia.[91] Explain side effects in terms that patients understand: document this in the notes.

Acknowledgements

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Editors: Longmore, Murray; Wilkinson, Ian B; Turmezei, Tom; Cheung, Chee Kay
Title: *Oxford Handbook of Clinical Medicine, 7th Edition*

10

Infectious Diseases (ID)

Alternative name: Climate change poverty and pollution

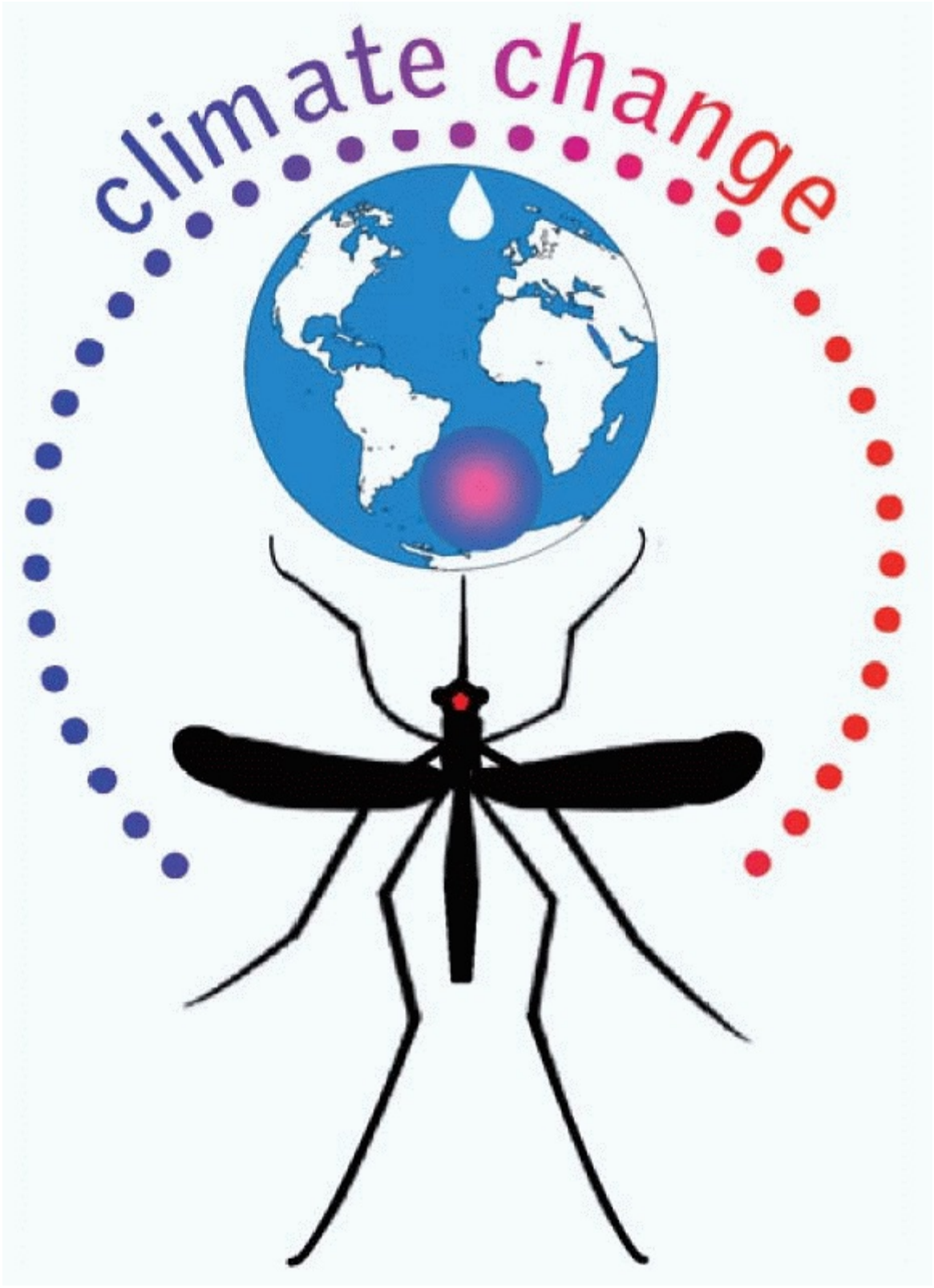


Fig 1. Interactions between pollution, global warming, poverty, and infection are often complex, and often fatal: WHO estimates that our warming climate, partly caused by CO_2 pollution, contributes to >150,000 deaths and 5 million illnesses/yr. Global warming compounds poverty, as poor areas

are most vulnerable to the effects of climate change, which often worsens access to clean water, and promotes spread of mosquito-borne illness, eg malaria.[1] Example: climate change→unstable housing→domestic chaos→needle sharing ± random sex→ HIV.[2] ▸France has a unique plan for both issues: a tax on air travel (a big cause of CO_2 emissions) to raise funds to fight HIV in developing nations.[3]

UK notifiable diseases[ND] ▸Inform the Consultant in Communicable Disease Control (CCDC).

Anthrax

Cholera

Diphtheria

Dysentery (amoebiasis, typhoid, and paratyphoid)

Encephalitis

Food poisoning

Leprosy

Leptospirosis

Malaria

Measles

Meningitis (acute)

Meningococcal sepsis

Mumps

Ophthalmia neonatorum

Plague

Poliomyelitis

Rabies

Relapsing fever

Rubella

Scarlet fever

Smallpox; tetanus

Tuberculosis

Typhus

Viral haemorrhagic fevers, eg yellow fever; Lassa fever

Viral hepatitis

Whooping cough

UK Health Protection Agency www.hpa.org.uk. 020 7759 2700; webteam@hpa.org.uk

Getting the balance right in studying infectious diseases

It is not possible for any ID chapter to be constructed so that it has the right balance throughout the world. Many of our readers come from communities where tetanus and malaria are daily problems—whereas, in UK consulting rooms, chest, GU, and ENT infections are likely to dominate.

In parts of Malawi, for example, 70% of adults are HIV+ve,[4] and most patients cannot even begin to mount an immune response to approach the classic descriptions beloved of standard textbooks (eg there is meningititis without meningism, and pneumonia without fever etc etc)—and medicine ***is*** (so it seems) no more than the pathology of immunosuppression.

In Western hospital specialist ID practice, the chief problems are:

- Respiratory tract infections (p152-60, and *Emergencies*, p800)
- Hospital acquired infections, eg p154, p408 (MRSA and *C. difficile*) & p238
- Infections in immunocompromised hosts, eg febrile neutropenia (p336)
- Infections associated with general surgery (p556 & p562)
- Infections in intensive care unit patients (examples on p548 & p613)
- Osteomyelitis (OHCS p696) and prosthetic joint infections (OHCS p706)
- HIV/AIDS (p396-402)
- Illness in a returning traveller (p378).

All these, however, may be trumped by the arrival of pandemic flu which will change everything (p155).

But in all areas and in all times, the pitfalls are the same: not taking time to find out about your patient—where he has been, what his hobbies are (and his work), and whom he or she has had contact with. Always have a high index of suspicion for TB, and always remember that ID rarities are often very treatable.

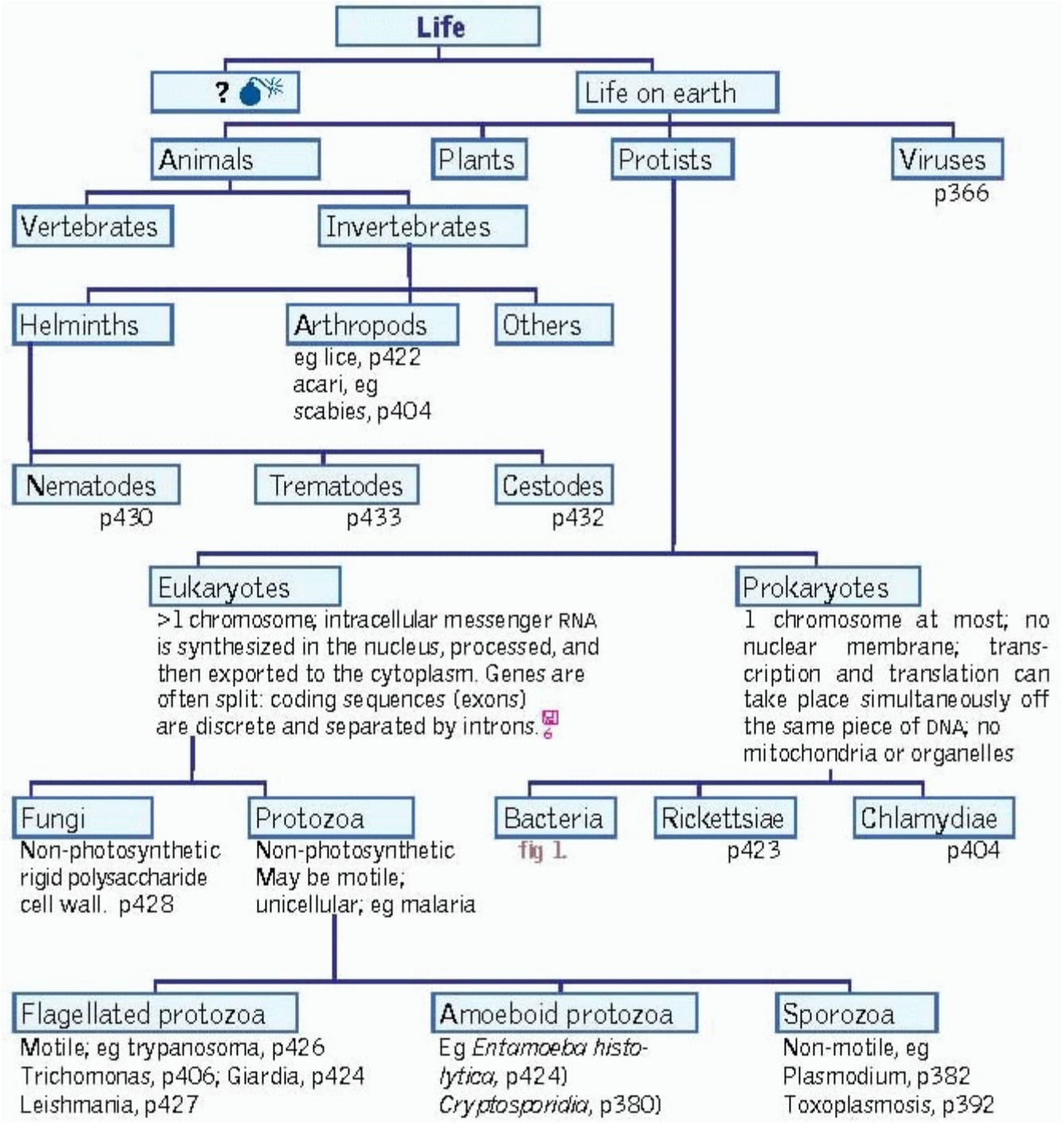
Know your local emerging diseases (p378) and your local multi-resistant organisms, and remember that it is common to have more than one infection.

▸ *Two heads are better than one: so when in doubt, get help.* The best help will often be well-endowed microbiology and imaging departments. In many places these are an impossible luxury—one chest X-ray can cost more than the entire yearly health budget allocated to each patient.[5] If this is your predicament, try not to give up the unequal struggle: bring your microscope to the bedside (p373) and hope for, and campaign for, better times.

Sources

Many sources have contributed to this chapter—none more generously laid at our disposal than the images belonging to Professor Steve Upton from the university of Kansas. His web site provides very useful educational material, much of it in the form of an quiz. See www.ksu.edu/parasitology/546tutorials.

The classification of pathogens



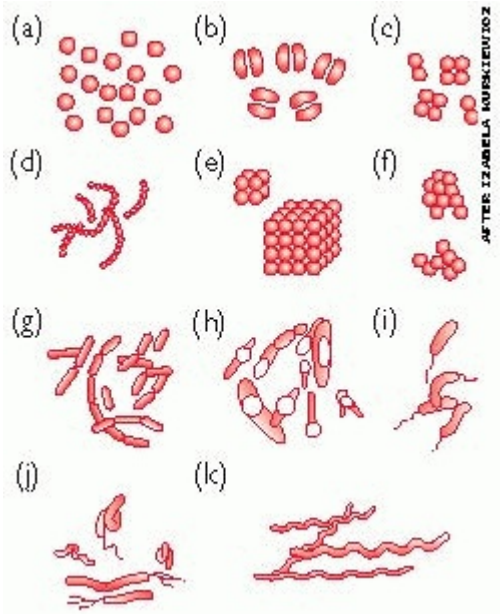


Fig 1. ***Bacteria:*** **a** coccus, **b** diplococcus (gonococcus), **c** tetrad of cocci, **d** streptococcus, **e** sarcina (cube of 8), **f** staphylococci in random

arrangement. ***Rods***: **g** bacterium, **h** bacillus. ***Spiral:*** **i** vibrio (cholera), **j** spirillium, **k** spirochaete (syphilis).[7]

Controversies

▸Exist at *every* taxonomic level…

What is life?

If a thing is organic and converts nutrients into progeny it is alive. If it does not do this, it is either non-living, dead, dying, or male. The average mind is always surprised to learn that long before birth, baby girls have their full complement of eggs for populating the next generation; but for biologists this fact is not so astounding: it is a proof of Aristotle's dictum that the defining essence of life is that it has a plan for its own survival and continuity.[8]

Are viruses alive?

How many kingdoms?

Seven, according to some: Archaebacteria, Eubacteria, Protozoa, Chromista (mainly photosynthetic; newly elevated to kingdomhood),[9] Plantae, Eumycota, Animalia. All Eumycota are fungi, and two of the phyla in Kingdom Chromista are also treated as fungi.[10]

Are kingdoms the highest taxonomic category?

No. There are 3 over-arching domains (or empires) according to some taxonomists: Archaea, Bacteria (also called Eubacteria), and Eucarya.[11]

Examples of pathogens from various types of bacteria

This table is not exhaustive; it is simply a guide for the forthcoming pages.

Gram positive cocci

Staphylococci (including MRSA, p408):

- coagulase +ve, eg *Staph. aureus*
- coagulase -ve, eg *Staph. epidermidis*

Streptococci[1] (p408):

- ß-haemolytic streptococci, eg *Strep. pyogenes* Lancefield[1] group A
- α-haemolytic streptococci
  - *Strep. mitior*
  - *Strep. pneumoniae* (pneumococcus)
  - *Strep. sanguis*
- Enterococci (non-haemolytic)[2]:
  - *Enterococcus mutans*
  - *E. faecalis*
- Anaerobic streptococci

[1] Streptococci are grouped by haemolytic pattern (α, ß-, or nonhaemolytic) or by Lancefield antigen (A-G), or by species. **Fig 1** shows Rebecca Lancefield (1895-1981) with her hand lens, typing streps with a variety of M protein-specific antibodies mixed with a streptococcal extract by detecting the precipitin in a pipet.

Gram positive bacilli (rods)

Aerobes

- *Bacillus anthracis* (anthrax: p409)
- *Corynebacterium diphtheriae* (p409)
- *Listeria monocytogenes* (p409)
- Nocardia species

Anaerobes:

- Clostridium
  - *C. botulinum* (botulism: p409)
  - *C. perfringens* (gas gangrene: p409)
  - *C. tetani* (tetanus: p412)
  - *C. difficile* (diarrhoea, p238)

Actinomyces: *Actinomyces israelii* (p409), *A. naeslundii A. odontolyticus, A. viscosus*

Obligate intracellular bacteria:

Chlamydia (p404, p154, OHCS p286)

- *C. trachomatis:* Tropical eye disease trachoma (OHCS p450)=serovars A-C GU/cervicitis (p405)=serovars B-K[12] lymphogranuloma ven. (p404)= L_{1-3}[13]
- *C. psittaci* causes psittacosis (p154)
- *C. pneumoniae* (atypical pneumonia)

Coxiella burnetii (p422)

Bartonella (p422)

Ehrlichia (p422)

Rickettsia (typhus, p423)

Legionella pneumophilia (p154)

Mycoplasma pneumoniae (p154)

Gram negative cocci

Neisseria: *Neisseria meningitidis*

(meningitis, septicaemia)

N. gonorrhoea (gonorrhoea,p406)

Moraxella: *Moraxella*

catarrhalis (pneumonia, p411)

Gram negative bacilli (rods)

Enterobacteriaceae (p380 & p410):

- *Escherichia coli*
- *Shigella* species (p414)
- *Salmonella* species (p414)
- *Citrobacter freundii; C. koseri*
- *Klebsiella pneumoniae; K. oxytoca*
- *Enterobacter aerogenes; E. cloacae*
- *Serratia marascens; Proteus mirabilis*
- *Morganella morganii*
- *Providencia* species; Yersinia *(Y. pestis Y. enterocolitica, Y. paratuberculosis*)

Pseudomonas aeruginosa(p410)

Haemophilus influenzae(p410)

Brucella species (p410)

Bordetella pertussis (p410)

Pasteurella multocida (p411)

Vibrio cholerae (p414)

Campylobacter jejuni(p380)

Anaerobes:

- *Bacteroides* (wound infections, p556)
- *Fusobacterium*
- *Helicobacter pylori* (p234)

Mycobacteria:

M. tuberculosis TB, p386

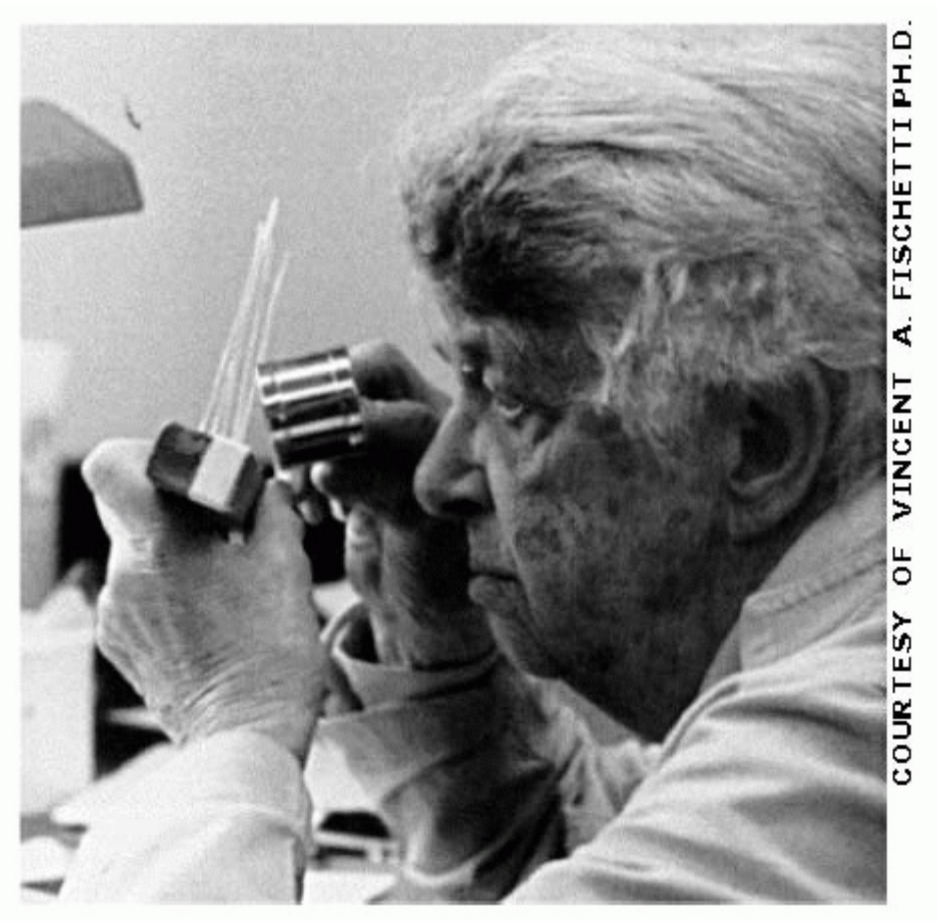
M. bovis & *M. leprae* (leprosy, p416)

'Atypical' mycobacteria:

- *M. avium intracellulare* (p398)
- *M. scrofulaceum, M. kansasii*
- *M. marinum*
- *M. malmoense*
- *M. xenopi, M. gordonae*
- *M. fortuitum, M. chelonae*
- *M. flavescens*
- *M. smegmatis-phlei*

Spirochaetes
(p418):

Treponema (syphilis; yaws; pinta)
Leptospira (Weil's dis.; canicola fever)
Borrelia (relapsing fever; Lyme dis.)



DNA viruses—
A) *Double-stranded DNA*

•	Papovavirus	Papilloma virus: human warts
		JC virus: Progressive multifocal leucoencephalopathy, PML
•	Adenovirus	>30 serotypes; 10% of viral respiratory disease 7% of viral meningitis
•	Human herpes viruses	Alphaherpesvirus$^{\alpha}$ (eg neurotropic) beta-$^{\beta}$ (eg epitheliotropic) and gammaherpesvirusγ (lymphotropic):

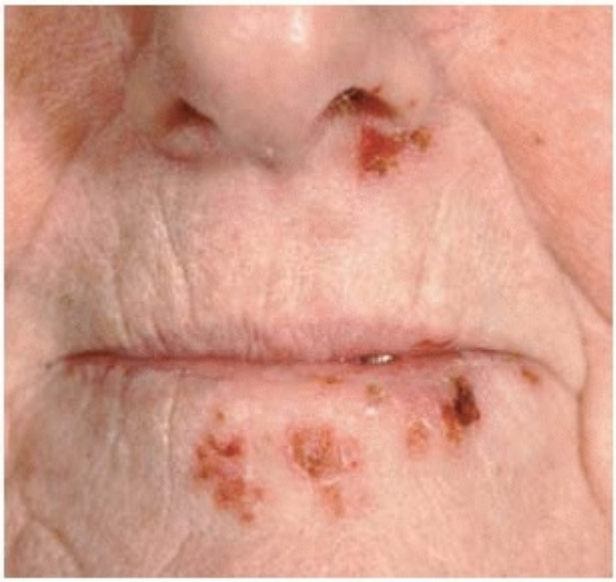


Fig 1. Oral herpes (HSV1)[14]

- Herpes simplex virus[α] (HSV) 1 & 2 (HHV-1 & HHV-2, p388)
- Herpes (varicella) zoster virus[α] (HHV-3, p388)
- Cytomegalovirus[β]—CMV, also called HHV-5, (p392)
- Herpes virus 6[β] & 7[β] (HHV-6 & 7): roseola infantum (mild, *OHCS* p143); also post-transplant, like CMV
- Epstein-Barr virus (EBV) (HHV-4, p389)[γ] - infectious mononucleosis (glandular fever)
- -Burkitt's lymphoma; nasopharyngeal carcinoma
- HHV-8: Kaposi's sarcoma (p694)
- Pox viruses
  - (1) Variola: smallpox (eradicated in 1979; some stocks left)
  - (2) Vaccinia, cowpox
  - (3) Orf, cutaneous pustules, caught from sheep
  - (4) Molluscum contagiosum, pearly umbilicated papules, typically seen in children or with HIV.
- Hepatitis B virus — See p394

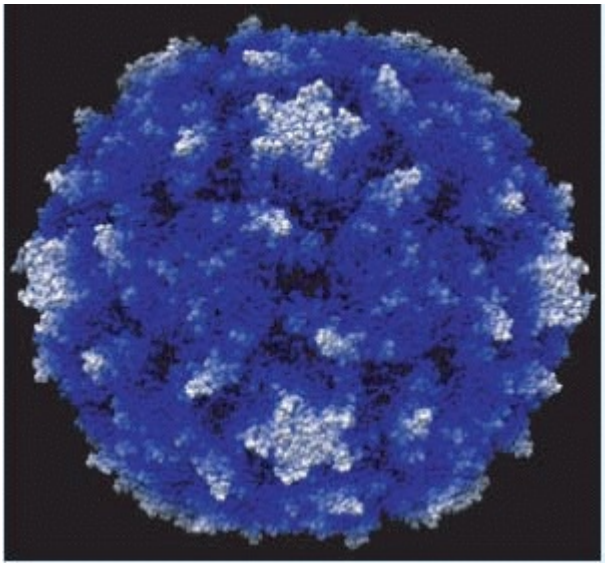
B) Single-stranded DNA

•	Erythrovirus (=parvovirus)	Erythema infectiosum (fifth disease, *OHCS* p142) 'slapped cheek' appearance ± aplastic crises

RNA viruses—
A) Double-stranded RNA

•	Reovirus	Eg rotavirus (p380), infantile gastroenteritis

B) Positive single-stranded RNA



(1)		Rhinovirus, common cold, >90 serotypes
(2)		Enterovirus (enteroviruses, esp echoviruses, are an important cause of meningoencephalitis and acute flaccid paralysis).[15] See *J Med Virol* 2006 **78** 98
	(i)	Coxsackie A (meningitis, gastroenteritis) Coxsackie B (pericarditis, Bornholm disease)

			(ii)	Hepatitis A virus
			(iii)	Echovirus (30% viral meningitis)
•	Picornavirus **(fig 2.)**		(iv)	Poliovirus, p420 (**fig 2** ©David Belnap; University of Utah & James Hogle; Harvard Med. School)
•	Coronavirus	Eg Urbani SARS-associated coronavirus (Dr Urbani described and died in an outbreak in Vietnam in 2003); ▸p155.		
•	Togavirus	(1)	Rubella; (2) Alphavirus	
		(3)	Flavivirus (yellow fever, dengue, hepatitis C)	

C) Negative single-stranded RNA

•	Orthomyxovirus	Influenza A, B, C
•	Paramyxovirus	Parainfluenza, mumps, measles, respiratory syncitial virus
•	Arenavirus	Lassa fever, some viral haemorrhagic fevers, lymphocytic-choriomeningitis virus (LCM)
•	Rhabdovirus	Rabies

•	Bunyavirus	Some viral haemorrhagic fevers

D) Retroviruses

•	Human immunodeficiency virus—HIV-1, HIV-2. Types A & B predominate in UK (p396)
•	Human T-lymphotropic virus—HTLV-I, HTLV-II. *HTLV-I* causes adult T-cell leukaemia/lymphoma (ATLL); a definite role in mycosis fungoides & Sézary syndrome is controversial. It is mostly asymptomatic, but 1-5% develop ATLL, a fatal expansion of virus-infected CD4+ T cells.$_{16}$ *HTLV-2* may be passed on by transfusions, injecting drug users, or sexually. It may cause tropical spastic paraparesis (p508). It is associated with ↑incidence of pneumonia and bronchitis, and arthritis.

Travel advice[1]

Most travel-related illness is not from infections, but due to accidents, violence, myocardial infarction etc. Most infections are due to ignorance or indiscretions.

▸ *Advice to travellers is more important than vaccination*: eg simple hygiene, malaria prophylaxis, and protective measures. Take time to advise travellers on the benefits of safer sex and the risks of HIV and other STDs. ***Malaria*** is a big killer; see p384 for prevention. ***Rabies:*** vaccinate if post-exposure vaccination is unlikely to be available (or their activities mean risk is ↑—or if they will be in a rabies area for >1month); seek immediate attention if bitten (wash the wound well); see p420. For ***cholera*** and ***traveller's diarrhoea***, see p414 & p380.

Vaccinations *L* = *live vaccine*	***Doses Needed***	***Gap between doses:***		***Booster interval***
		1st & 2nd	***2nd & 3rd***	
Yellow fever^{L}	1			10yrs
Typhoid SC (Typhim VI®)*	1			3yrs
Tetanus	3	4 weeks	4 weeks	10yrs
Polio	3	>4 weeks	>4 weeks	10yrs

Rabies pre-exposure	3	7 days	21 days	3yrs
Meningococcal disease	1			3yrs
Japanese encephalitis	3	1-2 weeks	2-4 weeks	2yrs
Tick encephalitis	3	1-3 months	9-12 months	3yrs
Hepatitis A (Havrix monodose®)	1	6-12 months		not needed
if 1-15yrs use Havrix Junior®	1	6-12 months		
Hepatitis B	3	1 month	5 months	not needed if anti HBs >10miu/mL
if travelling soon:	3	1 week	3 weeks	1yr

* If live oral form used, give 3 doses (1 capsule on alternate days, 1h ac, with a cool drink).

If only one attendance is possible, all is not lost (make up *en route*): *malaria prophylaxis/advice:* p384. Suggested vaccines:

Africa:

Meningitis, typhoid, diphtheria, tetanus, polio, hepatitis A ± yellow fever.

Asia:

Typhoid, diphtheria, tetanus, polio, hepatitis A. Consider rabies and Japanese encephalitis.

Meningitis and Hajj pilgrimage to Saudi Arabia:

All >2yrs old *must* be vaccinated against meningococcal meningitis with quadrivalent vaccine (serogroups A,C, Y & W135); must be <3yrs ago but not within the last 10 days. If 3 months-2yrs of age, give 2 doses of the A vaccine separated by 3 months.

S America:

Typhoid, diphtheria, tetanus, polio, hepatitis A ± yellow fever ± rabies.

Travel if immunocompromised:

Avoid live vaccines. Hepatitis B vaccine: p263.

Preventing traveller's diarrhoea

Water:

If in doubt, boil all water. Chlorination is OK, but doesn't kill amoebic cysts (get tablets from pharmacies). Filter water before purifying. It is important

to distinguish between simple gravity filters and water purifiers (which also attempt to sterilize chemically). Choose a unit which is verified by bodies such as the London School of Hygiene and Tropical Medicine (eg the MASTA[17] *Travel Well Personal Water Purifier*). Make sure that all containers are disinfected. Try to avoid surface water and intermittent tap supplies. In Africa assume that all unbottled water is unsafe. With bottled water, ensure the rim is clean and dry. Avoid ice. Other water-borne diseases include schistosomiasis (p433).

Food:

Hot, well-cooked food is best. Avoid salads and peel your own fruit. If you cannot wash your hands, discard the part of the food which you are holding (with bananas, careful unzipping obviates this precaution).[18] In those in whom traveller's diarrhoea might be serious, consider a standby course of ciprofloxacin.

Susceptibilities to antibiotics

Notes S=usually sensitive 2=S, but may be 2nd choice ? =may be resistant (esp. if hospital-acquired) R=resistance likely 0=not appropriate sources: OTM & GAT (Sanford)	Amoxicillin/amnicillin	Cefepime[19]	Cefotaxime[20]	Ciprofloxacin	Co-amoxiclav	Colis[21]
STAPH AUREUS	R	S	S	?	R	0
STREP PNEUMONIAE	?	S	?	?	?	0
STREP PYOGENESE	S	S	S	S	S	0
ENTEROCOCCUS FAECALIS	?	S	R	S	S	0
N. GONORRHOEA	?	S	S	S	?	0
N. MENINGITIDIS	S	S	S	S	S	0

H. INFLUENZI	?	S	S	S	?	0
E. COLI[24]	R	S	S	?	?	0
KLEBSIELLA	R	S	S	S	R	2
PROTEUS MIRABILIS	R	S	S	S	S	0
SERRATIA SPECIES[25]	R	S	S	S	R	0
PSEUDOMONAS AERUGINOSA[26]	R	?	R	?	R	2
ACINETOBACTER BAUMANNII[27]	R	R	R	R	R	2
BACTEROIDES FRAGILIS	R	R	R	R	R	0
CLOSTRIDIUM DIFFICILE	0	0	0	0	0	0

Penicillin-based antibiotics	***Usual adult dose:***	***In renal failure:***
Amoxicillin Uses as for ampicillin but better absorbed PO. For IV therapy, use ampicillin.	250-500mg/8h PO 3g/12h in recurrent or severe pneumonia	↓Dose if CC <10 (CC=creatinine clearance, mL/min)
Ampicillin Broader spectrum than penicillin; more		↓If CC <10, give

active against Gram -ve rods, but ß-lactamase sensitive. Amoxicillin is better absorbed PO.	500mg/4-6h IM/IV	doses every 12-24h
Benzylpenicillin = penicillin G Most streps, meningococcus, gonococcus, syphilis, gas gangrene, anthrax, actinomycosis, and many anaerobes.	300-600mg/6h IV, 2.4g/4h in meningitis. If dose >1.2g, inject at rate <300mg/min	Anaphylaxis risk <1:100,000; huge doses cause Na+↑± fits in renal failure
Co-amoxiclav Augmentin=amoxicillin 250 or 500mg + clavulanic acid 125mg confers ß-lactamase resistance so broader spectrum, but LFT↑ may rise.	1 tab/8h PO IV form: p411.	If CC 10-50, give 1 tab/12h; if CC <10, 1 tab/24h
Flucloxacillin For Gram +ve ßlactamase producers (staphylococci).	250-500mg/6h PO ½h before food. 0.5-2g/6h IV	Dose unaltered if CC >10
Phenoxymethylpenicillin (=pen. V) Like penicillin G but less active; use as Prophylaxis or to complete IV course.	250-500mg/6h PO; take ½h before food	In severe renal failure, give doses every 12h
Piperacillin Very broad spectrum including anaerobes & *Pseudomonas*. Inactive against *Staphs*. Reserve only for those with severe infection. May be used with aminoglycosides (but not in the same IVI).	Tazocin®= tazobactam 500mg + piperacillin 4g: dose: 4.5g/8h IV over 3-5min	↓Dose if CC↓: CC 10-50: 2.25g/6h CC <10: 2.25g/8h
Procaine penicillin (= procaine benzylpenicillin) Depot injection; good for syphilis; only available on a named patient basis in the UK.	Syphilis: 600mg/24h IM for 14d, gonorrhoea: start dose 3.6g if female, 2.5g if male	Dose unaltered in renal failure
Ticarcillin Very broad spectrum, eg *Pseudomonas, Proteus*. Use with an aminoglycoside; more active than azlocillin or piperacillin.	Timentin®=3g ticarcillin +200mg clavulanic acid. Dose: 3.2g/8h IV (/4h in severe infections)	If CC 10-50 dose is 1-2g/8h[] If CC < 10, dose is 1-2g/12h[]

Antibiotics: cephalosporins

Spectrum

Many cephalosporins are active against staphs (including β-lactamase producers), streps (except group D, *Enterococcus faecalis & faecium*), pneumococci, *E. coli*, some *Proteus*, *Klebsiella*, *Haemophilus*, *Salmonella*, and *Shigella*. 2nd generation drugs (cefuroxime, cefamandole) are active against *Neisseria* and *Haemophilus*. 3rd generation drugs (cefotaxime, ceftazidime, ceftriaxone) have better activity against Gram -ve organisms. Ceftazidime has less Gram +ve activity (esp. against *Staph aureus*) and is used in *Pseudomonas* infections.

Uses

Oral cephalosporins (cefaclor, cefalexin, cefuroxime axetil) have a role in UTI, pneumonia, and otitis media, but are not 1st-line (unless penicillin-allergic; but 10% will also be cephalosporin allergic). Their major use is parenteral, eg in surgical prophylaxis or post-op infection. 3rd-generations drugs (eg ceftriaxone) may be used in septicaemia.

SEs:

Hypersensitivity; warfarin potentiation.

Antibiotic	Adult dose	Notes For body surface area calculation, see *BNF*
Cefaclor	250mg (max 1g)/8h PO	No dose change in RF
Cefalexin	500mg/8h PO; Max: 4g/24h PO	↓Dose proportionately in RF if CC < 60 if CC <10: 750mg/24h
Cefepime[4]	1-3g/12h IVI	Good activity against *Pseudomonas*, enterobacter, other resistant Gram -ve organisms and *S. aureus*. If CC 10-50: 1-2g/12h; if CC ≤10: 1g/24h
Cefpirome[4]	1-2g/12h IV over 5min	Broad spectrum, used in polymicrobial infection; pyelonephritis; pneumonia. Not for MRSA (p408) or bacteroides. Good against enterobacter.[29] In renal failure, load with 1-2g, then if: CC 20-50: 500mg-1g/12h; if CC 5-20: 500mg-1g/24h
Cefixime	Syrup: ½-1yr: 3.75mL/d 1-4yrs: 5mL/d 5-10yrs: 10mL/d Adults: 200mg/12-24h	Syrup = 100mg/5mL. Active against streps, coliforms, *Haemophilus*, *Proteus* and anaerobes, staphylococci, *E. faecalis*, and *Pseudomonas* are resistant. In RF: normal dose if CC >20mL/min
Cefotaxime[3]	1-2g/8h IV/IM; max 3g/6h (gonorrhoea: 500mg stat)	Broad spectrum for serious infections only (pneumonia, meningitis). Unreliable activity against *Pseudomonas*. If CC <10, give 2g/24h max. If CC <5 give 1g stat, then halve dose.

Cefradine	250-500mg/6h PO or 500mg-1g/12h PO or 500mg-2g/6h IM/IV	Less active than cefuroxime In RF load with 750mg, then give 500mg at frequency dictated by CC: if CC > 20: 500mg/6h CC 5-20: 250mg/6h CC < 5: 250mg/50-70h
Ceftazidime[3]	UTI: 500mg-1g/12h Other: 1-2g/8h Max: 1g/8h if elderly Route: IV/IM but avoid IM if dose >1g	Broad spectrum, incl. most *Pseudomonas* but bad *vs* Gram +ves; for bad infections only; may help in blind [prescription take] of neutropenic sepsis[30] (cefepime is better).[31] In RF load with 1g, then if: CC 31-50: 1g/12h CC 16-30: 1g/24h CC 6-15: 500mg/24h CC ≤ 5: 500mg/48h
Ceftriaxone[3]	1-4g daily IM/IV; give ≤1g at each IM site. Use IVI, not IV, if dose >1g	Many Gram +ve and -ve infections. Used in meningitis (p370), pre-colonic surgery, and gonorrhoea. No activity against *Listeria*, enterococci, and *Pseudomonas*. Can use in RF if CC >10 (or limit dose to 2g/day and check levels)
Cefuroxime	250-500mg/12h PO 750mg-1.5g/8h IV/IM; Max IV: 3g/8h. Give per 12h if CC 10-50.	Broad spectrum & good Gram -ve activity. Used in: surgical prophylaxis; cholecystitis;[32] post-op infections; severe pneumonia.

Abbreviations:

RF = renal failure; CC= creatinine clearance; CC^M = CC/1.73m^2 body area; [4] = 4th generation cephalosporin; not all are available in the UK; [3]= 3rd generation.
Source: *GAT* 2006

Antibiotics: others

Antibiotic (and uses)	Adult dose	Notes CC=creatinine clearance, mL/min
Amikacin See gentamicin.	7.5mg/kg/12h IV; (~50% 12-18h if CC 10-50)[3]	Resistance growing, but less common than for gentamicin
Azithromycin See clarithromycin, also good against *N. gonorrhoea*.	500mg PO for 3d.	SE: see erythromycin.

Chloramphenicol Rarely used 1st-line. May be used in typhoid fever and *Haemophilus* infection. Also in blind [prescription take] of meningitis if patient allergic to both penicillins and cephalosporins. Avoid late in lactation and pregnancy.	12.5mg/kg/6h PO or IV; 25mg/kg/6h may be used in septicaemia or meningitis	SE (rare): marrow aplasia (check FBC often), neuritis, GI upset. Avoid long or repeated courses and in liver impairment or if CC <10mL/min. *Interactions*: warfarin, rifampicin, phenytoin, sulfonylureas, phenobarbital.
Ciprofloxacin Used in adult cystic fibrosis, typhoid, *Salmonella*, *Campylobacter*, prostatitis, and serious or resistant infections. Avoid overuse.	250-750mg/12h PO 200-400mg/12h IVI over ≥½h (over 1h, if 400mg used). If cc 10-50, give 50-75% of this dose.[4]	A good oral antipseudomonal agent. ß-lactamase-resistant. Halve dose if CC <10. SE: rashes, D&V, LFT ↑; potentiates theophylline.
Clarithromycin A macrolide, like erythromycin, used for: *S. aureus*, streptococci, *Mycoplasma, H. pylori*, *Chlamydia*, MAI (p399).	250-500mg/12h PO for 7-14d. *H. pylori:* 500mg /12h PO for 1wk as triple therapy (p235). MAI may need 12wks (p399) If cc 10-50 give 75%.[5]	Halve dose if CC <30. *Interactions:* ergot, warfarin, carbamazepine, theophyllines, zidovudine; never use with terfenadine or pimozide.
Clindamycin Active against Gram +ve cocci including penicillin resistant staph, and anaerobes.	150-300mg/6h PO; max 450mg/6h PO. 0.2-0.9g/ 8h IV or IM (by IVI only, if >600mg used)	Stop if diarrhoea occurs (pseudomembranous colitis, p239). Used in *Staph*. Bone/joint infection.
Co-trimoxazole Sulfamethoxazole 400mg + trimethoprim 80mg. 1st choice in *Pneumocystis jiroveci (=P. carinii*, p398), toxoplasmosis and nocardia. **NB:** can act against *S. aureus*.	960mg-1.44g/12h PO/IVI; see *Pneumocystis* (p398)	SE (mostly ∴ sulfonamide, elderly at ↑risk): jaundice; Stevens-Johnson syndrome; marrow depression; folate↓. If CC 15-30, halve dose. Avoid if CC <15. CI: G6PD deficiency.
Doxycycline Used in travellers' diarrhoea, *Chlamydia*, leptospirosis, syphilis, and brucellosis.	200mg PO on 1st day then 100mg/24h; max 200mg/d in severe infections	As for tetracycline, but may be used in renal failure.
Erythromycin Macrolide, used in penicillin allergy. Used 1st line in atypical pneumonia, p154.	250-500mg/6h PO (≤4g/d in *Legionella*). 6.25-12.5mg/kg/6h IVI (adult and child)	SE: D&V; phlebitis in IV use. Potentiates warfarin, theophylline, terfenadine, ergotamine, carbamazepine.

Fusidic acid/sodium fusidate Anti-staph agent (incl. some MRSA, p408); used in osteomyelitis.	500mg/8h PO; 500mg/ 8h IVI over 6h; avoid intravenous route if possible.	Combine with another anti-staphylococcal drug. SE: GI upset, reversible changes in LFTs.

Antibiotic (and uses):	**Adult dose**	**Notes (eg use in renal failure)**
Gentamicin Spectrum is wide but poor against streps & anaerobes, so use with a penicillin ± metronidazole. Synergy with ampicillin against enterococci. For serious Gram -ve infections or SBE prophylaxis.	▸p738. *Once daily IV dose* over 15min: 5.1mg/kg^{LBW} (7mg if very ill);[6] aim for **peak** serum level of 16-24µg/mL 1h after dose 3; **trough:** <1µg/mL; levels *not* needed if only one stat dose used, eg in UTI.	▸**Nomogram**, p738; ¾ dose if CC≈60mL/min.[7] ½ dose or avoid if CC ≈30-40 mL/min (get help). **Avoid:** prolonged use, concurrent furosemide, use in pregnancy/myasthenia gravis. ▸Do U&E often. **SE**: oto- and nephrotoxicity.
Imipenem (+cilastatin) Very broad spectrum: Gram +ve and -ve organisms, anaerobes and aerobes. ß-lactam stable.	250-500mg/6h IVI; if CC 50-90: ¼-½g/6-8h; if 10-50: ¼g/6-12h.[8] CC <5: dialyse. High doses risk seizures.	Pregnancy/lactation: avoid. SE: fits; D&V; myoclonus, eosinophilia, WCC↓, Coombs' +ve; LFT abnormal. See package insert eg if <70kg.
Linezolid An oxazolidinone antibiotic used against MRSA, VISA, & VRE[1]	600mg/12h PO/IVI over 1h (even if renal failure);[9] SE: D&V, gastritis, T°↑, tinnitus, neuropathy, WCC↓	May cause pancytopenia if ²2wks use; monitor FBC. CI: BP↑↑, phaeochromocytoma, carcinoid, thyrotoxicosis
Meropenem See imipenem.	½-1g/8h IVI, max 2g/8h (if CC 10-50, 1g/12h)	Causes fewer fits than imipenem.
Metronidazole 1st choice *vs* anaerobes, *Gardnerella, Entamoeba histolytica, & Giardia lamblia;* use PO in pseudomembranous colitis.	400mg/8h PO. PR dose: 1g/8h for 3d then 1g/12h. IVI dose: 500mg/8h for ≤7d	Disulfiram reaction with alcohol, interacts warfarin, phenytoin, cimetidine; care if LFT↑. Pregnancy/breast-feeding: avoid high-doses.

Minocycline Spectrum > tetracycline.	100mg/12h PO	As tetracycline, but more SE (hepatitis, pneumonitis).
Nitrofurantoin UTI.	50mg/6h PO with food	CI: CC <50.
Oxytetracycline	250-500mg/6h PO	See tetracycline.
Rifampicin^{UK} = rifampin^{US} Mycobacteria, prophylaxis in meningitis contacts.	Dose example: 450-600mg/24h PO before breakfast. See TB, p386	Caution in liver disease. Interferes with contraceptive Pill. SE: p386.
Teicoplanin See vancomycin, but not given PO.	IV/IM: 400mg/12h for 3 doses, then 200mg/24h	$t_{1/2}$ longer than vancomycin. (200mg/48h if CC 10-50)
Tetracycline Used in chronic bronchitis; 1st line in *Chlamydia*, Lyme disease, mycoplasma, brucellosis, rickettsia.	250-500mg/6h PO ac 500-1000mg/12h IVI (not if liver disease). IV preparation not available in UK.	Avoid if <12yrs old, in pregnancy, and if CC <50. Absorption ↓by iron, milk, and antacids. SE: photosensitivity, D&V.
Tobramycin As gentamicin; better against *Pseudomonas*.	1mg/kg/8h IVI Dose↓ in renal failure	Monitor levels; reduce dose if CC ≤50
Trimethoprim Used in UTI, COPD. Dose in prophylaxis: 100mg/24h PO.	200mg/12h PO	SE: depressed marrow, D&V. CC 10-50: 200mg/18h PO. CC <10: 200mg/24h PO.
Vancomycin PO: pseudomembranous colitis if metronidazole is contra-indicated; IV: MRSA or other Gram +ve organisms (not Erysipelothrix species).	125mg/6h PO; ½g/6h IVI over 1h or 1g/12h IVI over 100min; do peak level 2h post-IVI, eg after dose 3; aim for <30mg/L & <10mg/L pre-dose 4	In renal failure, get help; nomograms are available, eg[33] SE: renal and ototoxicity. Do not overuse (↑risk of multiple resistance, p408).

[1] MRSA, p408; VISA: vancomycin-intermediate resistance *S. Aureus*; VRE: vanco. resistant enterococci.

Blind [prescription take] for presumed septicaemia, pneumonia, etc

History:

A detailed history may reveal the source of infection: ask about respiratory, GI and GU symptoms; any travel or possible immunocompromise?

Examination:

Look at the temperature chart and examine for localizing signs.

Tests:

If time allows and the patient is not too ill, culture all possible sources before treating (blood, sputum, urine, faeces, skin/wound swabs, CSF, aspirates). Also check FBC, ESR, CRP, U&E, LFT, clotting, serology, malaria film, acute phase serum, save serum for virology, CXR, ABG (as clinically indicated). MSU/urine dipstick.

Prognosis:

Poor if very old or young, BP↓, WCC↓, P_aO_2↓, DIC, hypothermia.

Treatment:

Follow local guidelines. Change to the most appropriate drug once sensitivities are known. Treatment of most infections should not exceed 7d. Intravenous antibiotic therapy should preferably not exceed 48h; review the need and change to PO if possible. If in doubt, ask a microbiologist.

Infection	Treatment (*pen.=penicillin*, p368)
Urinary tract infection	Trimethoprim 200mg/12h PO
Cellulitis	Co-amoxiclav (or flucloxacillin + pen., p368)
Wound infection	Await swab result; if ill, flucloxacillin 1g/6h IV
Pneumonia	
Mild community-acquired	Amoxicillin 500mg/8h PO
Possible atypical pneumonia	Erythromycin 500mg/6h PO
Severe	

community-acquired	Cefuroxime 1.5g/8h IV + erythromycin 12.5mg/kg/6h IV
Hospital-acquired	Cefuroxime 1.5g/8h IV or Tazocin® 4.5g/8h IV[1]
Meningitis (p806)	
Meningococcus *Pneumococcus*[2]} *Haemophilus*	▸▸Ceftriaxone 2g/12h IV + benzylpenicillin 2.4g/4-6h slowly IV (1.2mg IM stat, prehospital)
Listeria	Add ampicillin 2g/4h IVI
If HSV encephalitis possible	Add aciclovir 10mg/kg/8h IVI
Endocarditis (p136)	
Empirical therapy	Flucloxacillin[] 2g/6h IV + gentamicin IV, p738
Strep. Viridans	Benzylpenicillin[2] + gentamicin IV
Enterococcus faecalis	Amoxicillin[2] + gentamicin IV
Staph. aureus or *epidermidis*	Flucloxacillin[2] + gentamicin IV
Prosthetic valve	Vancomycin + gentamicin + rifampicin

Osteomyelitis/Septic arthritis	Flucloxacillin 1g/6h IV then clindamycin PO
Septicaemia	
Urinary tract sepsis	Cefuroxime 1.5g/8h IV + gentamicin IV 5mg/kg *once daily* is typical max dose; rarely, 7mg/kg is needed, less if obese; p738
Intra-abdominal sepsis	Cefuroxime 1.5g/8h IV + metronidazole 500mg/8h IVI
Meningococcal sepsis	▸▸Ceftriaxone 2g/12h IV
Neutropenic sepsis	Tazocin® 4.5g/8h IV[1] over 3-5min + netilmicin eg 6mg/kg IV once daily
Skin or bone source	Flucloxacillin 1g/6h IV
Unknown cause	Cefuroxime 1.5g/8h IV + gentamicin 5.1-7mg/kg IV once daily, p738 + metronidazole 500mg/8h IVI

▸All IV doses should be given slowly, eg over 5mins.

[1] Tazocin = piperacillin 4g (p763) + tazobactam 500mg.

[2] Use vancomycin if penicillin-allergic, or you suspect resistance to penicillins (eg MRSA)

Using a side-room laboratory (near-patient testing)

The main advantage of doing your own lab work is that it enables you to have intelligent chats with lab staff, and encourage their diligence (lab staff make errors out of boredom; amateurs make errors out of ignorance). The great thing is to understand the sources of error—and allow for them at the bedside.[34]

Urine

Get used to microscoping your own urines. Dipstick analysis is OK but misses casts etc (p278). If dipstick +ve for leucocytes, nitrites, blood, or protein, send for culture and testing for antibiotic sensitivities. If +ve for glucose, suspect diabetes. If heavily positive for protein, check 24h collection for protein.

Blood

Use universal precautions: all specimens could be HBV, HCV, or HIV +ve. To make a ***thick blood film*** (malaria diagnosis), use fresh whole blood: a small blob should be spread out somewhat untidily to cover ~1cm2, thinly enough for watch hands to be seen through. The untidiness is helpful to the microscopist because it provides areas of varying thickness, some of which will be ideal for what is often a tricky task. Label and allow to dry. To make a ***thin blood film***, put 1 drop of blood near one end of the slide. Take another slide, place its end in the drop of blood, angled at 45°. Push the slide away from you to spread the blood into a thin film (practice makes perfect!). Allow the film to dry, fix in methanol for 5s, then stain as follows.

Leishman's stain:

Cover with 10 drops of Leishman's stain. After 30s add 20 drops of water. Leave for 15min. Pick up the slide with forceps (to avoid purple fingers) and rinse in fast-flowing tap water—for 1s only. Allow to dry. Now examine under oil immersion. Note red cell morphology. Do a differential white count. Polymorphs have lobed nuclei. Lymphocytes are small (just larger than red cells) and round, having little cytoplasm. Monocytes are larger than lymphocytes, but similar, with kidney-shaped nuclei. Eosinophils are like polymorphs, but have prominent pink-red cytoplasmic granules. Basophils are rare, and have blue granules. See p309 & p317 for images. Learn to use a white cell counting chamber—don't expect this to be as accurate as electronic methods.

Field's stain

is easy to use and gives good (and quick) results for malaria, and allows detection of trypanosomes and filaria. Dip the slide in solution A for 5s and solution B for 3s. Dip in tap water for 5s after each staining. Stand to dry. Examine thick films for at least 5min before saying that it is negative. NB: ward ***serology tests***, eg *Para*Sight F® are available for *P. falciparum*, but cannot replace microscopy as they are not 100% sensitive[35] and parasites are not quantified (needed to plan treatment).

Pus (Gram stain)

Make a smear; fix by gentle heat. Flood slide with cresyl violet for 30 seconds (s). Wash in running water. Flood with Lugol's iodine for 30s. Wash with running water. Decolourize with acetone for 1-3s until no blue colour runs out. Counterstain for 30s with neutral red or safranin. Wash and dry. Gram +ve organisms appear blue-black; Gram -ve ones look red, but are easier to miss.

Near-patient chemistry

In one sense this is less taxing than the above tests— the skill lies in the people who made the reagents easy to use. A problem is quality control and the black box effect: when we put a strip into a machine, eg to measure cardiac enzymes, we cannot see the workings of the black box: it just gives a deceptively accurate-looking figure. Frequent calibration of equipment is only a partial answer to this. It is only after you have spent a long time trying to get good results from near-patient analysers, and comparing paired samples with the lab, that one appreciates the reproducibility, and reliability of the formal lab. ▸Speed of reporting is useless if you cannot trust the results.[36]

Drug abuse and infectious diseases

▸Always consider this when there are evasive answers or unexplained findings, especially in younger patients. Ask direct questions: 'Do you use any drugs? Have you ever injected drugs? Does your partner use any drugs? Do you share needles? Have you ever had an HIV test? How do you finance your drugs?' List drugs used, and prescribed drugs, with names of prescriber.

Behavioural clues:

- Temporary resident seen by GP 'Just passing through your area'.
- Demands analgesia/antiemetics. Knows pharmacopoeia well: 'I just need some pethidine for my renal colic/sickle-cell crisis'.
- Erratic behaviour on the ward; unexplained absences; mood swings.
- Unrousable in the mornings; agitation from day 2.
- Heavy smoking; strange smoke smells (cannabis, cocaine, heroin).

Physical clues:

- Acetone or glue smell on breath (solvent abuse).
- Small pupils (opiates), reversed by naloxone.
- Needle tracks on arms, groin, legs, between toes; IV access hard.
- Abscesses and lymphadenopathy in nodes draining injection sites.
- Signs of drug-associated illnesses (endocarditis, p136; AIDS, p396, viral hepatitis).

Common and possible presentations in drug abusers

Unconscious	p774 Benzodiazepines (if in ITU consider flumazenil 0.2mg IV over 15s then 0.1mg/min as needed, to 1mg (2mg if on ITU).

Psychosis or agitation	Ecstasy (p827), LSD, amphetamine, anabolic steroids, benzodiazepines. Haloperidol may help (p13).
Asthma or dyspnoea	Is there opiate-induced pulmonary oedema? NB: Asthma may follow the smoking of heroin.
Lung abscess	Right-sided endocarditis (Staph) until proved otherwise.
PUO	Is it endocarditis, eg with no cardinal signs (p136)?
Fever/PUO/shivering/ headache	Do blood cultures; start eg gentamicin (p371 & p738).
Hyperpyrexia	p827
Abscesses	If over injection site, then often of mixed organisms. Eg on injecting suspended tablets into groin.
DVT	Any compression damage (compartment syndrome)? Do CK.
Pneumonia	Pneumococcus, haemophilus, TB, pneumocystis (p398).
Tachyarrhythmia	(If young); cocaine, amphetamines, endocarditis.
Jaundice	Hepatitis A, B, or C; anabolic steroids (cholestasis).
'Glandular fever'	May be presentation of HIV seroconversion illness.
Osteomyelitis	Including spinal. *Staph. aureus*/Gram -ve organisms.

Constipation	If severe, opiate abuse may be the cause.
Blindness	Consider fungal ophthalmitis ± endocarditis.
Runny nose	Opiate withdrawal (+colic /diarrhoea, yawns, lacrimation, dilated pupils, insomnia, piloerection, myalgia, mood↓; can occur in neonates if mother is an opiate abuser); cocaine use.
Neuropathies	(And any odd CNS signs) Consider solvent abuse.
Infarctions	(eg of spinal cord, brain, heart): suspect cocaine use.

The vocabulary of drug abusers [37]

The first step in helping a drug abuser is to communicate. To understand what he or she is telling you, the following may be helpful.

Amphetamines	Speed; whiz; Billy; pink champagne; crystal methamphetaime = 'meth' or 'chalk'
Amyl-nitrate	Goldrush; poppers; snappers
Barbiturates	Barbs; idiot pills
Cocaine	Coke; Charlie; uncle; the white; the nice; snow; rock; crack; nuggets; wash; gravel
Dihydrocodeine	DFs

Drug-induced sleep	Gauching; nodding; going on the nod
Drug intoxication	Stoned; off it; bladdered; ripped; wiped out; off my box
Heroin	Smack; the nasty; gear; brown; scag; hit; Harry
Ecstasy (MDMA)	E; X; echo; disco biscuit; love drug; XTC
Heroin with ecstasy	Party pack (2-for-1 deal when pusher's business is low)
Febrile reaction	Bad hit
Filter	A bud (usually a cigarette tip, through which drugs are drawn before being injected)
Injecting	Hitting up; jacking up; cranking; having a dig (skin popping/muscle popping/failed) (pocket shot)
(subcutaneous/IM/failed) (subclavian)	
Ketamine	Special K (Home Office class C drug, like cannabis); a ‘K hole’ is a dissociative state (hole in consciousness, p477)—may be a ketamine prelude to ‘ego death’.
LSD	Acid; trips; cardboard; tabs
Marijuana	Weed; pot; draw; ganja; grass; resin; Mary; hash
Methadone	Mud

Needles	Spikes; nails
Obtaining drugs	Score (selling drugs=deal)
PCP	Angel dust; KJ; ozone; missile
Physeptone ampoules	Amps
Prostitution	Working the block/square; doing business; on the game; on the batter; flogging one's golly
Prostitute's client	Mush; punter
Shooting gallery	Supervised surroundings for injecting (conforming with some mythical British Standard of Hygiene)
Shoplifting	Grafting
Smoking heroin	Chasing the dragon (bonging=smoking cocaine)
Syringes	Works; tools (barrel of a syringe=gun)
Temazepam	Temazies
Tourniquet	Key
Wanted by police	‘On me toes’; keeping head down

White heroin	China white
Withdrawing from opiates	Turkeying, clucking
Zopiclone	Zim-zims

General management of recreation drug users on the ward

A non-judgemental approach will produce better cooperation and may avoid self-discharge. Establish firm rules of acceptable ward behaviour. NSAIDs are useful for pain relief. Don't prescribe benzodiazepines or clomethiazole. Methadone may be needed if opiate addicts develop unacceptable withdrawal signs or symptoms in hospital. Get help.

Commercial sex workers need an STD screen, speculum exam (OHCS p242), and cervical cytology as carcinoma-*in-situ* is common (OHCS p273). Screen for syphilis (p419), HIV (p396) and hepatitis B (vaccination, p263, use gloves); give safe sex and safe injection advice. ▸Liaise with community teams. See OHCS p362.

Pyrexia of unknown origin (PUO)

Contrary to Gustave Flaubert, most fevers are not caused by plums, melons, April sunshine, etc.,[38] but by our immune responses to self-limiting viral infections resulting in production of interferons and cytokines. A PUO is defined as a fever for >3wks, eg resisting diagnosis after a week in hospital. Signs of bacteraemia include confusion, renal failure, neutrophilia, ↓plasma albumin,[39] and ↑CRP, p678.

Causes[40]

Infection (23%); connective tissue diseases (22%); tumours (20%); drug fever (3%); miscellaneous (14%). PUOs resist diagnosis in 25% of patients.

- Infections *Abscesses* (lung, liver, subphrenic, perinephric, pelvic); empyema; *bacteria* (*Salmonella, Brucella, Borrelia*, leptospira, p418); rheumatic fever; SBE/IE (may be culture -ve, eg Q fever); TB (CXR may be normal, so culture sputum & urine); other *granulomas* (actinomycosis, toxoplasmosis); *parasites* (eg amoebic liver abscess, malaria, schistosomiasis, trypanosomiasis); fungi; HIV; typhus.[41] Asking ***'Where have you been'*** is vital: find an expert on that area, or else you will miss diagnoses you may have never heard of, eg melioidosis (*Burkholderia*, p435, the chief cause of fatal bacteraemic pneumonia in parts of SE Asia).
- Neoplasms Especially *lymphomas* (any pattern: Pel-Ebstein fever, p344, is rare). Occasionally *solid tumours* (GI; renal cell). Patients may be unaware of fever.
- Connective tissue disease Rheumatoid arthritis, polymyalgia rheumatica, Still's disease, giant cell arteritis, SLE, PAN, Kawasaki disease.
- Others Drugs (T°↑ may occur months after starting but remits within days of stopping; eosinophilia is a clue); pulmonary embolism; stroke; Crohn's; ulcerative colitis; sarcoid; amyloid; familial Mediterranean fever—recurrent polyserositis (peritonitis, pleurisy) + fevers, abdominal pain, and arthritis; treat with colchicine; cause: gene defect, eg at 16p13.[42]

Examples of intermittent fevers

Always think of malaria; septicaemia (eg from diverticular disease); UTI; pelvic inflammatory disease; IE/SBE; TB; filarial fever—and rarities, eg: amyloid; *Brucella*; occult thromboembolism;[43] Castleman's disease.[44]

- *Daily spikes:* Abscess; TB;[45] schistosomiasis. *Twice-daily spikes:* Leishmaniasis.[46]
- *Saddleback fever* (eg fever for 7d, then normal for 3d): Colorado tick fever; Borrelia; Leptospira; dengue; Legionnaire's disease;[47] Ehrlichia[48] (p422).
- *Longer periodicity:* Pel-Ebstein (eg from lymphoma, p344).
- *Remitting* (diurnal variation, not dipping to normal): Amoebiasis; malaria; Salmonella; Kawasaki disease; CMV; TB.[49]

History

Work; hobbies; sexual activities; eating raw animals; drug abuse; immunosuppression; distant travel (▸p378); animal (or people) contacts; bites; cuts; surgery; rashes; diarrhoea; drugs (eg non-prescription); immunization; sweats; weight↓; lumps; and itching.

Examine:

Teeth; rectum; vagina; skin lesions; lymph nodes; hepatosplenomegaly (p624); nails; joints; temporal arteries; retina (Roth spots of SBE/IE, **fig 1**).

Symptom-patterns

Dialogue with experts ± decision support to diagnose fever with any other symptom. See www.emispdp.com.

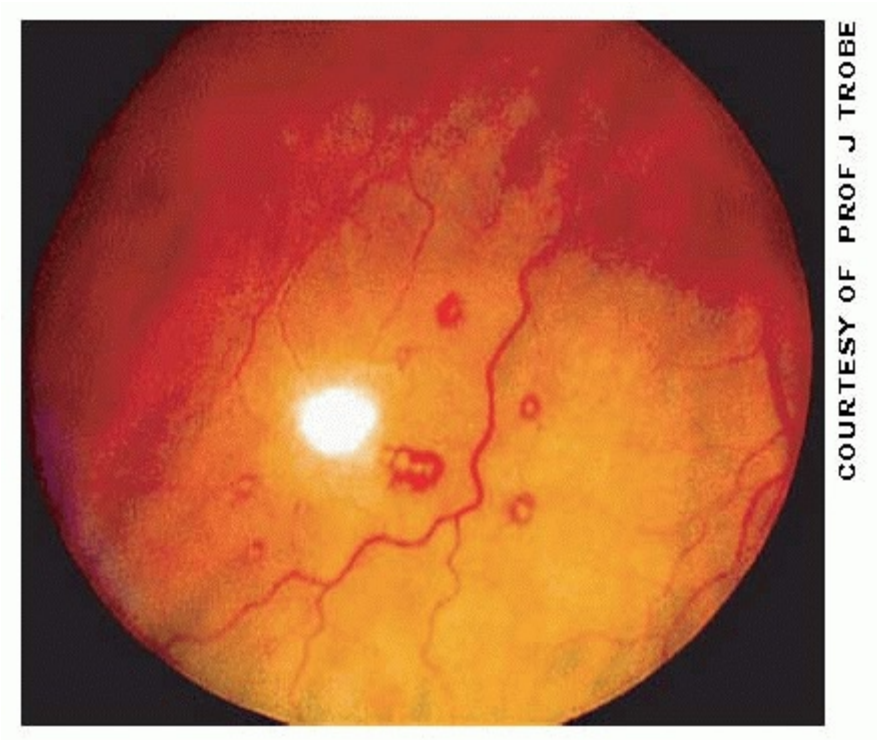


Fig 1. Roth spots: △△: micro-infarcts from hypertension, HIV,[50] connective tissue disease, anaemia, Behçet's, viraemia, hypercoagulability.

Stages in the investigation of PUO

Stage 1

(the 1st days): FBC; ESR; U&E; LFT; CRP; FBC; blood cultures (several, from different veins, at various times; prolonged culture for Brucella); baseline serum for virology; HIV; sputum MC&S (specify TB); MSU; stools (ova; cysts; parasites); CXR.

▸If 'septicaemic' but blood culture -ve, exclude malaria, and typhus, p423.

Stage 2

Repeat history/exam daily for new symptoms and newly-remembered symptoms or travel history. Protein electrophoresis; CT (chest; abdomen). Rheumatoid factor; ANA; antistreptolysin titre; Mantoux; ECG; marrow; lumbar puncture. Consider withholding drugs, one at a time for 48h each. Consider temporal artery biopsy (p542). HIV tests.

Stage 3

Follow leads uncovered, eg echocardiography; CT; IVU; liver biopsy; exploratory laparotomy; bronchoscopy. Repeat serology (any change since 1st sample?).

Stage 4

?Treat for TB, endocarditis, vasculitis, or trial of aspirin/steroids.

New and newly re-emerging infectious diseases

Many diseases preoccupying consultants in infectious diseases are new or newly re-emerging: food-borne *E. coli*, waterborne *Cryptosporidium*, airborne Legionnaire's disease, blood-borne hepatitis C, and HIV have come to the fore only in the last 30 years. Why have these years been so tumultuous in the ID world? The short answer is greed and exploitation. Examples: 1) Each year we consume 4 centuries-worth of animal and plant life,[51] so promoting ecological instability. 2) Economic drive builds dams (↑breeding grounds for vectors by orders of magnitude) and forces land development, putting people closer to vectors, eg ticks, mosquitoes, and rodents. Intensive farming makes it easier for infectious agents to jump the species barrier. Examples of viruses recently crossing species barriers to humans are hantavirus, haemorrhagic fever viruses, arboviruses, Nipah & Hendra viruses, avian influenza, monkeypox virus, SARS (p155), and CJD, p688). Consider also these 9 interacting causes:[52]

1. Famine and war (± threats of bioterrorism, eg with anthrax and smallpox).
2. Unprecedented movements of peoples, their animals and their parasites mixing genes, cultures, customs, and behaviour, eg eating raw molluscs and crabs facilitates toxoplasma, trematode, cestode and nematode zoonoses.
3. Microbial adaptation and change making antibiotics less successful.

4. Human susceptibility to infection (increased immunocompromise).
5. Climate change leading to shifting ecosystems and economic disaster (p362).
6. Human demographics (economic development and land use)—and related to an increasing world population (rising at ~86 million per year).
7. Tourism and commerce. West Nile virus, for example, reached New York from its ancestral home in the Middle East on a bird carried by a ship or plane.[53] With SARS, the precise tourists, businessmen, and doctors who took the virus from Hong Kong to Hanoi, Singapore, and Toronto have been identified.[54]
8. Technology and industry—easy to blame, but also part of the solution. Food security for millions living on <$1/day depends on increasing rice yields through high-tech genetic manipulation to produce insect- and saline resistant rice. Good crops from disease-free plants mean disease-free people.
9. Breakdown of public health measures with poverty and social inequality.

Can we win against infectious diseases?

No! All we can do is live with them. To help us do this in ways which are not too destructive, we need robust public health surveillance institutions, political will, quarantine laws, and above all, openness and cooperation. SARS and its spread emphasize this in a graphic way: as the Chinese and other less-than-open societies have found out, when it comes to reporting infectious diseases, lying means dying.

Winning or losing is the wrong image: infectious diseases have made us who we are. The ability of genomes to produce and emit DNA/RNA sequences allows *horizontal* transmission of genes, and is one of the main motors of evolution.[55]

GREED≈GLOBAL WARMING≈EMERGING DISEASES=POVERTY≈WAR

Diagnosing the tropical traveller

Tropical medicine emergency advice[UK]

Liverpool 0151 708 9393, London 020 7388 9600, Birmingham 0121 766 6611. In every ill traveller, consider:

1. ***Malaria*** (p382 & p384): Fever, rigors, headaches, dizziness, 'flu symptoms, diarrhoea, thrombocytopenia. *Complications:* anaemia, renal failure, pulmonary oedema, cerebral oedema. *Diagnosis:* serial thick and thin blood films. **NB:** Mosquitoes may stowaway in luggage causing malaria in non-tropical areas.[56]
2. ***Typhoid*** (p414): Presents with fever, relative bradycardia, abdominal pains, dry cough, constipation, lymphadenopathy, headache, splenomegaly ± rose spots (rare). *Complication*: GI perforation. *Diagnosis*: blood or marrow culture.
3. ***Dengue fever (DF)*** (p420): Presents with fever, headache, myalgia, rash (flushing or petechial), thrombocytopenia, and leucopenia. *Diagnosis:* serology.
4. ***Amoebic liver abscess*** (p424): T°↑, jaundice, RUQ pain. Do ultrasound.

Examine all over: any bites/eschar, p423? Do serology, thick films & blood cultures.

▸ ***Know your locally re-emerging diseases!*** Examples: TB, Lyme disease, leptospirosis, malaria, typhus, cholera, salmonella, hepatitis A, shigella, mumps, measles, brucellosis.[57] **NB:** A visit to the tropics doesn't preclude mundane fevers, eg 'flu.

Jaundice

Think of viral hepatitis, cholangitis, liver abscess, leptospirosis, typhoid, malaria, dengue fever, yellow fever, haemoglobinopathies.

Gross splenomegaly

Malaria, visceral leishmaniasis (kala-azar).

Diarrhoea & vomiting

(p380 & p238) *E. coli* (Travellers' diarrhoea) is commonest. Consider *Salmonella*, *Shigella*, *Campylobacter*, *Giardia lamblia*, *Vibrio cholerae*, etc. (p380). See p238 for general management. If diarrhoea prolonged, consider protozoal infection of small bowel or tropical sprue (p272). In HIV: cryptosporidia, microsporidia, and *Isospora belli* (need special stains—see **fig 1**, OPPOSITE).

Hepatosplenomegaly

See p624; malaria; *Brucella*; typhoid; typhus; leishmaniasis.

Respiratory symptoms

Common respiratory pathogens (p154), typhoid, *Legionella*, TB, Q fever, histoplasmosis, Löffler's (p696), HIV ± pneumocystosis. Do CXR & P_aO_2.

Arthritis

Gonococcus; septicaemia; viruses (Ross river, Chikungunya *et al* p421).[58]

Erythema nodosum

(p267) Causes: streps, TB, leprosy, fungi, Crohn's disease, ulcerative colitis, sarcoidosis, pregnancy, drugs (sulfonamides, contraceptive steroids).

Anaemia

Hookworm, malaria, kala-azar, haemolysis, malabsorption.

Skin signs

Scabies (itchy allergic rash + burrows, eg in finger web-spaces; p404 & OHCS p608), orf (pustules), molluscum contagiosum (pearly, punctate, papules), leprosy (p416, anaesthetic, hypopigmented areas), tropical ulcers, typhus ('eschar' =scab), leishmaniasis (ulcers/nodules), onchocerciasis (itchy nodules), myiasis (nodules—larvae of various insects), drug reactions. Transitory migratory swellings: gnathostomiasis, Calabar swellings (loa loa, p431), urticaria, contact dermatitis.

Acute abdomen

Perforating typhoid ulcer, toxic megacolon in amoebic or bacillary dysentery, sickle-cell crisis, ruptured spleen.

Rarities to consider

▸ Use local emergency isolation policy.

- ***Rabies*** (p420) and other CNS viral infections, eg encephalitis (p388 & p807).
- ***Yellow fever:*** (p420) Suspect in travellers from Africa.
- ***Lassa fever:*** Occurs in Nigeria, Sierra Leone, or Liberia. ***Signs:*** Fever; exudative sore throat; face oedema; collapse. ▲: PCR/EM; serology. **[prescription take]:** Isolate and refer.
- ***Marburg and Ebola virus:*** Seen in Sudan, Zaire, Kenya. ***Signs:*** Fever, myalgia, D&V, pleuritic pain, hepatitis, shock, and bleeding tendency. A maculopapular rash appears on day 5-7 and desquamates in <5d. Patients may bleed from all orifices and gums.[59] ▲: PCR or electron microscopy; serology. [prescription take]: Isolate and refer.[60]
- ***Viruses causing haemorrhage:*** Dengue, Marburg, Lassa, Ebola, Crimea-Congo fever, haemorrhagic fever with renal syndrome, yellow fever. ▸See p420.

▸Travel details (areas visited; immunization; prophylaxis; disease exposure) are very important, even if you cannot interpret yourself, so seek expert opinion *early*.

Incubation times for fever in the tropical traveller[61]

▸The incubation times below are typical, but considerable variation occurs.

<14 days	14 days to 6wks	>6wks
Undifferentiated fever		
Malaria	Malaria	Malaria
Typhoid	Typhoid	Hepatitis B or E
Leptospirosis	Leptospirosis	Kala-azar

Dengue fever	Hepatitis A or E	Lymphatic filariasis
Rickettsiae	Acute schistosomiasis	Schistosomiasis
Acute HIV infection	Acute HIV infection	Amoebic liver abscess
Fever with CNS signs		
Viral and bacterial meningitis and encephalitis	East African Trypanosomiasis	Rabies
East African trypanosomiasis	Rabies	
Poliomyelitis		
Fever with chest signs		
Influenza	Tuberculosis	Tuberculosis
Legionellosis	Q fever	
Q fever		
Acute histoplasmosis		
SARS		
Fever with diarrhoea, p380		

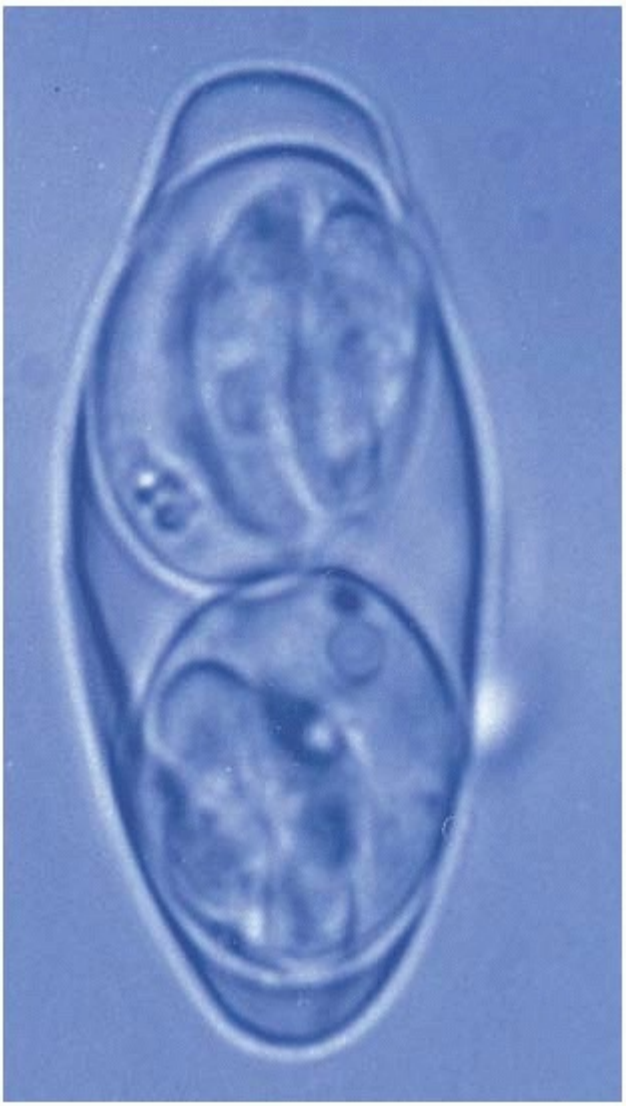


Fig 1. Sporulated (infective) oocyst of the protozoan *Isospora belli*;[62] oocysts are passed unsporulated, but can sporulate in 1-3 days, depending on T°, and the presence of molecular oxygen.[63]

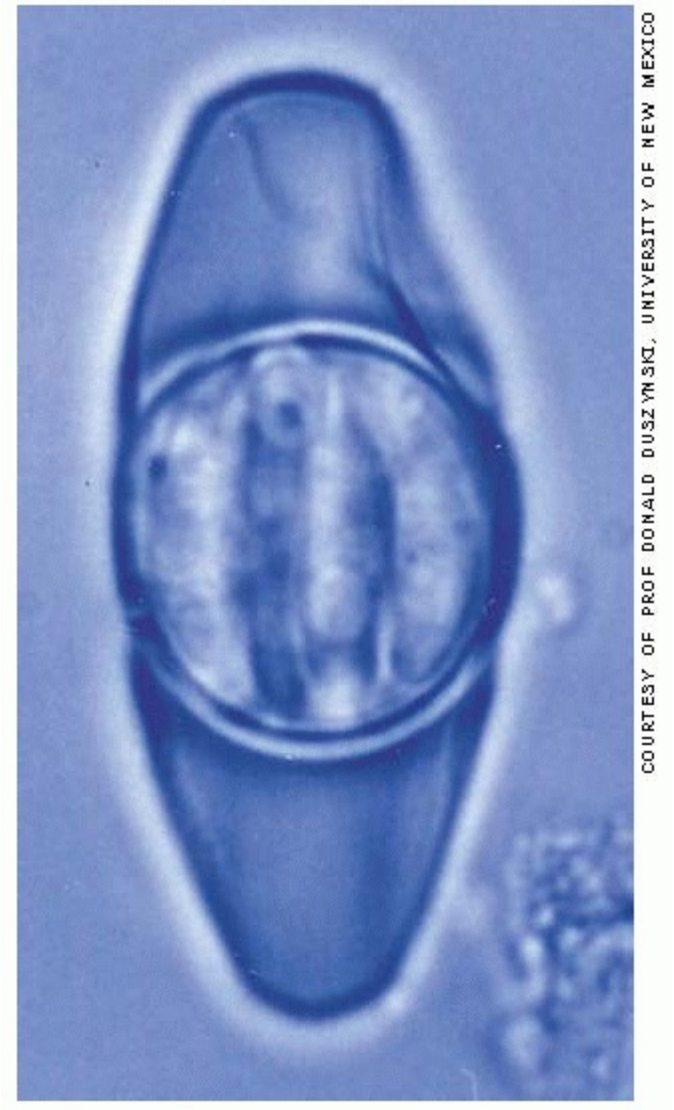


Fig 2. A unique feature of *I. belli* oocysts is that some develop irregularly, having 1 sporocyst with 8 sporozoites (Duszynski 1999).[64] Isosporiasis is an AIDS-defining illnesses (diarrhoea ± haemorrhagic colitis).

Gastroenteritis

Ingesting certain bacteria, viruses, and toxins is a common cause of D&V (p74 & p238). Contaminated food and water are common sources, but often no specific cause is found. Ask about details of food and water taken, cooking method, time till onset of symptoms, and whether fellow-diners were affected. Ask about swimming, canoeing, etc. **NB:** *Food poisoning is a notifiable disease (*p363*) in the* UK.

Organism/Source	Incubation	Clinical features	Notes/sources of infection
Staph. Aureus	1-6h	D&V, P, hypotension	Meat
Bacillus cereus	1-5h	D&V	Rice
Red beans	1-3h	D&V	

Heavy metals, eg zinc	5min-2h	V, P; with zinc, (delayed fever ± 'flu-like features after exposure at work)	
Scrombotoxin	10-60min	D, flushing, sweating erythema, hot mouth	Fish
Mushrooms	15min-24h	D&V, P, fits, coma, hepatic and renal failure	Image: p423
Salmonella	12-48h	D&V, P, fever, septicaemia	Meat, eggs, poultry
C. perfringens	8-24h	D, P afebrile	Meat
C. botulinum	12-36h	V, paralysis	Processed food
C. difficile	1-7d	Bloody D, P, GI perforation; toxic megacolon; hospital acquired (1000 deaths/yr^{UK})	Antibiotic-associated; and getting more virulent (eg strain BI/NAP1 with 20-fold ↑ in toxin A & B production).[65]
Vibrio parahaemolyticus	12-24h	Profuse D; P, V	Seafood
Vibrio cholerae	2h-5d	See p414	Water*
Campylobacter	2-5d	Bloody D, P, T°↑	Milk, poultry, water*
Listeria		Meningoencephalitis; 'I've got flu'; miscarriages	Cheese, pâtés

E. coli type 0157	12-72h	Cholera/typhoid-like;*	Haemolytic-uraemic syn, p300
Y. enterocolitica	24-36h	D, P, fever	Milk*
Cryptosporidium[1]	4-12d	D in HIV	Cow→water→man
Giardia lamblia	1-4wks	p424 (D, malabsorption)	*Nappies, cats,[66] dogs, crows[67]
Entamoeba histolytica	1-4wks	See p424	*
Noroviruses, eg Norwalk =SRVS (**small round structured viruses**)	36-72h	Fever, D & projectile V [68] 'winter vomiting illness'	Fecal-oral (vomit is infectious); very contagious, and common.
Rotavirus	1-7d	D&V, fever, malaise	* (RotaTeq vaccine ?available for infants aged from 6 weeks)
Shigella	2-3d	Bloody D, P, fever	Any food

V=vomiting; **D** = diarrhoea; **P** = abdominal pain.

* May be food- or water-borne.

[1] Cryptosporidium (**fig 1**) is a tiny fungus (5μm) causing diarrhoea/cramps—life threatening if HIV+ve; self-limiting if CD4 ≳100); if <100, 14L of diarrhoea can be lost/d (bad news). It's a UK crime to sell water with >1 oocyst/10L. Spread: unboiled water; cattle. If found in stool, quantify excretion. If [prescription take]needed, ask a microbiologist ([prescription take] often fails); optimize anti-HIV [prescription take]. Consider: nitazoxanide 0.5g/12h PO for 14d (if >12yrs old); azithromycin + paromomycin 1g/12h PO.

Tests

Stool microscopy/ culture

if from abroad, an institution, or in day care, or an outbreak is suspected. In these circumstances culture of the food source may help.

Prevention

Hygiene; if abroad, avoid unboiled/unbottled water, ice cubes, salads, and peel own fruit. Eat only freshly prepared hot food (or *thoroughly* rewarmed).

Management

Usually symptomatic. Maintain *oral fluid intake* (±oral rehydration sachets). For severe symptoms (but not in dysentery), give *antiemetics* (eg prochlorperazine 12.5mg/6h IM) + *antidiarrhoeals* (codeine 30mg PO/IM or loperamide 4mg stat, then 2mg after each loose stool). *Antibiotics are only indicated if systemically unwell, immunosuppressed or elderly*; resistance is common.

- Cholera: tetracycline reduces transmission.
- *Salmonella*: ciprofloxacin 500mg/12h PO, 200-400mg/12h IVI over 60min.
- *Shigella* & *Campylobacter*: ciprofloxacin as above.

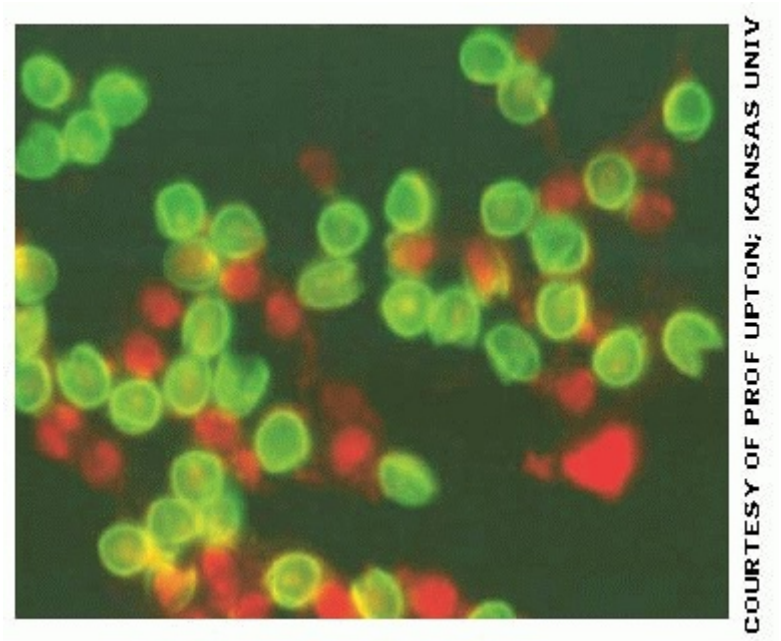


Fig 1 Indirect immunofluorescence (antibody 8F4 to the inner oocyst wall).

Immunization www.immunisation.nhs.uk

Active immunization

stimulates the immune system (humoral+cellular immunity).

Passive immunization

uses pre-formed antibody (nonspecific or antigen-specific).

Age	Immunization	(DoH[UK] 2006)

2 months	**Pediacel®**, ie 5-in-1 diphtheria + tetanus + acellular pertussis + inactivated polio + haemophilus B (HIB); if prem, still give at 2 mths; can give if ≤10 yrs if missed vacs + **Prevenar®** (7-valent pneumococcal).
3 months	**Pediacel®** + **Neisvac C®** or **Meningitec®** (Meningitis C vaccine)
4 months	**Pediacel®** + **Prevena®** + **Neisvav C or Meningitec®**
12 mths	**Menitorix®** (*H. influenzae* with meningitis C)
13 mths	**MMR II®**[L] or **Priorix ®**[L] (Measles, Mumps & Rubella) + **Prevenar®**
3¼-5yrs	**Repevax®** or **Infanrix-IPV®** (Diphtheria, tetanus, pertussis & polio) + **Priorix®**[L] or **MMR II®**[L]
13-18[+]yrs	**Revaxis®** (low-dose diphtheria, tetanus, inactivated polio; can also be used for primary vaccination if >10yrs).
Any age	**BCG[L]:** (not for everyone, since 2004[uk]) If at ↑risk of TB, eg for all in high-risk areas (eg London), or in groups at ↑risk, eg TB contact, or (grand)-parents or from high-prevalence country, ie >40/100,000/yr—or a visitor to such a country for >1 month. May start at 3 days old. ***Hepatitis B:*** p263; universal (WHO advice) or if at ↑risk. ***MMR***[L] may be given at any age the above is missed. One-off ***pneumococcal vaccine*** with 23-valent Pneumovax II® (**Prevenar®**×2, as above, if <2yrs old); yearly ***'flu vaccine*** if caring for a vulnerable person or if chronic heart, chest, liver, or renal disease; DM; immunosuppression (eg HIV +ve, cirrhosis, on chemotherapy, or spleen function↓, eg ∴ coeliac or sickle cell disease). Consider 2[nd] pneumococcal vaccine if at ↑risk after >5yrs.[69]
Adults	Tetanus and diphtheria booters (**Revaxis®**, as above). Travellers: p367.

▸*An acute febrile illness is a contraindication to any vaccine*. Give live vaccines either together, or separated by ≥3wks. Caution with live vaccines in patients who are immune-deficient (transplants, cancer chemotherapy, steroids, HIV infection)— seek expert advice. ▸*Contraindications to vaccines*: see OHCS p151.

▸**Bacille Calmette-Guérin (BCG)** Live attenuated anti-TB vaccine (works in up to 80% of subjects for ~10yrs, but there is much variation). Make a 7mm blanched weal between the top and middle 1/3 of arm (deltoid's insertion) or, for cosmetic reasons, the upper, outer thigh. Expect to feel marked resistance as the injection is given. If, during injection, propagation of the weal stops, you are going too deep: re-insert the needle. A swelling appears after 2-6 weeks, developing into a papule or small ulcer. Avoid air-occluding dressings. SE: pain, local abscess. CI: pyrexia, oral steroids, sepsis, or eczema at vaccination site, immune pareses (eg AIDS and malignancy).

Mantoux test

(p386) Offered to those at risk of TB (see BCG, above). It is now not routinely required for those <6yrs old being referred for BCG on the above criteria.

Travel

p367. Expert advice: *schools of tropical medicine*: London: 020 7636 8636; Liverpool: 0151 708 9393); National Travel Health Network and Centre, www.nathnac.org.

▸*Advice to travellers is more important than vaccination*: eg simple hygiene, malaria prophylaxis, and protective measures (mosquito nets, safe sex advice, etc).

Immunization in special situations

If *splenectomized/hyposplenic (eg sickle cell):* MCC; polyvalent pneumococcal; Hib; annual 'flu vaccine. *Chronic lung, heart, liver or kidney disease, diabetes:* pneumococcal; annual 'flu vaccine.

Further details

Hepatitis B (p263); 'flu; pneumococcal (p152); meningococcal (Mengivac® = group A & C), for short-term use, eg travel abroad. Leave ≥2wks after routine MCC before giving Mengivac®. Ideally this gap should be >6 months, but children <5yrs may not have responded well to their 1st dose of MCC.[70]

Malaria[ND]: clinical features and diagnosis

Malaria is one of the commonest causes of fever and illness in the tropics. ▸Check for it in any sick patient from an endemic area. *Plasmodium falciparum* kills ~1 million people each year. Summary of species differences:[71]

P. vivax: incubation 10-17 days, *'benign tertian malaria'*, symptoms 48hrly.

P. ovale: similar to *P. vivax*; except untreated infection lasts less long.

P. malariae: incubation 18-40 days, symptoms 72hrly, untreated infections ~20yrs

P. falciparum: incubation 7-10 days, symptoms 36-48hrly, fulminating disease.

Plasmodium protozoa, injected by the female *Anopheles* mosquito (~120 sporozoites/bite), multiply in RBCs (>10^8-10^{12} trophozoites per infection) causing haemolysis, RBC sequestration, and cytokine release. Protective factors: sickle-cell trait, Melanesian ovalocytosis, G6PD deficiency, certain HLA B53 allele (in many non-Europeans, enables killing of parasite-infected hepatocytes by cytotoxic T cells).

P. falciparum malaria Incubation:

~7-10d.[72] Most travellers present within 2 months.

Symptoms:

Non-specific flu-like prodrome: headache, malaise, myalgia, and anorexia followed by fever and chills ± faints. Classic periodic fever (peaking every 3rd day, ie tertian) and rigors are unusual initially.

Signs:

Anaemia, jaundice, and hepatosplenomegaly. No rash or lymphadenopathy.

Complications:

Cerebral malaria (p385): confusion; coma ± fits. Focal signs unusual. May have variable tone, extensor posturing; upgoing plantars, dysconjugate gaze; teeth-grinding. In children, seizures are common. Mortality: ~20%. *Metabolic (lactic) acidosis* giving laboured deep (Kussmaul's) breathing is also a major cause of death. *Anaemia* is common due to haemolysis of parasitized and unparasitized RBCs, and may be particularly severe in young children. *Hyperparasitaemia* (>5% of RBCs parasitized). *Hypoglycaemia* occurs in severe malaria (25% of children, 8% of adults), pregnancy, or with quinine therapy. *Acute renal failure* from acute tubular necrosis, sometimes with haemoglobinuria (*'blackwater fever'*), and *pulmonary oedema* (ARDS, p170) are important causes of death in adults. Shock may develop in severe malaria (*algid malaria*) from supervening bacterial septicaemia, dehydration or, rarely, splenic rupture. In pregnancy, the risk of death (mother or fetus) is high (OHCS p27). Use chemoprophylaxis in pregnant women in endemic areas of transmission.

Benign malaria

has a very low mortality. The acute febrile illness is very similar to that of uncomplicated *falciparum* malaria. Incubation periods may be longer: 5-10% of *P. malariae* malaria presents over 1yr after infection. Complications: Relapse occurs as parasites lie dormant in the liver (*P. vivax* and *ovale*) or at low levels in the blood (*P. malariae*). Nephrotic syndrome (glomerulonephritis) may occur in chronic *P. malariae* infection.

Diagnosis

Serial thin & thick blood films (needs much skill, don't always believe -ve reports, or reports based on thin film examination alone); if *P. falciparum*, what is the level of parasitaemia? Rapid stick tests now available if microscopy cannot be performed or previously treated seriously ill patient: see p373 for *Para*Sight F®. Serology not useful. Other tests: FBC (anaemia, thrombocytopenia), clotting (DIC, p336), glucose (hypoglycaemia), ABG/lactate (lactic acidosis) U&E and creatinine (renal failure), urinalysis (haemoglobinuria, proteinuria, casts), blood culture.

Poor prognostic signs

(Severe *falciparum* malaria) Age <3yrs, pregnancy, respiratory distress, fits, coma, absent corneal reflexes, papilloedema, pulmonary oedema, HCO_3^- <15mmol/L, plasma or CSF lactate >5mmol/L, glucose <2.2mmol/L, hyperparasitaemia (>5% RBCs or 250,000/μL), Hb <5g/dL, DIC, creatinine >265μmol/L.[73] If ≥20% (or $>10^4$/μL) of parasites are mature trophozoites or schizonts, the prognosis is poor, even if few parasites seen (reflects critical mass of sequestered RBCs[74]); malaria pigment in >5% of neutrophils.[75]

Malaria prophylaxis: a rough guide for adults and children

Age	Weight (kg; a better guide than age)	Chloroquine (base) weekly (mg)	Proguanil daily (mg)	Mefloquine weekly (mg)	Doxycycline daily (mg)
<12wks	<6	37.5	25	—	—
<1yr	6-9.9	75	50	62.5	—
1-3yrs	10-15.9	112.5	75	62.5	—
4-7yrs	16-24.9	150	100	125	—
8-12yrs	25-44.9	225	150	187.5	—
~Adult	>45	300	200	250	100

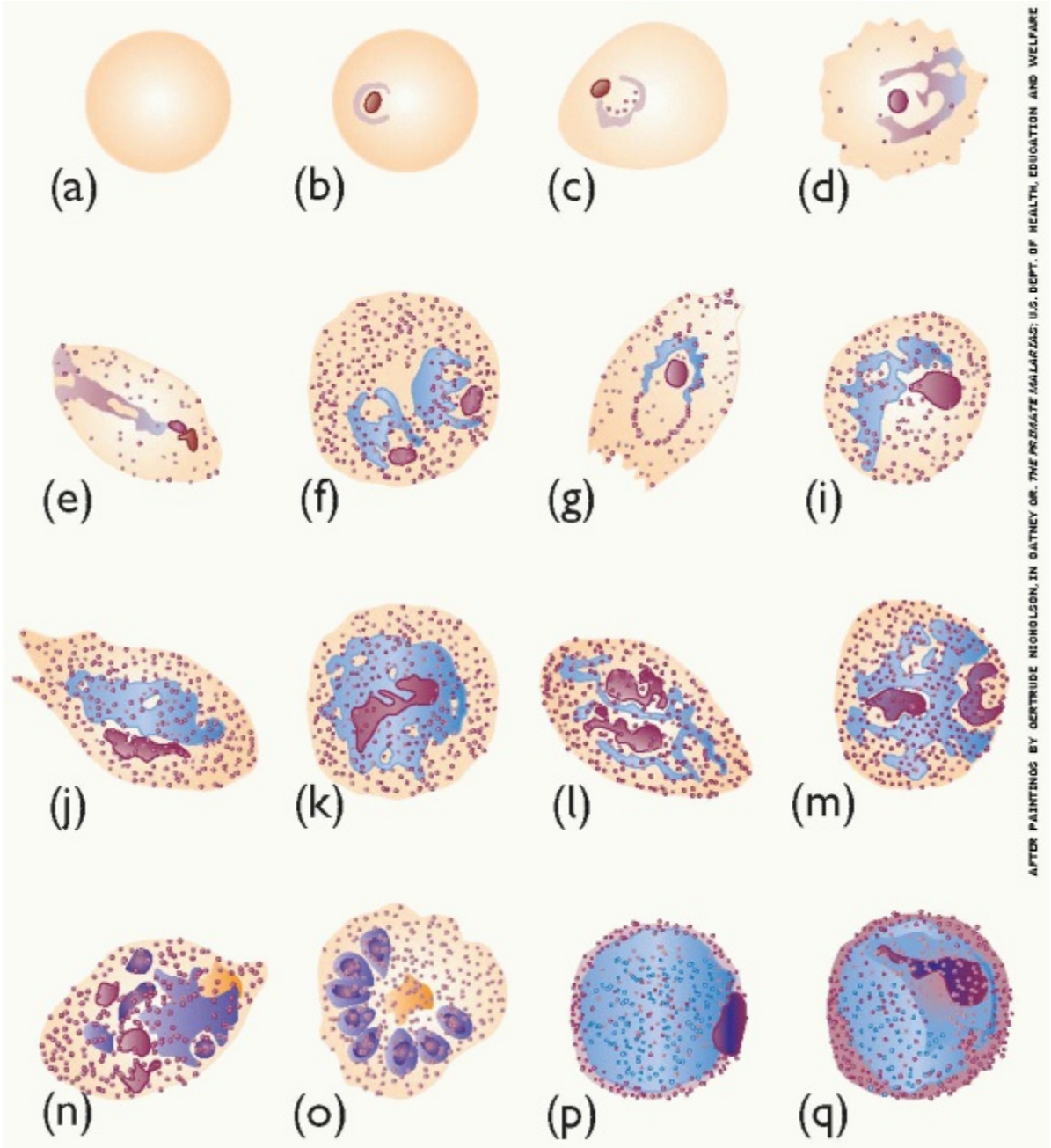


Fig 1. *P. ovale*:[76] **(a)** RBC; **(b-m)** trophozoites; in **(g)**, the RBC is fimbriated and oval, giving the species its name; **(l-o)** schizonts, ie segmentation; **(p-q)** ♀ & ♂ gametocytes.

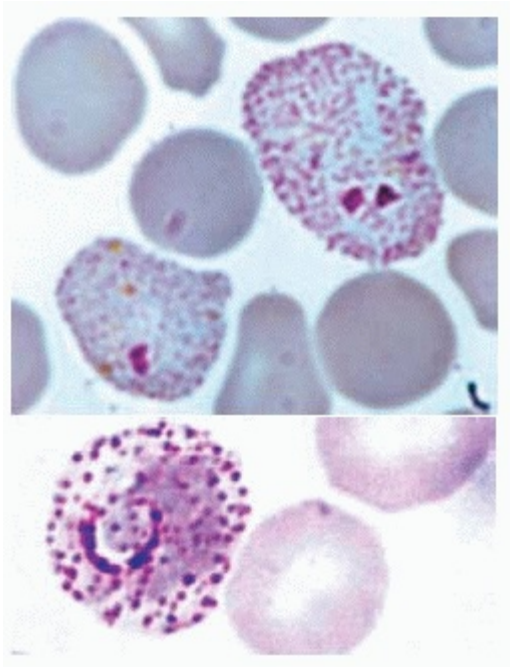


Fig 2. *P. vivax*[77] ring forms partly hidden by Schuffner's dots[78]

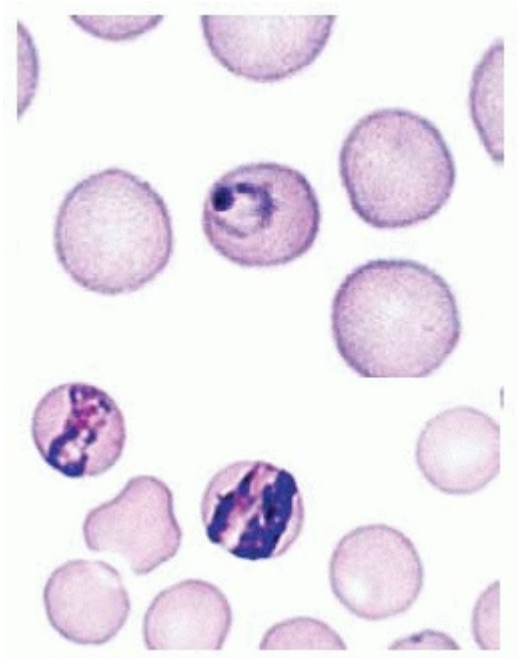


Fig 3. *P. malariae* ring & band forms from two specimens[79]

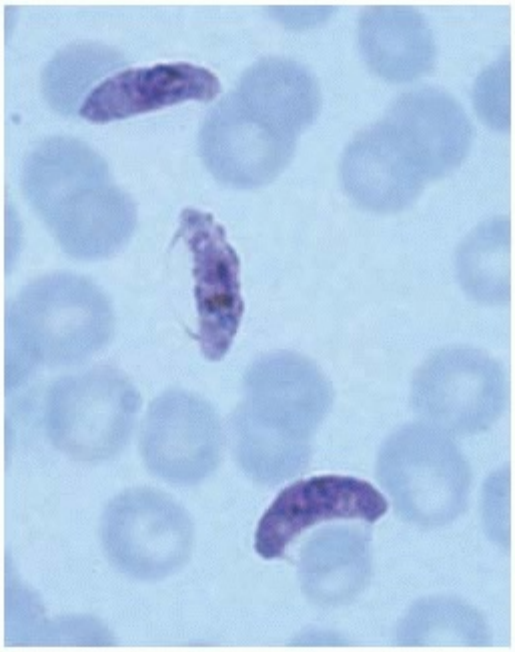


Fig 4. *P. falciparum* sausage-shaped gametocytes within RBC ghosts[80]

Fig 5. Ronald Ross who first described the malaria lifecycle[81]

Malaria: treatment and prophylaxis

Treatment

If species unknown or mixed infection, treat as *P. falciparum*. Nearly all *P. falciparum* is now resistant to chloroquine and in many areas is also resistant to Fansidar® (pyrimethamine + sulfadoxine). If in doubt consider as resistant. Chloroquine[82] is the drug of choice for benign malarias in most parts of the world, but chloroquine-resistant *P. vivax* occurs in Papua New Guinea, Indonesia, some areas of Brazil, Colombia, and Guyana.[83] Never rely on chloroquine if used alone as prophylaxis.

Falciparum malaria:

As multi-drug resistance is common, artemisinins-combinations are best (WHO).[84] Artemisinins are 'OK' in children and in 2nd & 3rd trimesters of

pregnancy. If able to swallow and no severe signs:[1] **artesunate (AS)-amodiaquine (AQ)**; if a fixed combination pill is available (AS 100mg + AQ 270mg), the dose is 2 pills once daily for 3d. If aged ~7-13yrs, it is 1 pill/d for 3d.[85] OR **artemetherlumefantrine** (Riamet®) 4 tabs/12h for 6 doses.[MET86] OR **dihydroartemisininpiperaquine** (2.1/16.8mg/kg daily for 3d, eg 3 Artekin® tabs/d)[87] OR **artesunate (4mg/kg/d for 3d) + mefloquine** (eg 5 Larium® tabs stat). These are better than **quinine** regimens (eg 600mg quinine salt/8h PO for 7d, + **doxycycline** 100mg/12h or **clindamycin** 450mg/8h for 5d).[88] If seriously ill,1 parenteral [prescription take] is needed (IVI for artesunate, IM for artemether)—▸▸see BOX; take to ITU (fluid monitoring is vital, and may require a CVP line). NB: Resistance to artemisinins may have started.[89]

Benign malarias:

Give chloroquine PO as 600mg base, 300mg 6h later, then 300mg/24h for 2d.[90] If *P. ovale*, give primaquine 15mg/24h for 14d (30mg/24h if *vivax*; CI pregnancy) after chloroquine to treat liver stage and prevent relapse. Screen for G6PD deficiency first.

Other treatments:

Tepid sponging + paracetamol for fever. Transfuse if severe anaemia. Consider exchange transfusion if patient severely ill. Treat 'algid' malaria as malaria + bacterial shock (p778). Monitor TPR, BP, urine output, blood glucose frequently. Daily parasite count, platelets, U&E, LFT.

Examples of prophylaxis[91]

▸***Prophylaxis does not give full protection***. Risks are very variable; get local advice. Avoid mosquito bites between dusk and dawn: wear long-sleeved clothes, use repellents (DEET), insecticide-treated bed nets.

Except for Malarone® and mefloquine , take drugs from 1wk before travel (to reveal any SE) and continue for 4wks after return. None are required if just visiting cities of East Asia. There is no good protection for parts of SE Asia.[92]

Prophylaxis:

Check up-to-date sources. *Caribbean, North Africa, Middle East:* chloroquine ± proguanil. *S. America, sub-Saharan Africa,* SE *Asia, Oceania:* mefloquine, doxycycline, or Malarone®. South Asia: *chloroquine + proguanil*. Indonesia and forests of Malaysia & Sarawak: *chloroquine + proguanil*. ▸If area has poor medical care and not pregnant, carry standby treatment course (eg Riamet®, Malarone®).

Adult prophylactic doses:

Chloroquine (base[2]): 300mg/wk PO. **Proguanil**: 200mg/24h PO. **Doxycycline**: 100mg/24h PO. **Mefloquine**: 250mg/wk PO for adults if no risk of pregnancy; start 2½ weeks before travel. **Malarone**®: 1 tablet/24h PO starting 1d before travel, and continuing till 7d after return from malarious area (other prophylactic drugs need to be continued for 4 weeks).

Antimalarial SE:

Chloroquine: headache, psychosis, retinopathy (chronic use). *Fansidar®:* Stevens-Johnson syndrome, erythema multiforme, LFT↑, blood dyscrasias. *Primaquine:* Epigastric pain, haemolysis if G6PD-deficient, methaemoglobinaemia. *Mefloquine:* Nausea, dizziness, dysphoria, insomnia, neuropsychiatric signs, long *t*½. Ideally start prophylaxis 3wks prior to travel to reveal any SE. Avoid mefloquine if: • Low risk of chloroquine-resistant malaria, eg East African coastal resort • Past or family history of epilepsy, psychosis • Need for delicate work (pilots[etc]) • Risk of pregnancy within 3 months of last dose. Interactions: quinidine, halofantrine. *Malarone*®: Abdominal pain, nausea, headache, dizziness.

Cerebral malaria (*P. falciparum*)

Falciparum malaria is one of the great killers, because it is swift and difficult to treat: so get expert help in anyone who could have travelled abroad particularly in the last few months, who is feverish with ↓consciousness. But fever is not *always* a feature of malaria, and signs may be unusual if prophylaxis has been given, and is partly effective. The central event in severe *Falciparum* malaria is sequestration of parasitized erythrocytes in the microvasculature of vital organs. Death rate: ~1 million deaths/yr, worldwide.[93]

Key questions

What is the parasite count, the plasma bicarbonate and the creatinine? Are there complications: shock (algid malaria), metabolic acidosis, hypoglycaemia, renal failure, or acute respiratory distress syndrome (ARDS, p170).

Treatment

Take advice. Transfer to ITU. Give **artesunate** (if *immediately* available[1]) or **quinine** (dihydrochloride) 20mg salt /kg IV (max 1.4g) over 4h, then after 8h give 10mg/kg (max 700mg) over 4h every 8h (or give by constant IVI of 30mg/kg/d after loading dose).[2] Give IV until the patient can swallow; complete the course orally. Monitor for hypoglycaemia. **Artemether** (3.2mg/kg followed by 1.6mg/kg daily) is another alternative. In the UK, artemether is available on a named patient basis: get local advice. Don't wait for an ideal drug if a good alternative is to hand: delay is fatal.[94]

If swallowing OK and no complications (shock; ARDS, renal failure) give either:

a. **Artemether**-lumefantrine (80/480mg twice daily for 3d with food).
b. **Malarone**® (atovaquone + proguanil; 4 tabs once daily for 3d with food).
c. **Quinine** (600mg salt/8h PO for 7d), with either doxycyline 200mg daily or clindamycin 600mg/12h for 7d PO.

[1] **Artesunate** dose 2.4mg/kg as a bolus at 0, 12 & 24h, then daily. It is not universally available, but works better than quinine (15% mortality *vs* 22%), and has fewer SEs, White N 2005 *Lancet* 366 717[RTO]

ITU monitoring in cerebral malaria

▸▸ Fluid requirements vary widely; careful fluid management is critical. Haemofilter early if renal failure. Ventilate early if pulmonary oedema.
▸▸ Consider exchange transfusion in very seriously ill patients if feasible.

▸▸ Monitor blood lactate (or bicarbonate) and glucose: quinine may cause hypoglycaemia. Also do LFT and clotting studies and cross-match blood if haematocrit <20%.

▸▸ Repeated U&E (and arterial blood gases if ARDS).

▸▸ Arrange repeated skilled microscopy to monitor the parasite counts.[95]

Expect a >75% decrease in the parasite count by 48h of treatment.

Pitfalls

- Failure to take a full travel history, including stop-overs in transit and failure to check if the patient has already received treatment which might make the blood smear negative.
- Delay in treatment while seeking lab confirmation.
- Failure to examine enough blood films before excluding the diagnosis.
- Belief that drugs will work, when the parasite is often one step ahead.
- Not having IV quinine available immediately. (Quinidine is an alternative.)
- Not observing *falciparum* patients closely for the first few days.
- Forgetting that malaria is an important cause of coma, deep jaundice, severe anaemia, and renal failure in the tropics.

[1] Prostration, consciousness↓, fits, respiratory distress, unable to drink, uncontrolled vomiting, macroscopic haemoglobinuria, jaundice, systolic BP ≤ 70mmHg, bleeding/DIC, inability to sit or stand.

Tuberculosis (TB)[ND]: TB-with-HIV: p397; BCG: p381

TB kills 2 million people/yr; it is the cause of death of most people with HIV. TB is why the poor stay poor—and then die. If HIV+ve, risk↑ if CD4 cell count↓; ESR↑; many coinfections; poor nutrition; high viraemia.[96] UK incidence 7000/yr; 350 deaths/yr.

Diagnosis

Whenever TB is suspected, try hard to get the relevant clinical samples (sputum, pleural fluid, pleura, urine, pus, ascites, peritoneum, or CSF) for culture to establish the diagnosis and drug sensitivities. **Active case-finding:** ▸Get advice on testing contacts. In high-incidence areas, most transmission (≳80%) occurs outside the household—so it may be necessary to spread your net wide.[97]

Microbiology:

Send multiple sputum for MC+S for AFB (acid-fast bacilli), pleural aspiration and biopsy (p752) if there is an effusion. If sputum is negative, bronchoscopy with biopsy and bronchoalveolar lavage may be helpful. Biopsy any suspicious lesions in liver, lymph nodes or bone marrow. AFB are bacilli that resist acid-alcohol decolourization under Ziehl-Neelsen (ZN) staining. Cultures undergo prolonged incubation (up to 12 weeks) on Lowenstein-Jensen medium.

TB PCR:

Allows rapid identification of rifampicin (and likely multi-drug) resistance. Occasionally useful for diagnosis in sterile specimens.

Histology:

The hallmark is the presence of *caseating granulomata*.

CXR signs:

Consolidation, cavitation, fibrosis, and calcification in pulmonary TB.

Immunological

evidence of TB may be helpful:

- *Tuberculin skin test:* TB antigen is injected intradermally and the cell-mediated response at 48-72h is recorded. A positive test indicates that the patient has immunity. It may indicate previous exposure or BCG. A strong positive test probably means active infection. *False negative tests* occur in immunosuppression, including miliary TB, sarcoid, AIDS, lymphoma.
- *Mantoux test:* Serial dilutions of TB antigen provide 1, 10, and 100 tuberculin units (TU), respectively. The test is +ve if it produces ≥10mm induration, and -ve if <5mm. This test is overrated in diagnosing TB and its use is controversial.
- If active TB is strongly suspected, use 1 TU. If it is positive, infection is likely. Otherwise, interpret in the clinical context.

Treatment of pulmonary TB

Before treatment:

Stress importance of compliance/concordance (helps the patient and prevents spread of resistance). Check FBC, liver, and renal function. Test colour vision (Ishihara chart) and acuity before and during treatment as ethambutol may cause (reversible) ocular toxicity.

▸Patients often forget to take pills, so consider *supervised* therapy as follows:

- ***Initial phase*** (8wks on 4 drugs depending on susceptibilities):
  1. Rifampicin 600-900mg (child 15mg/kg) PO 3 times/wk.
  2. Isoniazid 15mg/kg PO 3 times/wk max 900mg + pyridoxine 10mg/24h.
  3. Pyrazinamide 2.5g PO (2g if <50kg) 3 times/wk (child 50mg/kg).
  4. Ethambutol 30mg/kg PO 3 times a week for 2 months, or streptomycin 0.75-1g/24h IM (see BNF; child 15mg/kg/24h).
- ***Continuation phase*** (16wks on 2 drugs) rifampicin and isoniazid at same doses. Rifinah 300®=rifampicin 300mg + isoniazid 150mg; get advice about resistance.
- Give pyridoxine throughout treatment.
- Steroids are indicated in meningeal and pericardial disease.

Main side-effects

▸Seek help in renal or hepatic failure, or pregnancy.

Rifampicin: Hepatitis (a small rise of AST is acceptable, stop if bilirubin rises), orange discolouration of urine and tears (contact lens staining), inactivation of the Pill, 'flu-like syndrome with intermittent use.

Isoniazid: Hepatitis, neuropathy, pyridoxine deficit, agranulocytosis.

Ethambutol: Optic neuritis (colour vision is the first to deteriorate).

Pyrazinamide: Hepatitis, arthralgia (CI: acute gout; porphyria).

WHO's/G8 'Stop TB' plan

Sputum smear microscopy *et al* for all; directly observed therapy (**DOT**) in front of a health worker for 6 months; aiming to treat 50 million people over 10yrs, and to reduce the required duration of therapy to 8 weeks.[98]

Chemoprophylaxis for asymptomatic tuberculous infection

Immigrant or contact screening may identify patients with TB without symptoms or radiographic changes. In such patients, chemoprophylaxis may be useful to kill the infective organisms and prevent possible disease progression at a later date. This involves administration of one or two anti-TB drugs for shorter periods than for symptomatic disease (eg rifampicin and isoniazid for 3 months, or isoniazid alone for 6 months). Suitable patients for chemoprophylaxis include adults with documented recent tuberculin conversion, and some young immigrants (16-34yrs) who are Mantoux +ve, without prior BCG vaccination.[99]

▸Seek expert advice, or consult the latest British Thoracic Society guidelines (www.brit-thoracic.org.uk).

▸In all cases, standard anti-TB therapy should be initiated once any evidence of active disease (clinical or radiographic) is found.

Prophylaxis and dealing with latent TB

Primary prophylaxis against TB is indicated in some HIV +ve patients. In Africa, ~50% of those with HIV develop TB, and 80% with TB are HIV +ve. Isoniazid (eg 300mg/d PO; children 5mg/kg, max 300mg; give with pyridoxine) is the most often used. Duration of prophylaxis is debated; 9 months is probably correct for isoniazid,[100] lifelong prophylaxis is probably not helpful.[101] ▸Seek expert advice early. If prophylaxis is not used, monitor clinical state and CXR.

Indications for primary prophylaxis:

- If the patient has not had BCG and the Mantoux test is >5mm.
- If BCG vaccinated (>10yrs ago), consider prophylaxis if Mantoux >10mm.
- If there is recent exposure to someone with active TB.

TB meningitis (TBM)

▸Ask about recent contact with TB.

Prodrome

Fever, headache, vomiting, drowsiness, meningism, and delirium often worsening over 1-3 weeks (rarely many months) ± seizures.

CNS signs:

Tremor, papilloedema; cranial nerve palsies.

Diagnosis:

LP (p806—the 1st few LPs may be normal); TB PCR; Look for immunosuppression (HIV) and TB elsewhere (CXR etc). CT (obstructive hydrocephalus and basal enhancement). There may also be CNS tuberculomas.[102] △△: Pyogenic meningitis, histoplasmosis, glioma, CNS lymphoma, abscess, toxoplasmosis, neurocysticercosis, sarcoidosis, hydatid, and late syphilis.[103] [prescription take]: **Isoniazid** + **rifampicin** for 12 months, with

pyrazinamide and **streptomycin** during the 1st 2 months is often used (OTM). Ethambutol or ethionamide are alternatives to streptomycin. Add pyridoxine 25-50mg/24h PO to regimens using isoniazid to prevent neuropathies.[104] In adults, daily single doses of 300mg of isoniazid, 600mg of rifampicin, and 1500mg of pyrazinamide is adequate. Higher doses are unnecessary and can cause hepatotoxicity. Always check sensitivities of the causative organism, and discuss the chances of multi-drug resistant TB with a microbiologist. TBM with resistance to isoniazid and rifampicin is likely to be fatal.[105] There is a role for **dexamethasone** (eg for 1st month),[106] but tuberculomas may start to appear.[107] **Mannitol** for ICP↑ (p813).[108]

Complications:

Hydrocephalus (may need surgery).[109] Cognition↓. Salt wasting states (hyponatraemia with high urinary Na+ excretion and oddly high urine output even when dehydrated—it responds to fludrocortisone).[110]

Anti-TB drug use in liver and renal failure[111]

▸Monitor U&E +LFT before and after starting. In liver failure, get expert help. If creatine clearance=10-50mL/min: **Rifampicin**: ↓dose by 50%. **Ethambutol**: same dose every 36h (not /24h). No dose change for **ethionamide** or **isoniazid**.

Herpes virus infections

Herpes infections are like medical education: once you've had it, no one can ever take it away from you—and some people just can't help passing it on.

Herpes simplex virus (HSV)

Manifestations of primary infection:

1. ***Genital herpes:*** HSV I or II (I is now overtaking II). Flu-like prodrome, then grouped vesicles/papules develop around genitals, anus, or throat. These burst forming shallow ulcers (heal in ~3wks). Also: urethral discharge ± dysuria (esp if ♀); urinary retention. OHCS p268. ***Tests:*** PCR. **[prescription take]:** Give analgesia + famciclovir 250mg/8h (500mg if immunocompromise) PO for 5 days (recurrences: eg 1g/12h, 2 doses only, self-initiated[1]).[] If frequent (≥6/yr) or severe recurrences, continuous aciclovir ≤400mg/12h PO. *Prevention:* Condoms—even for oral sex.
2. ***Gingivostomatitis:*** Ulcers filled with yellow slough appear in the mouth.
3. ***Herpetic whitlow:*** Abrasions allow virus to enter the finger, causing a vesicle.
4. ***Herpes gladiatorum:*** Vesicles wherever HSV is ground into the skin by force.
5. ***Eczema herpeticum:*** HSV infection of eczematous skin; usually children.
6. ***Herpes simplex meningitis:*** This is uncommon and usually self-limiting (typically HSV II in women during a primary attack).
7. **HSV *keratitis:*** Corneal dendritic ulcers. *Avoid steroids*. See OHCS p416.
8. ***Systemic infection*** eg fever, sore throat, and lymphadenopathy may pass unnoticed. If immunocompromised, it may be life-threatening with fever, lymphadenopathy, pneumonitis, and hepatitis.
9. ***Herpes simplex encephalitis:*** Usually HSV I. Spreads centripetally, eg from cranial nerve ganglia, to frontal and temporal lobes. ▸*Suspect if* fever, fits, headaches, odd behaviour, dysphasia, hemiparesis, or coma or brainstem encephalitis, meningitis, or myelitis. △: Urgent PCR on CSF (CT/MRI or EEG may show temporal lobe changes but are non-specific and unreliable; brain biopsy rarely required). Seek expert help: careful fluid balance to minimize cerebral oedema, p812; ▸▸*prompt* aciclovir, eg 10mg/kg/8h IV for ≥10d, saves lives. Mortality: 19%.

Tests:

Rising antibody titres in 1° infection; culture; PCR for fast diagnosis.

Recurrent HSV:

Dormant HSV in ganglion cells may be reactivated by illness, immunosuppression, menstruation, or sunlight. Cold sores (perioral vesicles) are one manifestation. Aciclovir cream may be disappointing.

Varicella zoster

Varicella (=**chickenpox**) is a contagious febrile illness with crops of blisters of different ages starting on the back. Complications, eg purpura fulminans/DIC (get help; ▸▸may need heparin[112]), pneumonitis, and ataxia are commoner in pregnancy and adults than in children.[113] *Incubation:* 11-21d. *Infectivity:* 4d before the rash until all lesions are scabbed (~1 week). OHCS p144. After infection, virus is dormant in dorsal root ganglia. Reactivation causes **shingles** (affects 20% at some time; esp. if old or immunosuppressed). Pain in dermatomal distribution precedes malaise and fever by some days. See p446.

Shingles [prescription take]:

Most will want antivirals (hoping to ↓risk of post-herpetic neuralgia); if seen early, give aciclovir eg 800mg 5 times a day PO for 5-7d. If immunocompromised, give 10mg/kg/8h slowly IVI for 10d. Alternatives: valaciclovir; famciclovir (more expensive; fewer SEs). Paracetamol ± amitriptyline (start with 10mg at night) for pain. If the conjunctiva is affected, apply 3% aciclovir ointment 5 times a day. Beware iritis. Measure acuity often. Say to report *any* visual loss at once. SE of aciclovir: renal impairment (check U&E) vomiting, urticaria, encephalopathy. ***Post-herpetic neuralgia*** in affected dermatomes can last years, and is hard to treat, and intolerable. Try amitriptyline or gabapentin (±carbamazepine, phenytoin, topical capsaicin counter-irritant); last resort: ablation of the ganglion; refer to a pain clinic.

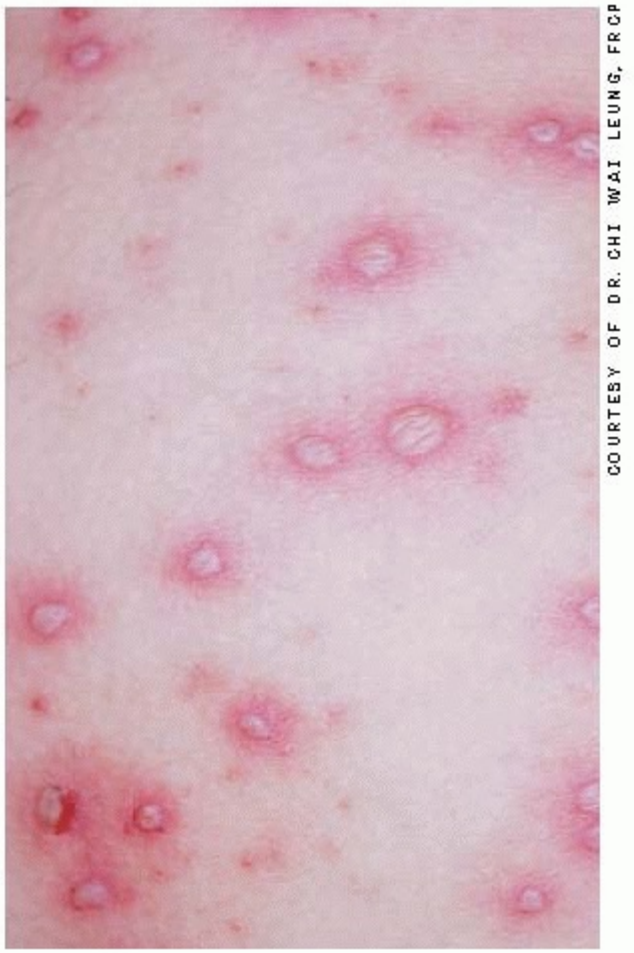


Fig 1. Chickenpox close-up.

Infectious mononucleosis (glandular fever)

This is a common disease in the young which may be unnoticed or cause acute illness. Spread: saliva or droplet (presumed). Incubation 4-5wks. Cause: Epstein-Barr virus (EBV, a DNA herpesvirus) infection of B-lymphocytes, causing proliferation of T-cells ('atypical' mononuclear cells) which are cytotoxic to EBV-infected cells. The latter are 'immortalized' by EBV infection and can, very rarely, proliferate in a way indistinguishable from immunoblastic lymphoma in immunodeficient individuals (whose suppressor T-cells fail to check multiplication of these B-cells).

The Patient

Sore throat, T°↑, anorexia, malaise, lymphadenopathy, palatal petechiae, splenomegaly, hepatitis, haemolysis.

Complications—CNS:

•Meningitis •Encephalitis •Ataxia[114] •Cranial nerve lesions (eg VII, bilateral in 40%[115]) ± Guillain-Barré syndrome •Neuropathy •Depression/fatigue for a few for months, depending in part on features present at onset (eg less fit pre-morbidly, no delay in Monospot® becoming +ve, and need for rest bed-rest—as determined by the patient).[116] Fatigue is also part of 'severe chronic active EBV infection', eg with anaemia, platelets↓ and severe hepatosplenomegaly.[117]

Others:

Thrombocytopenia (±pancytopenia with a megaloblastic marrow),[118] ruptured spleen, splenic haemorrhage, upper airways obstruction (may need observation on ITU), hepatitis (± fulminant hepatic failure[119]), secondary infection, myo- or pericarditis, pneumonitis/fibrosis[120], renal failure, autoimmune haemolysis, and erythema multiforme. All are rare (or very rare).

Blood film

shows a lymphocytosis (eg 20% of WBC) and atypical lymphocytes (large, irregular nuclei, **fig 1**). These may occur in many viral infections (CMV, HIV, parvovirus, dengue), toxoplasmosis, typhus,[122] leukaemia, lymphoma, drug hypersensitivity, and lead poisoning.

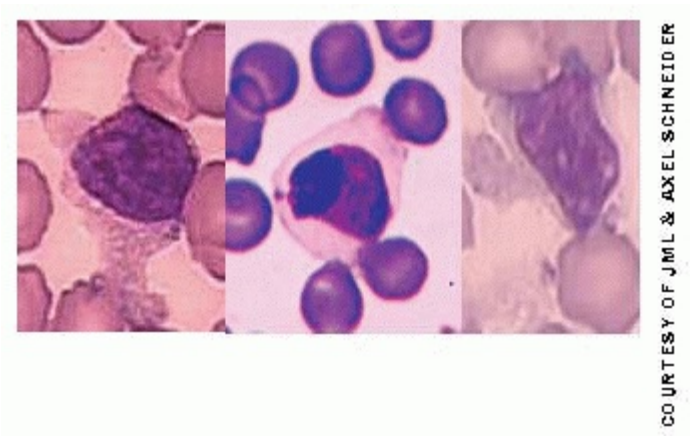


Fig 1. Atypical lymphocytes flowing around RBCs; dark cytoplasm at contact points.[121]

Heterophil antibody tests

(Monospot®; Paul-Bunnell): Heterophil antibodies develop in 90% of patients by week 3, disappearing after ~3 months (≲1yr).[123] They agglutinate sheep RBCs and can be absorbed (and thus agglutination is prevented) by ox RBCs, but not guinea-pig kidney cells. This pattern distinguishes them from other heterophil antibodies. These antibodies do not react with EBV or its antigens.

False +ve

Monospot® tests may occur in hepatitis, parvovirus infection, lymphoma, leukaemia, rubella, malaria, carcinoma of pancreas, and SLE.[124]

Other false trails:

Older patients may have little pharyngitis or adenopathy, but fever & LFT↑ are more prolonged, often with no telltale lymphocytosis or atypical lymphocytes.[125] So, if Monospot -ve, they may be subjected to dangerous over-investigation unless you request EBV-specific IgM—implies current infection (IgG reflects past infection). PCR may reveal ↑↑serum EBV DNA levels and warn of fulminant infection.[126]

Differential diagnosis

Streptococcal sore throat (may coexist), CMV, viral hepatitis, HIV seroconversion illness, toxoplasmosis, leukaemia, diphtheria.

Treatment

Avoiding alcohol 'to protect the liver' is traditional, but we can find no evidence to support this ban. Prednisolone PO is recommended (rarely) for severe symptoms or complications such as severe thrombocytopenia[127] (eg 60mg on day 1, tapering quickly); its use is non-standard. *Never give ampicillin or amoxicillin for sore throats as they often cause a severe rash in those with acute* EBV *infection.*

EBV oncogenicity

Lymphoma[128] (eg post-transplant);[129] **nasopharyngeal cancer** (esp. in Asia), **leiomyosarcoma**[130] and **oral hairy leucoplakia** (p230; aciclovir-responsive).

Other EBV-associated diseases

Crescentic glomerulonephritis;[131] **haemophagocytic syndrome** (EBV over-activates T-cells & macrophages, with overproduction of cytokines, eg causing fatal coagulopathy[132] ± central pontine myelinolysis).[133] The EBV **Gianotti-Crosti rash** (self-limiting papular acrodermatitis of childhood) consists in pale or red monomorphous 1-10mm papules and plaques placed symmetrically over extensor faces of limbs, buttocks, and face (also caused by streps, hepatitis B, HIV, echo, coxsackie, and respiratory syncitial viruses).

forlag.fadl.dk/sample/derma/images/447.htm

Influenza

This is the most important viral respiratory infection because of its frequency and complication rate, particularly in the elderly. In pandemics (1918, 1957 & 1968), millions die, particularly when new strains evolve (see BOX). WHO classification specifies: type/host origin/geographic origin/strain no./year of isolation/subtype, eg A/Swine/Taiwan/2/87/ (H3, N2)—see **fig 1**. **Spread** is by droplets. **Incubation period** 1-4 days. **Infectivity** 1 day before to 7 days after symptoms start.

Immunity

Those attacked by one strain are immune to that strain only.

Symptoms

Fever, headache, malaise, myalgia, prostration, nausea, vomiting, conjunctivitis/eye pain (even photophobia). Also depression.

Tests

Serology

(paired sera; takes >2wks).

Culture

(1wk, from nasopharyngeal swabs).

PCR:

(eg 36h; sensitivity 94.2%; specificity ~100%).[134]

Complications

Bronchitis (20%[135], pneumonia (esp. *Staph. aureus*), sinusitis, otitis media, encephalitis, pericarditis, Reye's syndrome (coma, LFT↑).

[prescription take] Bed rest ± aspirin. If severe pneumonia, take to ITU to prevent hypoxia and shock (cover *strep pneumoniae* and resistant staphs, eg **ciprofloxacin** & **co-amoxiclav**).[136]

Antivirals:

Zanamivir (**Relenza®**, an inhaled neuraminidase inhibitor) shortens attacks by ~36h; it is active against influenza types A and B. It is not a panacea; consider if complications would be bad (cardiovascular or chronic respiratory, renal disease; DM; immunosuppression; ≳65yrs old: see www.nice.org.uk). Dose: 2 blisters (2×5mg)/12h for 5d (before any other inhalers); start only if within 48h of symptom onset. **NB:** Inhalation is not an ideal route, eg if elderly. SE: bronchospasm; oropharyngeal oedema.[137] *Ensure your patient knows how to use the diskhaler*.

Oseltamivir (***Tamiflu®***) eg 75mg/12h PO for 5d is an alternative (if >13yrs old). **SE**: D&V, dyspepsia, headache, insomnia, dizziness, conjunctivitis, epistaxis, rash; rarely hepatitis, Stevens-Johnson, p703 ± ?flawed reports of hallucinations in children.[138]

M2 ion channel blockers (amantadine, rimantadine) are of low efficacy: don't use in seasonal flu in healthy people.[139]

SE:

Hallucinations. Use in pandemics is unclear.

Prevention

•Use whole ***trivalent vaccine*** (from inactivated viruses), reserving split (fragmented virus) for those <13yrs old. It is prepared from current serotypes and takes <2wks to work.

Indications:

Diabetes; COPD; asthma (not if mild), heart, renal or liver failure; immunosuppression (eg splenectomy or on steroids); haemoglobinopathies, medical staff; those ≳65yrs old and their carers, especially in institutions.[140] The logistics of vaccinating all those in the at-risk groups pose a challenge in ageing populations. In addition, *routine* vaccination of children may be worthwhile (might save ~100 deaths/yr).

Dose:

0.5mL sc (once). In children repeat after 6wks (½ dose if <3yrs old).

SE:

Mild pain or swelling (17%). T°↑, headaches, and malaise are in ≲10%. Guillain-Barré and pericarditis are rare. *Vaccine efficacy* is 'modest' (eg relative risk of pneumonia falls from 1 to 0.88 after vaccination for the elderly living in the community; all cause mortality *is* slightly reduced).[141]

•***Oseltamivir*** Only use as **prophylaxis** after formal notice that influenza A or B is circulating ***and*** >1yrs old ***and*** <48h since exposure ***and*** in at-risk group, above. It is ***not*** needed if vaccinated >2wks ago with a well-matched vaccine ***unless*** living in a rest- or nursing-home *et al* when it can be used ***whatever*** the vaccination status.[142] Dose: 75mg/d (if 24-40kg, 60mg/d; 16-23kg, 45mg/d)—all for ≥10d. (If not in an at-risk group, UK guidelines allow us to give private prescriptions for prophylaxis.)

The common cold (coryza)

Rhinoviruses are the main culprits (>80 strains), and cause a self-limiting nasal discharge (which becomes mucopurulent over a few days).

Incubation:

1-4d.

Complications:

(6% in children) Otitis media, pneumonia, febrile convulsions.

[prescription take]: None is usually needed. If nasal obstruction in infants hampers feeding, try 0.9% saline nose drops. Zinc gluconate yields conflicting results in trials.[143] [RCT][144]

The ART of making and breaking new pandemics

When an animal source of virus couples with human virus (reassortment[1]) to form a novel hybrid with efficient replication and person-to-person transmission —a pandemic is born. Millions of deaths occur if the human population is naive (no previous immunological exposure) and the new strain is highly pathogenic. What can we do? The first clusters may be containable, but once transmission is established, quarantine is probably futile and the pandemic will become global.[1] Nevertheless some strategic planning is possible:

- Buy time during spreading epidemics by moving free range chickens in-doors. (this was done in 2005-6, eg in Holland, to slow spread of H5N1 avian 'flu).
- Quarantine restrictions around clusters of animal infections, eg a 3km zone where entry and exit are banned, with movements restricted in a further 10km monitoring zone with checking of residents, and their birds destroyed.[145]
- Stock-pile vaccine (if it can be made in time), antivirals, and vital supplies. Masks are recommended by WHO when health workers are within 1 metre of a probably-infected person (eg on entering a room with such patients).[146]
- Seamless international co-operation with WHO and bodies such as the European Centre for Disease Prevention—eg to cancel mass events.
- Self-isolation at the 1st sign of human illness—and improved personal hygiene.
- Simulated exercises before the event to enhance preparedness.

Prevention, containment, health systems response, and communications

This 4-part response to flu pandemics depends on how far we have progressed down the pandemic path. Preceding any pandemic there is an ***interpandemic period*** (no new subtypes in humans but circulating animal virus may pose a risk) and then a ***pandemic alert period***. 2006, for example, began with the *first phase* of the pandemic alert period, characterized by 'human infections with a new subtype, [with] rare instances of spread to a close contact'. The next phase is 'small clusters of highly localized spread' (virus isn't well adapted to humans). The last phase before any ***pandemic phase*** of sustained transmission is one of large clusters of human-to-human spread, with full transmissibility less developed.

Orthomyxoviridae[RNA] divide into 2 genera: influenza A and B viruses—and influenza C, distinguishable by antigenic differences between their nucleoproteins (NP) and matrix (M) proteins. Influenza B & C are almost exclusively isolated from man (rarely pigs & seals). Influenza A infects many birds and mammals; they are subtyped by surface glycoproteins (haemagglutinin, HA) and neuraminidase (NA). So far, 15 different HAs (H1 to 15) and 9 NAs (N1 to 9) have been found among all influenza viruses.[147]

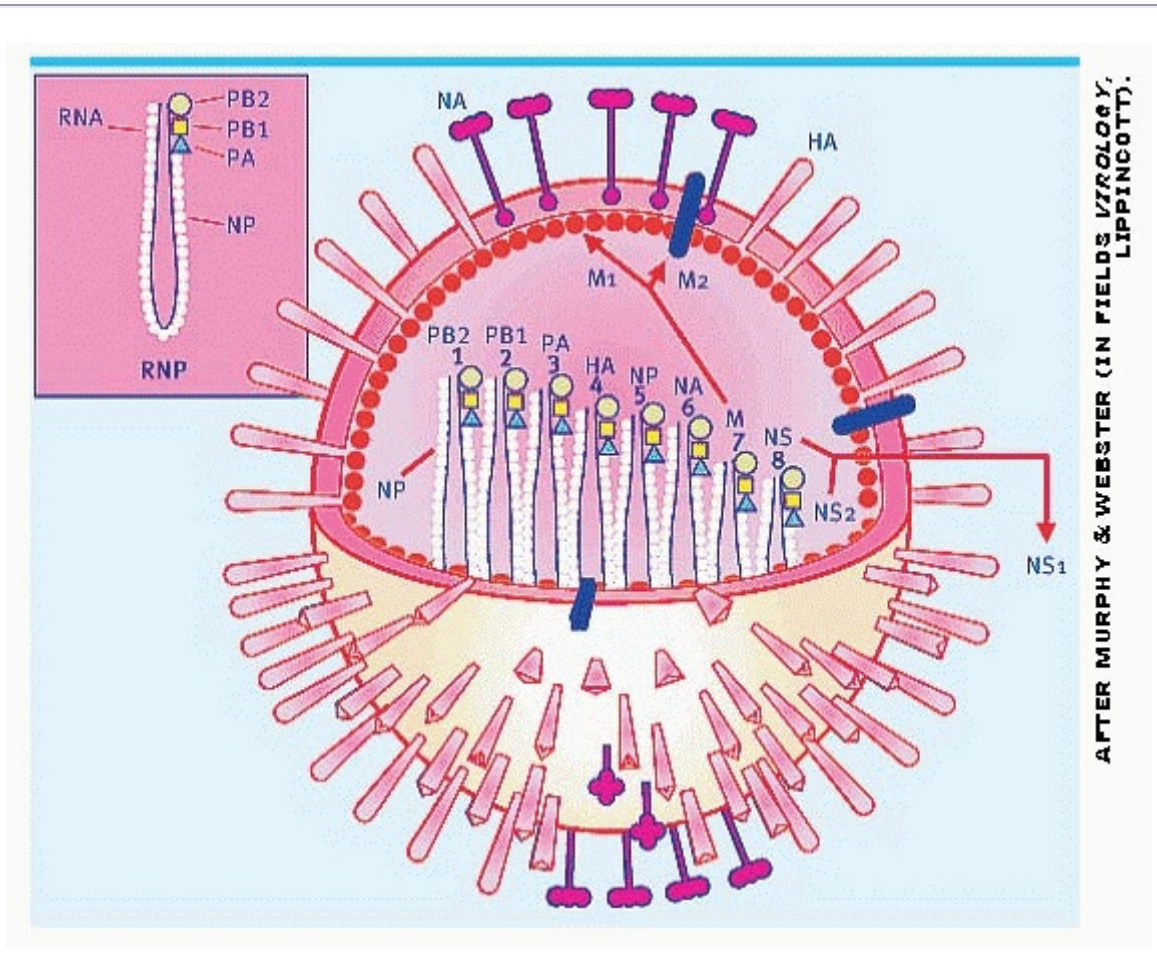


Fig 1. Influenza **A.**

Toxoplasmosis

The protozoan *Toxoplasma gondii* infects via gut (poorly-cooked meat), lung, or broken skin. Life-cycle: **fig 1**. In humans, the oocysts release trophozoites, which migrate widely, with a predeliction for eye, brain, and muscle. Toxoplasmosis occurs worldwide, but is common in the tropics. Infection is lifelong. HIV may reactivate it.

The Patient

▸*In any granulomatous uveitis or necrotizing retinitis, think of toxoplasmosis, especially in the immunosuppressed.* Most infections are asymptomatic: in the UK 50% have been infected by 70yrs. Symptomatic acquired toxoplasmosis resembles infectious mononucleosis, and is usually self-limiting. Eye infection, usually congenital, presents with posterior uveitis, often in the 2nd decade of life, and may cause cataract. In the immunocompromised (eg AIDS), myocarditis, encephalitis, focal neurological signs, stroke or fits may occur.

Tests

Acute infection is confirmed by a 4-fold rise in antibody titre over 4wks or specific IgM (unreliable if HIV+ve). Reactivation of latent toxoplasmosis in HIV presents problems (you may need to look for toxoplasma antigen and IgG).[148] PCR may be rewarding.[149] Parasite isolation is difficult; lymph node or CNS biopsy may be diagnostic. CT: characteristic multiple ring-shaped contrast-enhancing CNS lesions.

Treatment

Often none is needed: seek expert advice.[150] If the eye is involved, or in the immunocompromised, pyrimethamine 200mg PO on day one then 75mg/d PO for 4wks, + sulfadiazine ≤1g/6h PO *may* be needed. SE: renal stones. Folinic acid 10-20mg/d until 4wks after resolution. ▸If pregnant, get expert help. Sampling of fetal cord blood, eg at 21wks for IgM indicates severe infection. For HIV: p396.

Congenital toxoplasmosis

(OHCS p34) May cause abortion, neonatal seizures, choroidoretinitis, (**fig 2**), hydrocephalus, microcephaly, or cerebral calcification. Worse prognosis if early infection.

Cytomegalovirus (CMV)

CMV may be acquired by direct contact, blood transfusion, or organ transplantation. After acute infection, CMV becomes latent but the infection may reactivate at times of stress or immunocompromise. If immunocompetent, primary infection is usually asymptomatic, but acute hepatitis may occur. In transplant recipients or post marrow transplantation: fever > pneumonitis > colitis > hepatitis > retinitis. In AIDS: retinitis > colitis > CNS disease. (> = 'is commoner than')

Diagnosis

of acute CMV infection is difficult; virus growth is slow and there may be prolonged CMV excretion from a distant source of infection. Serology is good; specific IgM indicates acute infection (unreliable if HIV +ve). CMV PCR (including quantitative tests) of blood/CSF/broncho-alveolar lavage is available.

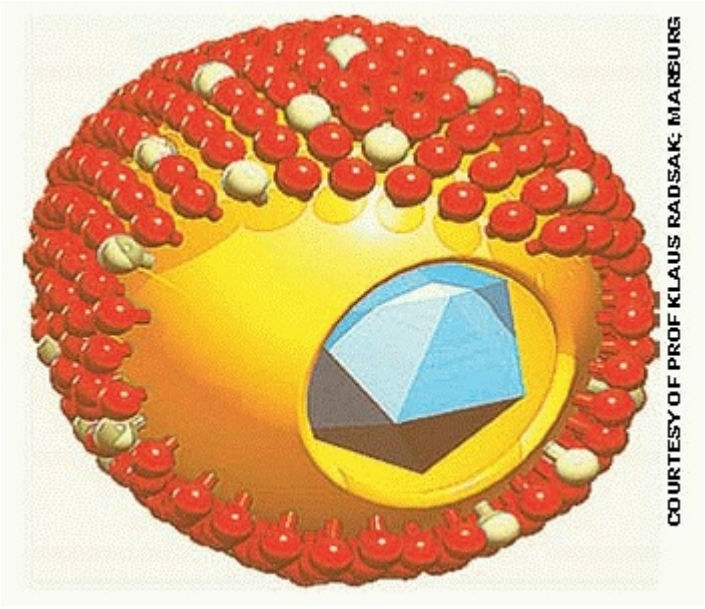


Fig 1. CMV.

Treat

only if serious infection (eg immunocompromised), with ganciclovir 5mg/kg/12h IVI over 1h via a central line. Alternatives: oral valganciclovir, foscarnet. Immunization is being explored. For CMV in HIV, see p398.

Prevention post-transplantation[151]

If seropositive pre-op, ganciclovir, eg 2.5mg/kg/d IV for the first 2 post-op weeks. If sero-ve pre-op, valaciclovir 2g/6h PO for 90d reduces incidence and delays onset of CMV disease.[152] Use CMV-ve, irradiated blood when transfusing transplant recipients, leukaemics, or HIV patients.

Congenital CMV

(OHCS p34) Look for: jaundice, hepatosplenomegaly, and purpura. Chronic defects include mental retardation, cerebral palsy, epilepsy, deafness, and eye problems. Treatment: none is established.

Complications

GU CMV reactivation in HIV +ve men leads to ↑ semen levels of HIV.[1]

***T. gondii:* a subtle parasite**

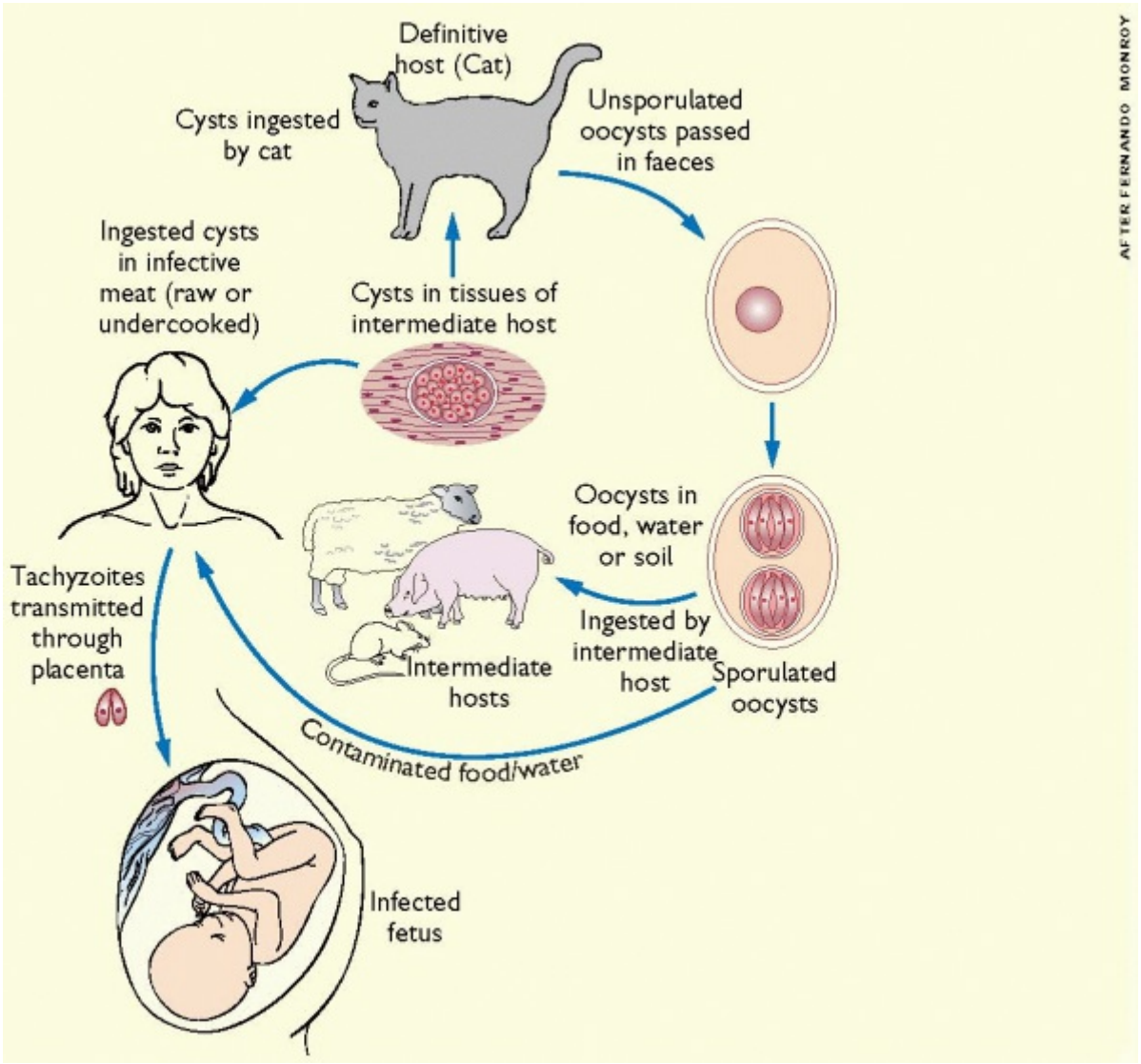


Fig 1. Oocysts in cat faeces can stay in the soil for months, where animals such as rats eat them. They get infected, and, under the direction of *Toxoplasma* in the amygdala, these rats lose their innate fear of cats, and so tend to get eaten. So parasites ensure their success by facilitating their jump from the intermediate to the definitive host.[153]

Humans with toxoplasmosis may show these features

- Confusion, seizures, and signs of brainstem or spinal cord injury.
- *A latent* phase of toxoplasmosis is recognized, as is subtle personality change. Loss of fear of cats is *not* reported in us, but there are changes in

willingness to accept group moral standards, in proportion to the latent period's length.[154]

- Meningoencephalitis + localizing signs (fever + headache → drowsiness → coma → death, eg over a days or weeks). CSF: mild lymphocytic pleocytosis & protein ↑.
- Multifocal myelin loss, and microglial nodules.
- *Pseudotumour cerebri* syndrome: transient intracranial hypertension.
- Space-occupying mass with ICP↑ mimicking a tumour or a brain abscess.
- Multiple mass lesions that can be the cause of hemisensory abnormalities, hemiparesis, cranial nerve palsy, aphasia, and tremors.

In some areas, eg India, toxoplasmosis is the major HIV-associated CNS infection.[155]

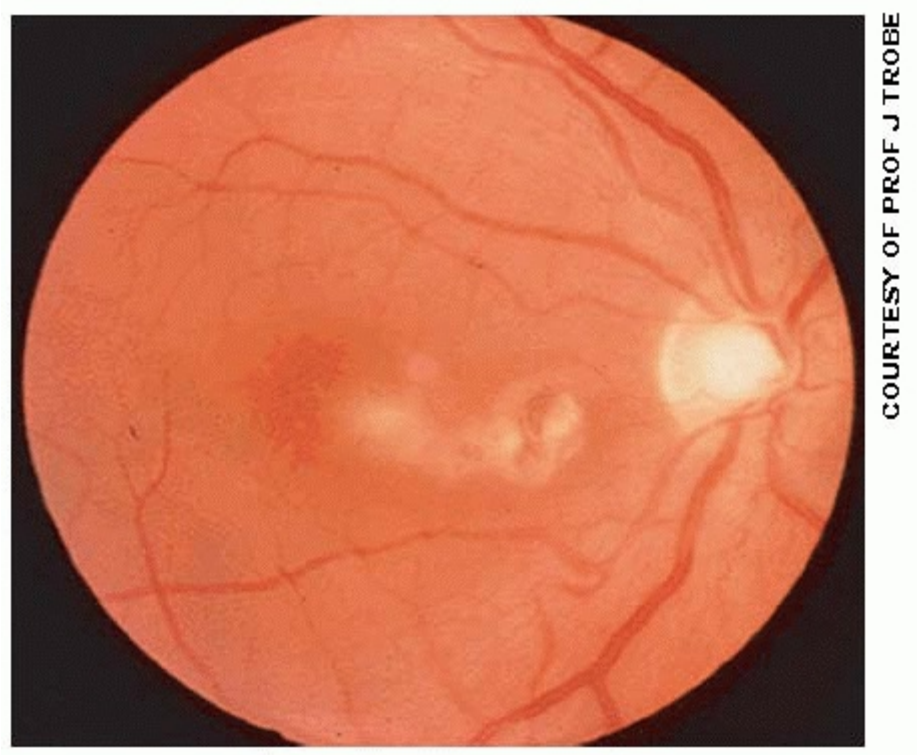


Fig 2. Retinal toxoplasmosis.[158]

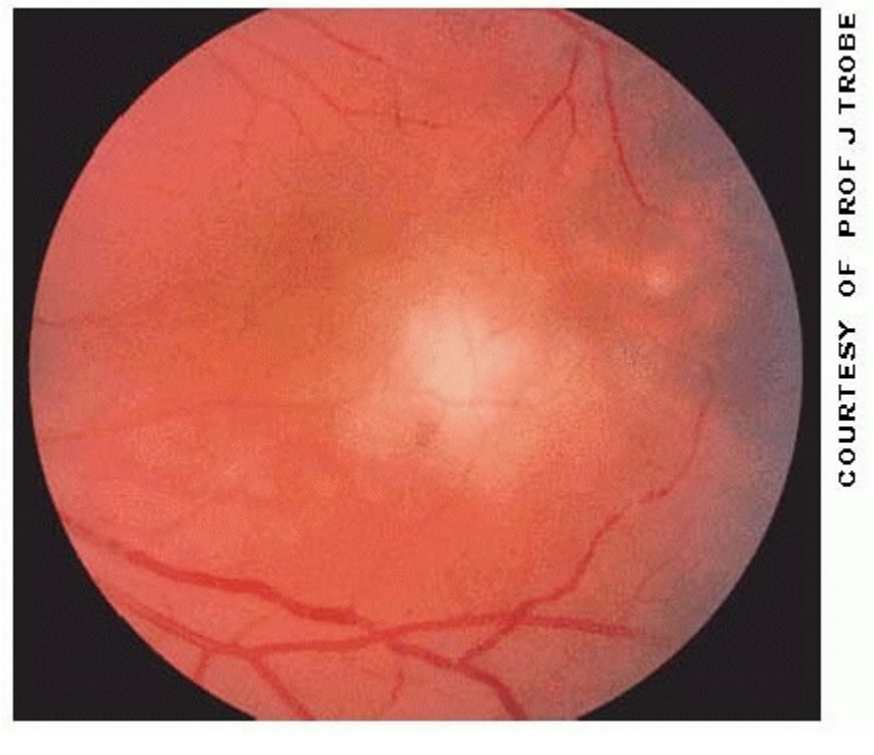


Fig 3. Ill-defined yellow infiltrates. △△: toxoplasmosis; herpes simplex/zoster; syphilis; sarcoidosis; leukaemia.[156]

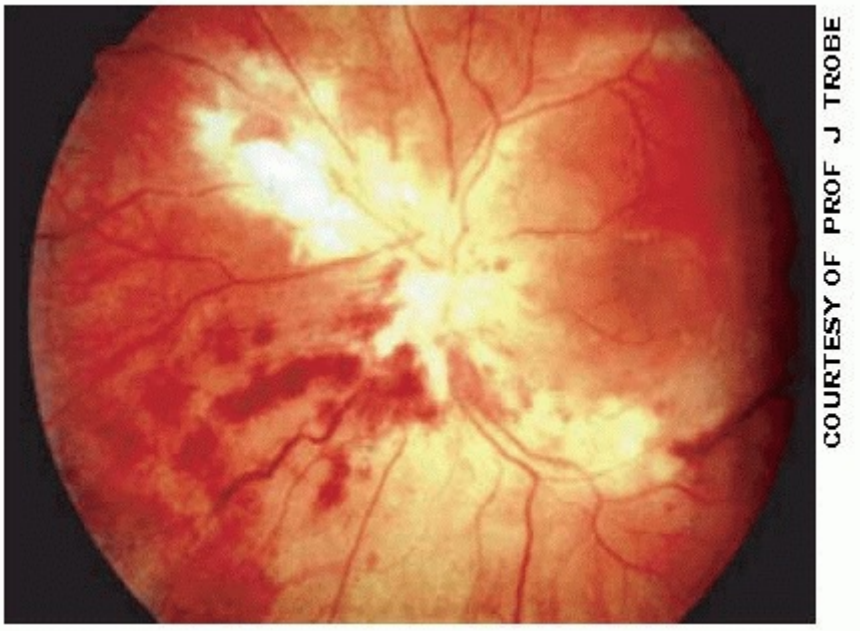


Fig 4. In HIV this 'pizza-pie' fundus means CMV retinitis. If CD4↓↓, re-examine in 2 days; ▸is it progressing?[157]

Viral hepatitis

Hepatitis A virus (HAV)

RNA virus.

Spread:

Faecal-oral, often in travellers or institutions. Most infections occur in childhood.

Incubation:

2-6wks.

Symptoms:

Prodromal symptoms include fever, malaise, anorexia, nausea, arthralgia. Jaundice develops ± hepatomegaly, splenomegaly, and adenopathy.

Tests:

Serum transaminases rise 22-40d after exposure. IgM rises from day 25 and signifies recent infection. IgG remains detectable for life.

Treatment:

Supportive. Avoid alcohol. Rarely, interferon-α for fulminant hepatitis.

Prevention:

Passive immunization with normal human immunoglobulin (0.02mL/kg IM) gives <3 months' immunity to those at risk (travellers, household contacts). Active immunization is with Havrix Monodose®, an inactivated protein derived from HAV.

Dose:

if >16yrs old, 1 IM dose (1mL to deltoid) gives immunity for 1yr (10yrs if further booster is given at 6 months). Use Havrix Monodose Junior® if 1-15yrs old.

Prognosis:

Usually self-limiting. Fulminant hepatitis occurs rarely. Chronic liver disease does not occur.

Hepatitis B virus

(HBV, a DNA virus.)

Spread:

Blood products, IV drug abusers (IVDU), sexual intercourse, direct contact.

Risk groups:

IVDU & their sexual partners; health workers; haemophiliacs and their carers (exposure to blood products—also morticians/embalmers); haemodialysis (and chronic renal failure); the sexually promiscuous; foster carers; close family members of a carrier or case; staff or residents of day care or longterm institutions/prisons; babies of HBsAg +ve mothers; adopted child from endemic area.

Endemic in:

Far East, Africa & Mediterranean.

Incubation:

1-6 months.

Signs:

Resemble hepatitis A but extrahepatic features are more common, eg arthralgia, urticaria.

Tests:

HBsAg (surface antigen) is present from 1 to 6 months after exposure. HBeAg (e antigen) is present for 1½-3 months after the acute illness and implies high infectivity. The persistence of HBsAg for >6 months defines carrier status and occurs in 5-10% of infections (chronic infection). Antibodies to HBcAg (anti-HBc) imply past infection; antibodies to HBsAg (anti-HBs) alone implies vaccination. HBV PCR allows monitoring of response to therapy.

Vaccination

(▸p263) may be universal in childhood or just for high-risk groups. Passive immunization (specific anti-HBV immunoglobulin) may be given to non-immune contacts after high-risk exposure.

Treatment:

Supportive. Avoid alcohol. Chronic HBV may respond to interferon-× or other antivirals, eg lamivudine, adefovir.[159] Immunize sexual contacts.

Complications:

Fulminant hepatic failure (rare); relapse; prolonged cholestasis; chronic hepatitis (5-10%); cirrhosis; hepatocellular carcinoma (HCC: 10-fold ↑risk if HBsAg +ve, 60-fold ↑risk if both HBsAg and HBeAg +ve);[160] glomerulonephritis; cryoglobulinaemia.

Hepatitis C virus (HCV)

RNA flavivirus.

Spread:

Blood, IVDU, sexual, acupuncture.[1] UK prevalence: 200,000-466,000.[161] Early infection is often mild/asymptomatic. ~85% develop chronic infection; 20-30% get cirrhosis within 20yrs; a few get hepatocellular cancer (HCC).

Tests:

LFT (AST: ALT <1:1 until cirrhosis develops, p274), anti-HCV antibodies, recombinant immunoblot assay, HCV-PCR; liver biopsy if HCV-PCR +ve to assess liver damage and need for [prescription take]. Do HCV genotype (BOX).

Drugs:

Interferon-α + ribavirin in chronic infection; peginterferon-α is better than IFN-α.[162] IFN-α in acute infection may ↓ progression to chronic disease.[163]

Hepatitis D virus (HDV)

Incomplete RNA virus, exists only with HBV.

Spread:

Coinfection or superinfection with HBV.

Clinical features:

Increased risk of acute hepatic failure and cirrhosis.

Tests:

Anti-HDV antibody.

Treatment:

Interferon-α has limited success in treatment of HDV infection.

Hepatitis E virus (HEV)

RNA virus. Similar to HAV. Common in India. High mortality in pregnancy.

Diagnosis:

Serology. No effective treatment/vaccine.

Hepatitis GB

Parenterally transmitted. Causes asymptomatic post-transfusion hepatitis. One type (HGB-C) can cause fulminant liver failure.

△△ Alcohol; drugs; toxins; EBV/CMV; leptospirosis; malaria; Q fever; syphilis; yellow fever, chronic hepatitis (eg alcohol; drugs; autoimmune hepatitis, p260; Wilson's, p257).

Serological markers of HBV infection

	Incubation	Acute	Carrier	Recovery	Vaccinated
LFTs		↑↑↑	↑	Normal	Normal
HbsAg	+	+	+		
HbeAg	+	+	+/-		
Anti-HBs				+	+
Anti-Hbe			+/-		
Anti-HBc IgM		+	+/-		

Anti-HBC IgG		+	+	+	

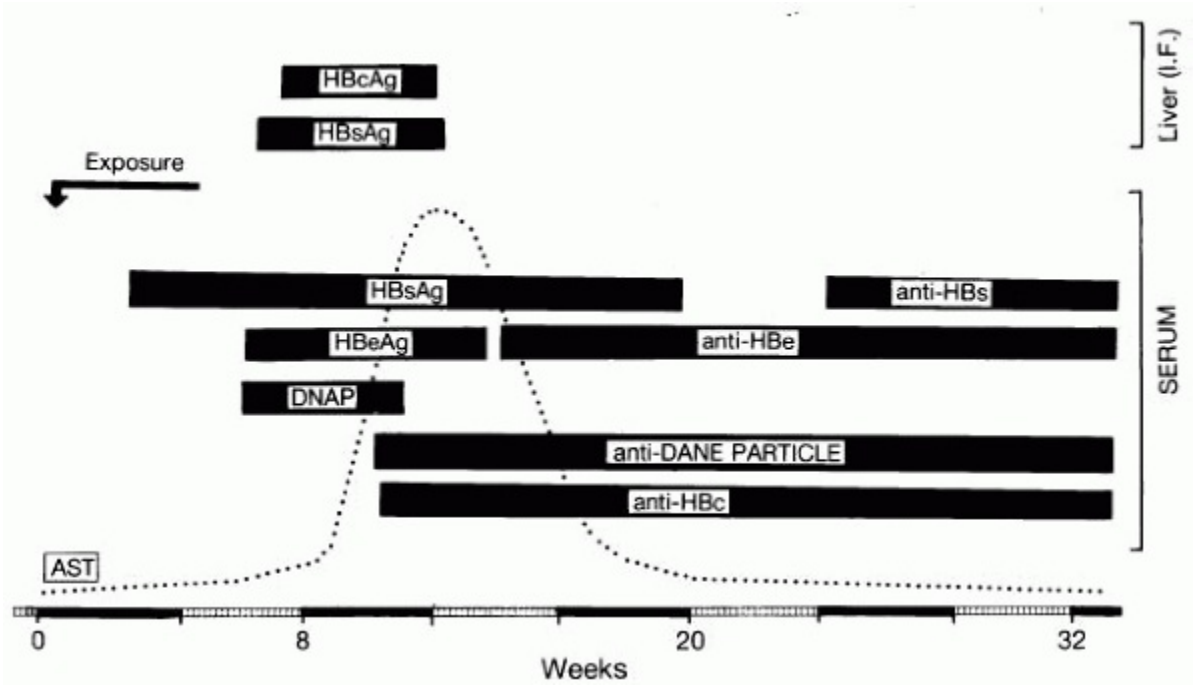


Fig 1. Virological events in acute hepatitis B in relation to serum aminotransferase (AST) peak. IF=immunofluorescence; Ag=antigen; HBS=hepatitis B surface; HBc=hepatitis B core; HBe=hepatitis B e antigen; DNAP=DNA polymerase.

Using ribavirin with peginterferon-× in HCV: *NICE* advice

This combination is indicated in moderate and severe chronic hepatitis C infection if liver biopsy shows necro-inflammation and fibrosis. Efficacy is less if: •HCV genotype G1, 4, 5, or 6 is involved[1] •↑Viral load •Older patients •Excessive delay before [prescription take] starts •Blacks (*vs* Caucasians) •Males •HIV+ve.

NB: Pegylated interferon has an inert tail retarding its elimination (hence it may be given SC once weekly). Giving these drugs is a specialist role, so the main thing is for non-specialists is to know the contraindications, to prevent inappropriate referral. **CI:** •Allergy to or past use of interferon •Autoimmune hepatitis •Severe liver dysfunction or decompensated cirrhosis •Age <3yrs •Severe, unstable or uncontrolled heart disease in past 6 months •Past severe psychiatric conditions (esp. depression) •Pregnancy/lactation •Haemoglobinopathies (a contra-indication to ribavirin).

HIV and hepatitis C

HCV prevalence is ~7% for sexually transmitted HIV and >90% for IV drug abuse transmission. Untreated HIV seems to accelerate the progression of HCV-induced liver fibrosis. Given the safety and efficacy of co-therapy with peginterferon + ribavirin and the bad effects of chronic hepatitis C, all HIV/HCV co-infected patients should be evaluated for therapy.[164]

Human immunodeficiency virus (HIV)

Over 40 million people are HIV +ve (5 million/yr; 3 million deaths/yr); over half are in Africa and there is markedly increasing transmission in eastern Europe. HIV-1 (a retrovirus) is responsible for most cases worldwide. HIV-2, a related virus, causes a similar illness, perhaps with a longer latent period. >3 million have acquired immunodeficiency syndrome (AIDS); most are women and children in Africa. Not all the news in Africa is bad: prevalence is falling in Kenya, for example (prevalence falling from 10% in the 1990s to 7% now).[165] UK *incidence:* >7250/yr—more heterosexually acquired than homosexually since 1999.[166]

Transmission

Sexual (75%, oral, in 3-7%[167][168]), infected blood, IV drug abuse or perinatally (vertical transmission causes ~600,000 child deaths/yr: see OHCS p34).

Immunology

HIV binds, via its gp120 envelope glycoprotein, to CD4 receptors on helper T-lymphocytes, monocytes, macrophages, and neural cells. CD4 +ve cells migrate to the lymphoid tissue where the virus replicates producing billions of new virions. These are released, and in turn infect new CD4 +ve cells. As infection progresses depletion or impaired function of CD4 +ve cells ↓immune dysfunction.

Virology

(RNA retrovirus). After entry into the cell, the viral reverse *transcriptase* enzyme makes a DNA copy of the RNA genome. The viral *integrase* enzyme then integrates this into the host DNA. The core viral proteins are initially synthesized as large polypeptides that are cleaved by the viral *protease* enzyme into the enzymes and building blocks of the virus. The completed virions are then released by budding. The number of circulating viruses (viral load) predicts progression to AIDS.

Stages of HIV infection

Acute infection

is often asymptomatic. ***Seroconversion*** may be accompanied by a transient illness 2-6wks after exposure: fever, malaise, myalgia, pharyngitis, maculopapular rash or meningoencephalitis (rare). A period of ***asymptomatic infection*** follows although 30% of patients will have ***persistent generalized lymphadenopathy (PGL)***, defined as nodes >1cm diameter at ≥2 extrainguinal sites, persisting for 3 months or longer. Later, constitutional symptoms develop: T°↑, night sweats, diarrhoea, weight↓, ± minor opportunistic infections, eg oral candida, oral hairy leucoplakia, herpes zoster, recurrent herpes simplex, seborrhoeic dermatitis, tinea infections. This collection of symptoms and signs is referred to as the **AIDS-*related complex (ARC)*** and is regarded as a prodrome to AIDS. **AIDS** is a stage in HIV infection characterized by the presence of an indicator disease (p398). CD4 count is usually <200 × 10^6/L (prognosis ~2yrs if untreated).

Diagnosis

Look for anti-HIV antibodies in serum. Acute infection is detectable by finding P24 antigen or HIV RNA by PCR and precedes the appearance of IgM and IgG (within 3 months). During the asymptomatic period, there are high titres of IgG to core and envelope proteins. As immunodeficiency develops, IgG titre to core protein falls, and P24 antigenaemia recurs. Rapid diagnostic kits for detecting anti-HIV antibodies are available.[169] The OraQuick® test uses oral fluid, and may be bought over the counter in some places; but false +ves are a problem.[170] **HIV *subtypes*** A & B predominate in the UK; type D (commoner in Africa)[171] & hybrid/recombinant strains carry a worse prognosis as they bind to immune cells more readily.

Prevention

Blood screening; **disposable equipment**; **perinatal antiretrovirals** for HIV+ve mothers ± **Caesarean birth ± bottle-feeding** (may ↓mortality if hygiene poor).

▸*A 'stop-HIV' sexual manifesto:*

Accurate *accessible* **HIV tests** and **information** (eg TV, wind-up radios, eg in Africa; HIV issues in soap-operas are most influential).[172] Well-rehearsed **sexual negotiation** skills. **Condoms** for *all* sexual contact, or **abstinence** (but…"I'd rather be dead than abstain"[173]). **Reframing of our bodies as a route to intimacy** rather than as instruments of gratification always entailing penetration. **Fewer sexual partners**. NB: 3 *simultaneous* partners is more risky than 6 *serial* partners. ↓**Alcohol use** (to avoid risky behaviour). NB: a randomized trial (unblind!) found that **circumcision** prevented 65% of HIV infections over 1½yrs. N=3128 heterosexuals <25yrs[174]

This didn't control for glans hygiene (washing/foreskin retraction if uncircumcised). It is not a reliable preventive: uncircumcised men must not behave as if they are safe.

HIV and TB: a prime example of the complex interaction between HIV, diseases of poverty, and multi-drug resistance (MDR-TB)

TB is a common, serious, but treatable complication of HIV. 30-50% of those with AIDS in the developing world also have TB. Morbidity due to HIV/AIDS/TB leads to disastrous losses in productivity, and a poorly trained workforce due to absenteeism from work & training. Health budgets become unbalanced in trying to treat these preventable diseases—if only the context was not one of poverty and ignorance. Economies become uncompetitive, there is higher labour turnover, hence unstable national budgets and politics.[175] Other interactions of HIV and TB:[MET][176]

- Mantoux tests may be negative and the presentation of TB may be atypical.
- Increased reactivation of latent TB.
- Previous BCG vaccination does not prevent development of TB.[177]
- Smears may be -ve for AFB. Smears that are +ve often have few AFB. This makes culture very important (and vital to characterize drug resistance).
- Atypical CXR, eg lobar or bibasal pneumonia, hilar lymphadenopathy.
- Extrapulmonary and disseminated disease is much more common.
- TB [prescription take] in poor countries entails a 4-drug initial phase (2 months of rifampicin, isoniazid, pyrazinamide & ethambutol) and a 2-drug continuation phase (4 months of rifampicin & isoniazid, or 6 months of isoniazid & ethambutol). HIV is known to increases case fatality and rates recurrent TB after this regimen.[178]
- There is ↑toxicity (D&V, hepatitis, rash neuropathy) from combining anti-TB and anti-HIV drugs (eg stavudine, lamivudine & nevirapine as twice-daily generic tablet, often used in resource-poor/WHO HAART, p401). NB: it may be best to delay HAART until 1-2 months after TB [prescription take] is started (unless CD4 <100×10^6/L).[179]
- As HAART reconstitutes CD4 counts, paradoxical worsening of TB symptoms may occur (the 'immune reconstitution inflammatory response', IRIS).[180]
- HIV may or may not necessitate lifelong prophylaxis with isoniazid,[181] but either way, regular clinical monitoring is vital.

▸Directly observed treatment strategy (DOTS) prevents MDR-TB.[182] In areas where MDR-TB is common, DOTS-plus (use of 2nd-line drugs) may be a solution.[183]

▸Respiratory isolation is vital if TB patients are near HIV +ve people. Nosocomial (hospital-acquired) and MDR-TB are major problems worldwide, affecting HIV +ve and HIV -ve people. Mortality is ~80% in patient-to-patient spread. Test TB cultures against 1st and 2nd line agents; 5+ drugs may be

needed in MDR-TB:[184]

First line antitubercular agents:		Second line antitubercular agents:	
Isoniazid	Streptomycin	Ofloxacin	Aminosalicylic acid
Rifampicin	Amikacin	Ciprofloxacin	Clarithromycin
Pyrazinamide	Kanamycin	Cycloserine	Azithromycin
Ethambutol	Capreomycin	Ethionamide	

Reducing MDR-TB

Chief goals: early identification; full treatment; isolation.[185]

- Early isolation of suspected patients. A suspicious CXR or a past history of MDR-TB is enough. Don't wait to prove the diagnosis.
- The ability to obtain Ziehl-Nielsen (ZN)/auramine stains 24h a day.
- Directly observing and confirming that patients take all prescribed drugs.
- Wearing of special masks by staff and the patient if s/he leaves the isolation room (avoid this if possible).
- Sputum induction/expectoration being confined to isolation rooms.
- Doors to isolation rooms having automatic closing devices.
- Providing negative air pressure in isolation rooms.
- Only stop isolation after ≥3 sputum samples are AFB -ve on culture for MDR-TB.
- Frequent tuberculin skin surveillance tests for workers and contacts.

Guidelines on MDR-TB are under review. Discuss treatment with a microbiologist, and refer early to a consultant in infectious diseases. Specific advice is available from the British Thoracic Society and the USA National Institutes of Health.

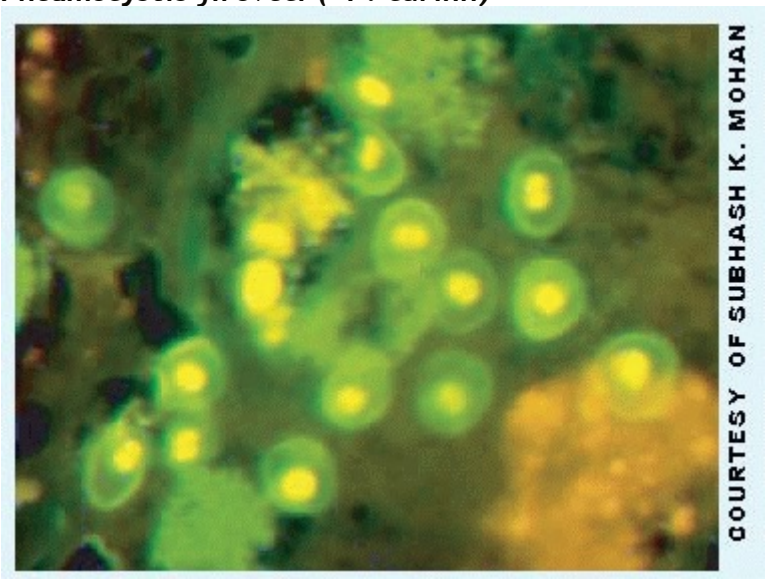
Complications of HIV infection

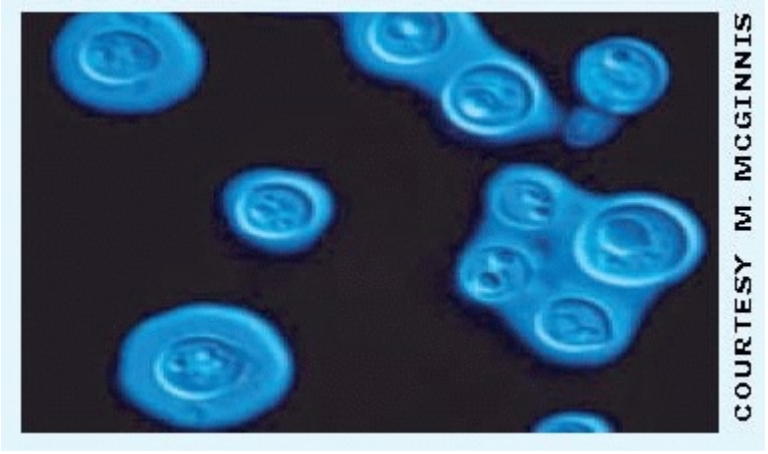
▸All patients with a new diagnosis of HIV should have a tuberculin test and be tested for toxoplasma, CMV, hepatitis B/C, and syphilis serology, to identify past or current infections that may develop as immunosuppression progresses.

- **Pulmonary** ***Pneumocystis jiroveci (=P. carinii)*** pneumonia: this fungus is the commonest life-threatening opportunistic infection in AIDS (p154). [prescription take]: high-dose co-trimoxazole IV (60mg/kg/12h for 14d PO or IV; special monitoring must be available) or pentamidine by slow IVI for 2-3wks. Steroids are beneficial if severe moderate to hypoxaemia. ***Primary prophylaxis:*** If CD4 count <200×10^6/L: co-trimoxazole 960mg/24h PO—reducible to 480mg to improve tolerance or 960mg on alternate days (3 times a week), or 960mg/12h on alternate days (3 times a week). Secondary prophylaxis is essential after 1st attack until CD4 count >200×10^6/L.[186] Other pathogens include ***pyogenic bacteria*** (atypical presentation); ***M. tuberculosis*** (p386); ***M. avium intracellulare*** (MAI); ***fungi*** (*Aspergillus*, cryptococcus, histoplasma); **CMV**. Also: ***Kaposi's sarcoma***, lymphoma, lymphoid interstitial pneumonitis, and non-specific pneumonitis.
- **Gut** Oral pain may be caused by ***candidiasis***, HSV or aphthous ulcers, or tumours. ***Oral Candida*** is treated with nystatin suspension/pastilles or amphotericin lozenges. ***Oesophageal*** involvement causes dysphagia ± retrosternal discomfort. [prescription take]: fluconazole, ketoconazole, or itraconazole PO for 1-2 weeks. Relapse is common. **HSV** and **CMV** also cause oesophageal ulceration which may be difficult to differentiate from *Candida* by barium studies. ***Anorexia and weight loss*** are common in HIV infection. **LFT ↑** ***and hepatomegaly*** are common; causes include drugs, viral hepatitis, AIDS sclerosing cholangitis, or MAI. **MAI** causes fever, night sweats, malaise, anorexia, weight↓, abdominal pain, diarrhoea, hepatomegaly, and anaemia. *Diagnosis:* blood cultures, biopsies (lymph node, liver, colon, bone marrow). [prescription take]: ethambutol + clarithromycin + rifabutin/rifampicin (box). *Primary prophylaxis:*[187] eg azithromycin 1200mg weekly, while CD4 <100×10^6/L. ***Chronic diarrhoea*** may be caused by bacteria (*Salmonella*, *Shigella*, *Campylobacter*, *atypical mycobacteria*, *C. difficile*), protozoa (*Cryptosporidium* p380, *Microsporidium*, *Isospora belli* **fig 1** p379, *cyclospora*), or viruses (CMV, *adenovirus*). ***Perianal disease*** may be from recurrent HSV ulceration, perianal warts, squamous cell Ca (rare). Kaposi's sarcoma (p694) and lymphomas can also affect the gut.

- **Neurological *Acute* HIV** is associated with transient meningoencephalitis, myelopathy, and neuropathy. ***Chronic* HIV** is associated with several CNS syndromes: AIDS-related dementia, HIV-related meningitis, CMV encephalitis, PML, p366,[1] and vacuolar myelopathy. ***Toxoplasma gondii*** (p392) is the main CNS pathogen in AIDS, presenting with focal symptoms/signs. CT/MRI shows ring-shaped contrast enhancing lesions. Treat with pyrimethamine (and folinic acid) + sulfadiazine or clindamycin for 6 months. Lifelong secondary prophylaxis is needed. Pneumocystis prophylaxis also protects against toxoplasmosis.[188] ***Cryptococcus neoformans*** (p428) causes a chronic meningitis, eg with no neck stiffness. **[prescription take]**: See box.
- ***Tumours*** affecting the CNS include primary cerebral lymphoma, B-cell non-Hodgkin's lymphoma. CSF JC virus PCR is useful in distinguishing lymphoma from PML.
- **Eye CMV *retinitis*** (acuity↓ ± blindness) may affect 45% of those with AIDS. Fundoscopy shows characteristic 'mozzarella pizza' signs, **fig 4** p393. ***Primary induction* [prescription take]**: Valganciclovir 900mg/12h PO with food for 21d—or ganciclovir IV or foscarnet, or cidofovir, or ganciclovir-containing intraocular implants (**NB:** risk of post-op retinal detachment, one implant does not prevent disease in the other eye). The need for maintenance therapy may be reviewed if CD4 $\gtrsim 100\times10^6$/L— eg after immune restoration by HAART (p402), if retinitis is inactive.[189]
- **TB** p386.
- **Leishmaniasis** p427.
- **Kaposi's sarcoma** p694.

Managing opportunistic infections in HIV

Infection	Treatment/side-effects/prophylaxis
Tuberculosis	The most lethal opportunistic infection; ▸p386. If no active infection, prophylaxis may be needed if significant exposure, or tuberculin skin test >5mm induration (isoniazid 300mg/day + pyridoxine 50mg/day PO; get expert local help, eg on how long to continue prophylaxis for).[190]
Pneumocystis jiroveci (=P. carinii)  Fig 1. PCC (fluorescent satin × 1000)[191]	***Co-trimoxazole*** (=trimethoprim 1 part + 5 parts sulfamethoxazole) 120mg/kg/d IVI in 3-4 divided doses for 14d. (SE: nausea, vomiting, fever, rash, myelosuppression) **or *Pentamidine isetionate*** 4mg/kg/d by slow IVI for 14-21d (SE: BP↓, hyper- or hypoglycaemia, renal failure, hepatitis, myelosuppression, arrhythmias). ***Prednisolone*** 40-60mg PO daily (reducing dose) if severe hypoxia. ***2nd line agents:*** primaquine + clindamycin, trimetrexate + calcium folinate, atovaquone. *Secondary prophylaxis,* eg co-trimoxazole 480mg/24h PO; same dose as 1° prophylaxis, essential after 1st attack.
	Local [prescription take]: ***Nystatin*** pastilles or ***amphotericin*** lozenges/6h. *Systemic [prescription take]* ***if mucosal:*** ***Fluconazole*** 50-100mg/d PO for 7-30d; ***if***

Candidiasis (See figures on p429)	***invasive:*** 400mg/d for eg 8wks (SE: nausea, hepatitis, platelets↓) **or** ***ketoconazole*** **or** ***itraconazole*** (SE: CCF, nausea, hepatitis). ***Amphotericin B*** (p160) is for *severe* systemic infection. Relapse is common.
Toxoplasmosis (**fig 2**, p392)	***Sulfadiazine*** 1g/6h (or ***clindamycin*** 600-1200mg/6h) + ***pyrimethamine*** eg 25mg/8h PO + folinic acid 15mg/d. *Secondary prophylaxis:* halve doses.
Cryptococcal meningitis  Fig 2. Cryptococcus neoformans (india ink)[192]	***Amphotericin B*** IV‘(p160)’+ flucytosine 25mg/kg/6h PO” for 14d IV. 20% mortality. Normalizing ICP (repeated LPs ± shunts) may help. Give secondary prophylaxis (fluconazole) until CD4 >150×10^6/L and cryptococcal antigen -ve. [193] Diagnosis: India ink stain (**fig 2**); CSF culture; cyptococcal antigen in blood & CSF. Note that the capsule is an essential virulence factor for this yeast.
CMV retinitis (**fig 2** on p392)	Induction: ***ganciclovir*** 5mg/kg/12h IV for 14-21d (SE: myelosuppression) or ***foscarnet*** 60mg/kg/8h IV for 2wks, then reduce. SE: U&E↑↓, ulcers. Alternatives: ***valganciclovir*** 900mg/12h PO for 3wks, then 900mg/24h PO **or** ***cidofovir:*** start with 5mg/kg IV once weekly for 2wks (with probenecid & IV fluids), then reduce to alternate weekly doses. Oral ganciclovir (1g/8h with food) is less good. Maintenance [prescription take] may be discontinued in some patients with CD4 >150×10^6/L.
MAI *Mycobacterium avium intracellulare* (=MAC, *M. avium* complex, p398).	***Clarithromycin*** 500mg/12h + ***ethambutol*** 15mg/kg/d + ***rifabutin***” 300mg/d ± ***ciprofloxacin*** 500mg/12h, all PO. Prophylaxis if CDC <50/mm^3: ***azithromycin*** 1.2g/wk PO.
	Prophylaxis: 23-valent pneumococcal

Strep. pneumoniae	vaccine, p152.[194]

What every doctor should know about HIV

Preventing HIV spread

▸Promote *lifelong* safer sex, barrier contraception, and reduction in partner numbers. Videos, followed by interactive discussions, is one way to double condom use. Another way is the *100% condom programme* involving distribution of condoms to sex establishments, with enforcement. Such programmes are estimated to have prevented 2 million HIV infections in Thailand.

- Warn everyone about dangers of sexual tourism/promiscuity. Teach skills in sexual negotiation. Explain how alcohol can undermine safe sex messages.
- Introduce drug users to needle exchange schemes ('don't share needles').
- Vigorous control of other STDs can reduce HIV incidence by 40%.
- Strengthen awareness of STD clinics (and support them in their work).
- Reduce unnecessary blood transfusions.
- Encourage HIV tests in pregnancy (±Caesarean sections if +ve, OHCS p34).[1]

[1] Without interventions, rate of vertical transmission is 15-20%; prolonged breastfeeding doubles this, falling to <2% with antiretroviral prophylaxis, elective Caesars and bottle feeding. 2006 data

Post-exposure prophylaxis

(eg needle-stick injury; split condom and HIV+ve)[195] Seroconversion rate post-needle-stick: ~0.4% (HIV); 30% for hep B if HBeAg +ve.

- Wash well. If needle-stick, encourage bleeding; do not suck or immerse in bleach.
- Note name, address, and clinical details of 'donor'.
- Report incident to Occupational Health and fill in an accident form.
- Store blood from both parties (HIV, HBV & HCV tests). Immunize (active & passive) against hepatitis B at once, if needed. Counsel (HIV risk <0.5% if 'donor' is HIV +ve) and test recipient at 3, 6, and 8 months (seroconversion may take this long).
- Weigh risks by questioning 'donor'; if HIV+ve, what is the CD4 and viral load count? Before prophylaxis, do a pregnancy test. Get informed consent. Was there a large inoculum? Was injury deep? (Mucous membrane exposure carries very low risk.) Give 4wks of drugs, if possible within 1h of exposure: ***Low-risk:*** No antiviral medication. ***Higher-risk:*** Typically zidovudine 250mg/12h + lamivudine 150mg/12h, and particularly for worst episodes (deep puncture from wide-bore needle causing bleeding), indinavir 800mg/8h OR nelfinavir 750mg/8h, all PO.

HIV test counselling

If in doubt, get help from a genitourinary clinic.

- Determine level of risk (eg unprotected sex; sex overseas).
- Discuss test benefits: partner protection; avoiding vertical transmission; getting [prescription take].
- What are the difficulties? Will you tell family and friends? Explain possible effects on: job, mortgage, insurance (we have no obligation to disclose HIV status).
- Do post-test counselling (eg to re-emphasize ways to ↓risk exposure).
- *Counselling throughout* HIV *illness:* A key issue when a person is dying from HIV is making a will. Legal help may be needed on housing, employment, and guardianship of children. Making advance directives needs special skill. Domiciliary genitourinary teams, GP, and hospices help with terminal care all have a role.

Acute seroconversion

As HIV gets more treatable, recognizing this early phase becomes more important. Signs are similar to infectious mononucleosis (eg lymphadenopathy, myalgia, rash and headache); perform tests if there are unusual signs, eg oral candidiasis, recurrent shingles, leucopenia, or CNS signs (antibody tests may be negative but viral p24 antigen and HIV RNA levels are ↑ in early infection). As ever, the first best 'test' is to take a thorough history. If you *do* identify acute seroconversion illness, get expert help—and advise unambiguously on preventing transmission. It is not known if early therapy is worthwhile.[196]

Questions for when you are seeing HIV+ve people

- Have you been to an STD clinic? (STDs promote spread of HIV).
- Are you using condoms?
- What is your CD4 cell count/HIV-1 RNA level? (viral load helps plan start of antiretrovirals; CD4 <200, <100, and <50/mm^3 prompt prophylaxis for *Pneumocystis*, *Toxoplasma*, and *Mycobacterium avium* complex, respectively).
- What is your CMV and toxoplasma titre? (if -ve, counsel to avoid infection, eg no uncooked meat; avoid cats etc).
- Recent CXR? (eg TB; pneumocystosis).
- Recent cervical smear? (risk of neoplasia↑).[197]

Aims of highly active antiretroviral therapy (HAART) & other strategies

- HAART aims to suppress plasma HIV RNA concentrations below the limit of detection and restore immune function. This is not a cure as latent replication-competent provirus in resting CD4+ T lymphocytes and persistent (but cryptic) viral replication remain intact.[198] Life-long suppression of plasma HIV RNA is problematic—hence the need for strategies to *eradicate* HIV.
- Enfuvirtide (a 'fusion inhibitor' eg 90mg/12h SC) intensifies HAART by blocking the last step in the 3-part process by which virus enter cells (attachment →coreceptor binding →fusion). It modestly increases rate of decay of the number of cells containing replication-competent HIV.[199]
- In theory, these effects can be helped by any therapy which blocks histone deacetylase 1 (HDAC1 mediates virion production). This is the rationale behind studies of HDAC1 blockers such as valproic acid—which has been shown ↓frequency of resting cell infection (mean reduction 75%).[200]
- ▸HAART should be part of a holistic, integrated, individualized care plan proceeding with management of co-morbidities eg malnutrition, malaria etc.[1]

Monitoring HIV infection

There is more to monitoring HIV than periodic measurements of the CD4 count. Plasma **HIV *RNA levels*** strongly predict progression to AIDS and death, whatever the CD4 count. This test typically involves quantitative reverse transcriptase PCR to amplify DNA copies of the target RNA. HIV patients in the lowest quartile of viral load (HIV RNA ≤4530 copies/mL) have an 8% chance of progressing to AIDS in 5yrs compared with 62% in those in the highest quartile (>36,270 copies/mL). Clinical benefit from anti-HIV agents depends not only on improving the ***CD4 count*** but also from decreasing HIV RNA to undetectable levels.

When to treat HIV infection

Long-term studies of various different populations with HIV and involving clinical endpoints such as death are few or lacking. In general, start drugs if:

- Any patient diagnosed with AIDS, or with severe/recurrent HIV-related illness.
- Any patient with CD4 count $\lesssim 200\times10^6$/L ($\lesssim$275 *might* be a better threshold).[201]
- Asymptomatic with CD4 count of 200-350 × 10^6/L and a high viral load.
- Asymptomatic with a CD4 count of 200-350 × 10^6/L which is falling rapidly.

Morbidity data suggest these levels may be too stringent in determining eligibility.[202]

Do CD4 counts and HIV RNA levels to monitor treatment, eg every 3 months. There is an argument for changing treatment if HIV RNA level rebounds (>500 copies/mL on two consecutive tests), if there is a consistent fall in the CD4 count, or if new symptoms occur. The new regimen should include at least two drugs new to the patient. Request resistance tests, eg genotyping for HIV reverse transcriptase/protease mutations (if available). **NB:** Multi-drug therapy imposes difficulties both in terms of timing of doses and interactions with other drugs.

Resource-limited settings

Where HIV is most prevalent, CD4 counts are too expensive. A reasonable alternative is the TLC—the total lymphocyte count: a TLC of 1400/μL≈a CD4 count of 200/μL as far as risk of mortality from HIV goes.[203]

Useful web link: British HIV association: www.bhiv.org.

Antiretroviral agents

This is an expensive luxury for most of the world's HIV patients. In many ways *all* anti-HIV treatment is experimental so perhaps the best question to ask is not *what is the best treatment for* HIV but *which is the most appropriate trial to enter my patient into?* ▸Seek expert help early.

▸**HAART** (**h**ighly **a**ctive **a**nti-**r**etroviral **t**herapy) involves combining two nucleoside analogue reverse transcriptase inhibitors (NRTI) with *either* a protease inhibitor (PI) *or* a non-nucleoside reverse transcriptase inhibitor (NNRTI) *or* (in patients with relatively low viral loads) abacavir.[204] One example of comparative data: efavirenz-tenofovir-emtricitabine is better than efavirenz-zidovudine-lamivudine.[205][206]

Nucleoside analogue reverse transcriptase inhibitors (NRTI)

- ***Zidovudine (azidothymidine, AZT)*** was the first anti-HIV drug. Dose: 250-300mg/12h PO or 1-2mg/kg/4h IV. SE: anaemia, leucopenia, gastrointestinal disturbance, fever, rash, myalgia. Stop treatment if ↑LFT, hepatomegaly, lactic acidosis. CI: anaemia, neutropenia, breast-feeding.
- ***Didanosine (DDI; Videx EC®)*** 250mg/24h PO if wt <60kg; 400mg/24h if ≥60kg. SE: pancreatitis, peripheral neuropathy, hyperuricaemia, GI

disturbance, retinal and optic nerve changes, liver failure. Stop treatment if significant rise in LFT or amylase. CI: breast-feeding.

- ***Lamivudine (3TC)***[207] is a well-tolerated antiretroviral. Dose: 150mg/12h PO, take without food. se: see zidovudine, but less common. Stop if ↑LFT, hepatomegaly, lactic acidosis, pancreatitis.
- ***Emtricitabine (FTC)*** It is like lamivudine, but is also active against hepatitis B.[208]
- ***Stavudine (D4T)*** 40mg/12h PO if weight ≥60kg; 30mg/12h PO if <60kg. Stop if neuropathy or ↑LFT.
- ***Tenofovir*** 245mg/24h PO. SE: see lamivudine.
- ***Abacavir*** 300mg/12h PO. SE: hepatitis, lactic acidosis, hypersensitivity syndrome (3-5%)—rash, fever, vomiting; may be fatal if rechallenged.

Protease inhibitors (PI)

slow cell-to-cell spread, and lengthen the time to the first clinical event. PIs are often given with low dose ritonavir (100mg/12hr PO), which appears to enhance drug levels. All PIs are metabolized by the cytochrome p450 enzyme system. They may therefore increase the concentrations of certain drugs by competitive inhibition of their metabolism, if administered concomitantly.[209] PIs can cause metabolic syndrome (dyslipidaemia, hyperglycaemia, insulin resistance).

- ***Indinavir*** 800mg/8h PO, 1h before or 2h after a meal. SE: dry mouth, taste disturbance, rash, pruritus, hyperpigmentation, alopecia, nephrolithiasis, anaemia, neutropenia, myalgia, paraesthesiae, ↑LFT.
- ***Ritonavir*** Start with 300mg then ↑ to 600mg/12h PO. SE: see indinavir.
- ***Saquinavir*** 1g/12h PO within 2h of a meal. SE: oral ulcers, paraesthesiae, myalgia, headache, dizziness, pruritus, rash, pancreatitis.
- ***Nelfinavir*** 750mg/8h PO. SE: hepatitis, neutropenia, flatulence, ↑CK.
- ***Lopinavir/Ritonavir (Kaletra®)*** is probably superior to nelfinavir.[210] Dose: 400mg (+100mg ritonavir)/12h PO. SE: see saquinavir.
- **Others:** ***amprenavir*** 1200mg/12h PO (it has a new pro-drug, ***fosamprenavir***). SE: see saquinavir; ***atazanavir***; ***tipranavir***.

Non-nucleoside reverse transcriptase inhibitors (NNRTI)

These may interact with drugs metabolized by the cytochrome p450 enzyme system, which they either induce or inhibit depending on the concomitantly administered drug.[211]

- ***Nevirapine*** 200mg/24h for 2wks, then 200mg/12h PO. Resistance emerges readily. SE: Stevens-Johnson syndrome, toxic epidermal necrolysis, hepatitis.
- ***Efavirenz*** Dose: 600mg/24h PO. SE: rash, insomnia, dizziness. Avoid in pregnancy.

Golden rules in HIV therapy

- Start HAART early, ideally before CD4 count <200 × 10^6/L.
- Explain to patients that regimens are complex and negotiate strict adherence. Take time to harmonize pills with the patient's expectations and lifestyle.
- Is the patient suitable to include in an on-going research trial?
- Aim for no more than twice-daily dosing, if possible.
- Use ≥3 drugs (minimizes replication and cross-resistance). No dual therapies.
- Monitor plasma viral load & CD4 count; *what seems like elimination of* HIV *often turns into reactivation when treatment stops*. Aim for undetectable viral loads 4 months after starting HAART. Suspect poor adherence if viral load rebounds.
- If viral loads remains high despite good adherence, if there is a consistent fall in CD4 count, or if new symptoms occur, change to a new combination of anti-HIV drugs and request resistance tests, eg genotyping for HIV reverse transcriptase/protease mutations (if available).
- Stay informed about new drugs, and emerging classes of drugs.

Standard regimens and some practical problems

- Other illnesses: no ddI if **pancreatitis**. If **polyneuropathy**, avoid d-drugs (ddI, ddC, d4T). **Non-insulin-dependent diabetes** may need insulin with PIs. Hepatotoxicity risk is ↑ for nevirapine or ritonavir if there are **liver problems**.
- Common initial regimens consist of two nucleoside analogues, combined with either a protease inhibitor, an NNRTI or a third nucleoside analogue.[212]
- Managing highly antiviral-experienced HIV-infected patients is complicated by drug resistance, patient intolerabilities, drug interactions and quality-of-life issues. So potent regimens need expert input to maximize activity against resistant virus, eg enfuvirtide and tipranavir/ritonavir, have shown promising results in HAART regimens in those with extensive treatment histories and resistance profiles, if used in combination with other active agents.[213]
- A few studies on simplification have been completed: for example, switching from complex regimes to didanosine-tenofovir-efavirenz provides a virological suppression rate at 12 months similar to that seen in patients who do not change from more complex therapy (and may obviate dyslipidaemias).[214]

- Combination tablet examples: Trizivir® is abacavir 300mg, lamivudine 150mg, and zidovudine 300mg. Combivir® is zidovudine with lamivudine.

'3-by-5'→'10-by-10': free access to antiretroviral drugs?

When WHO announces targets such as '***3-by-5***' (3 million extra to get HIV [prescription take] by 2005) or, when this failed, '***10-by-10***' (100% availability of free HIV drugs by 2010), some people look on with scepticism, confident of failure. This is very clever, but misses the point, which is to save lives *and* raise awareness by pushing the HIV pandemic (which judges us all) up political agendas and to spur governments into action. Looked at it this way, WHO has had a major impact, with 300,000 lives saved, and, in some places, prevalences falling (eg in Kenya from 14% in 1997 to ~4% in 2006). In some places, wards full of people dying of AIDS have emptied as drugs enable people get off their knees and start *living* with HIV.[215] From 2006, as a result of debt-cancellation and pressure from Médecins Sans Frontières, all people in Nigeria have access to free antiretroviral therapy. But sometimes drugs remain in warehouses beyond their expiry date—owing to corruption, and lack of blood tests for monitoring.[216]

Can HIV [prescription take] save lives rather than just postpone death? Of course: if drugs keep a mother alive, her offspring stand a chance. In one chilling study from Gambia 100% of babies who lost their mother died within a year.[217]

WHO initiatives also make HIV less taboo. If people know that HIV is a condition which can be managed, and not a death-warrant, a culture of passive dependency is replaced by one of interdependence, initiative, and practical optimism. This really is a better definition of health than being disease-free.

★★ CYNICS BEWARE ★★ Don't always blame th e drug companies.

Sexually transmitted infections/diseases (STI/STD)

▸Refer early to genitourinary medicine clinic (GUM) for full microbiological investigation and contact tracing and notification. Most clinics see patients immediately during the working day; some offer an on-call service. Avoid giving antibiotics until seen in GUM clinic or at least discussed. For HIV, see p398.

UK incidence

is rising alarmingly, by >10%/yr as 'safer sex' practices are being ignored. Prevalence of chlamydia is ~11%[UK] (>104,000 cases new cases of genital *Chlamydia*); 22,320 cases of gonorrhoea[UK], and >2250 cases of syphilis.[218]

History

Ask about timing of last intercourse; contraceptive method; sexual contacts; duration of relationship; sexual practices and orientation; past sexual infections; menstrual and medical history; antimicrobial therapy.

Examination

Detailed examination of genitalia including inguinal nodes and pubic hair. Scrotum, subpreputial space, and male urethra. PR examination and proctoscopy (if indicated); PV and speculum examination.

Signs

Vaginal/urethral discharge (p406), genital lesions: herpes (p388); syphilis (p419); *Chlamydia* (BOX). Genital warts (OHCS p268). Salpingitis (OHCS p286). Lice (OHCS p608).

Tests

Refer to GUM clinic. Urine: dipstick and MSU for MC+S. Ulcers: take swabs for HSV culture (viral transport medium) and dark ground microscopy for syphilis (***T. pallidum***). Urethral smear for Gram stain/culture for ***N. gonorrhoeae*** (send quickly to lab in Stuart's medium); urethral swab for ***Chlamydia*** (free tests also available from UK chemists, see BOX). High vaginal or swab in Stuart's medium for microscopy/culture (***Candida, Gardnerella vaginalis,*** anaerobes, ***Trichomonas vaginalis)***; endocervical swab for ***Chlamydia trachomatis. Chlamydia*** (an obligate intracellular bacteria) is the trickiest STD to diagnose as it is asymptomatic, difficult to culture, and serology may be unhelpful as it cross-reacts with *C. pneumoniae*. Nucleic acid amplification assays (eg urine ligase chain reaction, PCR) are quite good screening tests, with sensitivity >90%. Other tests: include ***Chlamydia*** antigen and nucleic acid probe assays.[219]

Blood tests:

Syphilis, hepatitis, and HIV serology after counselling.

Follow-up

At 1wk & 3 months, with repeat smears, cultures, and syphilis serology.

Scabies

(Sarcoptes scabei, an arachnid*)* Spread is common in families.

The patient:

Papular rash (on abdomen or medial thigh; itchy at night) + burrows (in digital web spaces and flexor wrist surfaces).

Incubation:

~6wks (during which time sensitization to the mite's faeces and/or saliva occurs). Penile lesions produce red nodules.

Diagnosis:

Tease a mite out of its burrow with a needle for microscopy. This may fail but if a drop of oil is placed on the lesion, a few scrapes with a scalpel may provide faeces or eggs.

[prescription take]:

▸Treat all the household. Give written advice (OHCS p608). Apply 5% permethrin over whole body including scalp, face, neck and ears (BNF); wash off after 8-12h; repeat after 7d. Use 5% cream on hands if washed before the 8h elapses. Remember to paint *all* parts, including soles (avoid eyes); wash off after 24h.

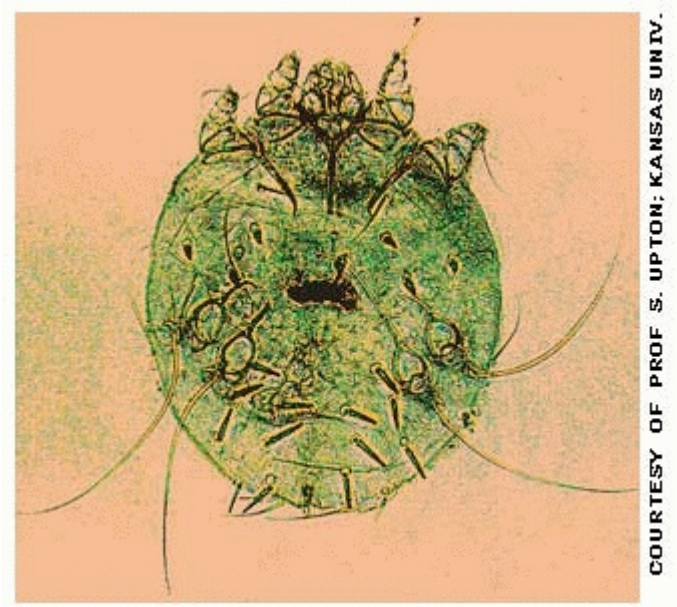


Fig 1. *Sarcoptes scabei.*[220]

Lymphogranuloma

Signs:

Inguinal lymphadenopathy + ulceration

Causes:

Lymphogranuloma venereum (*Chlamydia trachomatis;* serovar L_2 causes proctitis too, eg in HIV +ve European men),[221] chancroid (*Haemophilus ducreyi*),[1] or granuloma inguinale (*Klebsiella (Calymmatobacterium) granulomatis*, ie donovanosis). The latter causes extensive, painless, red genital ulcers and pseudobuboes (inguinal nodes abscess), with possible elephantiasis ± malignant change.

Diagnosis:

'closed safety-pin' inclusion bodies in cytoplasm of histiocytes.

[prescription take]:

doxycycline 100mg/12h PO until all lesions epithelialized—or azithromycin, erythromycin, or tetracycline.

Chlamydia screening to prevent pelvic inflammatory disease NICE 2006

Genital *Chlamydia trachomatis* is the commonest STI in the UK (>104,000 diagnoses in GUM clinics/yr). Highest rates are in men and women <24yrs old — implying longterm morbidity, as salpingitis, infertility, or ectopic pregnancy will occur in 2-4%.[222] These 2006 data (n=43,751) are at odds with older NICE data, casting doubt of some of NICE's strategies (below).

Shame, **embarrassment** about discussing STIs with partners, **lack of appointments**, and having to go **out of one's way** to be sensible are the main obstacles. Dialogue is the key; you can help by talking frankly with your patients about sex: see OHCS p328. As part of implementing the UK **National Chlamydia Screening Programme**, UK high street pharmacies (Boots) offer **free chlamydia tests** (NHS funded) or those aged 16-24yrs (eg in London,

and if +ve, to their partners, of *any* age). Uptake of this service is patchy and it may be hard to sustain. Colleges, prisons, and armed forces are also targeted.[223] NB: Only 0.5% of young adults respond to **mass media campaigns** inviting them in for screening.

Free home-based urine test kits may be distributed to garages, hairdressers, and supermarkets with results texted to **mobile phones**—removing the need to provide embarrassing samples at the doctor's surgery.

Walk-in STI clinics and **late-opening GP clinics** allow *prompt* treatment of uncomplicated genital chlamydial infection: **azithromycin** 1g PO as a single dose.

NICE advocates **opportunistic screening** of young adults (eg with nucleic acid amplification tests on urine) *wherever* they present to primary care, irrespective of presenting symptoms.[224] This might halve the incidence of pelvic inflammatory disease. Issues about efficient contact tracing are unresolved. NB: There is no good evidence to support using screening to halt transmission, of to reduce rates of orchitis,♂ ectopic pregnancy or infertility.

LEAPING OVER BARRIERS WHICH PERPETUATE STDS

Vaginal discharge and urethritis

Non-offensive vaginal discharge may be physiological. Most which are smelly or itchy are due to infection. Foul discharge may be due to a foreign body (eg forgotten tampons, or beads in children). ▸Discharges rarely resemble their classical descriptions. ▸Untreated GU inflammation ↑viral shedding of HIV-1 in semen 3-fold.

Thrush (Candida albicans)

Thrush is the commonest cause of discharge and is classically described as white curds. The vulva and vagina may be red, fissured, and sore. The partner may be asymptomatic.

Risk factors:

Pregnancy, immunodeficiencies, diabetes, the Pill, antibiotics.

Diagnosis:

Microscopy: strings of mycelium or oval spores. Culture on Sabouraud's medium.

Treatment:

A single imidazole vaginal pessary, eg **clotrimazole** 500mg, + cream for the vulva (and partner) is convenient. Alternative: 1 dose of **fluconazole** 150mg PO. Reassure that thrush is not necessarily sexually transmitted. Recurrent thrush: see OHCS p284.

Trichomonas vaginalis

(TV) Produces vaginitis and a thin, bubbly, fishy smelling discharge. It is sexually transmitted. Exclude gonorrhoea (which may coexist). The motile flagellate may be seen on wet film microscopy, or cultured.

[prescription take]:

Metronidazole 400mg/12h PO for 5 days or 2g PO stat. Treat the partner. If pregnant, use the 5-day regimen.

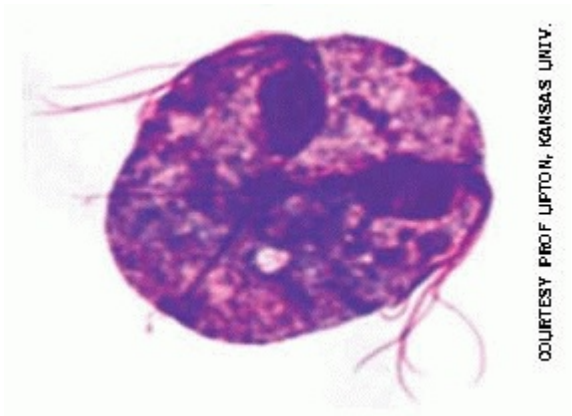


Fig 1. *T. vaginalis*.[225]

Bacterial vaginosis

causes a fishy smelling discharge. The vagina is not inflamed. Itch is rare. Vaginal pH is >5.5, hence alteration of bacterial flora ± overgrowth, eg of

Gardnerella vaginalis, *Mycoplasma hominis*, peptostreptococci, *Mobiluncus* and anaerobes, eg *Bacteroides* species with too few lactobacillae. There is ↑risk of pre-term labour and amniotic infection if pregnant.

Diagnosis:

Stippled vaginal epithelial 'clue cells' on wet microscopy. Culture.

[prescription take]:

OHCS p286; eg **metronidazole** 400mg/12h PO for 5d, or **clindamycin** cream.

Gonorrhoea

Neisseria gonorrhoea (gonococcus, GC) can infect any columnar epithelium, eg urethra, cervix, rectum, pharynx, conjunctiva. Incubation: 2-10d. ♂: Urethral pus ± dysuria; tenesmus; proctitis ± discharge PR if gay. ♀: Often asymptomatic, but may have vaginal discharge, dysuria, proctitis. Pharyngeal disease is often asymptomatic.

Complications—Local:

Prostatitis, cystitis, salpingitis, epididymitis, Bartholinitis.

Systemic:

Septicaemia, eg with petechiae, hand/foot pustules, arthritis; Reiter's syndrome; SBE (rare).

Obstetric:

Ophthalmia neonatorum[ND] (OHCS p36).

Long-term:

Urethral stricture, infertility.

[prescription take]:

Cefixime, eg 400mg PO stat (or **ciprofloxacin** 500mg stat PO, but resistance is a problem in eg in 36% in N England). Treat for chlamydia too (eg **doxycyline** 100mg/12h PO for 7d, or a stat dose of **azithromycin** 1g PO) as 50% of patients with urethritis or cervicitis also have *C. trachomatis*. Trace contacts (refer to special clinic). No intercourse or alcohol until cured.

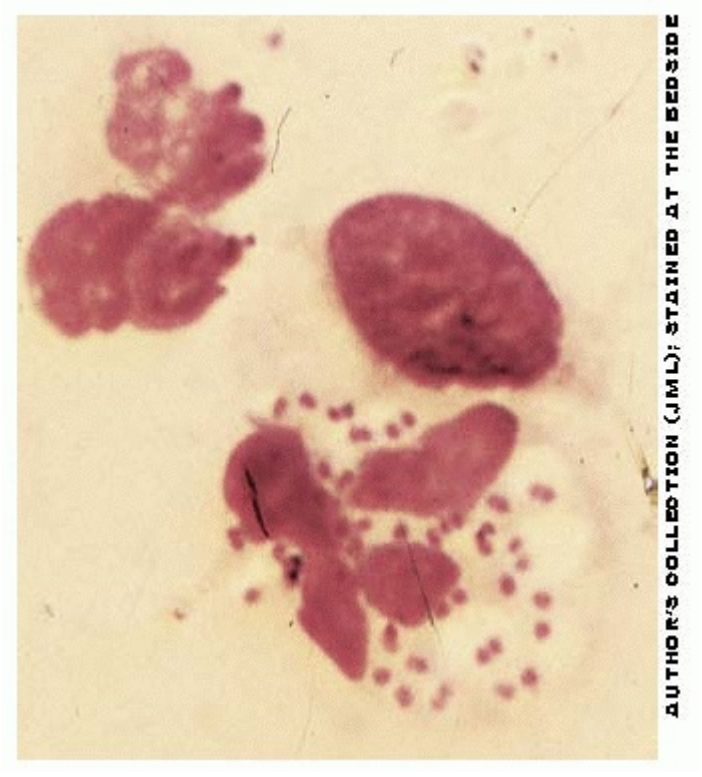


Fig 2. Gonococci in neutrophils; pairs of diplococci (long axes parallel)—here stained at the bedside by Field's stain (p373).[226]

Non-gonococcal urethritis

is commoner than GC. Discharge is thinner and signs less acute, but this may not help diagnosis. Women (typically asymptomatic) may have cervicitis, urethritis, or salpingitis (pain, fever, infertility). Rectum and pharynx are not infected.

Organisms:

C. trachomatis (▸special swabs are needed, OHCS p286); *Ureaplasma urealyticum*; *Mycoplasma genitalium*; *Trichomonas vaginalis*; *Gardnerella*; Gram -ve and anaerobic bacteria; *Candida*.

Complications:

Similar to local complications of GC. *Chlamydia* may cause Reiter's syndrome and neonatal conjunctivitis.

Treatment:

1 week of **doxycycline** 100mg/12h PO. A single dose of **azithromycin** 1g PO is an alternative where compliance is likely to be problematic. Trace contacts. Avoid intercourse during treatment and alcohol for 4 weeks.

Non-infective urethritis

Traumatic; chemicals; cancer; foreign body.

When do antibiotic guidelines become outdated?

The emergence of antibiotic resistance amongst pathogens represents one of the main obstacles in the fight against infectious diseases. Antibiotic guidelines, which exist on local, regional, and national levels help ensure optimal therapy, but must be continually updated in the vain task of trying to keep up with pathogens. To monitor resistance patterns, sample infective isolates from different UK regions are collected centrally and tested against a variety of antibiotics to determine their sensitivities to the different drugs (as measured by the minimal inhibitory concentration (MIC) of drug required to prevent organism growth in culture). Such results can highlight the need to revise antibiotic guidelines.

One example is the emergence of ciprofloxacin resistance in *Neisseria gonorrhoeae* isolates in England and Wales. Resistance was found in 36% of isolates from N England in 2004-5—a big rise from 10% of isolates in 2002, and 3% in 2001, and 2% in 2000. National guidelines aim for chosen drugs to eliminate gonococcal infection in >95% of patients. Ciprofloxacin, previously 1st-line, now has to be replaced by cephalosporins (eg cefixime) in new guidelines.[227]

Miscellaneous Gram positive bacteria

Staphylococci

When pathogenic, these are usually *Staph. aureus*. Typically, they infect skin, lids, or wounds. Severe *Staph. aureus* infections are: pneumonia, osteomyelitis; septic arthritis; endocarditis; septicaemia. Production of ß-lactamase which destroys many antibiotics (p368, p369, p370) is the main problem. *Staph. aureus* toxins cause food poisoning (p380) and toxic shock syndrome toxin (TSST-1): shock, confusion, fever, a rash with desquamation, diarrhoea, myalgia, CPK↑, platelets↓ (associated with the use of hyperabsorbent tampons). *Staph. epidermidis (albus*) is recognized as a pathogen in the immunocompromized, particularly in connection with IV lines or any prosthesis. When isolated from a culture, *Staph. epidermidis* can usually be assumed to be a contaminant. It is often enough to remove infected lines. Deep *Staph.* infections need ≥4wks of flucloxacillin 500mg/6h IV ± removal of foreign bodies, eg prostheses.

Methicillin-resistant Staph. aureus (MRSA)

is a high-profile hospital-acquired infection, causing pneumonia, septicaemia, wound infections, and death (risk ↑5-fold),[228] but MRSA only accounts for ~6% of total hospital acquired infection (~300,000/yr in England, with ~5000 deaths). ≳17 sub-types. NB: *C. difficile* and glycopeptide-resistant enterococci are just as bad. In the UK it is mandatory to record all infections; despite stringent efforts rates are rising in 40% of UK hospitals—eg related to overcrowding, the inability to close affected wards, poor barrier-nursing facilities, and faulty hygiene (eg not washing hands between patients). Carriage rates (nasal): 1-10%. Risk factors: HIV, dialysis, being on ITU. MRSA is community-acquired in up to 40%. [prescription take]*:* Discuss with a microbiologist. Vancomycin or teicoplanin are used, but strains with reduced sensitivity (vancomycin-intermediate *Staph. aureus* (VISA)—↓sensitivity to *both* drugs) have emerged.[229] Here, linezolid or quinupristin/dalfopristin (Synercid®) may be effective. Preventive measures:

- Isolate recently admitted patients with suspected MRSA. Group MRSA cases on one ward (impractical if hospital has to run at 100% capacity).
- Wash your hands and your stethoscope! (also TV remote controls, etc).
- Ask about the need for eradication (with *mupirocin*).
- Be meticulous in looking after intravascular catheters when on ITU.
- Surveillance swabs of patients and staff during outbreaks.
- Use gowns/gloves when dealing with infected or colonized patients. Masks may be needed during contact with MRSA pneumonia.

Streptococci

Group A streps (eg ***Strep pyogenes***) are common pathogens, causing wound and skin infections (eg impetigo, erysipelas, OHCS p598), tonsillitis, scarlet fever[ND], necrotizing fasciitis (p592), toxic shock, or septicaemia. Late complications are rheumatic fever and post-streptococcal glomerulonephritis.

Strep. pneumoniae (pneumococcus, Gram +ve diplococcus) causes pneumonia, otitis media, meningitis, septicaemia, peritonitis (rare). Resistance to penicillin is a problem. ***Strep. sanguis***, ***Strep. mutans***, and ***Strep. mitior*** (of the 'viridans' group), ***Strep. bovis***, and ***Enterococcus faecalis*** all cause endocarditis. ***Enterococcus faecalis*** also causes UTI, wound infections, and septicaemia. ***Strep. mutans*** is a very common cause of dental caries. ***Strep. milleri*** forms abscesses, eg in CNS, lungs, and liver. Most streps are sensitive to the penicillins, but ***Enterococcus faecalis*** and ***Enterococcus faecium*** may present some difficulties. They usually respond to a combination of ampicillin and an aminoglycoside, eg gentamicin (p371 & p738). Vancomycin-resistant enterococci (VRE) have been reported. Some strains of VRE are sensitive to either teicoplanin or Synercid®; all appear to be sensitive to linezolid (p370).[1]

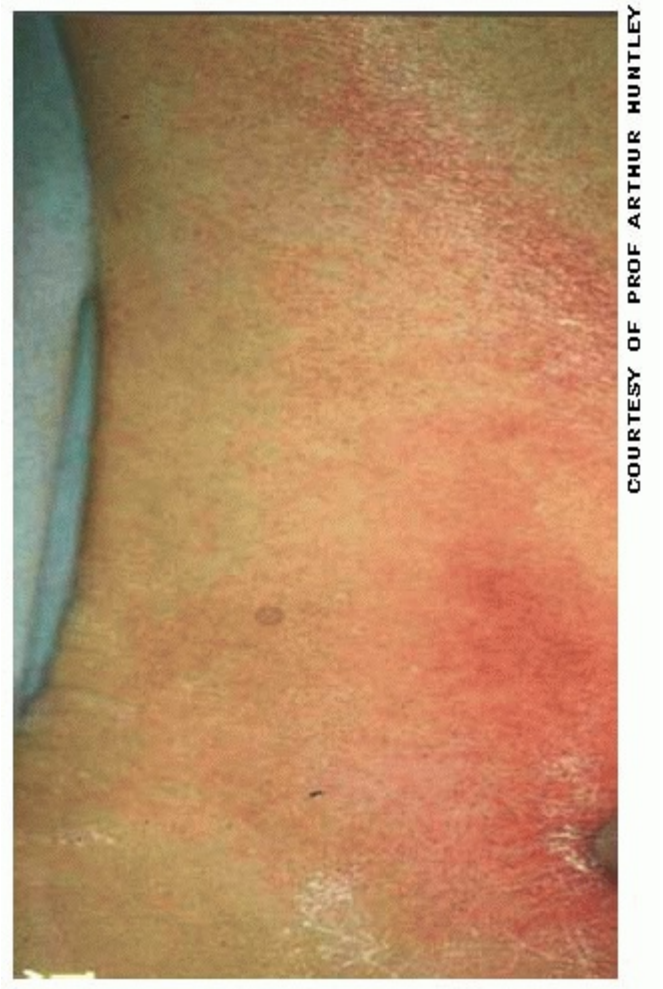


Fig 1. Streptococcal ascending lymphangitis from an infected (diabetic) ankle ulcer.[230]

[1] See reports of vancomycin-resistant *S. aureus* (VRSA), containing a *vanA* resistance gene.

Anthrax[ND]

(Bacillus anthracis)

Occurs in Africa, Asia, China, Eastern Europe, and Haiti. Spread is by handling infected carcasses; well-cooked meat poses *no* risk. Terrorists have used long-lasting anthrax spores (from the ear of a cow that died near Oxford in 1937)[231] as a biological weapon.[232]

Signs:

Common form: local cutaneous black pustule (anthrax=ανθηραξ=coal in Greek). Oedema may be a striking sign ± fever and hepatosplenomegaly. May cause lung or GI anthrax with dyspnoea ± big GI bleeds or meningoencephalitis.

Tests:

CXR (wide mediastinum). Gram stain is sometimes diagnostic (Gram +ve rod).

[prescription take]:

Cutaneous disease: ciprofloxacin 500mg/12h PO for up to 60d. *Pulmonary or* GI *anthrax:* Ciprofloxacin 400mg/12h IVI + clindamycin 900mg/8h IVI + rifampicin 300mg/12h IVI. Switch to oral drugs when able; treat for 60d.

Prevention:

Immunize animals at risk, and enforce sound food-handling and carcass-hygiene policies.[233]

Diphtheria[ND]

is caused by *Corynebacterium diphtheriae* toxin.

Signs:

tonsillitis ± a pseudomembrane over the fauces and lymphadenopathy ('bull neck'). ENT details: OHCS p158.

[prescription take]:

Erythromycin 10-12mg/kg/6h IVI.

Prevention:

p381. Give non-immune contacts erythromycin 500mg/6h PO for 10d *before* swab results known.

Listeriosis

is caused by *Listeria monocytogenes*, a Gram +ve bacillus with an odd ability to multiply at low temperatures. Possible sources of infection include p[prescription take]tés, raw vegetables, unpasteurized milk, and soft cheeses (brie, camembert, and blue vein types). It may cause a non-specific 'flu-like illness, pneumonia, meningoencephalitis, ataxia, rash, or PUO, especially in the immunocompromised, in pregnancy, where it may cause miscarriage or stillbirth, and in neonates.[234]

Diagnosis:

Culture blood, placenta, amniotic fluid, CSF, and any expelled products of conception. ▸*Take blood cultures in any pregnant patient with unexplained fever for ≥48*h. Serology, vaginal, and rectal swabs don't help (it may be a commensal here).

Treatment:

Ampicillin IV (erythromycin if allergic) + gentamicin; see p368 & p371 for doses.

Prevention in pregnancy:

- Avoid soft cheeses, p[prescription take]tés, and under-cooked meat.
- Observe 'use by' dates.
- Ensure reheated food is piping hot; observe standing times when using microwaves; throw away any left-overs.

Nocardia species

cause subcutaneous infection (eg Madura foot) in warm climes, and, if immunocompromised, abscesses (lung, liver, cerebral). Microscopy: branching chains of cocci.

[prescription take]:

Trimethoprim 5mg/kg/8h IVI + sulfamethoxazole 25mg/kg/8h IVI for 3wks[] (do serum levels) then reduce. 2nd-line: imipenem ½g/6h IVI + amikacin.

Clostridia

Tetanus p412. ***C. perfringens*** causes wound infections and gas gangrene ± shock or renal failure after surgery or trauma (p592).

[prescription take]:

Debridement is vital; benzylpenicillin 1.2-2.4g/6h IV + clindamycin 900mg/8h IVI, antitoxin and hyperbaric O_2 may also be used. Amputation may be necessary. *Clostridia* food poisoning (p380).

C. difficile:

Diarrhoea (the cause of pseudomembranous colitis following antibiotic therapy, p239).

C. botulinum:

(Botulism) *C. botulinum* toxin blocks release of acetylcholine causing descending flaccid paralysis. Botulism is not spread from one person to another. There are 2 adult forms of botulism: food-borne and wound botulism. ▸*Risk is high in IV drug abusers* if heroin is contaminated with *C. botulinum*.

Signs:

Afebrile, flaccid paralysis, dysarthria, dysphagia, diplopia, ptosis, weakness, respiratory failure. Autonomic signs: dry mouth, fixed or dilated pupils.

Tests:

Find toxin in blood samples or, in wound botulism, identify *C. botulinum* in wound specimens by prompt referral to a reference lab. Samples include: serum, wound pus, swabs in anaerobic transport media (in the UK, phone 020 8200 6868).[235]

[prescription take]:

Get help (on ITU). IM botulism antitoxin works if given early (eg 50,000U of types A & B + 5000U of type E). Also give to those who have ingested toxin but are as yet asymptomatic. *C. botulinum* is sensitive to benzylpenicillin and metronidazole. In the UK, if out of hours, antitoxin is sourced via CDSC doctors (tel. 020 7210 300).[236]

Actinomycosis

is caused by ***Actinomyces israelii***. Usually causes subcutaneous infections, forming sinuses with pus which contains sulfur granules—eg on the jaw (or IUCDs, OHCS p298). It may cause abdominal masses (may mimic appendix mass).

[prescription take]:

Benzylpenicillin (p368) for ≥2wks post-clinical cure. Liaise with surgeons.

Miscellaneous Gram negative bacteria

Enterobacteria

Some are normal gut commensals, others environmental organisms. They are the commonest cause of UTI and intra-abdominal sepsis, especially post-operatively and in the acute abdomen. They are also a common cause of septicaemia. Unusually, they may cause pneumonia (especially ***Klebsiella***), meningitis, or endocarditis. These organisms can be sensitive to ampicillin and trimethoprim but resistance is growing. Resistance of *K. pneumoniae* to amikacin is seen in 50% (in some places), ceftazidime (90%) and tobramycin (90%)[237] so imipenem may be needed. ***Salmonella*** & ***Shigella*** are discussed on p380 & p414.

Pseudomonas aeruginosa

is a serious pathogen (esp. if immunocompromised and in cystic fibrosis). It causes pneumonia, septicaemia, UTI, wound infection, osteomyelitis, and cutaneous infections. The main problem is its increasing antibiotic resistance.

Treatment:

Piperacillin (p368) or mezlocillin + an aminoglycoside. Ciprofloxacin, ceftazidime, and imipenem (p371) are useful against *Pseudomonas*.

Haemophilus influenzae

typically affects unvaccinated children usually <4yrs old. It causes otitis media, acute epiglottitis, pneumonia, meningitis, osteomyelitis, and septicaemia. In adults it may cause exacerbations of chronic bronchitis.

[prescription take]:

Unreliably sensitive to ampicillin; cefotaxime is more reliable. Capsulated types tend to be much more pathogenic than non-capsulated types.

Prevention:

Immunization with HIB vaccine (p381) has resulted in a dramatic fall in incidence.

Plague[ND]

Cause:

Yersinia pestis.

Incubation:

1-7d. ***Bubonic plague*** presents as suppurating lymphadenopathy (buboes).

Pneumonic plague:

'Flu-symptoms, dyspnoea, cough, copious, bloody sputum, septicaemia, and a fatal haemorrhagic illness (± buboes).

Diagnosis:

Phage typing of bacterial culture, or a 4-fold rise in antibodies to F antigen.[239]

[prescription take]:

Isolate suspects; streptomycin 15mg/kg/12h IM for 10d. If in 1st 1/3 of pregnancy, amoxicillin 250-500mg/8h PO; if later in pregnancy, co-trimoxazole 480mg/12h PO; children: co-trimoxazole.[240] Staying at home, quarantine (inspect daily for 1wk), insect sprays to legs and bedding, and avoiding dead animals helps stop spread.

Post-exposure prophylaxis:

Doxycycline 100mg/12h PO for 7d.

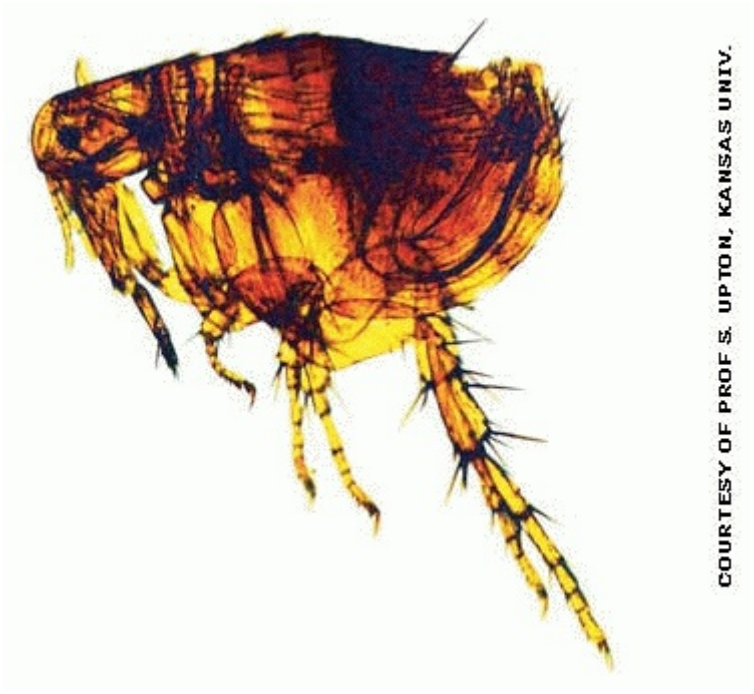


Fig 1. Rat fleas (*Xenopsylla cheopis*) spread plague; also cat fleas ± human-to-human droplet spread.[238]

Prevention:

Vaccines give no instant protection (multiple doses may be needed).

Brucellosis

This zoonosis (carried by domestic animals) is common in the Middle East. Typically affects vets or farmers. Cause: ***B. melitensis*** (the most virulent), ***B. abortus***, ***B. suis***, or ***B. canis***. Symptoms may be indolent and last for years—eg fever (PUO), sweats, malaise, anorexia, vomiting, weight loss, hepatosplenomegaly, constipation, diarrhoea, myalgia, backache, arthritis, sacroiliitis, rash, bursitis, orchitis, depression.

Complications:

Osteomyelitis, SBE/IE (culture -ve), abscesses (liver, spleen, lung), meningoencephalitis.

Diagnosis:

Blood culture (≥6wks but rapid culture systems available, contact lab); serology: if titres equivocal (eg >1 : 40 in nonendemic zones) do ELISA ± immunoradiometric assays; pancytopenia.

Treatment:

Doxycycline 100mg/12h PO for 6 weeks + streptomycin 1g/d IM for 2-3wks (↓relapse rate from 2-10% *vs* >20%).[241] If a child, get expert help.

Whooping cough[ND]

is caused by ***Bordetella pertussis***. It begins with a prodromal catarrhal, fever, and cough. After a week or so, the child develops the characteristic paroxysms of coughing and inspiratory whoops. Most children recover well, although the illness may last months. Some, especially the very young, may

develop pneumonia (±bronchiectasis) or convulsions and brain damage.

[prescription take]:

Erythromycin, given early, if only to limit spread. *Immunization* (p381) has not controlled the disease in Europe: incidence in adults doubled over a recent 5yr period.[242]

Pasteurella multocida

is acquired via domestic animals, eg cat or dog bites. It can cause skin infections, septicaemia, pneumonia, UTI, or meningitis.

[prescription take]:

Co-amoxiclav, p368 eg is 1g/6-8h IV over 3-4 min (expressed as amoxicillin).

Yersinia enterocolitica

In Scandinavia, this is a common cause of a reactive, asymmetrical polyarthritis of the weight-bearing joints, and, in America, of enteritis. It also causes uveitis, appendicitis, mesenteric lymphadenitis, pyomyositis, glomerulonephritis, thyroiditis, colonic dilatation, terminal ileitis and perforation, and septicaemia.

Diagnosis:

Serology is often more helpful than culture, as there may be quite a time-lag between infection and the clinical manifestations. Agglutination titres >1 : 160 indicate recent infection.

Treatment:

None may be needed or ciprofloxacin 500mg/12h PO for 3-5d.

Moraxella catarrhalis

(Gram -ve diplococcus) is an increasingly recognized cause of pneumonia, exacerbations of COPD, otitis media, sinusitis, and septicaemia.

Treatment:

Clarithromycin 500mg/12h PO.

Tularaemia

is caused by ***Francisella tularensis*** (Gram -ve bacillus), which may be acquired by handling infected animal carcasses. It causes rash, fever, malaise, tonsillitis, headache, hepatosplenomegaly, and lymphadenopathy. There may be papules at sites of inoculation (eg fingers).

Complications:

Meningitis, osteomyelitis, SBE/IE, pericarditis, septicaemia.

Diagnosis:

Contact local microbiologist for advice. Only use laboratories with safety cabinets suitable for dangerous pathogens. Swabs and aspirates must be transported in approved containers.

Treatment:

Gentamicin or streptomycin 7.5-10mg/kg/12h IM for 2wks. Oral tetracycline may be suitable for chemoprophylaxis.

Prevention:

Find the animal vector; reduce human contact with it as far as possible. Vaccination may be possible for high-risk groups.

Cat scratch disease

Mostly due to ***Bartonella henselae*** (a small, curved, pleomorphic, Gram negative rod) or ***Afepilis felis***. Think of this when any three of the following coexist: an inoculating cat scratch; regional lymphadenopathy (with negative lab tests for other causes of lymphadenopathy, p64); positive cat scratch skin test antigen response; or microabscesses in lymph nodes. In HIV-infected patients, the skin lesions may resemble Kaposi's sarcoma.

Treatment:

Usually resolves spontaneously within 1-2 months. One trial found that azithromycin ↑speed of resolution of lymph nodes.[243] Other drugs that have been used include ciprofloxacin, rifampicin and co-trimoxazole. Usually unresponsive *in vivo* despite susceptibility *in vitro*.

See also **Spirochaetes** p418; ***Neisseria*** p368, and ***Legionella*** p154.

Tetanus[ND]

Essence

Tetanospasmin, *Clostridium tetani's* exotoxin, causes muscle spasms and rigidity, cardinal features of tetanus (='to stretch').

Incidence

~50 people/yr in the UK. Mortality: 40% (80% in neonates).

Pathogenesis

Spores of *C. tetani* live in faeces, soil, dust, and on instruments. A tiny breach in skin or mucosa, eg cuts, burns, ear piercing, banding of piles, may admit the spores. Diabetics are ↑risk. Spores then germinate and make the exotoxin. This travels up peripheral nerves and interferes with inhibitory synapses.

The Patient

15-25% will have no evidence of recent wounds. Signs appear from 1d to several months from the (often forgotten) injury. There is a prodrome of fever, malaise, and headache before classical features develop: *trismus* (=lockjaw; Greek trismos = grinding, hence difficulty in opening the mouth); *risus sardonicus* (a grinlike posture of hypertonic facial muscles); *opisthotonus* (**fig 1**); *spasms* (which at first may be induced by movement, injections, noise, etc., but later are spontaneous; they may cause dysphagia & respiratory arrest); autonomic dysfunction (arrhythmias ± wide fluctuations in BP).

Differential diagnosis

is dental abscess (both cause trismus), rabies, phenothiazine toxicity, and strychnine poisoning. Phenothiazine toxicity usually only affects facial and tongue muscles; if suspected, give benzatropine 1-2mg IV.

Poorer prognosis

Short incubation; trismus leads to spasms in <48h; neonates; elderly; postinfective; postpartum (a big cause of maternal mortality worldwide).

Treatment

▸▸Get help on ITU. ABC (may need tracheostomy & ventilation). Monitor ECG + BP + SpO_2 (keep >92%, eg with O_2 mask + reservoir); careful fluid balance.

- **Human tetanus immunoglobulin** (HTIG) 5000-10,000U IVI to neutralize toxin.
- Aim to keep the patient asleep but rousable to obey simple commands. **Diazepam** 5-20mg/8h PO (mild disease) or, to control spasms, 0.05-0.2mg/kg/h IVI (≲140mg/d) ***or*** **phenobarbital** 1.0mg/kg/h IM or IV + **chlorpromazine** 0.5mg/kg/6h IM (IV bolus is dangerous) starting 3h after the phenobarbital. If this fails to control the spasms, paralyse and ventilate (get anaesthetist's help). Dose example (OTM): **pancuronium** 2-4mg IV/1/2-2h (or by continuous IVI).

Prevention

Active immunization with tetanus toxoid is part of the 3-stage vaccine during the 1st year of life (eg Pediacel®, p381). Boosters are given on starting school and in early adulthood. Once 5 injections have been given, revaccinate only at the time of significant injury, and consider a final 1-off booster at ~65yrs.[244]

Primary immunization of adults:

0.5mL tetanus toxoid IM repeated twice at monthly intervals. In the UK, the formulation is Revaxis®, p381.

Wounds:

Any cut merits an extra dose of 0.5mL toxoid IM, unless already fully immune (a full course of toxoid or a booster in last 10yrs). If non-immune: 2 further injections (0.5mL IM) at monthly intervals. If partially immune (ie has had a toxoid booster or a full course >10yrs previously), a single booster is enough.[245]

Human tetanus immunoglobulin:

Give if non-immune or partially immune, defined above if wound is dirty, old (>6h), infected, devitalized, or soil-contaminated. Give 250-500 units IM, using a separate syringe and site to the toxoid injection.

- ▸ If immune status is unknown, assume that the patient is nonimmune. Routine infant immunization started in 1961, so many adults are at risk.
- ▸Hygiene education and wound debridement are of vital importance.

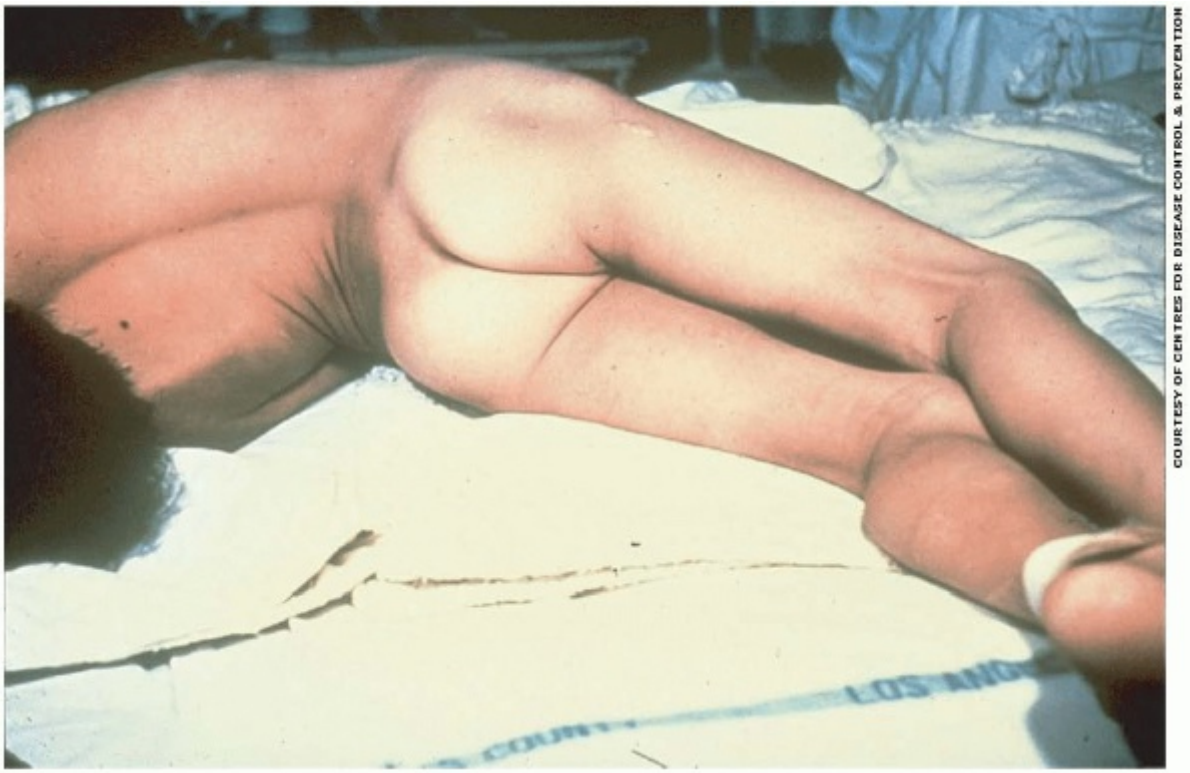


Fig 1. Spasm causing opisthotonus (arching of body with neck hyperextension).[246]

Enteric fever[ND]

Typhoid and paratyphoid

are caused by ***Salmonella typhi*** and ***S. paratyphi*** (types A, B, and C), respectively. (Other *Salmonella* cause D&V: p380 & p238.)

Incubation:

3-21d.

Spread:

Faecal-oral. 1% become chronic carriers.

Presentation:

Usually malaise, headache, high fever with relative bradycardia, cough, and constipation (or diarrhoea). CNS signs (coma, delirium, meningism) are serious. Diarrhoea is more common after the 1st week. Rose spots occur on the trunk of 40%, but may be very difficult to see. Epistaxis, bruising, abdominal pain, and splenomegaly may occur.

Tests:

First 10d: blood culture; later: urine/stool cultures. Bone marrow culture has highest yield (infiltration may cause ↓platelets & WCC). LFT↑. Widal test unreliable. DNA probes and PCR tests have been developed, but are not widely available.

Treatment:

Fluid replacement and good nutrition. There is good evidence that fluoroquinolones (eg ciprofloxacin 500mg/12h PO for 6d) are the best antimicrobial treatment for typhoid. Chloramphenicol is still used in many areas: 1g/8h PO until pyrexia diminishes, then 500mg/8h for a week and 250mg/6h to make up 14d (can be shorter). Other alternatives: cefotaxime, azithromycin, or amoxicillin (if fully susceptible). In severe disease, give IV ciprofloxacin or IV cefotaxime for 10-14d. In encephalopathy ± shock, give dexamethasone 3mg/kg IV stat, then 1mg/kg/6h for 48h. Drug resistance is an increasing problem, even with ciprofloxacin, eg due to mutations in the DNA gyrase enzyme of *S. typhi*.[247]

Complications:

Osteomyelitis (eg in sickle-cell disease); DVT ; GI bleed or perforation; cholecystitis; myocarditis; pyelonephritis; meningitis; abscess. Infection is said to have cleared when 6 consecutive cultures of urine and faeces are -ve. Chronic carriage is a problem; treat if at risk of spreading disease (eg food handlers). Ciprofloxacin 500mg/12h PO for 6 weeks; cholecystectomy may be needed.

Prognosis:

If untreated, 10% die; if treated, 0.1% die.

Vaccine:

p381.

Bacillary dysentery[ND]

Shigella

causes abdominal pain and bloody diarrhoea ± sudden fever, headache, and occasionally neck stiffness. CSF is sterile. UK school epidemics are usually mild (often ***S. sonnei***), but imported dysentery may be severe (often ***S. flexneri*** or ***S. dysenteriae***).

Incubation:

1-7d.

Spread:

Faecal-oral.

Diagnosis:

Stool culture.

Treatment:

Fluids PO. Avoid anti-diarrhoeal drugs. Drugs: ciprofloxacin 500mg/12h PO for 3-5d. Imported shigellosis is often resistant to several antimicrobials: sensitivity testing is important for all enteric fevers. There may be associated spondyloarthritis (p537).

Cholera[ND]

Caused by ***Vibrio cholerae*** (Gram negative comma-shaped rod, **fig 1**, on p364). Pandemics or epidemics may occur, eg outbreaks in Angola and the 1990s epidemic in S America and Bangladesh (Bengal *Vibrio cholerae 0139*).

Incubation:

From a few hours to 5d.

Spread:

Faecal-oral.

Presentation:

Profuse (eg 1L/h) watery ('rice water') stools, fever, vomiting, and rapid dehydration (the cause of death).

Diagnosis:

Stool microscopy and culture.

Treatment:

Strict barrier nursing. Replace fluid and salt losses meticulously (0.9% saline IVI if shocked), add 20mmol/L K+ until U&E known (avoid plain Ringer's lactate: it may cause fatal K+↓). Oral rehydration with WHO formula (20g glucose/L) is not so effective as cooked rice powder solution (50-80g/L) in reducing stool volume.[248] Its high osmolarity (310mmol/L vs 200mmol/L) is also unfavourable to water absorption. A dose of ciprofloxacin 1g PO may reduce fluid loss.[249]

Prevention:

Only drink boiled or treated water. Cook all food well; eat it hot. Avoid shellfish. Peel all vegetables. Heat-killed vaccine (serovar O1) gives limited protection, and is no longer needed for international travel; newer vaccines are non-standard.[250]

Whose deaths really matter? Enteric fevers suggest an answer

In 2006, DNA analysis of pulp in the teeth of Athenians dying in the great plague of 430BC revealed that the cause was typhoid fever.[251] 30% of Athenians died, including Pericles, their leader. He gave us the Parthenon, juries, free theatre, and, in his own immortal oratory, the notion that it is better to die resisting than to live in submission.[252] This is definitely *not* the right approach to infectious diseases: Pericles should have promulgated a third way: neither victory nor submission, but, more subtly, *accommodation*, or something even more symbiotic.

For the next 23 centuries, typhoid fever carried on killing, teaching us nothing much, until noon on 23 April 1851, when a little-known girl was quietly expiring in Malvern. Her name was Annie Darwin, her father's, Charles. Annie was his favourite fun-loving daughter, and with her lingering enteric death Darwin gave up all belief in a just and moral universe. Thus unimpeded, his mind was able to frame and compellingly justify the most devastating answer to the oldest question: that we are here by accident, thanks to natural selection, the survival of the fittest, and the 'wasteful, blundering, low & horridly cruel works of nature'.[1]

The next significant enteric death was 3 summers later at 40 Broad Street, in the Parish of St James, London, where a child became ill with diarrhoea in August, 1854, dying on September 2. Her mother rinsed the soiled nappies into the house drains. These led within feet of the supply to the Broad Street pump. Both the drain and the pump's well had faulty brickwork allowing the waters to mix. From this confluence sprung the discipline of Public Health, for many of the 500 or so ensuing late summer deaths from cholera clustered around this Broad Street pump, as diagrammed by the local doctor, Dr John Snow. He used his now famous diagrams locating each death to motivate the Board of Guardians of St James's parish at its meeting of Sept. 7th 'In consequence of what I said, the handle of the pump was removed the following day'[2]—so inaugurating the control of cholera. If Snow were alive today, he might be busy unplugging all our carbon-emitting power-stations (as killing as cholera), but note that Snow worked through committees to save his countless lives, not by direct action.

These events illustrate two counter-intuitive truths: knowledge of the microscopic cause of a disease is not required for public health measures to succeed (*Vibrio cholerae* was as yet undiscovered)—and even the most parochial Church Council is capable of prompt and decisive action affecting the lives of millions, when informed by an intelligent doctor in command of the facts.

There is one metaphysical truth revealed by these enteric deaths, which would not have escaped Pericles had he only taken the trouble to become a medical student for long enough to realise that his overvalued ideal of heroism is often pointless.[3] Pericles never gave his condolences to parents who lost their sons in battle, because, he said, a hero's death was the finest thing that could befall a man. We meet many heroic deaths on our wards, but they seem oddly pointless in retrospect. This is why we award the palm to Annie, whose unheroic death so transforms the inner landscapes of the mind. And with her in mind, we can confidently relieve our patients of the notion that they must die fighting.

[2] J Snow 1854 *Med Times Gaz* **9** 321. Snow (a teetotaller, a vegetarian, and a virgin) is unfairly portrayed as secular saviour; he was really just the man on the spot who took logical decisions.

[3] If you doubt that heroism is often pointless, visit the Somme where lies buried the old lie '***dulce et decorum est pro patria mori***'. Wilfred Owen (1893-1918) wrote in a letter to his mother: 'The famous Latin tag [Horace] means *It is sweet and meet to die for one's country.* Sweet! and decorous! …'

Leprosy[ND]

▸The diagnosis of leprosy (Hansen's disease) must be considered in all who have visited endemic areas who present with painless disorders of skin and nerves. It is not just a tropical disease, and may occur in the USA, eg in Texas, Louisiana, and California, as well as Hawaii and Puerto Rico.

Mycobacterium leprae

affects millions of people in the Tropics and subtropics. Since the widespread use of dapsone, and WHO elimination campaigns, prevalence has fallen (from 0.5% to 0.4/10,000 in Uganda; from 11% to 4/10,000 in parts of India).[253] Incidence remains stable, however, at about 800,000 new cases/yr worldwide, many of whom are children.

The Patient

The incubation period is months to years, and the subsequent course depends on the patient's immune response. If the immune response is ineffective, '*lepromatous*' or '*multibacillary*' disease develops, dominated by foamy histiocytes full of bacilli, but few lymphocytes. If there is a vigorous immune response, the disease is called '*tuberculoid*' or '*paucibacillary*', with granulomata containing epithelioid cells and lymphocytes, but few or no demonstrable bacilli. Between these poles lie those with 'borderline' disease.

Skin lesions:

Hypopigmented anaesthetic macules, papules, or annular lesions (with raised erythematous rims). Erythema nodosum (**fig 1** p267) occurs in 'lepromatous' disease, especially during the 1st year of treatment.

Nerve lesions:

Major peripheral nerves may be involved, leading to much disability. Sometimes a thickened sensory nerve may be felt running into the skin lesion (eg ulnar nerve above the elbow, median nerve at the wrist, or the great auricular nerve running up behind the ear).

Eye lesions:

▸*Refer promptly to an ophthalmologist*. The lower temperature of the anterior chamber favours corneal invasion (so secondary infection and cataract). Inflammatory signs: chronic iritis, scleritis, episcleritis. There may be reduced corneal sensation (V nerve palsy), and reduced blinking (VII nerve palsy) and lagophthalmos (difficulty in closing the eyes; *lagos* is Greek for hare), ± ingrowing eyelashes (trichiasis).

Diagnosis

Biopsy a skin lesion; *in vitro* culture is not possible. As an incidental curio, armadillo (or mouse) foot-pad culture works, but don't taunt your lab by requesting this test! Split skin smears for AFB are +ve in borderline or lepromatous disease. Classification matters: it reflects biomass of bacilli, influencing treatment: the more organisms, the greater the chance that some will be drug resistant. Other tests: neutrophilia, ESR↑, IgG↑, false +ve rheumatoid test.

Treatment[254]

Ask a local expert about: • Resistance patterns, eg to dapsone, when ethionamide may (rarely) be needed • Using prednisolone for severe complications • Is surgery ± physiotherapy needed as well as drug therapy? In the UK, seek advice from the panel of Leprosy Opinion. In other areas, the administration of some drugs should be supervised (S) whereas others need no supervision (NS). For multibacillary and borderline disease, WHO advises rifampicin 600mg PO

monthly (S), dapsone 100mg/24h PO (NS), and clofazimine 300mg monthly (S) + 50mg/24h (NS) for 2yrs. In paucibacillary leprosy, rifampicin 600mg monthly (S) and dapsone 100mg/24h (NS) for 6 months. In single skin lesion paucibacillary disease, single-dose therapy (rifampicin 600mg, ofloxacin 400mg, minocycline 100mg, all PO, together) is advised.

▸Beware sudden permanent *paralysis* from nerve inflammation caused by dying bacilli (± *orchitis*, *prostration*, or *death*); this 'lepra reaction' may be mollified by thalidomide (***NOT*** if pregnant). Liaise urgently with a leprologist. Supervised therapy may be problematic as many patients find it hard to attend (nomads, jungledwellers). WHO has proposed 'accompanied' multi-drug therapy, where someone close to the patient takes responsibility for ensuring treatment compliance. This strategy is controversial.[255]

What is more communicable than leprosy?

This page is dedicated to Joseph deVeuster of Kalawao, Molokai, in Hawaii, who befriended sufferers of leprosy in a remote pacific colony. Here the leprosy victims, arriving by ship, were sometimes told to jump overboard and swim for their lives, so frightened were the sailors of this island of contagion. But when they arrived they found a friend who was both doctor and priest to them, whose self-imposed duty was to build their homes, their churches—and their coffins. Without any distinction of race or religion, he gave a voice to the voiceless, building a unique community where the joy of being together gave people new reasons for living.

It is said that after spilling hot water painlessly on his foot, he diagnosed his own leprosy. After that, his sermons beginning 'We lepers…' had added veracity.

He gave everything to leprosy—and leprosy took all it could from him, including, on April 15th 1889, his life.

We may look upon that water flowing over his foot not so much as a death sentence, but as one of those initiation ceremonies devised by ancient shamans who realized that it was by these close encounters with death that we augment our spirituality, and so are able to heal.

Joseph deVeuster also invalidates all our definitions of health, and, more importantly, he demonstrates that optimism works and is more communicable than leprosy, proving that there is nothing that cannot be transcended.

Why are doctors and lepers similar? Both will eventually stop feeling unless cherished.

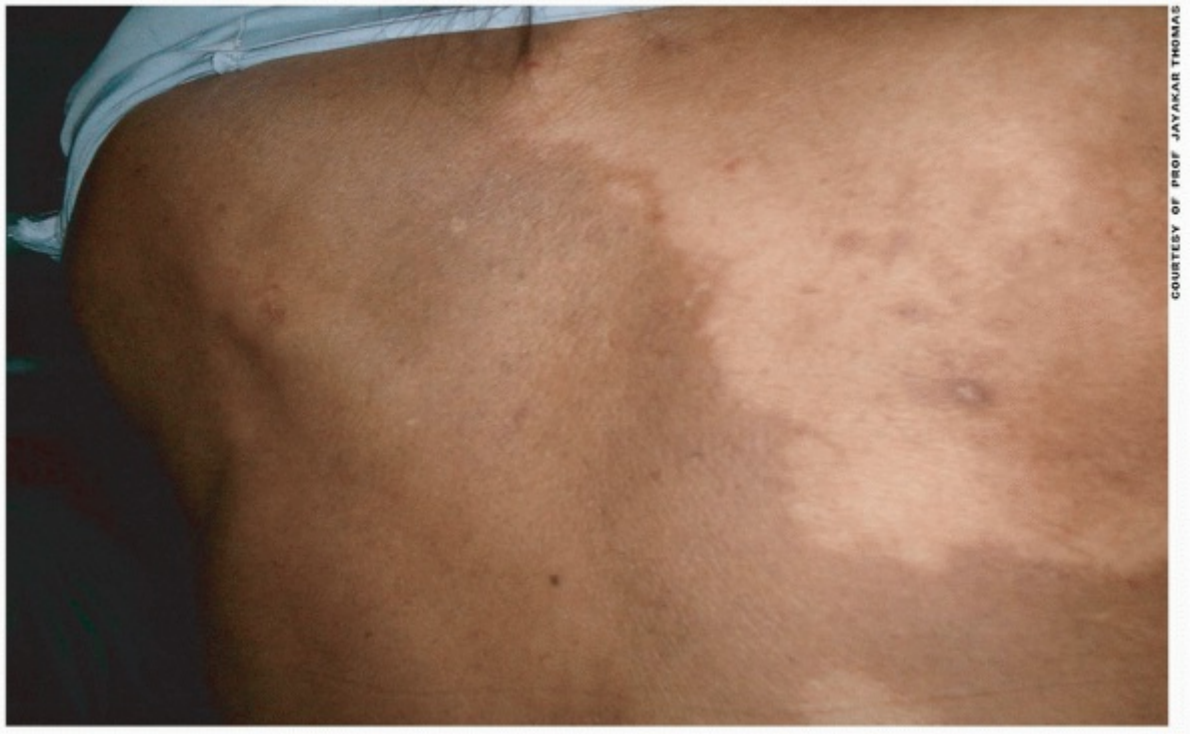


Fig 1. Think of leprosy in everyone with anaesthetic hypopigmented macules or plaques. Could this be vitiligo? No: vitiligo is more demarcated and **de**pigmented (chalk white).[256] See **fig 4** on p547.

Spirochaetes

Lyme disease[257]

is a tick-borne infection caused by *Borrelia burgdorferi*. Although famously described in Lyme (Connecticut) it is now global, eg New Forest.[UK] ▸≤75% remember the tick bite.

Signs:

Cognition↓; lymphadenopathy; arthralgia/arthritis; myocarditis; heart block; meningitis; ataxia; amnesia; cranial nerve palsies; neuropathy; lymphocytic meningoradiculitis (Bannwarth's syndrome). If the problem is a '?Lyme' skin condition, eg ACA (below) erythema migrans target lesions (p546) you need to ask about Bell's palsy[etc] *years* ago.

△:

Clinical ± serology; if -ve do, PCR/LP.

[prescription take]:

Skin rash: doxycycline 100mg/12h PO (amoxicillin or penicillin V if <8yrs or pregnant) for 14-21d. Later complications: high-dose IV benzylpenicillin, ceftriaxone.

Prevention:

Keep limbs covered; use insect repellent; tick collars for pets; check skin often when in risky areas. Vaccination is available eg if living in high-risk areas. Advice differs on prophylaxis after a tick bites. A single dose of doxycycline 200mg PO given within 72h of a bite is effective prophylaxis; in highly endemic areas, this may be worthwhile (eg if risk is >1%).

Removing ticks:

Suffocate tick with, eg petroleum jelly, then remove by grasping close to mouth parts and twisting off; then clean skin. Skin complications: **acrodermatitis chronica atrophicans** (ACA; skin is as 'thin as cigarette paper'); **borellia lymphocytoma** manifests eg as a blue/red discolouration of the earlobe; **erythema migrans**, p546.

Fig 1. *Amblyomma americanum*

Endemic treponematoses

Yaws

is caused by *T. pertenue* (serologically indistinguishable from *T. pallidum*). It is a chronic granulomatous disease prevalent in children in the rural Tropics. Spread is by direct contact, via skin abrasions, and is promoted by poor hygiene. The primary lesion (an ulcerating papule) appears ~4wks after exposure. Scattered secondary lesions then appear, eg in moist skin, but can be anywhere. These may become exuberant. Tertiary lesions are subcutaneous gummatous ulcerating granulomata, affecting skin and bone. Cardiovascular and CNS complications do not occur.

Pinta

(*T. carateum*) affects only skin; seen in Central and S America.

Endemic non-venereal syphilis

(*bejel; T. pallidum*) is seen in Third World children, when it resembles yaws. In the developed world, *T. pallidum* causes *syphilis* (p419).

Diagnosis:

Clinical.

[prescription take]:

Procaine penicillin (p368).

Weil's disease[ND]

is caused by ***Leptospira interrogans*** (eg serogroup *L. icterohaemorrhagiae*). Spread is typically by contact with infected rat urine, eg in slums or while swimming, canoeing or cycling through puddles. After an incubation of 2-20d there is abrupt fever, myalgia/myositis, cough, chest pain ± haemoptysis—

then recovery, or jaundice, meningitis, uveitis, and renal failure.

△: Blood culture +ve only up to day 4 of illness; serology.

[prescription take]:

IV penicillin or amoxicillin. Prophylaxis: doxycycline 200mg/wk *may* have a role—eg for water sports in dangerous places.

Canicola fever

is an aseptic meningitis caused by *Leptospira canicola*.

Relapsing fever[ND]

This is caused by *Borrelia recurrentis* (louse-borne) or *B. duttoni* (tick-borne). It typically occurs in pandemics following war or disaster, and may kill millions.

Incubation:

4-18d.

Presentation:

Abrupt onset fever, rigors, and headache. A petechial rash (which may be faint or absent), jaundice, and tender hepatosplenomegaly may develop. Serious complications include myocarditis, hepatic failure, and DIC. Crises of very high fever and tachycardia occur. When the fever abates, hypotension due to vasodilatation may occur and be fatal. Relapses occur, but are milder.

Tests:

Organisms are seen on Leishman-stained thin or thick films.

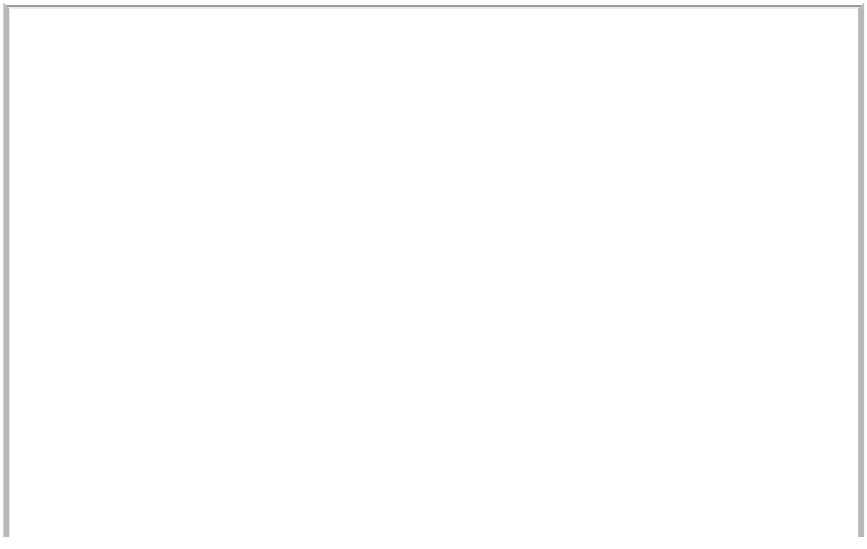
Treatment:

Tetracycline 500mg PO or 250mg IV as a single dose (but for 10d for *B. duttoni*). Alternative: doxycyline 100mg/12h PO. The Jarisch-Herxheimer reaction (p419) is fatal in 5%: meptazinol 100mg IV slowly is given as prophylaxis with the tetracycline, repeated 30min later (with the chill phase) and during the flush phase (if systolic BP <75mmHg). Delouse the patient and their clothes.[258] Doxycycline (p370) is useful prophylaxis in high-risk groups.

Syphilis: the archetypal spirochaetal disease

▸*Any anogenital ulcer is syphilis until proven otherwise*. UK incidence is rising, eg >2254 new infections/yr.[260] In a recent 5-yr period, rates rose by 213% in heterosexual men, 1412% in men who have sex with men, and 22% in women, with serious outbreaks in London & Manchester[261] as safe-sex messages are forgotten, ignored, or trounced.[262] *Treponema pallidum* (**fig 1**) enters via a graze, during sex. All features are due to an endarteritis obliterans. *Incubation:* 9-90d. 4 stages:

- *Primary syphilis:* Macule at site of sexual contact forms a painless hard ulcer (*primary chancre;* it is very infectious).
- *Secondary syphilis:* Occurs 4-8wks after the chancre: rash (trunk, face, palms, soles), malaise, lymphadenopathy, T°↑, alopecia, condylomata lata (flattened, sometimes moist papules around or beyond the genitals),[263] palatal or buccal snail-track ulcers; rarely hepatitis, meningism, nephrosis, and uveitis.
- *Tertiary syphilis* follows >2yrs latency (when patients are non-infectious): there are *gummas* (granulomas in skin, mucosa, bone, joints, viscera, eg lung, testis).
- *Quaternary syphilis Cardiovascular:* Ascending aortic aneurysm/aortic regurgitation. *Neurosyphilis: **(a)** Meningovascular:* Cranial nerve palsies, stroke; ***(b)** General paresis of insane (GPI):* Dementia, psychoses (fatal untreated; treatment *may* reverse it); ***(c)** Tabes dorsalis:* Sensory ataxia, numb legs, chest, and bridge of nose, lightning pains ('like a bolt from the blue'), gastric crises, reflex loss, plantars↑↑, Charcot's joints (p508). *Argyll Robertson pupil* (p70).



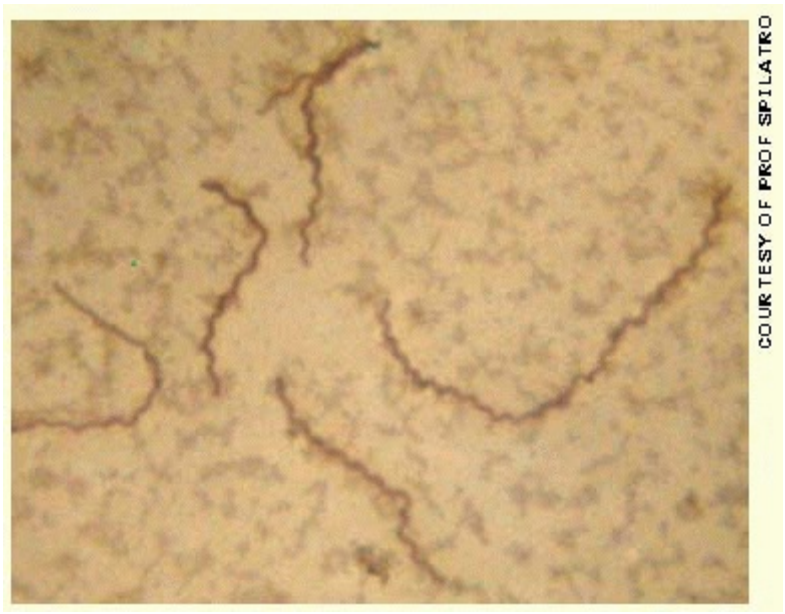


Fig 1. *T. pallidum.*[259]

Cardiolipin antibody:

Not treponeme-specific. Detectable in primary disease but wanes in late syphilis. Indicates active disease and becomes -ve after treatment. *False* +ve*s* (with -ve treponemal antibody): pregnancy, immunization, pneumonia, malaria, SLE, TB, leprosy. *Examples:* **venereal disease research laboratory slide test** (**VDRL**), **rapid plasma reagin** (**RPR**), **Wassermann reaction** (**WR**).

Treponeme-specific antibody:

Positive in 1° disease, remains so despite treatment. *Examples:* ***T. pallidum*** **haemagglutination assay** (**TPHA**), **fluorescent treponemal antibody (FTA)**, *T. pallidum* **immobilization test** (**TPI**). Non-specific, also +ve in non-venereal yaws, bejel, or pinta.

ELISA:

Syphilis ELISA IgG and ELISA IgM.

Other tests

In 1° syphilis, treponemes may be seen by *dark ground microscopy* of chancre fluid; serology at this stage is often -ve. In 2° syphilis, treponemes are seen in the lesions and both types of antibody tests are positive. In late syphilis, organisms may no longer be seen, but both types of antibody test usually remain +ve (cardiolipin antibody tests may wane). In neurosyphilis, CSF antibody tests (particularly FTA and TPHA) are +ve. If HIV+ve, serology may be negative during syphilis reactivation. PCR may help.

Treatment:

Contact tracing; screening for other sexual infections (eg HIV) Procaine **penicillin** (=procaine benzylpenicillin) 600mg/24h IM for ~28d (14d in early syphilis), or **doxycycline** 200mg/12h PO for 28d (100mg/12h PO for 14d in early syphilis). Beware *Jarisch-Herxheimer reaction:* Fever, pulse↑, and vasodilatation hours after the 1st dose of antibiotic. It is thought to be from sudden release of endotoxin. Commonest in 2° disease; most dangerous in 3°. Consider steroids. If HIV+ve, penicillin may not stop neurosyphilis; consult microbiologist.

Congenital syphilis:

OHCS p35.

Poliomyelitis[ND]

Polio is a highly contagious picornavirus (**fig 1** BOX), though only a small proportion of patients develop any illness from the infection.

Spread:

Droplet or faeco-oral.

The Patient:

7 days' incubation, then 2 days' 'flu-like prodrome, leading to a 'preparalytic' stage: fever, tachycardia, headache, vomiting, neck stiffness, and unilateral tremor. In <50% of patients this progresses to the paralytic stage: myalgia, lower motor neurone signs, and respiratory failure—*with no sensory signs*.

Tests:

CSF: WCC↑, polymorphs then lymphocytes, otherwise normal; paired sera (14 days apart); throat swab & stool culture identify virus.

△△*:*

Non-viral causes of flaccid paralysis: Borrelia; mycoplasma; diphtheria; botulism; heavy metals; transverse myelitis; polymyositis.

Natural history:

<10% of those with paralysis die. There may be *delayed progression* of paralysis (post-polio syndrome, PPS). *Risk factors for severe paralysis:* Adulthood; pregnancy; post-tonsillectomy; muscle fatigue/trauma during incubation period. *PPS* causes fatigue, weakness, joint and muscle pains, and worsening function (not necessarily in the sites originally affected). PPS management centres on just enough exercise to prevent wasting but no so much as to increase weakness in already damaged muscles.[264]

Vaccine:

p381.

Rabies[ND]

Rabies is a rhabdovirus spread by bites from any infected mammal, eg bats, dogs, cats, foxes, or raccoons (bites may go unnoticed[265]).

The Patient:

Usually 9-90 days' incubation, so give prophylaxis even several months after exposure. Prodromal symptoms: headache, malaise, abnormal behaviour, agitation, fever, and itching at the site of the bite. Progresses to 'furious rabies', eg with waterprovoked muscle spasms often accompanied by profound terror (hydrophobia). In 20%, 'dumb rabies' starts with flaccid paralysis in the bitten limb and spreads.

Pre-exposure prophylaxis

(eg vets, zoo-keepers, customs officials, bat handlers, travellers in rabies area for >1 month or at especial risk, or if access to post-exposure treatment is problematic): Give human diploid cell strain vaccine (1mL IM, deltoid) on days 0, 7, & 28, and again at 2-3yrs if still at risk.

Treatment if bitten where rabies is endemic

(if unvaccinated): Wash the wound well. ▸Seek help (UK *virus reference lab, tel.*: 020 8200 4400). Observe the biting animal to see if it dies (but it is possible that it may not die of rabies before the patient does).[266] Clean the wound. *If previously immunized:* give vaccine (1mL IM) on days 0 and 3. *If previously unimmunized:* give vaccine on days 0, 3, 7, 14, and 28 and human rabies immunoglobulin (20U/kg on day 0; half given IM and half locally infiltrated around wound). Rabies is fatal once symptoms begin (but survival has occurred, with optimal CNS/cardiorespiratory support). Vaccinate attending staff.

Viral haemorrhagic (and related) fevers[ND]

Yellow fever:

An epidemic arbovirus disease spread by *Aedes* mosquitoes (Brazil, Bolivia, Peru, and Central and West Africa). *Immunization:* p367. *Incubation:* 2-14d. *The Patient:* In mild forms, fever, headache, nausea, albuminuria, myalgia, and relative bradycardia. If severe: 3 days of headache, myalgia, anorexia ± nausea, followed by abrupt fever, a brief remission, then prostration, jaundice (± fatty liver), haematemesis and other bleeding, oliguria. *Mortality:* <10% (day 5-10). *Diagnosis*: ELISA. *Treatment:* Symptomatic.

Lassa fever[ND], *Ebola virus*[ND], *Marburg virus*[ND], & *dengue haemorrhagic fever*

(DHF—this 'unofficial' haemorrhagic fever is the commonest arbovirus disease).[267] They start with sudden headache, pleuritic pain, backache, myalgia, conjunctivitis, prostration, dehydration, facial flushing (dengue), and T°↑. Bleeding soon supervenes. There may be resolution, or renal failure, encephalitis, coma, and death.

[prescription take]:

Primarily symptomatic; ribavirin is useful in Lassa fever if given early in disease. ▸*Use special infection control measures (Lassa, Ebola, Marburg); get expert help at once.*

Polio: a tantalizing exercise in prevention and (near) eradication

- Pre-1950s, polio distribution was worldwide. In 1952, during an epidemic in Copenhagen, the cause of death was established as CO2 retention. Mechanical ventilation began in special centres—the birth of intensive care units.[268]
- 12 April 1955: vaccination starts with Salk's inactivated vaccine.
- 1958: Sabin donated his 3 attenuated strains to Chumakov in Moscow, who produced the 3 vaccines, giving them to 15 million people in 1 year.
- 1960s: the 3 vaccines were mixed, to produce a single oral polio vaccine.
- 1988: Estimated 350,000 cases worldwide, occurring in 125 countries. The Global Polio Eradication Initiative, aiming to protect children worldwide through vaccination, is launched; the aim was eradication by the year 2000.
- 1991: Transmission interrupted in the West.
- 1993: China starts national immunization days; >80,000,000 vaccinated in 2 days; in 1994 only 5 cases of virus-confirmed wild polio.
- 1994: WHO declares the Americas polio-free.
- 1997: 1 case of wild polio in all of Europe.
- 1999: Only 7090 cases, worldwide.
- 2000: WHO declares Western Pacific polio-free.
- 2001: 483 cases in 10 endemic countries.
- 2002: WHO declares Europe polio-free.

- 2004: 6 polio-endemic countries: Afghanistan; India; Niger; Nigeria; Pakistan.[269]
- 2006: Transmission re-established in: Nigeria, Sudan, Egypt, Central African Republic, Mali, Côte D'Ivoire, Somalia, Burkina Faso, Uttar Pradesh.[270][271]

Before 2005 most cases in the West were adult contacts of child vaccinees; these cases have stopped as live vaccine has been replaced by inactivated vaccine.

NB: Sabin viruses and their genetic revertants can cause chronic infection in immunodeficient people, who may shed neurovirulent virus in faeces for years. So programmes of oral vaccination should not continue one day longer than necessary to eliminate disease caused by wild virus.[272]

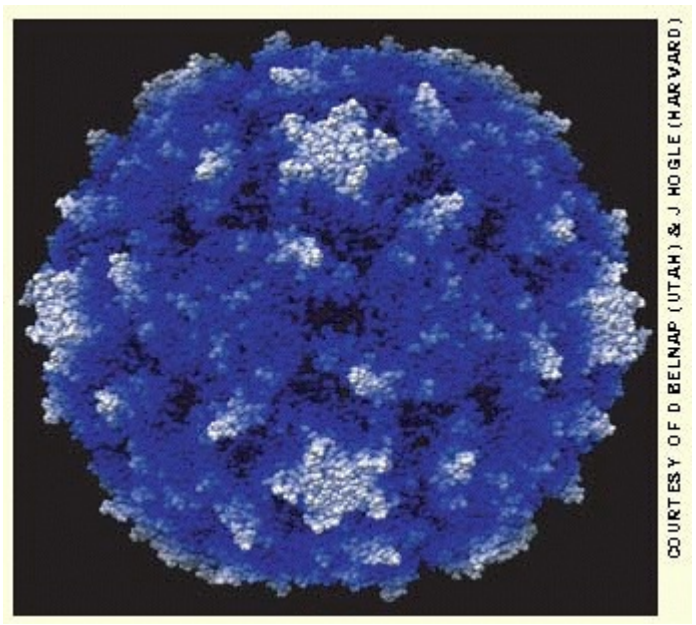


Fig 1. Poliovirus

Dengue fever (DF) and dengue haemorrhagic fever (DHF)

There is a global pandemic of this RNA flavivirus, related to poor vector control (*Aedes* mosquitoes), urbanization,[1] poor waste disposal, and rapid migrations bringing new strains (DEN-2) which become more virulent in those who have had mild dengue. Global warming is also important: a temperature rises of 1-3° increases transmission, leading to an extra 25,000 cases/yr. WHO_{data} Incidence: 50-100×10^6/yr; 250,000-500,000/yr get DHF.[2]

Infants typically have a simple febrile illness with a maculopapular rash. Older children/adults have flushing of face, neck, and chest or a centrifugal maculopapular rash from day 3—or a late confluent petechiae with round pale areas of normal skin—also headache, arthralgia, jaundice; hepatosplenomegaly; anuria.

Haemorrhagic signs:

(Unlikely if AST normal).[273] Petechiae, GI, gum or nose bleeds, haematuria; hypermenorrhoea.

Monitor:

BP; urine flow; WCC↓; platelets↓; PCV; +ve tourniquet test (>20 petechiae/inch^2) + PCV↑ by 20% are telling signs (rapid endothelial plasma leak is the key pathophysiology of DHF).

△△:

Chikungunya,[2] measles, leptospirosis, typhoid, malaria.

Exclusion:

If symptoms start >2wks after leaving a dengue area, or if fever lasts >2wks, dengue can be 'ruled out'.

[prescription take]:

Prompt IV resuscitation, eg Ringer's lactate. ▸▸If shocked (mortality 40%), give a bolus of 15mL/kg; repeat every ½h until BP rises, and urine flow at >30mL/h.[274]

Arthropod-borne bacteria

Q fever

is caused by ***Coxiella burnetii*** (100 cases/yr in the UK). It is so named because it was first labelled 'query' fever in workers in an Australian abattoir.

Epidemiology:

Occurs worldwide, and is usually rural, with reservoirs in cattle and sheep. The organism is resistant to drying and is usually inhaled from infected dust. It can be contracted from unpasteurized milk, directly from carcasses in abattoirs, sometimes by droplet spread, and rarely from tick bites.

Clinical features

Suspect Q fever in anyone with a PUO or atypical pneumonia. It may present with fever, myalgia, sweats, headache, cough, and hepatitis (± splenomegaly). 275 If the disease becomes chronic, suspect endocarditis (typically 'culture-negative'). This usually affects the aortic valve, but clinical signs may be absent. It also causes miscarriages and CNS infection.

Tests:

CXR may show consolidation, eg multilobar or slowly resolving. Liver function tests may be hepatitic and biopsy may show granulomata. Diagnosis is serological: phase I antigens suggest chronic infection; phase II antigens suggest acute infection. PCR may be used on tissue samples. CSF tests may be needed.

Treatment:

Get expert microbiological help.

Acute:

Tetracycline or doxycycline for 2wks. Minocycline, clarithromycin, ciprofloxacin (in pregnancy) and co-trimoxazole are used.

Chronic:

Ciprofloxacin + rifampicin for 2yrs ± valve replacement.

Prevention:

Vaccination for those whose occupation places them at high risk.

Bartonellosis

is caused by ***Bartonella bacilliformis***, a Gram -ve, motile, bacilluslike organism which parasitizes RBCS. Spread is by sandflies in the Andes, Peru, Equador, Colombia, Thailand, and Niger. Transient immunosuppression leads to other infections (eg *Salmonella*).

Incubation:

10-210 days (mean=60d).

Signs:

Fever, rashes, lymphadenopathy, hepatosplenomegaly, jaundice, cerebellar syndromes, dermal nodules (verrugas), retinal haemorrhages, myocarditis, pericardial effusion, oedema, and rarely, meningo-encephalomyelitis.

Tests:

Giemsa-stained blood films. Blood culture (prolonged). Coombs' -ve haemolytic anaemia, and hypochromic, macrocytic red cells with a megaloblastic marrow. CSF pleocytosis. Serological tests are not widely available.

Treatment:

Responds to penicillin, but chloramphenicol (p414) or ciprofloxacin (500mg/12h PO for 10d) are often used because of frequent association with salmonelloses. Steroids may be indicated if there is severe neurological involvement.

Cat scratch disease

(p411) is caused by ***Bartonella henselae***.

Trench fever

is caused by ***Bartonella quintana*** inoculated from infected louse faeces, not only in soldiers, but also in the homeless, and in alcoholics.

Clinical features:

Fever, headache, myalgia, dizziness, back pain, macular rash, eye pain, leg pain, splenomegaly, endocarditis (rare). In HIV-infected patients, the skin lesions may resemble Kaposi's sarcoma. It is not fatal; it may relapse.

Tests:

Blood culture, serology, PCR.

[prescription take]:

Doxycycline 100mg/12h PO for 15 days.

Ehrlichiosis

is caused by ***Ehrlichia chaffeensis***, an obligate intracytoplasmic Gram -ve organism, related to Rickettsia. It is spread by ticks. It causes fever, headache, anorexia, malaise, abdominal pain, epigastric pain, conjunctivitis, lymphadenopathy, jaundice, rash, confusion, and cervical lymphadenopathy.

Tests:

Leucopenia, thrombocytopenia, AST↑.[276] Serology/PCR are diagnostic.

Treatment:

May respond to doxycycline 100mg/12h PO for 7-14d.

Typhus: the archetypal rickettsial disease

Rickettsiae are parasitic bacteria that are obligate intracellular parasites; they are bigger than viruses but smaller than classical bacteria. They are carried by host arthropods and invade human mononuclear cells, neutrophils, or blood vessel endothelium ('vasculotropic'). All the cataclysmic events of the last century (war, revolution, flood, famine, genocide, and overcrowding) have favoured lice infestation. As a result, Rickettsia (especially typhus) have killed untold millions.

Pathology

Widespread vasculitis and endothelial proliferation may affect any organ and thrombotic occlusion may lead to gangrene.

Clinical features

▸**Think of typhus in all travellers or inhabitants of endemic areas who seem to have septicaemia, but have -ve blood cultures.**[277] Incubation: 2-23d. Infection may be mild/asymptomatic or severe/systemic, with sudden onset of fever, frontal headache, confusion, and jaundice. With some species, an *eschar* (dark crusty ulcer at the site of a bite) may be present. A rickettsial rash may be macular, papular, petechial, or haemorrhagic. Test: haemolysis, neutrophilia, thrombocytopenia, clotting abnormalities, hepatitis, renal impairment. Patients die of shock, renal failure, DIC (p650), or stroke.

- *Epidemic typhus (*R. *prowazeki): Spread:* human lice *Pediculus humanus* (**fig 1**) faeces are inhaled or pass through skin). It may recrudesce decades later (Brill-Zinsser disease). The rash is truncal, then peripheral (opposite to R. *rickettsii*).
- *Rocky Mountain spotted fever (*R. *rickettsii)* is tick-borne (**fig 2**). Endemic in Rocky Mountains & south east USA. The rash (seen in 90%) begins as macules on hands/feet, spreading and becoming petechial or haemorrhagic in 50%.
- *Tick typhus (*R. *conorii*; Mediterranean spotted fever) the chief imported rickettsial disease in the UK (endemic in Africa, the Mediterranean area, eg Croatia, and parts of Asia; sporadic in Laos, Korea etc). The rash starts in the axillae, becoming purpuric as it spreads. *Other signs*: Conjunctival suffusion; jaundice; deranged clotting; meningoencephalitis; cerebritis;[278] renal failure.
- *Scrub typhus (Orienta tsutsugamushi)* Most common in SE Asia. Signs: Eschar from chigger bite (75%); hepatomegaly (65%); cough (60%); lymphadenopathy (46%);[279] tachypnoea (35%); constipation (25%); abdominal pain (20%); oedema (20%); splenomegaly (15%); vomiting (15%); rash (15%); petechiae (5%); sudden deafness.[280] CXR: bilateral infiltrations (85%).[281] Blood: LFT↑ (90%); platelets↓ (80%); neutrophilia (60%); lymphocytosis ± atypical lymphocytosis (5%). Complications: pneumonia ± pulmonary oedema, meningitis, and shock.
- *Murine (endemic) typhus (*R. *typhi)* is spread by fleas from rats to humans. It is more prevalent in warm, coastal ports (eg Dalmatia, Laos).[282]
- *Rickettsialpox (*R. *akari)* Variegate rash: macular, papular, or vesicular.

Diagnosis

This is difficult as often the picture is non-specific, the organisms are difficult to grow, and traditional heterophil antibody Weil-Felix tests are insensitive and nonspecific. A rise in antibody titre in paired sera is diagnostic. Latex agglutination, indirect immunofluorescence, ELISAs and PCR are available (may be done on the eschar).[283] An accurate, rapid dotblot immunoassay is available for scrub typhus. Skin biopsy may be diagnostic in Rocky Mountain spotted fever.

Treatment

Doxycycline 100mg/12h PO/IV for 7d (or 48h after T° normal) **or** chloramphenicol 500mg/6h PO for 10-14d. Resistance has been reported in Thailand. Azithromycin 500mg (1 dose) may work in tick and scrub typhus.[284]

Poor prognostic factors

Older age, male, Black, G6PD deficiency.

The human louse

Fig 1. *Pedic*ulus humanus,[285] vector for epidemic typhus.

Fig 2 *Dermacentor variabilis* is one vector for Rocky Mountain spotted fever.

Fig 3 The 'dog tick'.

Some gastrointestinal protozoa

Giardia lamblia

is a flagellate protozoon, which lives in the duodenum and jejunum. Spread: faecal-oral (↑ risk if eg immunosuppression, travel, homosexuality, achlorhydria, playgroups,[286] and swimming)—or from pets or birds. Drinking water may be contaminated.

The patient:

Giardiasis is often asymptomatic. Lassitude, bloating, flatulence, abdominal pain, loose stools ± explosive diarrhoea are typical. Malabsorption, weight loss, and lactose intolerance may occur.

Diagnosis:

Repeated stool microscopy for cysts/trophozoites may be -ve. Duodenal fluid analysis (aspiration or absorption on to a piece of swallowed string, Enterotest ®) may be tried, or ELISA/PCR or therapeutic trial.

△△*:*

Any cause of diarrhoea (p378, p380, p580), tropical sprue (p272), coeliac (p272).

[prescription take]:

Scrupulous hygiene. Metronidazole 400mg/8h PO for 5d (avoid alcohol); if pregnant, paromomycin 500mg/6h PO. If treatment fails, check for compliance and consider treating *all* the family. If diarrhoea persists, avoid milk as lactose intolerance may persist for 6wks.

Fig 1. Giardia: the only diplomonadid to trouble us.[287]

Entamoeba histolytica

(amoebiasis) occurs worldwide. Spread: faecal-oral. Boil water and infected food to destroy cysts. Trophozoites may remain in the bowel or invade extra-intestinal tissues, leaving 'flaskshaped' GI ulcers. Presentation may be asymptomatic, with mild diarrhoea or with severe amoebic dysentery.

Amoebic dysentery[ND] may occur some time after initial infection. Diarrhoea begins slowly, becoming profuse & bloody. An acute febrile prostrating illness can occur but high fever, colic, and tenesmus are rare. May remit and relapse. *Diagnosis:* stool microscopy shows trophozoites, blood, and pus cells. Faecal antigen detection may also be useful. Serology indicates previous or current infection and may be unhelpful in acute infection. △△*: Non-pathogenic amoebae* (eg *Entamoeba dispar*) are common in the tropics (cysts are indistinguishable). *Bacillary dysentery* often starts suddenly; it may cause dehydration. Stools are more watery. *Acute ulcerative colitis* has a more gradual onset and the stools are very bloody. For other causes of bloody diarrhoea, see p414 & p238.

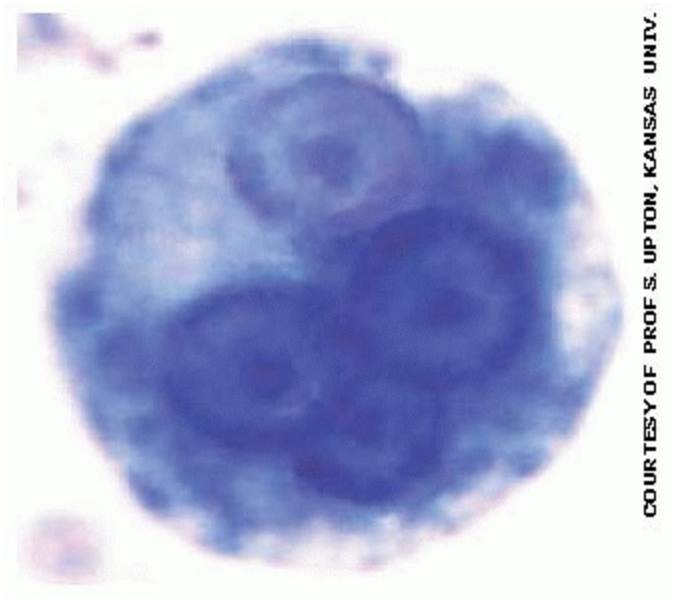


Fig 2. *E. histolytica* cyst with an endosome inside each of its 4 nuclei.[288]

Amoebic colonic abscess may perforate causing peritonitis.

Amoebomas are inflammatory masses, eg in the caecum (a cause of RIF masses).

Amoebic liver abscess is usually a single mass in the right lobe, and contains 'anchovy-sauce' pus. There is usually a high swinging fever, sweats, RUQ pain, and tenderness. WCC↑. LFT normal or ↑ (cholestatic). 50% have no history of amoebic dysentery. *Diagnosis:* ultrasound/CT ± aspiration; positive serology.

[prescription take]:

Metronidazole 800mg/8h PO for 5d for acute amoebic dysentery (active against vegetative amoebae), then diloxanide furoate 500mg/8h PO for 10d to destroy gut cysts (SES rare). Diloxanide is also best for chronic disease when *Entamoeba* cysts, not vegetative forms, are in stools. Amoebic liver abscess: metronidazole 400mg/8h IV for 10d; repeat at 2wks as needed; aspirate if no improvement within 72h of starting metronidazole; give diloxanide post-metronidazole. Extra-intestinal amoebiasis (including liver abscess) and symptomless amoebic cyst passers, metronidazole 400-800mg/8h for 5-10d (child 1-3 yrs: 100-200mg/8h; 3-7yrs 100-200mg/6h; 7-10yrs 200-400mg/8h).

Other GI protozoa

Cryptosporidium (p380), *Microsporidium* and *Isospora* (occur in AIDS, p398), *Balantidium coli*, and *Sarcocyscocystis*.

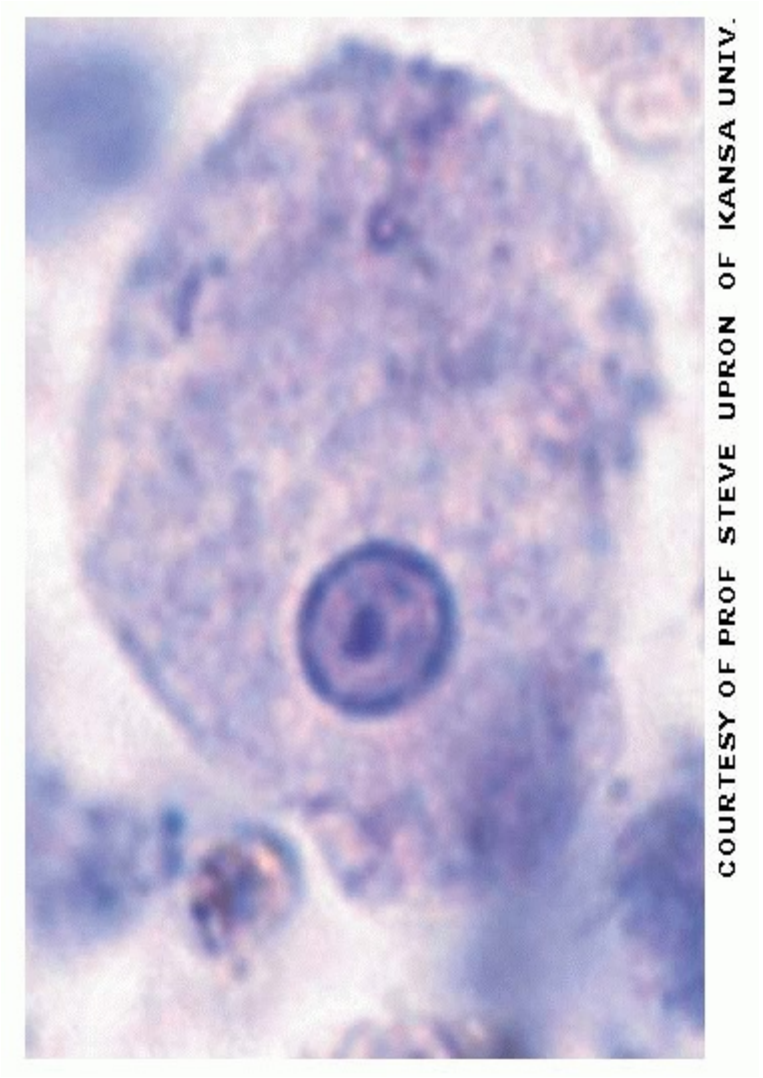


Fig 1. A trophozoite of *Entamoeba histolytica*[289]

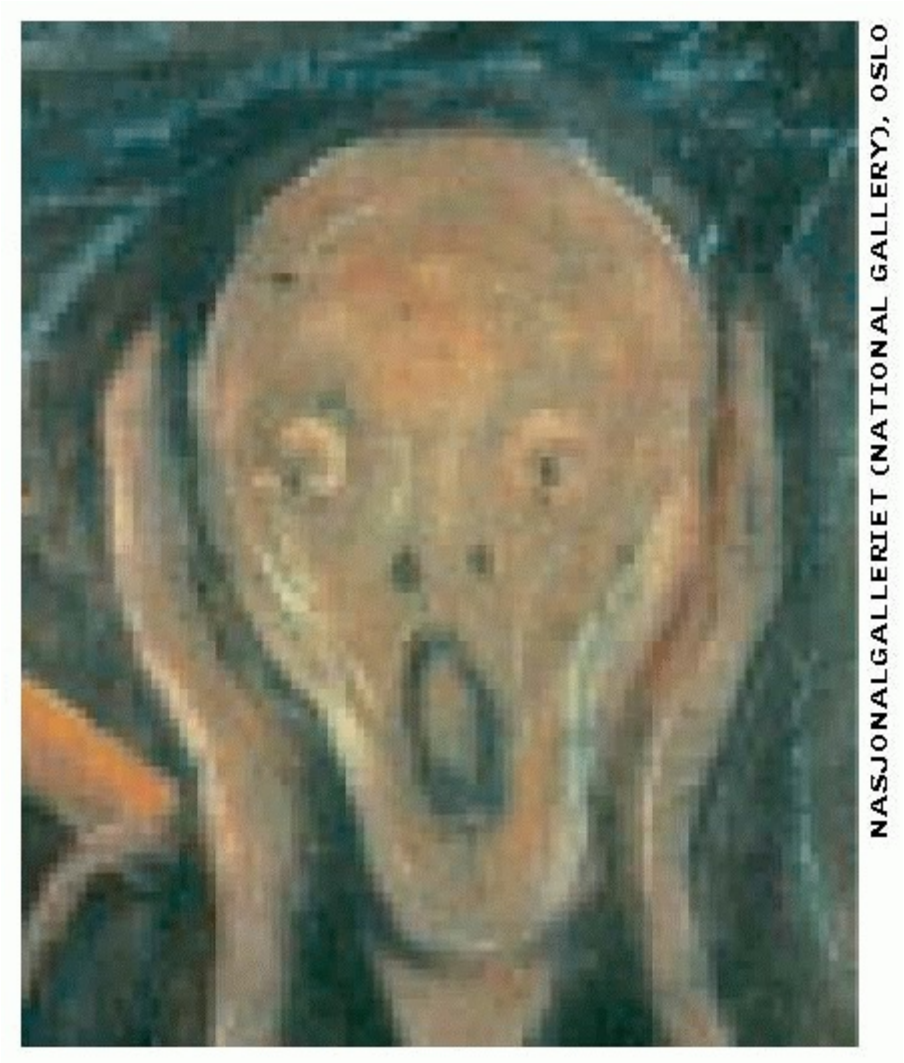


Fig 2. Edvard Munch, 1893 *The Scream*, crayon on paper

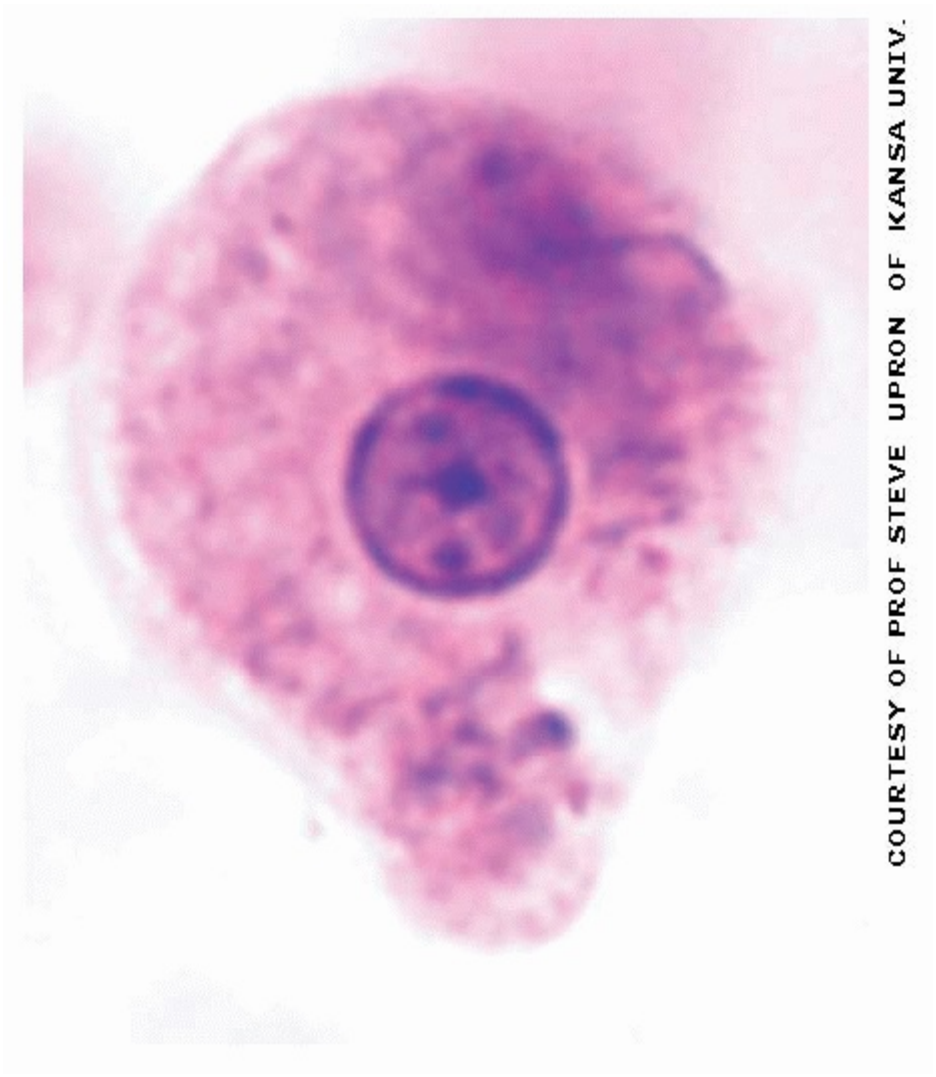


Fig 3. A 3rd trophozoite of *Entamoeba histolytica*.

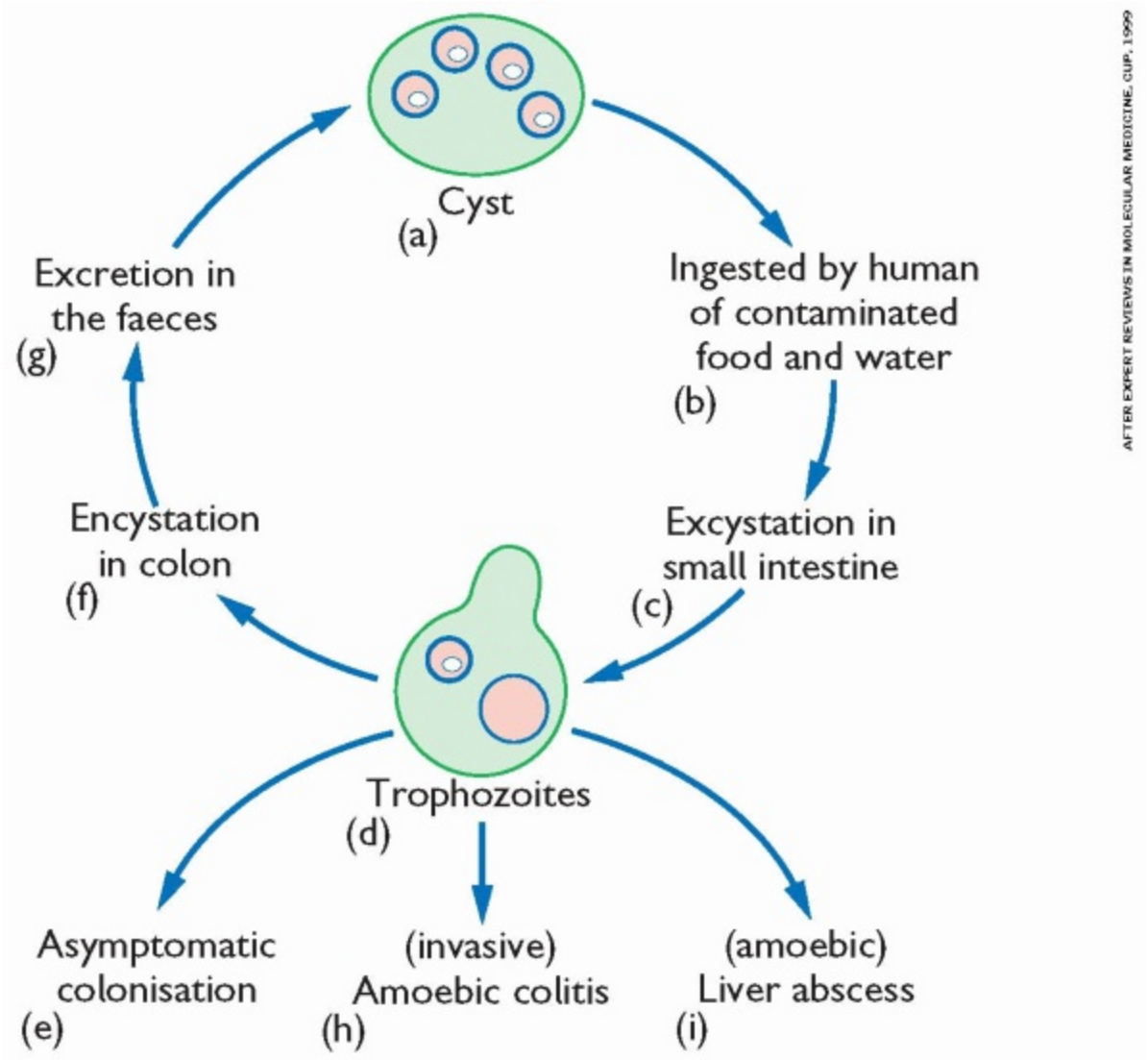


Fig 4. The life cycle of *Entamoeba histolytica* is in 2 stages: cysts and trophozoites. Cysts (10-15µm across) typically contain 4 nuclei; they are spread by ingesting faecally contaminated food or water. During excystation in the gut lumen, nuclear division is followed by cytoplasmic division, giving rise to 8 trophozoites. Trophozoites (10-50µm across) containing a single nucleus with a central karyosome, live in the caecum and colon. ~90% of individuals infected with *E. histolytica* are asymptomatic. Re-encystation of the trophozoites occurs in the colon, resulting in excretion of cysts in faeces and continuation of the life cycle.

Alternatively, trophozoites invade colonic epithelium, causing amoebic colitis (in ~10%). *E. histolytica* can spread haematogenously after breaching colon epithelium and can establish persistent extra-intestinal infection (eg amoebic liver abscess).[291]

Trypanosomiasis

African trypanosomiasis (sleeping sickness)

In West and Central Africa, *Trypanosoma gambiense* causes a slow, wasting illness with long latency. In East Africa, *T. rhodesiense* causes a more rapidly progressive illness. Trypanosome parasites, spread by tsetse flies, proliferate in blood, lymphatics, and CNS, causing progressive dysfunction, then death. Wars and famine caused an upsurge in the 1990s, now under control (prevalence ≲70,000) thanks to WHO, the Gates' foundation, Aventis, and Médecines Sans Frontières.[292]

Presentation:

A tender, subcutaneous nodule (*chancre*) develops at the site of infection. 2 stages follow:

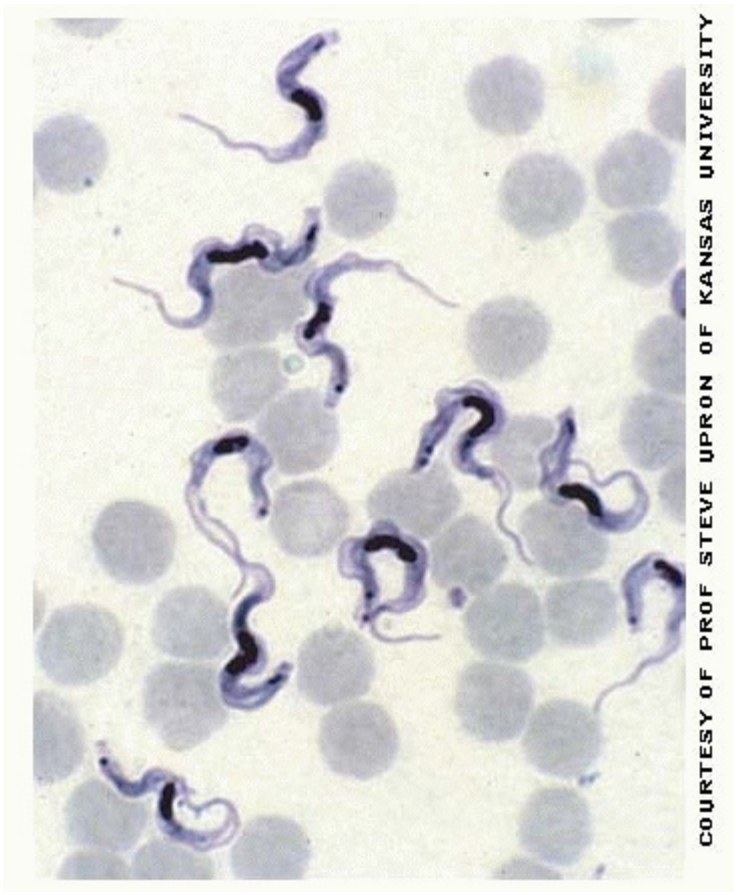


Fig 1. *T. gambiense*[293]

Stage I (haemolymphatic):

Non-specific symptoms including fever, rash, rigors, headaches, hepatosplenomegaly, lymphadenopathy, and joint pains. Winterbottom's sign (posterior cervical nodes↑) is a reliable sign, particularly in *T. gambiense* infections. In *T. rhodesiense* infections, this stage may be particularly severe, with potentially fatal myocarditis.

Stage II (meningoencephalitic):

Weeks (*T. rhodesiense*) or months (*T. gambiense*) after initial infection, convulsions, agitation, and confusion—and then apathy, depression, ataxia, dyskinesias, dementia, hypersomnolence, and coma occur.

Diagnosis:

Microscopy shows trypomastigotes in blood film, lymph node aspirate, or CSF. Serology is only reliable in *T. gambiense* infections.

Treatment:

▸Seek expert help. Treat anaemia and other infections first; then:

- Early (pre-CNS) phase: pentamidine isethionate 4mg/kg/d IM for 10d. SE: WCC↓, ↓BP, ↓Ca^{2+}, ↑creatinine, platelets↓. Alternative: suramin (SE: proteinuria, ↑creatinine).
- CNS disease: melarsoprol, eg '3 by 3' regimen IV: [294] 2-3.6mg/kg/d IV for three doses. Repeat at 7d and once more after 10-21d. SE: pruritus, Jarisch-Herxheimer-like reaction (p419), lethal encephalopathy in up to 10% (abnormal behaviour, fits, coma)—partly preventable with prednisolone (1mg/kg/24h, max 40mg/24h), starting the day before the first injection. Arseno-resistant trypanosomiasis was always fatal until the introduction of eflornithine. Dose example: 100mg/kg/6h IV over 1h for 14d. SE: anaemia, diarrhoea, seizures, leucopenia, hair loss. Eflornithine has a role in more severe cases (a drug developed on a not-for-profit basis). Inhibitors of sterol biosynthesis, cysteine proteases, other parasite biochemical pathways are being developed (with optimistic promises of free availability). [295]

American trypanosomiasis

(Chagas' disease) is caused by *T. cruzi*. Spread: blood-sucking reduviids (triatomine bugs, **fig 2**) in Latin America. Acute disease mostly affects children. An erythematous, indurated nodule (*chagoma*) forms at the site of infection which may then scar.

Signs:

T°↑, myalgia, rash, lymphadenopathy, hepatosplenomegaly ± unilateral conjunctivitis ± periorbital oedema (*Romaña's sign*) ± myocarditis/ meningoencephalitis. In up to 30%, progression to chronic disease occurs after a latency of eg 20yrs. Multiorgan invasion causes megaoesophagus (dysphagia, aspiration), megacolon (abdominal distension, constipation) ± dilated cardiomyopathy (p138); CNS lesions, eg if immunosuppressed (HIV, lymphoma).

Fig 2. Blood-sucking vector[296]

Diagnosis:

Acute disease: trypomastigotes may be seen in or grown from blood, CSF, or lymph node aspirate. Chronic disease: serology (Chagas' IgG ELISA).

Treatment:

Unsatisfactory. Nifurtimox 2mg/kg/6h PO for 120d or benznidazole (3.7mg/kg/12h PO for 60d) in acute disease (toxic, and eliminate parasites in ≲50%). Chronic disease can only be treated symptomatically. Surgery may be tried.[297]

Leishmaniasis

Leishmania are protozoa (**fig 1**, inset, with 2 RBCs, from a spleen aspirate) that cause granulomata. They are spread by sandflies and occur in Africa, India, Latin America, the Middle East, and the Mediterranean. Clinical effects reflect: 1 The ability of each species to induce or suppress the immune response, to metastasize, and to invade cartilage, and 2 the speed and efficiency of our own immune response. *L. major*, for example, is the most immunogenic and allergenic of cutaneous Old World *Leishmania*, and causes most necrosis. *L. tropica* is less immunogenic and causes less inflamed, slow-healing sores with relapsing lesions and a tuberculoid histology.

Cutaneous leishmaniasis

(oriental sore) A major disease affecting >300,000 people eg in Africa, India, and S America caused by *L. mexicana, L. major, L. tropica* or *L. amazonensis*.[1] Lesions develop at the bite site, beginning as an itchy papule; crusts fall off to leave an ulcer (*Chiclero's ulcer*). Most heal in ~2 (old world disease) to 15 months, with scarring (disfiguring if extensive). *L. mexicana* may cause pinna destruction (*Chiclero's ear*).

Fig 1.[298] Sandfly.

Diagnosis:

Microscopy and culture of aspiration from the base of the ulcer.[299]

[prescription take]:

May only be needed if unhealed by 6 months or lesion >4cm across (or multiple). Get help. Fluconazole 200mg/d PO for 6wks can work against *L. major*;.[300] or miltefosine 2.5mg/kg/d PO for 4wks (teratogenic); sodium stibogluconate (SbV, pentavalent antimony) intralesional (no agreed dose) or IV (10mg/kg/12h IV; max 850mg/d) for 28d; paromomycin, eg 14mg/kg/d IM for 60d + 10mg SbV/kg/d IM.[301]

[1] Visceralization may cause hepatitis & lymphadenopathy; *Trans* R *Soc Trop Med Hyg* 2006 100 79

Mucocutaneous leishmaniasis

(*L. brasiliensis*) occurs in S America. Primary skin lesions may spread to the mucosa of the nose, pharynx, palate, larynx, and upper lip and cause severe scarring. Nasopharyngeal lesions are called *espundia*. △*:* As parasites may be scanty, a Leishmanin skin test may be needed to distinguish the condition from leprosy, TB, syphilis, yaws, and cancer. Indirect fluorescent antibody tests and PCR tests are available. [prescription take]*:* Sodium stibogluconate (below). Treatment is unsatisfactory once mucosae are involved, so treat all cutaneous lesions early.

Visceral leishmaniasis

(kala-azar) Kala-azar means black sickness and is characterized by dry, warty, hyperpigmented skin lesions. It occurs in Asia, Africa, S America, and the Mediterranean. Cause: *L. donovani*, *L. chagasi*, or *L. infantum* (or rarely, 'visceralizing' of *L. tropica*[302]). Incubation: months to years. Protozoa spread via lymphatics from minor skin lesions and multiply in macrophages of the reticuloendothelial system (Leishman-Donovan bodies). There are 30 subclinical cases for every overt case. ♀:♂>3:1. It is HIV-associated.

The patient:

T°↑; sweats; burning feet; arthralgia; cough; epistaxis; abdo pain. *Signs:* Splenomegaly (96%); hepatomegaly (63%); lymphadenopathy; emaciation.

Diagnosis:

Leishman-Donovan bodies in marrow (80%), node, or splenic aspirates (95%). Hypersplenism (Hb↓, platelets↓, WCC↓), albumin↓, IgG↑; -ve Leishmanin skin

test. Solid-state serology for field use (K39 antigen). [303] Serology may be -ve if HIV+ve.

[prescription take]:

Get help. WHO regimen: sodium stibogluconate (Sb^V) 20mg/kg/24h IV/IM, up to 850mg/d, for 30d. SE: malaise, cough, substernal pain, arrhythmias, Hb↓, urea↑, LFT↑. Regimens are changing as 25% fail to respond or relapse, eg 10mg/kg SbV/8h for 10d, [304] without the 850mg limit. Alternative: pentamidine, eg 3-4mg/kg (deep IM) on alternate days, up to 10 doses. SEs may be fatal (BP↓, arrhythmias, glucose↓, diabetes in 4%). [305] Other agents: paromomycin, liposomal amphotericin B (AmBisome®). [306] Miltefosine (50mg/12h PO for 21d) is a promising oral alternative. *Post kala-azar dermal leishmaniasis* may occur months or years following successful treatment; lesions resemble leprosy.

Fungi

Pathogenic fungi either produce toxins or allergic reactions, or infect directly. They are *superficial* (pityriasis versicolor), *cutaneous* (tinea/ringworm; intertrigo; restricted to keratinized skin, hair & nails), *subcutaneous* (mycetoma; madura foot or sporotrichosis; [prescription take] is complex and may need limb amputation)—or *systemic* (from the lung, spreading to many organs (eg histoplasmosis; blastomycosis; coccidioidomycosis; fungal meningitis).

Superficial and cutaneous mycoses

Candida (**fig 3**). Dermatophytes (***Trichophyton***, ***Microsporum***, ***Dermatophyton***) cause tinea (ringworm). △: Skin scraping microscopy. [prescription take]: Topical clotrimazole 1%. Continue for 14d after healing. If intractable, try itraconazole (100-200mg/24h PO for 7d; SE: D&V; CCF), terbinafine (250mg/24h PO for 4wks) or griseofulvin 0.5-1g/24h (SE: agranulocytosis↓; SLE).

Fig 1. Candida intertrigo.[307]

Malassezia furfur

causes pityriasis versicolor: a macular rash which appears brown on pale skin and pale on tanned skin.

Diagnosis:

Microscopy of skin scrapings under Wood's light. [prescription take]: Ketoconazole 200mg/24h PO with food for 7d (also available as a cream); alternatively selenium sulfide lotion.

Systemic mycoses

Aspergillus fumigatus

may precipitate asthma, allergic bronchopulmonary aspergillosis (ABPA), or cause aspergilloma (p160). Pneumonia and invasive aspergillosis occur in the immunosuppressed. There is evidence that **voriconazole** is better than **amphotericin B** in invasive aspergillosis,[308] especially in cerebral aspergillosis.[309] Systemic ***candidiasis*** also occurs in the immunocompromised: consider this *whenever* they get a PUO, eg *Candida* UTI in DM or as a rare cause of prosthetic valve endocarditis. Do repeated blood cultures. If infection does not resolve when the predisposing factor (eg IV line) is removed, the treatment is **amphotericin B** IV (p180) or, if not neutropenic, **fluconazole** 400mg stat then 200mg/d PO. **Caspofungin** (70mg/d IVI if >80kg) is a new alternative.[310]

Cryptococcus neoformans

causes meningitis or pneumonia. It is commonest in the immunocompromised, eg AIDS, sarcoidosis, Hodgkin's, or on steroids. The history may be long and there may be features suggesting ICP↑, eg confusion, papilloedema, cranial nerve lesions.

Diagnosis:

Indian Ink CSF staining; blood culture. Cryptococcal antigen is detected in CSF and blood by latex tests. [prescription take]: **amphotericin B** IV over 4h (Fungizone®) 0.5-0.8mg/kg/d + **flucytosine** 37.5mg/ kg/6h PO until afebrile and culture -ve (≥2wks; 4 months if meningitis). Adjust flucytosine to give a peak level of 70-80mg/L; trough 30-40mg/L. When culture -ve, start fluconazole 200mg daily PO for 10wks. Monitor response clinically and serologically.

If HIV +ve:

See p399 for [prescription take]. It may be necessary to lower CSF pressure by ~50% by removing CSF. Secondary prophylaxis with fluconazole 200mg/d PO is needed until CD4 >150 × 10^6/L and cryptococcal antigen -ve (p398).

New World and Africa fungi

causing deep infection: ***Histoplasma species***, ***Coccidioides immitis***, ***Paracoccidioides brasiliensis*** & ***Blastomyces dermatitidis*** may be asymptomatic or cause acute or chronic lung disease, or disseminated infection. Histoplasma pneumonitis features arthralgia, erythema nodosum (**fig 1**, p546), and multiforme (p546). Chronic disease causes upper-zone fibrosis ± CXR coin lesions. Diagnosis: CXR, serology, culture, biopsy. [prescription take]*: Histoplasmosis:* **Amphotericin B** 0.7mg/kg/d IV for ~3-10d, eg if HIV+ve & severe; liposomal form may be better (+less renal failure), then **itraconazole** 200mg/12h PO for 12wks. *Paracoccidioides:* **Itraconazole** 200mg/d PO for 26wks. *Blastomycosis:* **Itraconazole**.

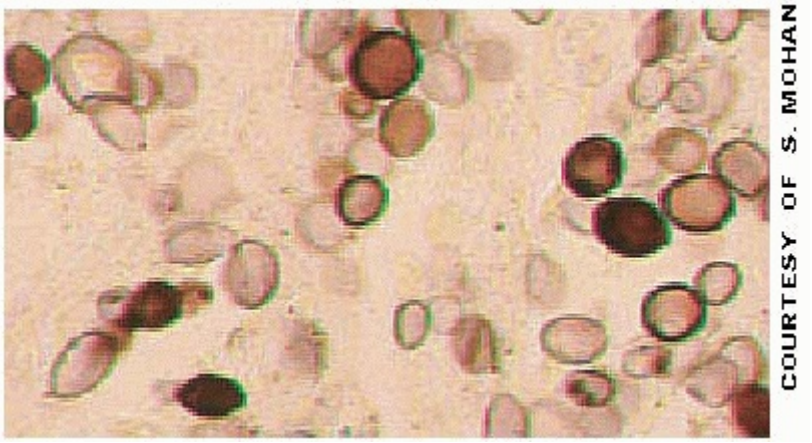


Fig 2. Histoplasma ×1000[311]

Candida on ITU: colonization → invasion → dissemination

Not everyone with +ve yeast cultures needs treatment: *Candida* is a common commensal (eg on skin, pharynx, or vagina, p230; p406) but if many sites (urine, sputum, or surgical drains) are colonized, risk of invasion rises, especially if:[312]

- Prolonged ventilation
- Broad-spectrum antibiotics
- Urinary catheters
- Immunosuppression
- Intravascular lines
- IV nutrition

Invasion implies fungus in normally sterile tissues. *Dissemination* involves infection of remote organs via the blood (eg endophthalmitis + fungi in lung or kidney). Consider IV amphotericin (OPPOSITE) or fluconazole (itraconazole if unresponsive) in these circumstances (esp. if your patient is deteriorating):[313]

- A single well-taken +ve blood culture—if risk factors present (above).
- Isolation of *Candida* from any sterile site except urine.
- Yeasts on microscopy on a sterile-site specimen, before cultures are known.
- Positive histology from normally sterile tissues in those at risk (above).
- Removal/change of IV lines is essential in patients with candidaemia.

▸Consult an ID physician/microbiologist before starting systemic antifungals.

Preventing fungal infections if immunocompromized

Fluconazole 50-400mg/24h after cytotoxics or radiotherapy, preferably started before onset of neutropenia, and continued for 1 week after WCC returns to normal.

Some facts about fungi

They differ from bacteria in having chitin in their cell walls, being able to undergo mitosis—and being larger than bacteria (eg 8µm across). They mostly reproduce by budding or germ tubes (**fig 6**), not fission.

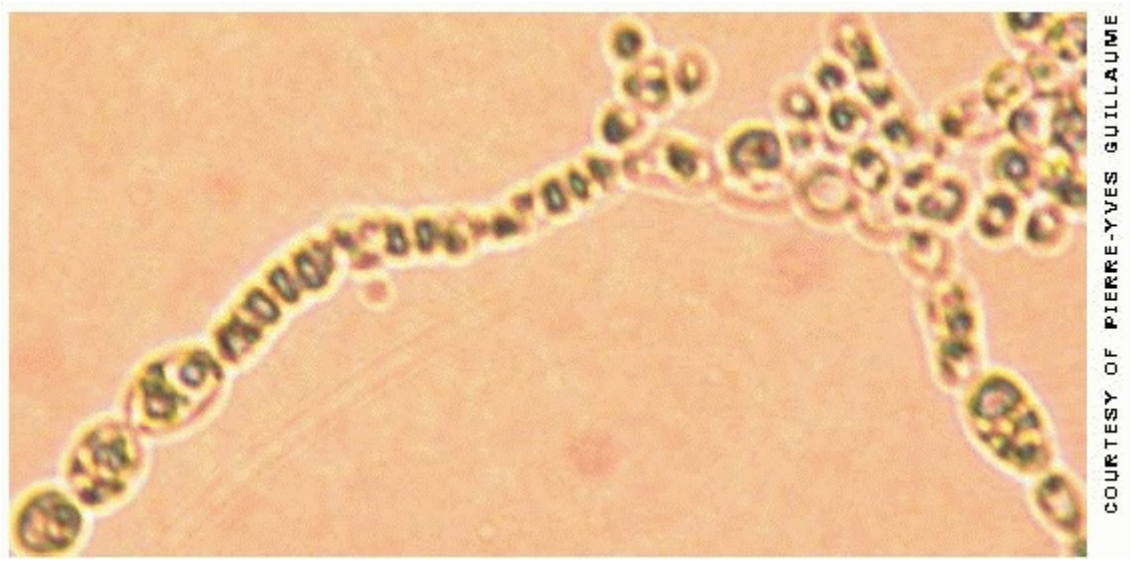


Fig 3. *Candida albicans*.[314] Yeasts usually occur as single cells or as clusters. Hyphae often occur in a mass of cells usually called moulds. A hyphal cell with cross-walls is called a mycelium. Some organisms grow as a yeast at 37°C but form mycelia at room temperature—ie they are dimorphic.

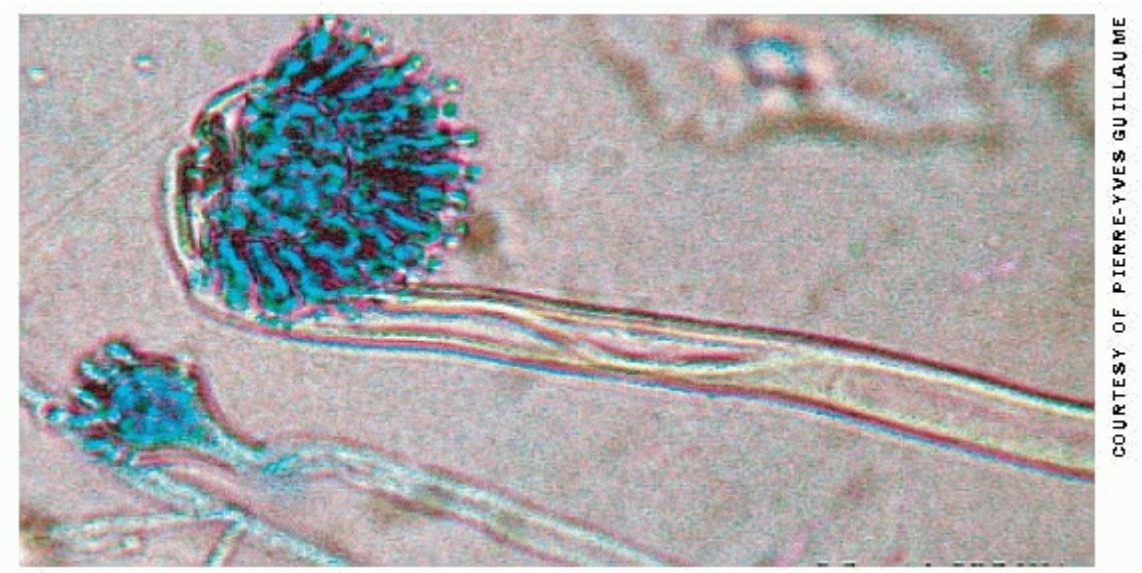


Fig 4. Aspergillus niger.[316] If spores are inhaled, aspergillosis can rarely occur, p161.[317]

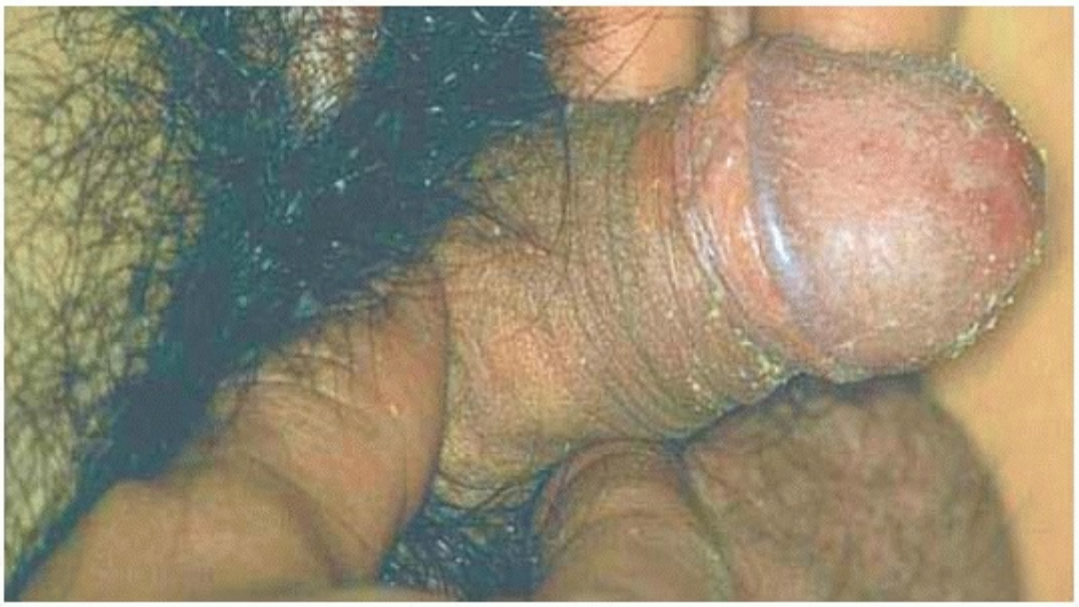


Fig 5. Candida of the glans.[320]

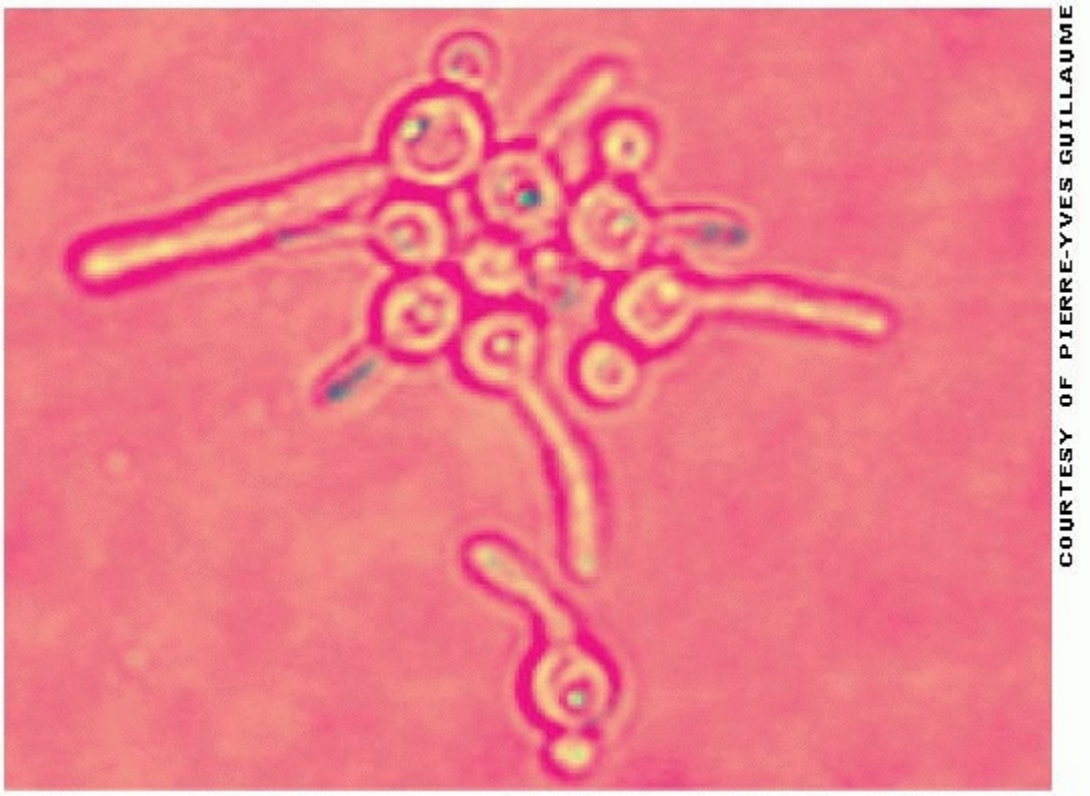


Fig 6. Germ tubes ×1000 emerging from dimorphhic *Candida albicans* blastospores[315]

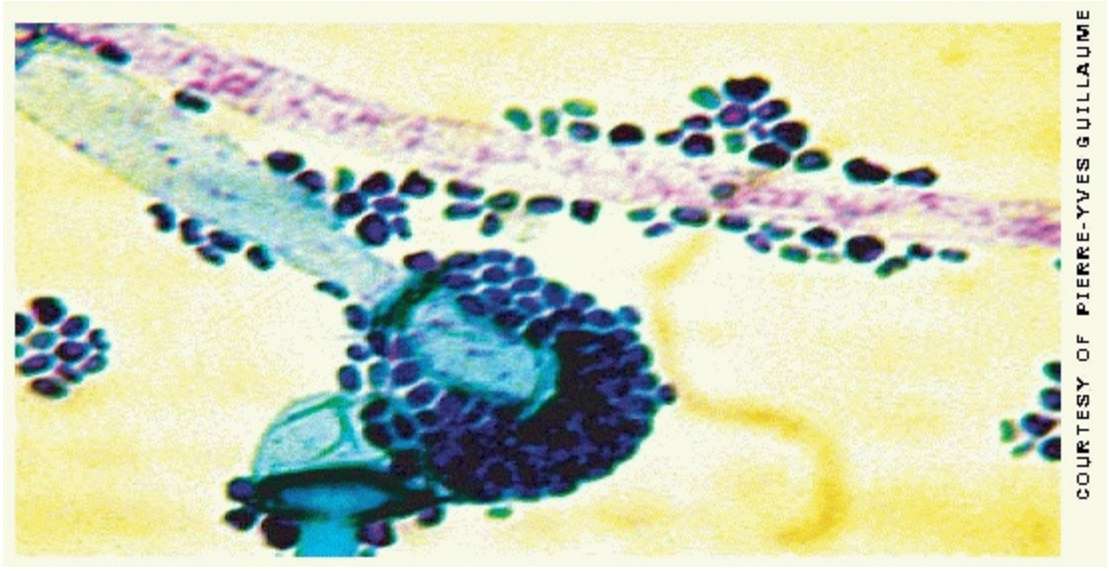


Fig 7. Mucor blastospores.[318] [319] Think of mucormycosis in diabetics with black pus in the nose ± proptosis/sinusitis or pneumonia. [prescription take]: amphotericin B; posaconazole (if available).

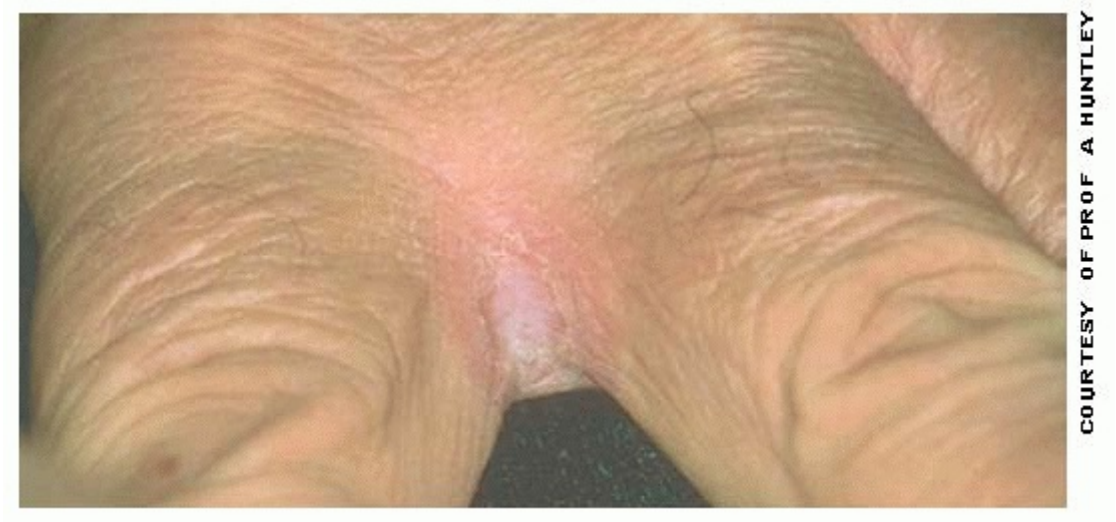


Fig 8. Web-space candida.[321]

Nematodes (roundworms)

1 billion people are hosts to nematodes (give or take a few hundred million[322]). Many live with us quite peacefully (even helpfully); but ascariasis can cause GI obstruction, hookworms can stunt growth, necatoriasis can cause anaemia, and trichuriasis causes dysentery/rectal prolapse. Mass use of albendazole 400mg/24h PO for 3d to school children or immigrants from endemic areas may be beneficial.

Necator americanus & Ankylostoma duodenale (hookworms)

occur in the Indian subcontinent, SE Asia, central/N Africa, and parts of Europe. Necator is also found in the Americas & sub-Saharan Africa. Many small worms attach to upper GI mucosa, causing bleeding (∴ Fe deficiency anaemia). Eggs are excreted in faeces and hatch in soil. Larvae penetrate feet, so starting new infections. Oral transmission of *Ankylostoma* occurs. △: Stool microscopy. [prescription take]: Mebendazole 500mg PO stat (1 dose) ± iron.

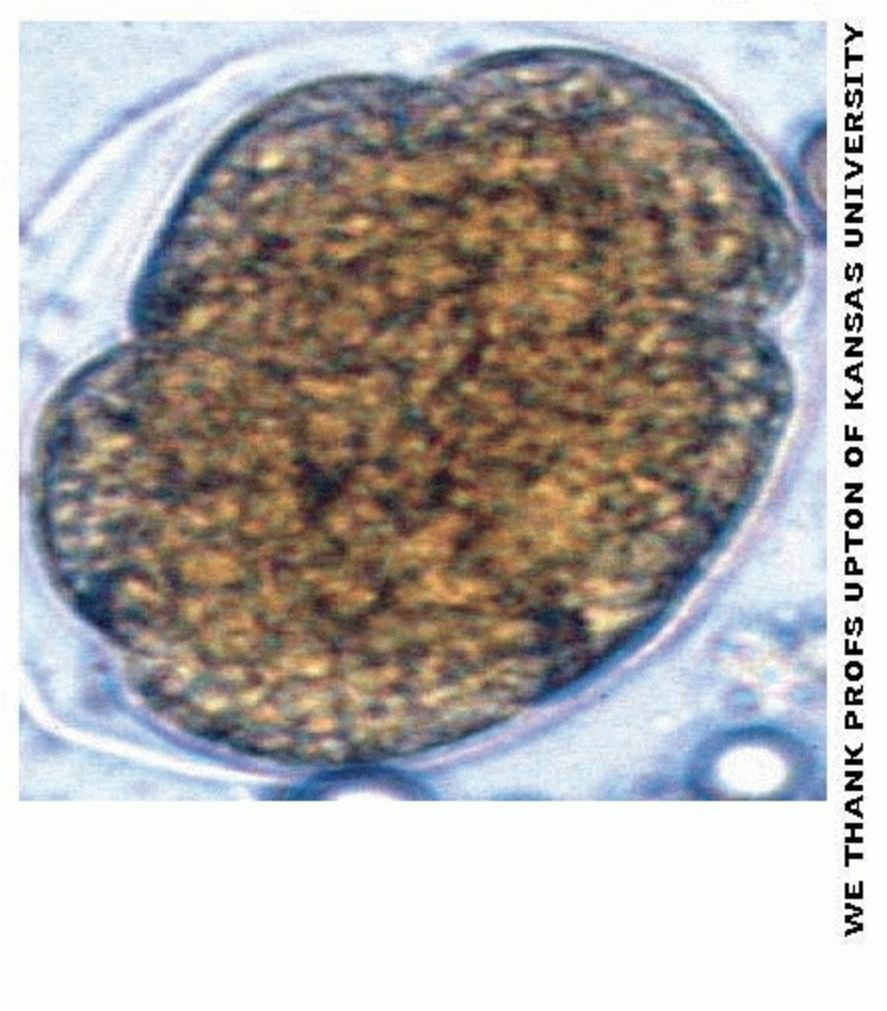


Fig 1. *Necator americanus* eggs ~70×38µm.

Strongyloides stercoralis

is endemic in the sub-tropics. Transmitted via skin, it causes migrating urticaria on thighs & trunk (*cutaneous larva migrans*) ± pneumonitis, enteritis/malabsorption (chronic diarrhoea/ abdominal; pain). Worms may take bacteria into the blood, causing septicaemia ± meningitis. △: Stool microscopy, serology, or duodenal aspiration. [prescription take]: Ivermectin 0.2mg/kg/24h PO for 48h. Hyperinfestation occurs in immunocompromize (on steroids; AIDS; consider albendazole 400mg/12h PO for 7-10d).

Ascaris lumbricoides

looks like a garden worm (*Lumbricus*). It has 3 finely toothed lips. Transmission is faecal-oral. It migrates through liver & lungs, settling in small bowel. Often asymptomatic; GI obstruction/perforation is rare. If in bile ducts, cholangitis or pancreatitis can result. Worms may be >25cm long with a hooked end if ♂. △: Stool microscopy (ova stain orange in bile); worms on barium X-rays; eosinophilia (?not if immunosuppressed). [prescription take]: Mebendazole 500mg PO stat (1 dose).

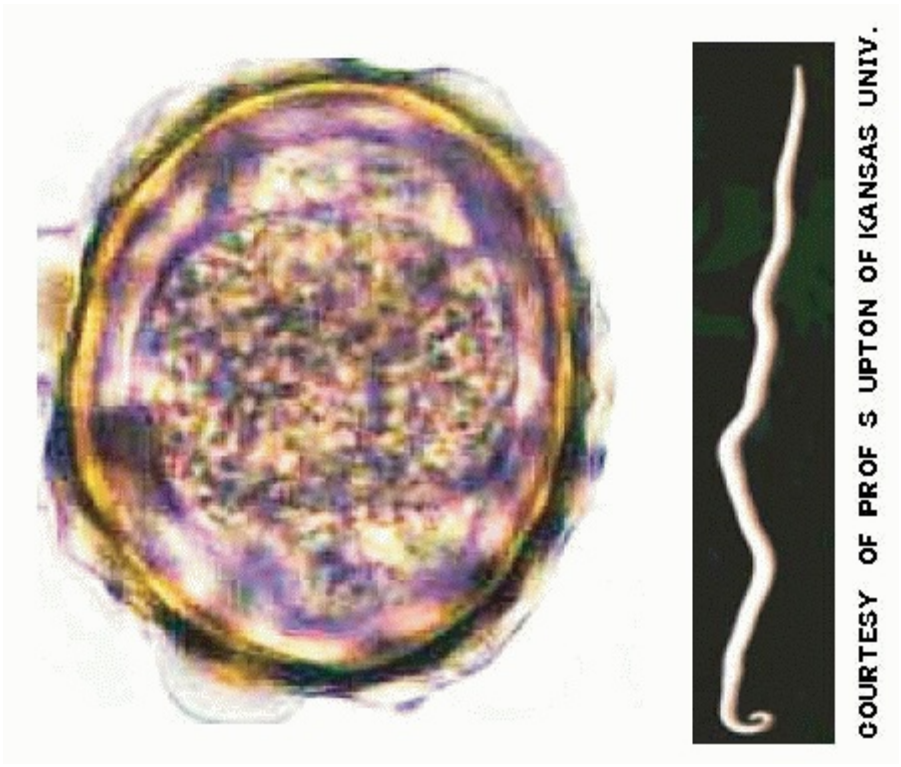


Fig 2. Ascaris eggs are 45×40µm.  

Enterobius vermicularis

(threadworm; ~9mm long; **fig 3**) causes anal itch as it leaves the bowel to lay eggs on the perineum. Apply sticky tape there to identify eggs (~55 × 25µm) microscopically. [prescription take]: Mebendazole 100mg PO stat. Repeat at 2wks if ≥2yrs. If aged <2yrs, try piperazine 0.3mL/kg/24h for 7d. Treat the whole family. *Hygiene is more important than drugs* as adult worms die after 6wks. Continued symptoms means *reinfection*.

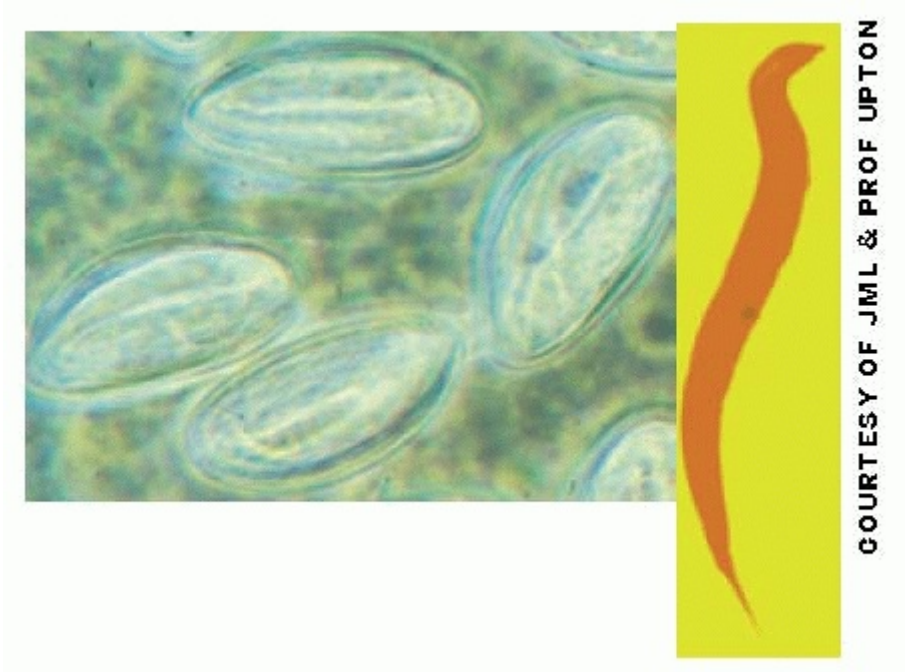


Fig 3. Enterobius: the folded worm is seen squirming in its egg. ♀ 

Trichuris trichiura

(whipworm) causes non-specific abdominal pain. △: Stool microscopy. [prescription take]: Mebendazole 500mg stat.

Trichinella spiralis

(worldwide) Transmitted by uncooked pork, it migrates to muscle, causing myalgia, myocarditis, periorbital oedema ± fever. [prescription take]*:* Albendazole 400mg/12h PO for 8-14d + prednisolone 40mg/d.

Toxocara canis

is the main cause of *visceral larva migrans*. It presents with eye granulomas (squint, blindness) or visceral signs (T°, myalgia, big liver, asthma, cough). △*:* Fundoscopy, serology, histology. [prescription take]: Mebendazole 100-200mg/12h PO for 5d. Severe lung, heart, or CNS disease may warrant steroids. In eye disease, visible larvae can sometimes be lasered. *Toxocara* is often contracted by ingesting dirt, so de-worm pets often (exclude from play areas).

Dracunculus medinensis

Guinea worm is the longest nematode (up to 70cm; in Ghana & Sudan); transmitted by water containing tiny crustaceans (copepods).[326] [prescription take]*:* Slow extraction of pre-emerging worms as they exit through the skin helped by metronidazole 400mg/d PO (±steroids). WHO eradication date is set for 2009.

Filarial infection

This is common—prevalence of lymphatic filariasis: 120 million worldwide.

1. **Onchocerciasis** is caused by ***Onchocerca volvulus*** and is transmitted by the black fly. It causes river blindness in 72% of some communities in Africa and S America, affecting 17 million worldwide. A nodule forms at the site of the bite, shedding microfilariae to distant skin sites which develop altered pigmentation, lichenification, loss of elasticity, and poor healing. Disease manifestations are mainly due to the localized host response to dead/dying microfilariae. Eye manifestations include keratitis, uveitis, cataract, fixed pupil, fundal degeneration, or optic neuritis/atrophy. Lymphadenopathy and elephantiasis also occur. *Diagnosis:* Visualization of microfilaria in eye or skin snips. Remove a fine shaving of clean, unanaesthetized skin with a scalpel. Put on slide with a drop of 0.9% saline and look for swimming larvae after 30min. [prescription take]*:* Ivermectin 0.15mg/kg stat, repeated eg 6-montly to suppress dermal and ocular microfilariae. If the eye is involved start prednisolone 1mg/kg/24h PO a few days before starting ivermectin (it's probably OK in pregnancy). Worm survival requires symbiosis with Wolbachia bacteria (susceptible to doxycycline 100mg/d PO for 4-6 weeks.
2. **Lymphatic filaria** occur in Asia, Africa, and S America and is transmitted by mosquito vectors. Acute infections cause fever and lymphadenitis. ***Wuchereria bancrofti*** causes lower limb lymphoedema (elephantiasis) and hydrocoeles. ***Brugia malaya*** causes elephantiasis below the elbow/knee. *Wuchereria* life cycle: a mosquito bites an infected human→ingested microfilariae develop into larvae→larvae migrate to mosquito's mouth→Biting of another human→ Access to bloodstream →Adult filariae lodge in lymphatic system. *Diagnosis:* Blood film (**fig 1**), serology. A rapid immuno-chromatographic fingerprick test can be used in the field. *Complications:* Immune hyperreactivity may cause tropical pulmonary eosinophilia (cough, wheeze, lung fibrosis, high eosinophil counts, IgE↑ and IgG↑). It is a major public health problem and is a WHO target for elimination by the year 2020 (starting with Nigeria, Samoa, and Egypt). The current elimination strategy involves mass treatment with one yearly dose of 2 drugs for 5yrs: **albendazole** (400mg) + *either* **ivermectin** (200µg/kg) *or* **diethylcarbamazine** (6mg/kg).[328] Giving diethylcarbamazine-fortified salt to families for 1yr, has also been found to be effective. [329]
3. **Loiasis** is caused by ***Loa loa***. Occurs in Africa; transmitted by the *Chrysops* fly. It causes painful 'Calabar' swellings of the limbs, eosinophilia, and may migrate across the conjunctiva. [prescription take]: Diethylcarbamazine 6mg/kg PO stat.

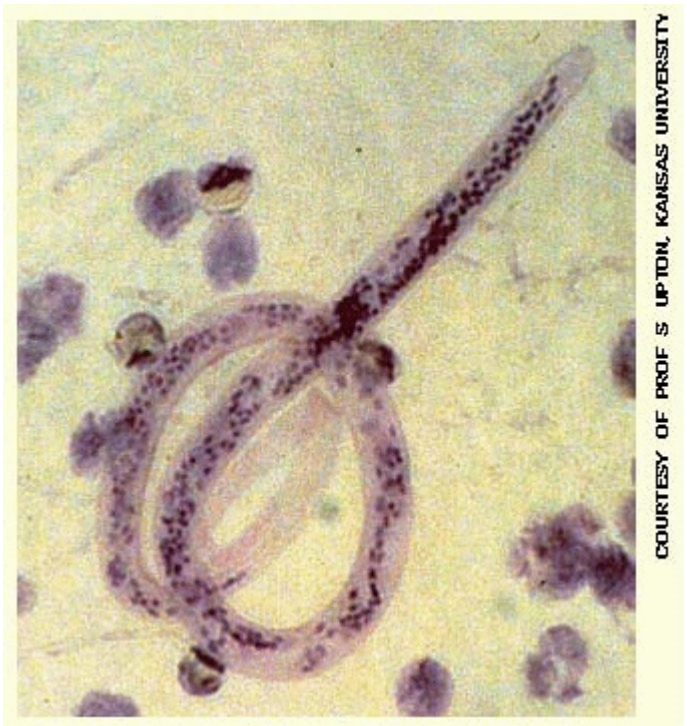


Fig 1. Blood smear of *Wuchereria bancrofti;* 290×8.5µm[327]

Cestodes (tapeworms)

Taenia solium

(pork tapeworm) infection occurs by eating uncooked pork, or from drinking contaminated water.[1] ***T. saginata*** is contracted from uncooked beef. Both cause vague abdominal symptoms and malabsorption. Contaminated food and water contain cysticerci which adhere to the gut and develop into adult worms. On swallowing the eggs of *T. solium* they may enter the circulation and disseminate throughout the body, becoming cysticerci within the human host (***cysticercosis***). This tapeworm encysts in muscle, skin, heart, eye, and CNS, causing focal signs. ***Subcutaneous cysticercosis*** causes subcutaneous nodules (arms, legs, chest). ***Ocular cysticercosis*** causes conjunctivitis; uveitis; retinitis; choroidal atrophy; blindness.

[1] While eating undercooked pork is the only way to acquire intestinal *T. solium*, any food contaminated by faeces from hosts infected with cysticerci can carry the eggs that may lead to development of cysticercosis. Even vegetarians are at risk. The lack of public awareness of this poses big problems.

Neurocysticercosis

is the chief cause of seizures in some places, eg Mexico. Other features: focal CNS signs, eg hemiplegia, odd behavioural, dementia—or no symptoms. Cysticerci may cluster like bunches of grapes ('racemose' form) in the ventricles (causing hydrocephalus) and basal cisterns (causing basal meningitis, cranial nerve lesions, and raised ICP). Spinal cysticerci may cause radicular or compressive symptoms (p458).

Diagnosis:

• Stool microscopy and examination of perianal swabs. • Serology: indirect haemagglutination test. • CSF: may show eosinophils in neurocysticercosis, and a CSF antigen test is available. • CT or MRI scan may locate cysts. • SXR and x-rays of soft tissues may show calcified cysts. [prescription take]: Get help (*tel:* 0151 708 9393[UK]). Niclosamide 2g PO in 2 doses, separated by 1h. Neurocysticercosis: albendazole 7.5mg/kg/12h PO with food, or praziquantel 17mg/kg/8h PO for 30d. Allergic responses to dying larvae should be covered by dexamethasone 12mg/day PO for 21d. Cimetidine (800mg/d PO) can ↑concentration of praziquantel. The role of steroids in the routine treatment of neurocysticercosis is controversial. **NB:** If CSF ventricles are involved, you may need to shunt before starting drugs. Drugs may worsen the acute phase of cysticercotic encephalitis.[331]

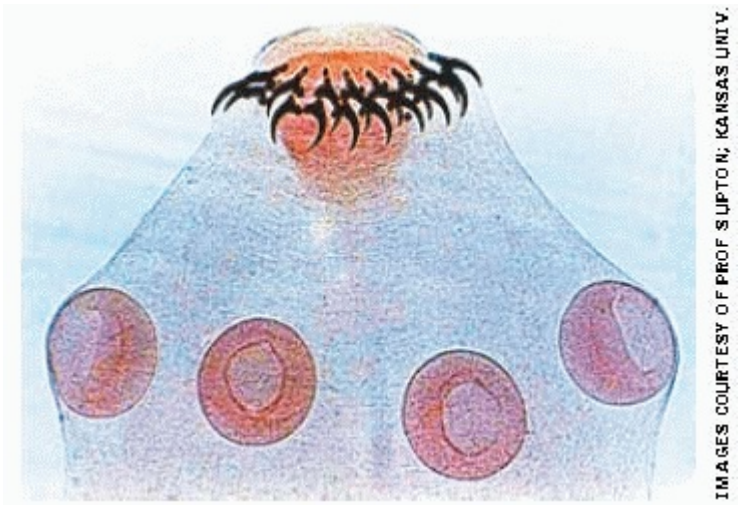


Fig 1. *Tinea solium* (note the two rows of hooks).[330]

Hymenolepis nana; H. diminuta

(dwarf tapeworm; rarely symptomatic). [prescription take]: Praziquantel 25mg/kg PO (1 dose; adults & children) or niclosamide 500mg/day for 3d.

Diphyllobothrium latum

(**fig 2**) is a fish tapeworm (via uncooked fish) causing similar symptoms to *T. solium*. [prescription take]: Niclosamide. It is a cause of vitamin B_{12}↓.

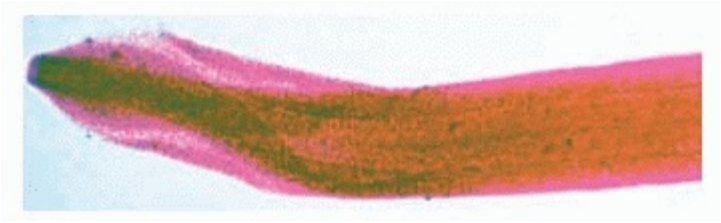


Fig 2.

Hydatid disease

(**fig 3**) Cystic hydatid disease is a zoonosis caused by eating eggs of the dog parasite ***Echinococcus granulosus*** (**fig 3**)[332] eg in rural sheep-farming regions. Hydatid is a public health problem in parts of China, Russia, Alaska, Wales, and Japan.

Signs:

Most cysts are asymptomatic, but liver cysts may present with hepatomegaly, obstructive jaundice, cholangitis, or PUO. Lung cysts present with dyspnoea, chest pain, haemoptysis, or anaphylaxis. Parasites migrate almost anywhere, eg CNS; or it turns up incidentally on CXR.

Diagnosis:

Plain X-ray, ultrasound, CT cysts. A good serological test has replaced the variably sensitive Casoni intradermal test. [prescription take]: Get help. 1st-choice: albendazole before & after drainage (if >60kg, 400mg/12h; if <60kg, 7.5mg/kg/12h with food). Excise/drain symptomatic cysts. Beware spilling cyst contents (causes anaphylaxis; give praziquantel here). The **PAIR** approach is often used: **p**uncture →**a**spirate cyst →**i**nject hypertonic saline → **r**e-aspirate after 25min—and continue albendazole for 28 days to prevent recurrence. (NB: Alveolar hydatid is caused by *E. multilocularis*.)

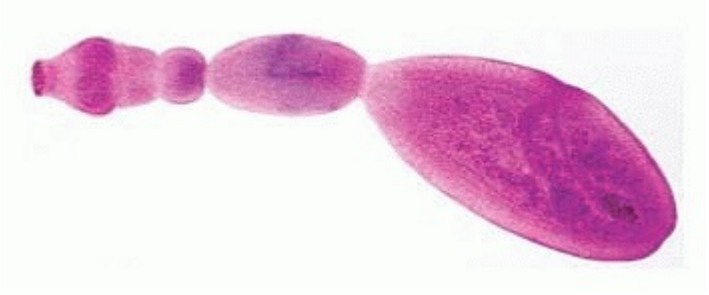


Fig 3. Hydatid[333]

Trematodes (flukes)

Schistosomiasis

(bilharzia) is the most prevalent disease caused by flukes (~200 million people in Africa; now also introduced to S America/Caribbean). Snail vectors release cercariae that penetrate skin, eg during paddling, causing itchy papular rashes ('swimmer's itch'). The cercariae shed their tails to become schistosomules and migrate via lungs to liver where they grow. ~2wks later, there may be fever, urticaria, diarrhoea, cough, wheeze, and hepatosplenomegaly ('Katayama fever'). In ~8wks, flukes are mature (14♂-20♀mm long), mate (**fig 1**), and migrate to resting habitats, ie bladder veins (*haematobium*) or mesenteric veins (*mansoni* & *japonicum*). Eggs released from these sites cause granulomata and scarring. Clinical signs reflect our immune response to eggs (type IV hypersensitivity, eg for *S. mansoni*).

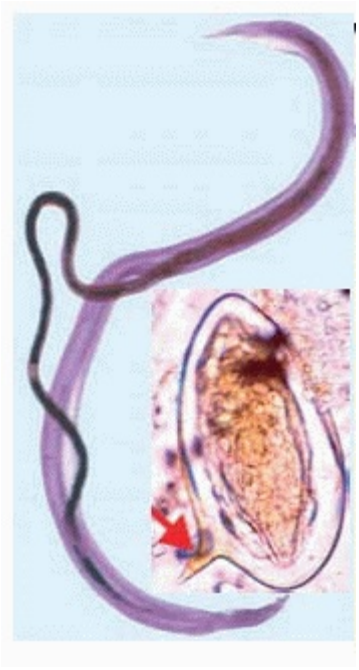


Fig 1. *S. mansoni* ♂/♀ mating; inset egg with sublateral spine (red arrow)

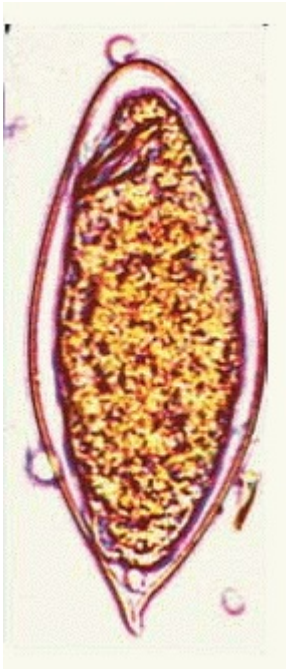


Fig 2. (enlarged) *S. haematobium*; terminal spine.[334]

The patient

S. mansoni: abdominal pain; D&V; later, hepatic fibrosis, granulomatous inflammation, anaemia,[1] and portal hypertension (transformation into true cirrhosis has not been well-documented). *S. japonicum*, often the most serious, occurs in SE Asia, tends to affect the bowel and liver, and may migrate to lung and CNS ('travellers' myelitis'). Urinary schistosomiasis (*S. haematobium*) occurs in Africa, the Middle East, and the Indian Ocean. Signs: frequency, dysuria, haematuria (± haematospermia), incontinence. It may progress to hydronephrosis and renal failure. There is an ↑risk of squamous cell carcinoma of the bladder.

Diagnosis

Eggs in urine (*S. haematobium;* **fig 2**, with 3 RBCs for scale) or faeces (*S. mansoni* & *japonicum*) or rectal biopsy (all types). AXR may show bladder calcification in chronic *S. haematobium* infection. Ultrasound (renal obstruction, hydronephrosis ± thickened bladder wall). Schistosoma ELISA is most sensitive.

Treatment

Praziquantel: 40mg/kg PO with food divided into 2 doses separated by 4-6h for *S. mansoni* & *S. haematobium*, or 20mg/kg/8h for 1d in *S. japonicum*. Sudden transitory abdominal pain ± bloody diarrhoea may occur shortly after. Oxamniquine is an alternative for *S. mansoni* infection. Artemether also shows promise, both for prophylaxis in high-risk groups, and as a synergist to praziquantel.[335]

Fasciola hepatica

(liver fluke) is spread by sheep, water, and snails. It causes T°↑, abdominal pain, diarrhoea, weight↓, jaundice, hepatomegaly, liver fibrosis and eosinophilia.

Tests:

Stool microscopy, serology. [prescription take]: Get help. Triclabendazole 10mg /kg PO, 1 dose, or bithionol 30mg/kg alternate days for 10-15 doses, max 2g/day IM.

Opisthorchis & *Clonorchis*

are liver flukes common in the Far East, where they cause cholangitis, cholecystitis, and cholangiocarcinoma.

Tests:

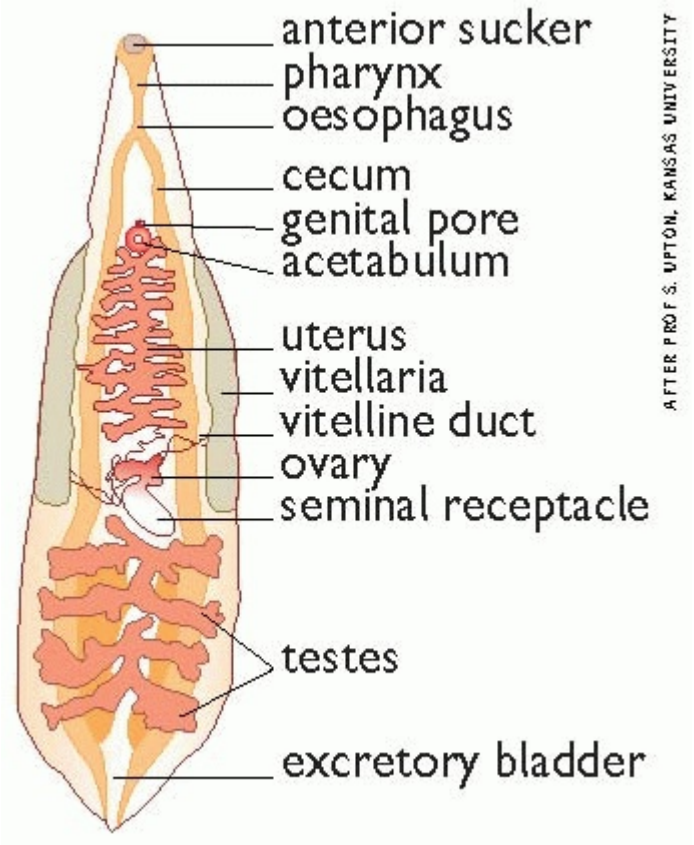
Stool microscopy. [prescription take]: Praziquantel 25mg/kg/8h PO for 1d.

Fasciolopsis buski is a big intestinal fluke ~7cm long causing ulcers or abscesses at the site of attachment. [prescription take]: Praziquantel 25mg/kg/8h PO for 1d.

Paragonimus westermani

(lung fluke) is got by eating raw freshwater crabs and crayfish. Parasites migrate through gut and diaphragm to invade lungs (hence cough, dyspnoea, haemoptysis, ± lung abscess/bronchiectasis). It occurs in the Far East, S America, and Congo; often mistaken for TB (similar signs & CXR).

Tests:



Sputum for CNS/lung lesions. [prescription take]: Praziquantel (25mg/kg/8h PO for 2d).

Fig 3. *Clonorchis sinensis*[336]

Exotic infections

Exotic infections may be ***community-acquired*** or ***nosocomial***, ie acquired in hospital. The increasing prevalence of immunosuppression, both drug induced and innate, and the widespread use of broad-spectrum antibiotics have resulted in an increase in exotic infections. New techniques such as PCR have enabled the identification of more putative infective agents.

The history—and a good gossip:

Don't expect to find the pertinent question in any textbook—eg "Are your carp well at present?" (Mycobacterium marinum skin infection)[337] or "Who has been licking your face recently?" (Pasteurella multocida);[338] "Has your dog been on holiday this year?" (monkeypox from prairie dogs); "Has your pet hedgehog lost weight?" (Salmonella);[339] "Did you have a stray pig living under your house when the monsoon started?" (pigs + standing water + mosquitoes " Japanese encephalitis).

When you suspect infection (T°↑, sweats, inflammation, D&V, WCC↑, or *any* unexplained symptom), ask about: • Foreign travel (recent and past) • Foreign bodies (hip prosthesis, heart valve) • Work or hobby or family exposure to infectious agents • Any bites/stings • Sexual exploits • Any necrotic tissue? • HIV risk or reason for immunosuppression (eg pregnancy; steroids) • Any pets, exotic or otherwise?

Diagnosis

Take appropriate cultures (blood, urine, stool, CSF) or swabs as clinically indicated. Liaise early with an infectious diseases physician or microbiologist. Consider CXR, ultrasound, or CT as clinically indicated. If the infection appears to be localized, consider surgical debridement ± drainage. Do not give up if you cannot culture an organism; tests may need to be repeated. Perhaps the organism is 'fastidious' in its nutritional requirement or requires prolonged incubation? Even if culture *is* achieved, it may be that the organism is pathogenic, or it could be a commensal (ie part of the normal flora for that patient). If culture is not possible, look for antibodies or antigen in the serum or other body fluids. It is generally agreed that a 4-fold increase in antibody titres in convalescence (compared with the acute sera) is indicative of recent infection, although not diagnostic. PCR is increasingly being used to make identifications; however, it is far from infallible, and contamination with DNA from the lab or elsewhere is a frequent problem.

Treatment

Empirical therapy (p372) may be needed if the patient is ill. *The table opposite is for reference purposes only:* no one can remember *all* the details about even the common infectious diseases, let alone rare ones. Check with a microbiologist for local patterns of disease and antibiotic sensitivity/resistance. *Antibiotic doses:* Penicillins (p368); cephalosporins (p369); gentamicin;[1] other agents (p370).

Organism

Acanthamoeba

Acinetobacter calcoaceticus

Actinobacillus actinomycetemcomitans

Actinobacillus lignieresii

Actinobacillus ureae

Aerococcus viridans

Aeromonas hydrophila

Afipia broomeae

Alcaligenes species

Arachnia propionica

Arcanobacterium

Babesia microti (protozoa)

Bacillus cereus

Bifidobacterium

Bordetella bronchiseptica

Burkholderia cepacia, etc (formerly pseudomonas)

Burkholderia pickettii

Burkholderia pseudomallei (formerly Pseudomonas pseudomallei)

Capnocytophaga ochracea & C. sputagena

Cardiobacterium hominis

Chromobacterium violaceum

Citrobacter koseri/diversus

Corynebacterium bovis/equi

Corynebacterium ovis

Corynebacterium ulcerans

Cyclospora ayetanensis

Edwardsiella tarda

Eikenella corrodens

Erysipelothrix rhusiopathia

Eubacterium

Flavobacterium meningosepticum

Flavobacterium multivorum

Gemella haemolysans

Helicobacter cinaedia

Kingella denitrificans kingae

Kurthia bibsonii/sibirica/zopfii

Lactobacillus

Megasphaera elsdenii

Mobiluncus curtisii/mulieris

Moraxella osloensis and M. nonliquefaciens

Neisseria cani

Neisseria cinerea/mucosa +

N. subflava; N. flavescens

Pasteurella multocida[340]

(Gram-ve rod)

Pasteurella pneumotrophica

Peptostreptococcus magnans

Plesiomonas shigelloides

Propionibacterium acnes

Prototheca wickerhamii[342] *& zopfii = achlorophyllous algae*

Providencia stuartii

Pseudomonas maltophilia

Pseudomonas putrefaciens

Rothia dentocariosa[344]

Serratia marcescens (may be non-pathogenic)[345]

Sphingomonas paucimobilis

Streptococcus bovis

Vibrio vulnificus

Site or type of infection IE=infective endocarditis

Corneal ulcers

UTI; CSF; lung; bone; conjunctiva

IE ; CNS; UTI; bone; thyroid; lung

Periodontitis; abscesses

CSF; IE; wounds; bone; lymph nodes

Bronchus; CSFpost-trauma; hepatitis

Empyema; UTI; CSF; bone; IE

IE ; CSF; cornea; bone; D&V; liver abscess

Marrow; synovium

Dialysis peritonitis; ear; lung

Actinomycosis; tear ducts; CNS

Throat; cellulitis; leg ulcer

PUO ± haemolysis if old/splenectomy

Wounds; eye; ear; lung; UTI; IE

Vagina; UTI; IE; peritonitis; lung

URTI; CSF(after animal contact)

Wounds; feet; lungs; IE ; CAPD; UTI ecthyma gangrenosa; peritonitis

CSF (formerly a pseudomonas)

Melioidosis: self-reactivating septicaemia + multiorgan, protean signs eg in rice-farmers, via water/soil in Papua, Thailand, Vietnam, Torres Straits

Oral ulcer; stomatitis; arthritis

Blood; cervical abscess

IE (=infective endocarditis)

Nodes; eye; bone; liver; pustules

CSF; UTI; blood; cholecystitis

IE ; CSF; otitis; leg ulcer; lung

Joints; liver; muscle; granulomata

Diphtheria-like ± CNS signs

Diarrhoea (via raspberries)

Cellulitis; abscesses; BP↓; dysentery via penetrating fish injuries

Sinus; ears; PEpost-jugular vein phlebitis (postanginal sepsis) via bites

Erysipelas-like (OHCS p598); IE

Wounds; gynaecologic sepsis; IE

Lungs; epidemic neonatal meningitis; post-op bacteraemia

Peritonitis (spontaneous)

IE; meningitis after neurosurgery

Proctitis in homosexual men

Throat; larynx; eyelid; joint; skin

IE (infective endocarditis)

Teeth; chorioamnionitis; pyelitis

Anaerobic Gram-negative coccus; IE

Vagina; uterus; septicaemia in cirrhosis

Conjunctiva; wound; vagina; UTI; CSF

CNS; bone; haemorrhagic stomatitis

Wounds from cat bites

IE; CNS; bone; post human bites or from peritoneal dialysis

Skin; bone; lung; CSF; UTI; pericarditis epiglottitis. From cat or dog bite

Wounds; joints; bone; CSF[341]

Bone/joint/discitis; wound; teeth; face

D&V; eye; sepsis post fishbone injury

Face; wounds; CSFshunts; bone; IE ;

liver granuloma (botyromycosis)

Subcutaneous granuloma; plaques; bursitis; adenitis; nodules

UTI; burn or lung infections stenotrop-homonas Wounds; ear; eye; lung; UTI; IE[343]

CSFpost CNSsurgery/head trauma

Appendix abscess; infective emboli

Wound; burns; lung; UTI; liver; CSF; bone; IE; red diaper/nappy syndrome

Superficial leg ulcer; CSF; UTI

IE if colon cancer; do colonoscopy

Wounds; muscle; uterus; fasciitis

Treatment example

Propamidine + neomycin

Gentamicin

Penicillin ± gentamicin

Ampicillin ± gentamicin

Ampicillin ± gentamicin

Penicillin ± gentamicin

Gentamicin

Imipenem or ceftriaxone

co-amoxiclav or cetazidime

Penicillin

Penicillin

Clindamycin + quinine

Gentamicin

Penicillin

Co-trimoxazole?

Ceftazidime

Clindamycin or gentamicin

Cefalosporin

Ceftazidime (14d) + Co-trimoxazole or co-amoxiclav for 3 months

Penicillin or ciprofloxacin

Penicillin + gentamicin

Erythromycin, chloramphenicol

Cefuroxime + gentamicin

Erythromycin + rifampicin

Penicillin

Penicillin + Diphtheria antitoxin

Co-trimoxazole

Cefuroxime + gentamicin

Penicillin + gentamicin

Penicillin

Penicillin

Penicillin

Cefuroxime

Penicillin + gentamicin

Ampicillin or gentamicin

Penicillin ± gentamicin

Penicillin

Cephalosporins, Penicillin

Metronidazole

Cephalosporins or ampicillin

Penicillin

Amoxicillin

Penicillin, cephalosporin

ß-lactam antibiotics or tetracyclines for >2weeks

Penicillin; cipro-/moxifloxacin

Penicillin or cephalosporins

Ciprofloxacin

Tetracycline or Penicillin

Amphotericin or Ketoconazole

Gentamicin

Co-trimoxazole or cefepine

Cefotaxime

Penicillin + gentamicin

Imipenem, ceftazidime, ciprofloxacin

Ceftazidime

Penicillin + gentamicin

Tetracycline, penicillin

Acknowledgements

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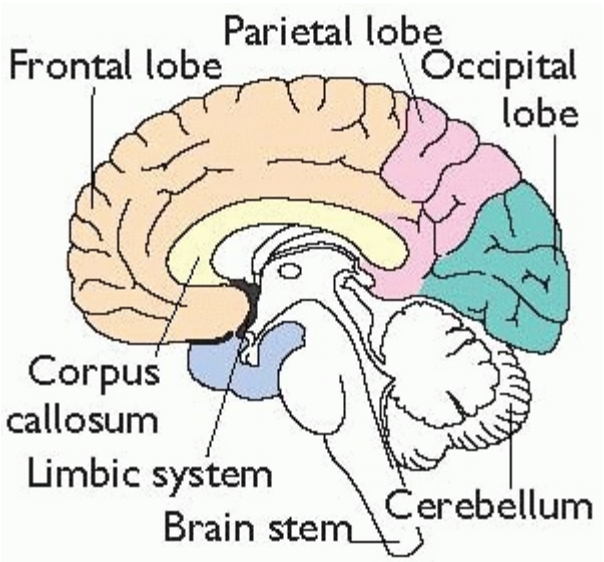
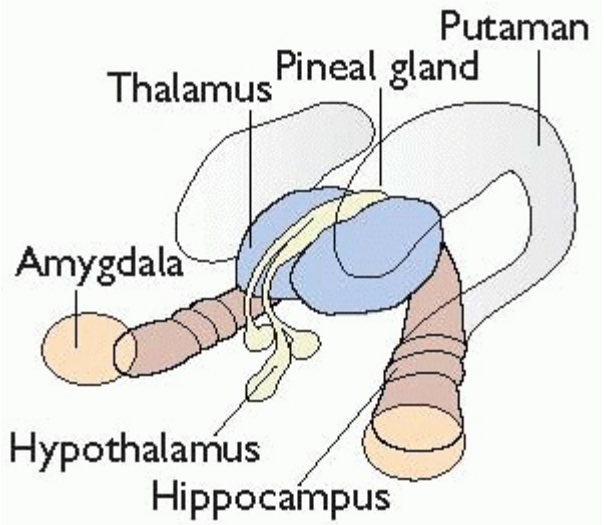
11

Neurology





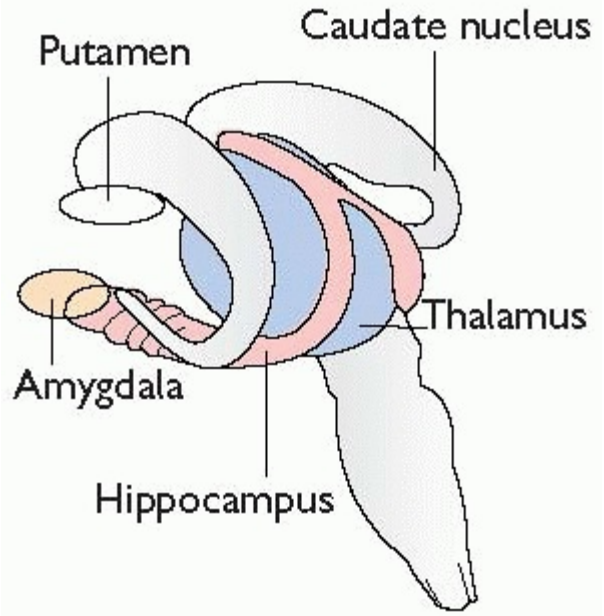


Fig 1. Cerebral hemispheres (top) and limbic system (middle & bottom) "We are very knowing. We know all sorts of other things…about how there isn't a unitary ego—how we're made up of conflicting, interacting systems." AS Byatt, *Possession*, p267.[1]

We dedicate this page to those carers who find themselves responsible for a friend or relative who has a chronic neurological illness, eg stroke, Parkinson's disease, Alzheimer's disease, or motor neurone disease. As a thought experiment, try spending a morning imagining that you are such a carer— eg trying to expunge the smell of soiled sheets from your clothes, while awaiting a visit from a neighbour, who said he would 'sit with him' so you can catch the bus into town, and, like a guilty hedonist, play truant from your role as nurse for a few sanity-giving hours of normal life. You wait. No one comes. You stop bothering about the smell on your clothes, and turn towards your husband, about to say something, but when your eyes meet his, you realize he does not recognize you—and you keep your thoughts to yourself. Knuckles whiten as you grasp his collar to lift him forward on the commode, and you seem to hear a mocking voice over your shoulder saying: '… so I see we're getting angry with him today, are we?' The ceaseless round from mouth to anus, from bed to chair, from twilight to twilight, continues, *ad infinitum*.

It is all we can do to spend *2 minutes* on this thought experiment, let alone a morning—or the rest of our lives. We need to be aware of the strategies we adopt to avoid involvement with the naked truth of the shattered lives, which like a tragic subplot, stand behind the farce of morning surgery or out-patients in which we hear ourselves for ever saying in plumy complacency: 'And how are *you* today Mrs Salt—your husband, I know… marvellous how you manage. You are a real support to each other. Let me know if I can do anything.' We pretend to be busy, we ensure that we *are* busy, we surround ourselves with students, with white coats, and a miasma of technical expertise—we surround ourselves with *anything* to ensure that there is no chink through which Mrs Salt can shine her rays of darkness. Poor Mrs Salt. Poor us—to be frightened of the darkness, panicking at the thought that we might not have anything to offer, or that we might be called to offer up our equanimity as a sacrifice to Mrs Salt. How dare one little grain upset our carefully contrived universe?

Respite care, medical charities, meals on wheels, laundry services, physiotherapy, occupational therapy (OT), transport, day care centres, clubs for carers, visits from district nurses or from a nurse-matron specializing in chronic diseases will go some way to mitigate Mrs Salt's problems. As ever, the way forward is by taking time to listen. Carers' needs evolve. First there is uncertainty, and the need for help in handling this. Next comes the moment of diagnosis with the numbness, denial, and anger that may follow. Then there may be an adjustment to reality, with frenzied searching for information and advice, or a careful titration by the carer of how much information he or she can handle.

Issues of driving, mobility, finance, sex, and employment are likely to occur throughout the illness, and advice will need to be constantly tailored to suit individual circumstances. But the best thing you can ever offer is the unwritten contract that, come what may, you will be there, available, often ineffectual, but incapable of being alienated by whatever the carer may disclose to you.

Revising for exams? You can skip this page, if you are *sure* your examiner is a narrow-minded bigot.

The chief questions of bedside neurology

Is there a **focal lesion** (illness of all cells in one part of the brain, eg a stroke)?—or:

- A **general insult**, eg trauma, encephalitis, anoxia, poisoning, or post-ictal states.
- **Widespread neurodegeneration** (may have specific local effects, eg amnesia).
- Loss of **a specific type of nerve cell**, eg motor neurone disease; subacute combined degeneration of the cord ($B_{12}\downarrow$, p320); loss of pre-Bötzinger neurones in the medulla causes central sleep apnoea (and death during sleep in the elderly).[2]
- A **disorder of function** (migraine; epilepsy) or **connectivity** (in autism, face processing areas do not connect well to fronto-parietal areas directing attention).[3]
- **Medically unexplained symptoms**, eg associated with psychological problems.

A key feature in determining if a focal lesion is present is lack of symmetry— eg one pupil dilated, or an upgoing plantar response.

Where is the lesion?

Localizing the lesion depends on recognizing patterns of cognitive, cranial nerve, motor, and sensory deficits occurring after lesions at different sites in the nervous system. Analyse cognitive, cranial nerve, and motor deficits first; the sensory examination is then used to confirm the site of the lesion.

Patterns of motor deficits

Weakness can arise from lesions of the cortex, corona radiata, internal capsule, brainstem, cord, peripheral nerves, neuromuscular junction, or muscle. Is the pattern upper or lower motor neurone (UMN or LMN; see BOXES)?

Cortical lesions may show an unexpected pattern of weakness involving all movements of a hand or foot, with normal or ↓tone—but ↑reflexes more proximally in the arm or leg will suggest an upper rather than lower motor neurone lesion.

Internal capsule and ***corticospinal pathway*** brainstem lesions cause contralateral hemiplegia with a pyramidal distribution of weakness (1st BOX). If the hemiplegia occurs with epilepsy, ↓cognition, or homonymous hemianopia (p441), the lesion is in a cerebral hemisphere. A cranial nerve palsy (III-XII) contralateral to a hemiplegia implicates the brainstem on the side of the cranial nerve palsy. ***Cord lesions*** causing paraplegia (both legs) or quadriparesis/tetraplegia (all limbs) are suggested by finding a motor and reflex level (ie muscles are unaffected above the lesion, show LMN signs *at* the level of the lesion, and UMN signs *below* the lesion). ***Peripheral neuropathies:*** (p494) Most cause a distal weakness (foot-drop; weak hand), but in Guillain-Barré syndrome weakness is often *proximal*. Involvement of a single nerve (mononeuropathy) occurs with trauma or entrapment (carpal tunnel, p495); involvement of several nerves (mononeuritis multiplex) is seen eg in DM.

Sensory deficits

Information about the site of a lesion is obtained chiefly from the distribution of sensory loss; the range of sensory modalities involved (pain, temperature, touch, vibration, and joint position sense) can also add information, as pain and temperature sensations travel along small fibres in peripheral nerves and tracts in the cord and brainstem. They are distinct from joint position and vibration sense, which travel in fibres in the large dorsal columns of the cord.

Distal sensory loss suggests a neuropathy and may involve all sensory modalities or be more selective, depending on the nerve fibre size involved in the peripheral nerve. Individual nerve lesions are identified by their anatomical territories which are usually more sharply defined than those of root lesions (dermatomes, p446), which often show considerable overlap. The hallmark of a cord lesion is a sensory level—ie an area of decreased or absent sensation below the lesion (eg the legs) with normal sensation above this level (eg in abdomen, trunk, and arms). Lateral cord lesions give a Brown-Séquard syndrome (p688) with dorsal column loss on the side of the lesion and spinothalamic loss in the other leg. Cervical cord lesions (eg syringomyelia, p508 or cord tumours) may cause selective loss of pain and temperature sensation with sparing of joint position sense and vibration (ie 'dissociated' sensory loss). Lateral brainstem lesions show both dissociated and crossed sensory loss with pain and T° loss on the side of the face ipsilateral to the lesion, and contralateral arm and leg sensory loss. Lesions above the brainstem give a contralateral pattern of generalized sensory loss. In cortical lesions, sensory loss is confined to more subtle and discriminating sensory functions (2-point discrimination and stereognosis).

UMN lesions (upper motor neurone)

These are caused by damage to motor pathways anywhere from motor nerve cells in the precental gyrus of the frontal cortex, through the internal capsule, brainstem, and cord, to the anterior horn cells in the cord. Typical characteristics are 'pyramidal'[1] in distribution, ie weakness involving physiological extensors of the arm (shoulder abduction; elbow, wrist, and finger extension; and the small muscles of the hand) and the flexors of the lower limb (hip flexion, knee flexion, and ankle dorsiflexion and everters). There is little muscle wasting and ***loss of skilled fine finger movements*** may be greater than expected from the overall grade of weakness. ***Increased tone*** (spasticity) develops in stronger muscles (eg arm flexors and leg extensors). It is manifest as resistance to passive movement that can suddenly be over-come (clasp-knife feel). There is ***hyperreflexia:*** reflexes are brisk; ***plantars are upgoing*** (+ve Babinski sign) ± ***clonus*** (elicited by rapidly dorsiflexing the foot; ≤3 rhythmic, downward beats of the foot are normal; more suggest an UMN lesion) ± a positive ***Hoffman's reflex***: brief flexion of thumb and index finger in a pincer movement following a flick to the pulp of the middle finger (it is a stretch reflex so the often-used way of flicking the finger *towards* the palm isn't ideal).[4] Neck extension is said to increase sensitivity of this test.[5] **NB:** UMN weakness affects ***muscle groups***, not individual muscles.

LMN lesions (lower motor neurone)

These are caused by damage anywhere from anterior horn cells in the cord, nerve roots, plexi, or peripheral nerves. The distribution of weakness corresponds to those muscles supplied by the involved cord segment, nerve root, part of plexus, or peripheral nerve. See p444. A combination of anatomical knowledge, good muscle testing technique, and experience is needed to distinguish, eg a radial nerve palsy from a C7 root lesion, or a common peroneal nerve palsy from an L5 root lesion (p444).[2] The relevant muscles show ***wasting*** ± spontaneous involuntary twitching (***fasciculation***), and feel soft and floppy, providing little resistance to passive stretch (***hypotonia/flaccidity***). ***Reflexes are reduced*** or absent, the ***plantars remain flexor***. The chief differential is weakness from primary muscle disease—here there is symmetrical loss, reflexes are lost later than in neuropathies, and there is no sensory loss. Myasthenia gravis (MG) causes weakness worsening with use of the affected muscles (↑fatigue); there is little wasting, normal reflexes, and no sensory loss—see p504. ***Reflexes and spinal cord level:*** p43. ***Spinal roots for each muscle:*** p444. For *mixed* LMN *and* UMN *signs*, see p459 (B_{12}↓, syphilis etc).

Muscle weakness grading (MRC classification)

Grade 0	No muscle contraction	**Grade 3**	Active movement against gravity
Grade 1	Flicker of contraction	**Grade 4**	Active movement against resistance
Grade 2	Some active movement	**Grade 5**	Normal power (allowing for age)

Grade 4 Covers a big range: **4-**, **4**, and **4+** denote movement against slight, moderate, and stronger resistance; avoid fudging descriptions—'strength 4/5 throughout' suggests a mild quadriparesis or myopathy. It is better to document 'poor effort' and the maximum grade for each muscle tested.

Cerebral artery territories

Knowledge of the anatomy of the blood supply of the brain helps in diagnosing and managing cerebrovascular disease (p462-470). Always try to identify the area of brain that correlates with a patient's symptoms and identify the affected artery.

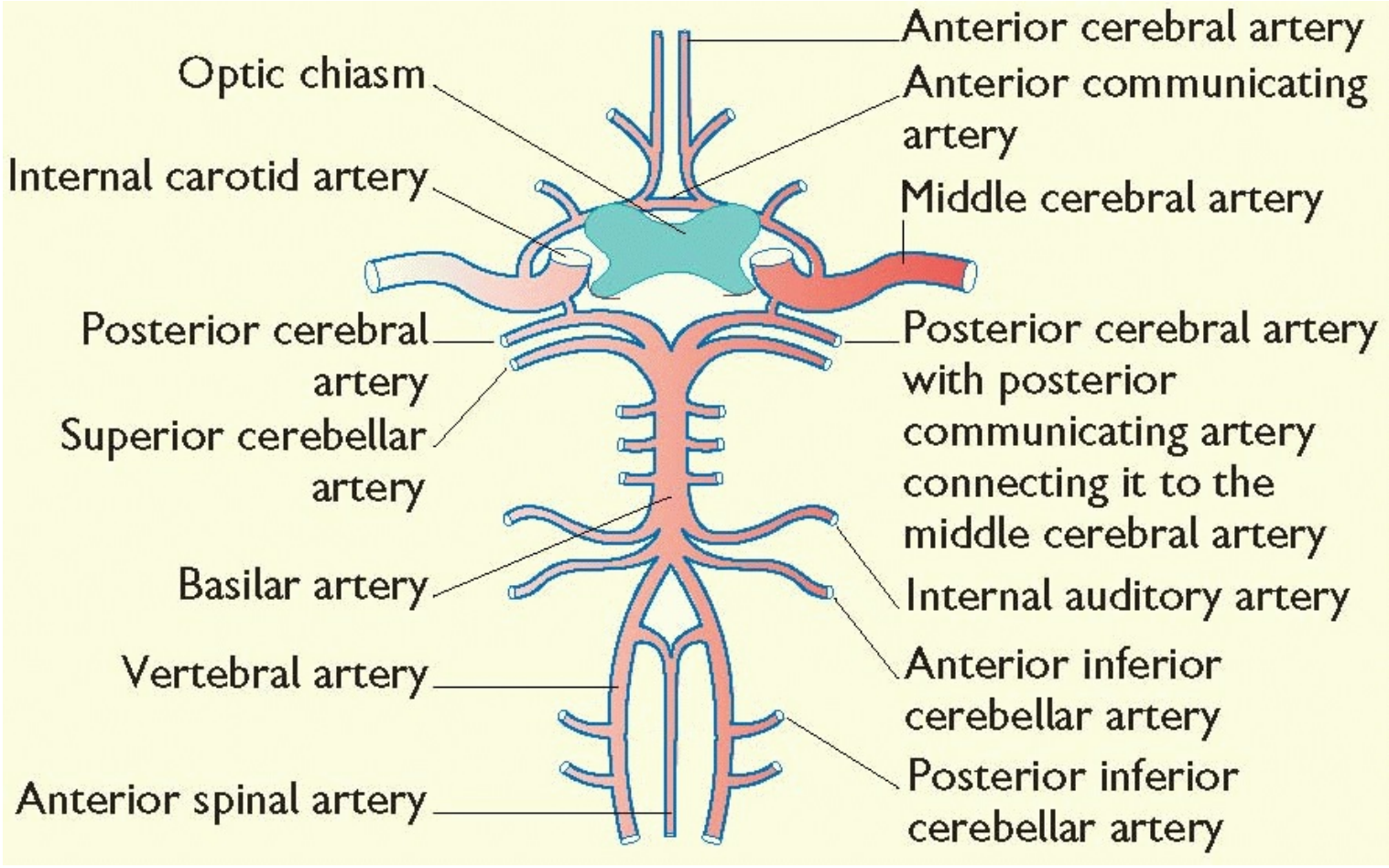
Cerebral blood supply

The brain is supplied by the two internal carotid arteries and the basilar artery (formed by the joining of the two vertebral arteries). These 3 vessels feed into an anastomotic ring at the base of the brain called the circle of Willis (below). This arrangement may lessen the effects of occlusion of a feeder vessel proximal to the anastomosis by allowing supply from unaffected vessels. The anatomy of the circle of Willis is, however, highly variable and in many people it cannot provide much protection from ischaemia due to carotid, vertebral, or basilar artery occlusion. Anastomotic supply from other vessels in the neck may mitigate occlusions of feeder vessels— occlusion of the internal carotid in the neck, eg may not cause infarction if flow from the external carotid artery enters the circle of Willis via its anastomosis with the ophthalmic artery.

Fig 1. Where (and what) is the lesion? Answer: p470.[6]

The circle of Willis at the base of the brain

see also CT on p471.



Footnotes in history: Willis

Thomas Willis (1621-75) is one of those happy Oxford heroes belonging to Christ Church College who hold a bogus DM degree—awarded in 1646 for his Royalist sympathies. He had a busy life inventing terms such as 'neurology' and 'reflex'. Not only has his name been given to his famous circle, but he was the first to describe myasthenia gravis, whooping cough, and the sweet taste of diabetic urine. He was the first person (few have followed him) who knew the course of the spinal accessory nerve. He is unusual among Oxford neurologists in that, at various times, he developed the practice of giving his lunch away to the poor. He also developed the practice of iatrochemistry: a theory of medicine according to which all morbid conditions of the body can be explained by disturbances in the fermentations and effervescences of its humours.

Arteries and CNS territories (see also figs 3 & 4, p733)

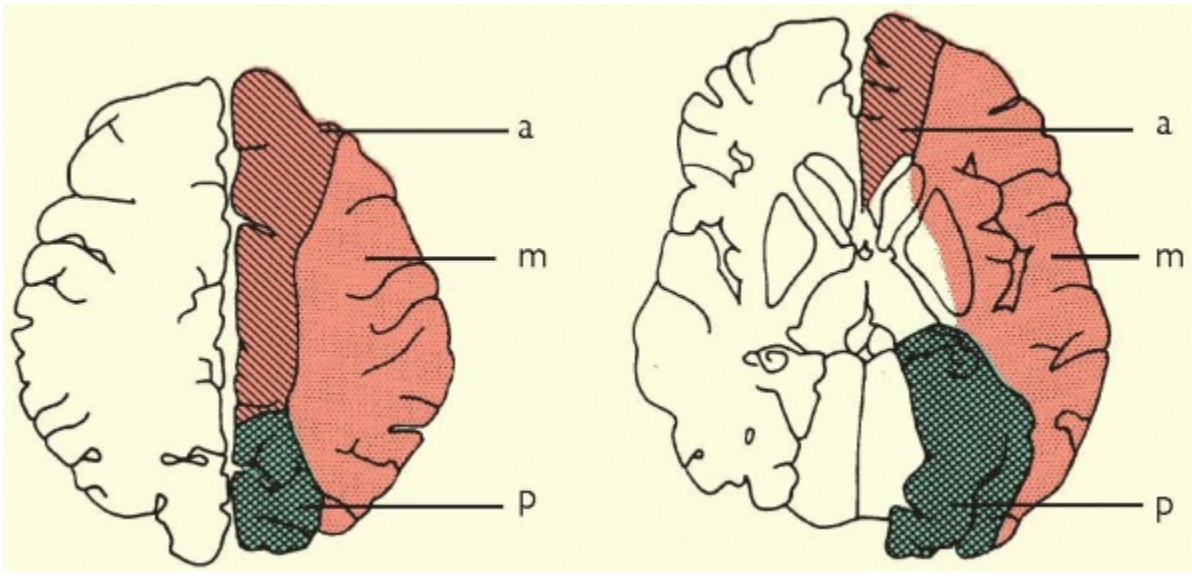


Fig 1. See text.

Carotid artery

Internal carotid artery occlusion may, at worst, cause total (and usually fatal) infarction of the anterior two-thirds of the ipsilateral hemisphere and

basal ganglia (lenticulostriate arteries). More often, the picture is similar to a middle cerebral artery occlusion (below).

Cerebral arteries

3 pairs of arteries leave the circle of Willis to supply the cerebral hemispheres; the anterior, middle, and posterior cerebral arteries. The anterior and middle cerebrals are branches of the carotid arteries; the basilar artery divides into the 2 posterior cerebral arteries. Ischaemia due to occlusion of any one of them may be reduced, if not prevented, by retrograde supply from meningeal vessels.

Anterior cerebral artery:

(**a** in Fig 1) Supplies the frontal and medial part of the cerebrum. Occlusion may cause a weak, numb contralateral leg ± similar, if milder, arm symptoms. The face is spared. Bilateral infarction can cause a kinetic mutism from damage to the cingulate gyri (also a rare cause of paraplegia).

Middle cerebral artery:

(**m** in Fig 1) Supplies the lateral (external) part of each hemisphere. Occlusion may cause: contralateral hemiplegia, hemisensory loss mainly of face and arm; contralateral homonymous hemianopia due to involvement of the optic radiation, cognitive change including dysphasia if the dominant hemisphere is affected, and visuo-spatial disturbance (eg cannot dress; gets lost) with non-dominant lesions.

Posterior cerebral artery:

(**p** in Fig 1) Supplies the occipital lobe; occlusion gives contralateral homonymous hemianopia (often with macula sparing).

Vertebrobasilar circulation

Supplies the cerebellum, brainstem, occipital lobes. *Occlusion cause:* hemianopia; cortical blindness; diplopia; vertigo; nystagmus; hemi- or quadriplegia; unilateral or bilateral sensory symptoms; cerebellar symptoms; hiccups; dysarthria; dysphasia; coma. Infarctions of the brainstem can produce various syndromes, eg *Lateral medullary syndrome* (occlusion of one vertebral artery or the posterior inferior cerebellar artery). It is due to infarction of the lateral medulla and the inferior cerebellar surface causing vertigo with vomiting, dysphagia, nystagmus, ipsilateral ataxia, soft palate paralysis, ipsilateral Horner's syndrome, and a crossed pattern sensory loss (analgesia to pin-prick on ipsilateral face and contralateral trunk & limbs).

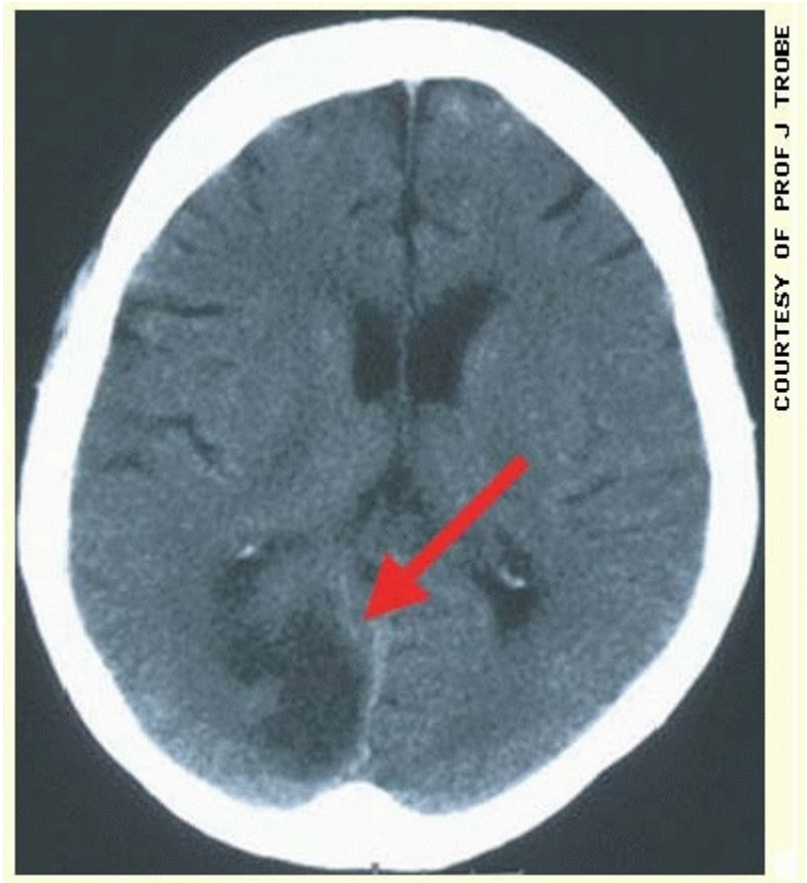


Fig 2. CT of stroke (arrow) in the distribution of the posterior cerebral artery.[7]

Subclavian steal syndrome:

Subclavian artery stenosis proximal to the origin of the vertebral artery may cause blood to be *stolen* by retrograde flow down this vertebral artery down into the arm, causing brainstem ischaemia typically after use of the arm. Suspect if the BP in each arm differs by >20mmHg.

Drugs and the nervous system

The brain is a gland that secretes both thoughts and molecules: both products are modulated by neurotransmitter systems. *Some target sites for drugs:*

1. Precursor of the transmitter (eg L-dopa).
2. Interference with the storage of transmitter in vesicles within the pre-synaptic neurone (eg tetrabenazine).
3. Binding to the post-synaptic receptor site (bromocriptine).

4. Binding to receptor-modulating site (benzodiazepines).
5. Interference with the breakdown of neurotransmitter within the synaptic cleft (monoamine oxidase inhibitors—MAOIs).
6. Reduce *reuptake* of transmitter from synaptic cleft into *pre-synaptic* cell (*selective serotonin reuptake inhibitors*, SSRIs, eg fluoxetine, OHCS p340). Also SNRI (serotonin and nonadrenaline reuptake inhibitors). Nonadrenaline may be more involved in the symptoms of anergia, fatigue and loss of drive in depression, and 5-HT may be more involved in the alteration in subjective mood and anxiety.[8]
7. Binding to presynaptic autoreceptors. There are 3 kinds of autoreceptors: neurotransmitter release modulators, synthesis modulators, and impulse modulators. These offer sites for intervention.[9] Augmenting antidepressant therapy with 5-HT autoreceptor antagonists such as pindolol is possible.[10]

The proven neurotransmitters include:

Amino acids

Glutamate & aspartate act as excitatory transmitters on NMDA & non-NMDA receptors—relevant in epilepsy and ischaemic brain damage. γ-aminobutyric acid (GABA) is mostly inhibitory.

Drugs enhancing GABA activity are used in:

Epilepsy (phenobarbital, benzodiazepines, vigabatrin); spasticity (baclofen, benzodiazepines).

Peptides

Opioids and substance P.

Histamine and Purines

(such as ATP) Clinical relevance is not clear.

Dopamine (DA)

Drugs enhancing DA activity:

Used in Parkinson's; hyperprolactinaemia; acromegaly. SE: vomiting; BP↓; chorea; dystonia; hallucinations and delusions.

Drugs which ↓ DA activity are used in:

Schizophrenia (OHCS p360, D_2 antagonists); delusions; chorea; tics; nausea; vertigo. SE: parkinsonism; dystonias; akathisia.

Serotonin

(5-hydroxytryptamine; 5HT) There are many types of receptors, eg: $5HT_{1-4}$. $5HT_1$ has 5 subtypes ($5HT_{1A-E}$).

Agonists:

$Lithium_{1A}$; $sumatriptan_{1D}$.

Partial agonists:

$Buspirone_{1A}$; LSD_2;

Antagonists:

$Ondansetron_3$, $pizotifen_{1\&2}$; $methysergide_{1\&2}$, $clozapine_{2C}$—known as low D_2-high $5HT_2$, while risperidone is high D_2-high $5HT_2$ (low D_2 means <60% D_2 occupancy at conventional doses; traditional antipsychotics are just high D_2, ie 60-80%).

Reuptake inhibitors:

Fluoxetine, sertraline, venlafaxine. Ecstasy increases nerve terminal 5HT release.[11]

Adrenaline (epinephrine) and non-adrenaline (norepinephrine)

4 receptor types: α1, α2, β1, β2. Norepinephrine is more specific for α-receptors but both transmitters affect all receptors. In the periphery: α-receptor stimulation leads to arteriolar vasoconstriction and pupillary dilatation; β1 stimulation to increase in pulse and myocardial contractility; β2 stimulation to bronchodilatation, uterine relaxation, and arteriolar vasodilatation.

Drugs enhancing adrenergic activity are used in:

Asthma (β2); anaphylaxis (adrenaline); heart failure (dobutamine); depression (MAOIs and tricyclics, the latter may act by increasing synaptic norepinephrine in the CNS).

Drugs reducing adrenergic activity are used in:

Angina, ↑BP, arrhythmias, thyrotoxicosis/anxiety (β1); ↑BP from phaeochromocytoma (α).

Acetylcholine

(Muscarinic and nicotinic receptors)

Centrally acting anticholinergic drugs are used in:

Parkinsonism, dystonias, motion sickness. Central toxic effects (especially in the elderly): confusion, delusions.

Peripheral antimuscarinic drugs are used in:

Asthma (ipratropium); incontinence; to dry secretions pre-op; to dilate pupils; to ↑ heart rate (atropine).

Peripheral cholinergic agonists used in:

Glaucoma (pilocarpine); myasthenia (anticholinesterases). SE: sweating, hypersalivation, colic.

Neurotransmitters and CNS drugs

Here we list drugs used to modify CNS transmitters. When prescribing bear in mind that: • The drug (or a metabolite) must be able to pass through the blood-brain barrier to have an effect. • The consequences of any sedative effects may be severe. • There will be short- and long-term side-effects (eg tardive dyskinesia with neuroleptic drugs). • Drugs may affect many neurotransmitters increasing therapeutic scope (and uncertainty). • One neurotransmitter may have many effects—eg midbrain dopamine neurones go awry in Parkinson's disease, schizophrenia, and in addiction to drugs and gambling, by affecting motor control, motivation, effort, reward, analgesia, stress, learning, attention, and cognition.[12]

Drugs ↑ activity (≈agonists)	**Drugs ↓ activity (≈antagonists)**
Dopamine (L-dopa)	
Pergolide; apomorphine; amantadine	Major tranquillizers
Bromocriptine (a D_2-agonist)	Benzisoxazoles (D_2) eg risperidone
Pramipexole (D_3) to do with mood behaviour & rewards	Some antiemetics
Selegiline (MAOI-B inhibitor)	
Non-adrenaline & adrenaline less (=norepinephrine & epinephrine)	

Salbutamol (β_2); adrenaline	Propranolol (β) (atenolol is mostly β_1)
?Tricyclic antidepressants	Clonidine (α_2-agonist)
MAOI	Phentolamine (α)

5HT

LSD and other hallucinogens	Pizotifen
Sumatriptan	Benzisoxazoles ($5HT_2$-antagonist) eg risperidone
Some tricyclic antidepressants eg trazodone	
Buspirone; lithium	Clozapine (*OHCS* p360 $5HT_{2A}$ antagonist)
Fluoxetine (*OHCS* p340)	Mianserin; ondansetron

Acetylcholine

Carbachol	Atropine; Scopolamine
Pilocarpine	Ipratropium
Anticholinesterases eg pyridostigmine	Benzhexol (=trihexyphenidyl) Orphenadrine; Procyclidine

GABA (inhibits other transmitters)

Baclofen (GABA-B) (GABA=gamma aminobutyric acid)	Alcohol abuse[1]: *acute effects* block
Benzodiazepines; valproate	
Barbiturates	*N*-methyl-D-aspartate (NMDA) receptors; *with chronic use*, numbers of NMDA receptors rise, mediating alcohol
Acamprosate (used in alcohol addiction; taurine & GABA analogue)[13]	

Glutamate[1]

(an excitatory amino acid)	Lamotrigine (used in epilepsy)
	Topiramate (used in epilepsy *et al.*)[1]
	Acamprosate (↓craving in alcoholics)
	Memantine (Alzheimer's, p478)
	Zonisamide (+ carbonic anhydrase activity, and modulates T Ca^{2+} channels)

New drugs are often aimed at multiple neurotransmitters, eg *risperidone* (blocks D_2, $5HT_2$, α1 and α2 adrenoceptors, *OHCS* p360). The smoking-cessation drug *bupropion* (=*amfebutamone*) is said to act by increasing dopamine in the mesolimbic system (mediates dependence) *and* via noradrenergic effects in the locus ceruleus (mediates symptoms of nicotine withdrawal).[14]

[1] Alcoholics have more glutamate binding sites, facilitating midbrain dopamine neurotransmission (pathways, which, in the ventral tegmental area, mediate alcohol's rewarding effects, eg craving). Topiramate facilitates GABA function, antagonizing glutamate at kainate receptors, and may ↓craving in alcoholism.

Testing peripheral nerves

Nerve root	Muscle	Test—by asking the patient to:
C3, 4	Trapezius	Shrug shoulder (via accessory nerve).
C5, 6, 7	Serratus anterior	Push arm forward against resistance; look for winging of the scapula, if weak.
C5, 6	Pectoralis major (p major) clavicular head	Adduct arm from above horizontal, and push it forward.
C6, 7, 8	P major sternocostal head	Adduct arm below horizontal.
C5, 6	Supraspinatus	Abduct arm the first 15°.
C5, 6	Infraspinatus	Externally rotate semi-flexed arm, elbow at side.
C6, 7, 8	Latissimus dorsi	Adduct arm from horizontal position.
C5,		

6	Biceps	Flex supinated forearm.
C**5**, 6	Deltoid	Abduct arm between 15° and 90°.
Radial nerve		
C6, **7**, 8	Triceps	Extend elbow against resistance.
C5, **6**	Brachioradialis	Flex elbow with forearm half way between pronation and supination.
C5, **6**	Extensor carpi radialis longus	Extend wrist to radial side.
C6, 7	Supinator	Arm by side, resist hand pronation.
C**7**, 8	Extensor digitorum	Keep fingers extended at MCP joint.
C**7**, 8	Extensor carpi ulnaris	Extend wrist to ulnar side.
C**7**, 8	Abductor pollicis longus	Abduct thumb at 90° to palm.
C**7**, 8	Extensor pollicis brevis	Extend thumb at MCP joint.
C**7**, 8	Extensor pollicis longus	Resist thumb flexion at IP joint.

Median nerve		
C6, 7	Pronator teres	Keep arm pronated against resistance.
C6, 7	Flexor carpi radialis	Flex wrist towards radial side.
C7, **8**, T1	Flexor digitorum superficialis	Resist extension at PIP joint (with proximal phalanx fixed by the examiner).
C7, **8**	Flexor digitorum profundus I & II	Resist extension at index DIP joint of index finger.
C7, **8**, T1	Flexor pollicis longus	Resist thumb extension at interphaÐlangeal joint (fix proximal phalanx).
C8, **T1**	Abductor pollicis brevis	Abduct thumb (nail at 90° to palm).
C8, **T1**	Opponens pollicis	Thumb touches base of 5th finger-tip (nail parallel to palm).
C8, **T1**	1st lumbrical/Interosseus (median & ulnar nerves)	Extend PIP joint against resistance with MCP joint held hyperextended.
Ulnar nerve		
C7, **8**,	Flexor carpi ulnaris	Flex wrist to ulnar side; observe tendon.

T1		
C7, **C8**	Flexor digitorum profundus III and IV	Resist extension of distal phalanx of 5th finger while you fix its middle phalanx.
C8, **T1**	Dorsal interossei	Finger abduction: cannot cross the middle over the index finger (tests index finger adduction too).[15]
C8, **T1**	Palmar interossei	Finger adduction: pull apart a sheet of paper held between middle and ring finger DIP joints of both hands; the paper moves on the weaker side.[1][16]
C8, **T1**	Adductor pollicis	Adduct thumb (nail at 90° to palm).
C8, **T1**	Abductor digiti minimi	Abduct little finger.
C8, **T1**	Flexor digiti minimi	Flex the little finger at MCP joint.

[1] Also, metacarpophalangeal joint flexion may be more on the affected side as flexor tendons are recruited—the basis of Froment's paper sign. Wartenberg's sign is persistent little finger abduction.

Lower limb Femoral nerve

L1, 2, 3	Iliopsoas (also supplied via L1, 3, & 3 spinal nerves)	Flex hip against resistance with knee flexed and lower leg supported: patient lies on back.
L2, 3, 4	Quadriceps femoris	Extend at the knee against resistance. Start with the knee flexed.

Obturator nerve		
L**2**, **3**, 4	Hip adductors	Adduct the leg against resistance.
Inferior gluteal nerve		
L**5**, S**1**, S2	Gluteus maximus	Hip extension (‘bury heal into the couch’)—with knee in extension.
Superior gluteal nerve[17]		
L**4**, **5**, S1	Gluteus medius & minimus	Abduction and internal hip rotation with leg flexed at hip and knee.
Sciatic (and common peroneal*) and sciatic (and tibial) nerves**		
*L**4**, 5	Tibialis anterior	Dorsiflex ankle.
*L**5**, S1	Extensor digitorum longus	Dorsiflex toes against resistance.
*L**5**, S1	Extensor hallucis longus	Dorsiflex hallux against resistance.
*L5, S1	Peroneus longus & brevis	Evert foot against resistance.
*L5, S1	Extensor digitorum brevis	Dorsiflex proximal phalanges of toes.

L5, **S1, 2	Hamstrings	Flex the knee against resistance.
**L4, 5	Tibialis posterior	Invert the plantarflexed foot.
**S1, 2	Gastrocnemius	Plantarflex ankle or stand on tiptoe.
L5, S1**, **2**	Flexor digitorum longus	Flex terminal joints of the toes.
**S1, 2	Small muscles of foot	Make the sole of the foot into a cup.

Quick screening test for muscle power

Shoulder	Abduction	C5	**Hip**	Flexion	L1-L2
	Adduction	C5-C7		Adduction	L2-3
Elbow	Flexion	C5-C6		Extension	L5-S1
	Extension	C7	**Knee**	Flexion	L5-S1
Wrist	Flexion	C7-8		Extension	L3-L4
	Extension	C7	**Ankle**	Dorsiflexion	L4

Fingers	Flexion	C8		Eversion	L5-S1
	Extension	C7		Plantarflexion	S1-S2
	Abduction	T1	**Toe**	Big toe extension	L5

Remember to test proximal muscle power: ask the patient to sit from lying, to pull you towards himself, and to rise from squatting (if reasonably fit).

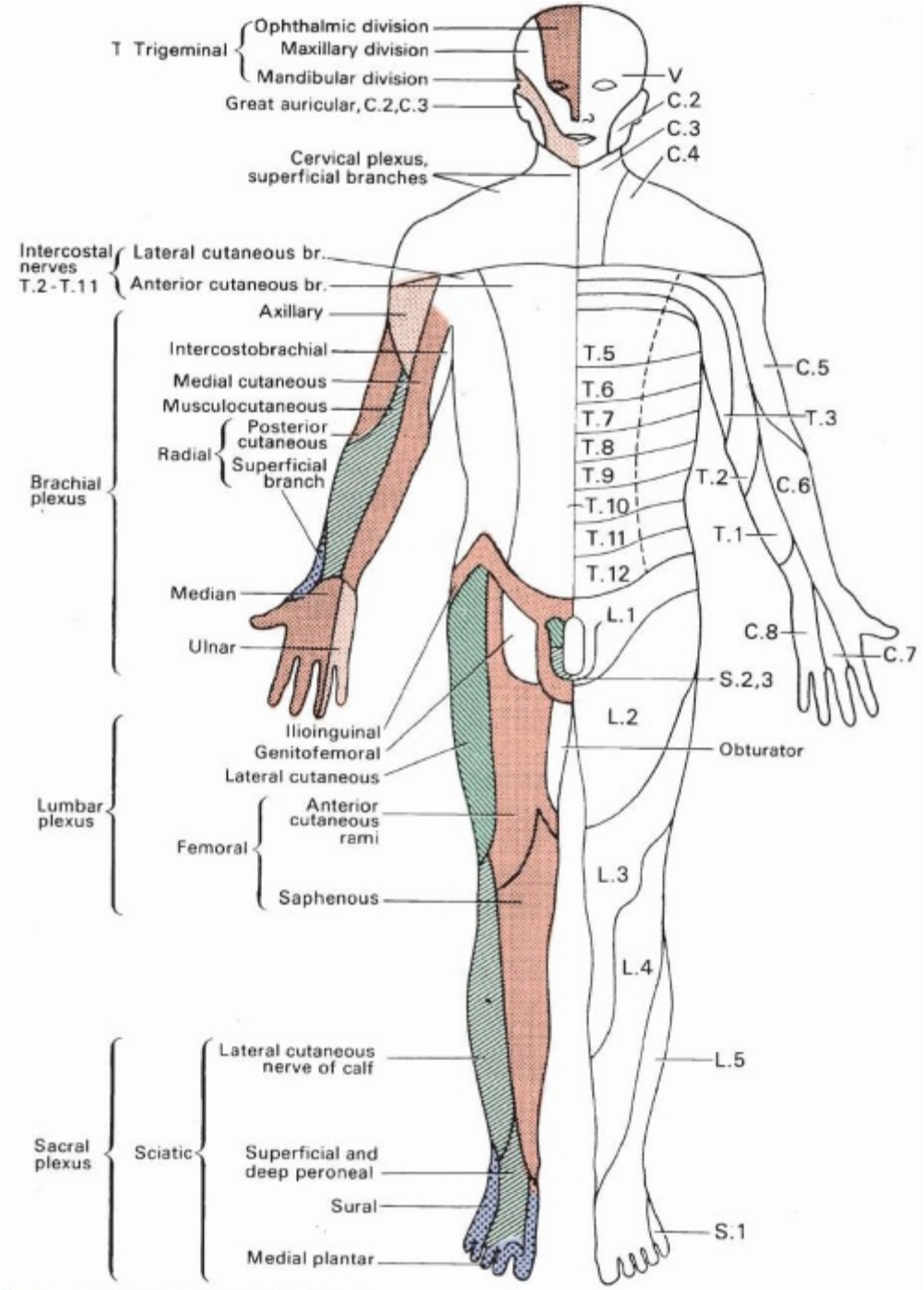
▸Observe walking—easy to forget, even if the complaint is of walking difficulty!

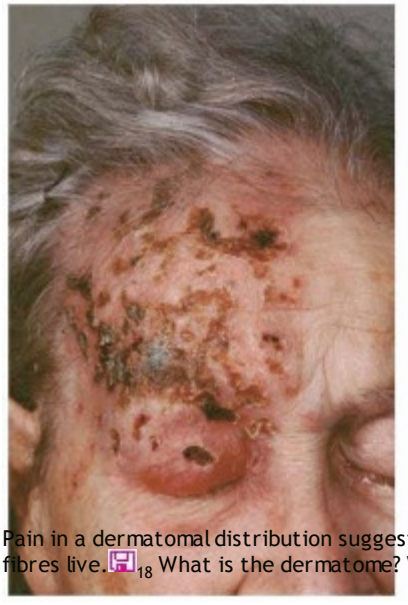
NB: root numbers in bold indicate that that root is more important than its neighbour.

▸Sources vary in ascribing particular nerve roots to muscles, and there is some biological variation in individuals. The above is a reasonable compromise, based on MRC/*Brain* 2001 guidelines: ISBN 0-7020-2512-7.

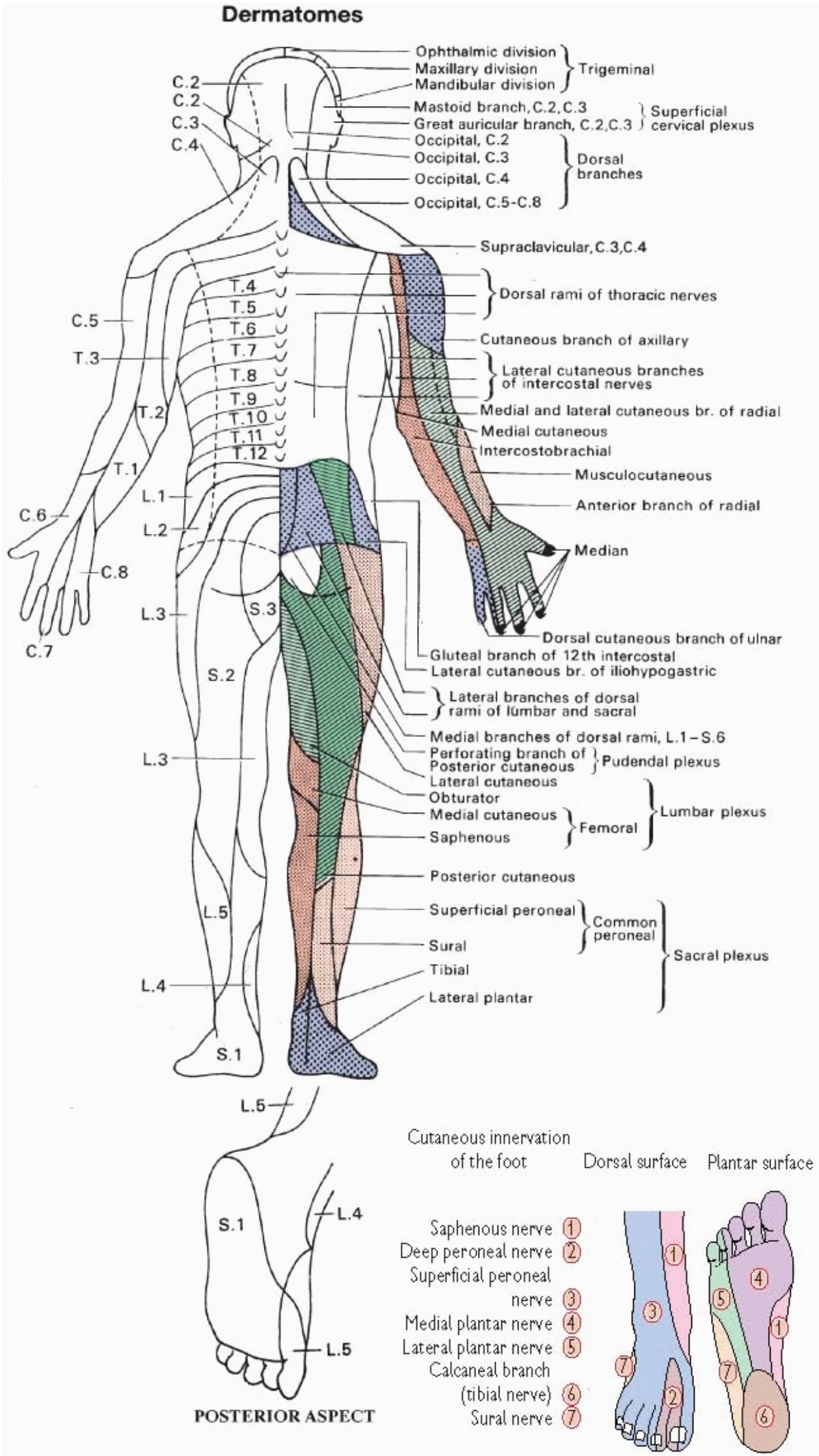
▸We don't react to nerve damage according to simple anatomy; eg ulnar neuropathy may initiate dystonic flexion or tremor of 4^{th} & 5^{th} digits by inducing a central motor disorder. [@8622720] [@2153273]

Dermatomes





Pain in a dermatomal distribution suggests a problem with a cranial nerve or dorsal root ganglion (radiculopathy) —where the cell bodies of sensory fibres live.[18] What is the dermatome? What is the lesion? See p388.


Dermatomes
Ophthalmic division
Maxillary division
Mandibular division
Trigeminal
Mastoid branch, C.2, C.3
Great auricular branch, C.2, C.3
Superficial cervical plexus
Occipital, C.2
Occipital, C.3
Occipital, C.4
Occipital, C.5-C.8
Dorsal branches
Supraclavicular, C.3, C.4
Dorsal rami of thoracic nerves
Cutaneous branch of axillary
Lateral cutaneous branches of intercostal nerves
Medial and lateral cutaneous br. of radial
Medial cutaneous
Intercostobrachial
Musculocutaneous
Anterior branch of radial
Median
Dorsal cutaneous branch of ulnar
Gluteal branch of 12th intercostal
Lateral cutaneous br. of iliohypogastric
Lateral branches of dorsal rami of lumbar and sacral
Medial branches of dorsal rami, L.1 – S.6
Perforating branch of Posterior cutaneous
Pudendal plexus
Lateral cutaneous
Obturator
Medial cutaneous
Saphenous
Femoral
Lumbar plexus
Posterior cutaneous
Superficial peroneal
Sural
Common peroneal
Tibial
Lateral plantar
Sacral plexus
C.2
C.2
C.3
C.4
C.5
T.3
T.2
T.1
C.6
C.8
C.7
T.4
T.5
T.6
T.7
T.8
T.9
T.10
T.11
T.12
L.1
L.2
L.3
S.3
S.2
L.3
L.5
L.4
S.1
L.5
S.1
L.4
L.5
POSTERIOR ASPECT
Cutaneous innervation of the foot
Dorsal surface
Plantar surface
Saphenous nerve 1
Deep peroneal nerve 2
Superficial peroneal nerve 3
Medial plantar nerve 4
Lateral plantar nerve 5
Calcaneal branch (tibial nerve) 6
Sural nerve 7

Headache

Every day, *thousands* of patients visit doctors complaining of headache; these consultations are rewarding as the chief skill is in interpreting the history, not in *taking* it, so much as in *allowing* it to unfold. Let patients tell you about all the headache's associations, or even *who* their headache is. Stress/tension headache is the usual cause of bilateral, non-pulsatile headache (± scalp muscle tenderness, but without vomiting or sensitivity to head movement). Here, stress relief, eg massage or antidepressants, may have more to offer than a neurologist. But some headaches are disabling and treatable (migraine, cluster headache), while others are sinister, eg space-occupying lesions, meningitis, subarachnoid haemorrhage (SAH), and giant cell arteritis. These are the headaches you must recognize:

Acute single episode

Meningitis	p806, eg fever, photophobia, stiff neck, rash, coma
Encephalitis	p807, eg fever, odd behaviour, fits, or consciousness↓
Tropical illness	p378, eg malaria, +ve travel history, 'flu-like illness
Subarachnoid	p470, haemorrhage → *sudden* headache ± stiff neck
Sinusitis	p562 in *OHCS*, eg tender face + coryza + post-nasal drip
Head injury	p810, cuts/bruises, consciousness↓; lucid interval, amnesia

Acute recurrent attacks

Migraine	p450, any pre-attack aura? Visual aura? Vomiting? Sensitivity to light, noise, or movement
Cluster headache	p449, typically nightly pain in one eye for ~8wks then OK for the next few months —then intermittently repeated
Glaucoma	p545, red eye; sees haloes, fixed big oval pupil; acuity↓

Recurrent (Mollaret's) meningitis	Suspect if T°↑ & fever; do LP + PCR for herpes simplex. Is there access to the subarachnoid space via a skull fracture, or a recurring cause of aseptic meningitis (SLE, Behçet's, sarcoid)?

Subacute onset

Giant cell arteritis	p542; tender scalp; ≳50yrs old; threat to vision; ESR↑

Chronic headache (pain for >15d/month for >3 months) [19]

Tension headache	'a tight band round my head'; stress at work / home, mood↓
Chronically ↑ICP	Eg worse on waking, focal signs, BP↑, pulse↓
Medication misuse	p448; medication misuse headache eg from analgesic overuse

Acute single episode

(eg meningitis, encephalitis, subarachnoid haemorrhage.) If the headache is acute, severe, felt over most of the head and accompanied by meningeal irritation (neck stiffness) ± drowsiness you must think of meningitis (p806), encephalitis (p807), or a subarachnoid (p470). Admit immediately for urgent CT (and, if -ve, LP, looking for blood products in the CSF).

After head injury

headache is common, eg at the site of trauma, or more generalized. It lasts ~2wks and is often resistant to analgesia. Bear in mind subdural/extradural haemorrhage (p474). Sinister signs are drowsiness, focal signs.

Sinusitis

causes dull, constant, aching pain over the frontal or maxillary sinus, with tender overlying skin ± postnasal drip. Ethmoid or sphenoid sinus pain is felt deep in the midline at the root of the nose. Pain is worse on bending over. Often occurs with coryza (p390). The pain lasts ~1-2 weeks. CT can confirm diagnosis (rarely needed).

Acute glaucoma:

Mostly elderly, long-sighted people. Constant, aching pain develops rapidly around an eye, radiating to the forehead.

Symptoms:

Markedly reduced vision, nausea, and vomiting.

Signs:

Red, congested eye; cloudy cornea; dilated, non-responsive pupil. Attacks may be precipitated by sitting in the dark, eg the cinema, dilating eye-drops or emotional upset. Seek expert help at once. If delay in treatment of >1h is likely, start IV acetazolamide, 500mg over several minutes.

Attacks of headache

Cluster headache (CH = migrainous neuralgia):

One theory (among many) is that this is caused by superficial temporal artery smooth muscle hyperreactivity to 5HT. There are related hypothalamic grey matter abnormalities. An autosomal dominant gene also has a role. Onset: any age; ♂:♀ ≥5:1, commoner in smokers. Pain occurs once or twice every 24h, each episode lasting 15-160min. Clusters typically last 4-12wks and are followed by pain-free periods of months or even 1-2yrs before another cluster begins. Sometimes it is chronic rather than episodic.

Symptoms:

Rapid onset severe pain around 1 eye which may become watery and bloodshot with lid swelling, lacrimation, facial flushing, and rhinorrhoea. Miosis ± ptosis (20% of attacks), being permanent in 5%. Pain is strictly unilateral and almost always affects the same side.

The father in extremis:

'...I am careful not to wake the children as I make my way down the stairs. If they were to witness my nightly cluster ritual, they would never see me the same way again. Their father, fearless protector, diligent provider, crawling about in tears, beating his head on the hard wood floor. The pain is so intense I want to scream, but I never do. I go down 3 flights of stairs where I can't be heard, and drop to my knees. I place my hands on the back of my neck, and lock my fingers together. I bind my head between my arms and squeeze as hard as I can in an attempt to crush my skull. I begin to roll around, banging my head on the floor, pressing my left eye with full force of my palm. I search for the telephone that has always been my weapon of choice for creating a diversion, and I beat my left temple with the hand piece. I create a rhythm as I strike my skull, cursing the demon with each blow...'[20]

[prescription take]:

Acute attack: 100% O_2 (7-15L/min for ~15min; specify 'non-rebreathable mask and short-burst delivery to give 100%';[21] CI: COPD)—or *sumatriptan* SC 6mg at the attack's onset. ***Preventives:*** Verapamil; lithium; steroids; methysergide (**SE:** retroperitoneal fibrosis).

Trigeminal neuralgia:

Paroxysms of intense, stabbing pain, lasting seconds, in the trigeminal nerve distribution eg from anomalous intracranial vessels compressing the trigeminal root. It is unilateral, typically affecting mandibular or maxillary divisions. The face screws up with pain (hence *tic douloureux*).

Triggers:

Washing affected area, shaving, eating, talking, dental prostheses.[22]

Typical patient:

♂ >50yrs old; in Asians ♀:♂ ≈2:1.[23]

Secondary causes:

Aneurysm, tumour, chronic meningeal inflammation, MS, zoster, skull base malformation (eg Chiari).[24] **MRI** is justifiable as secondary trigeminal neuralgia is not rare (~14%).[25]

Drugs:

Carbamazepine (start at 100mg/12h PO; max 400mg/6h; **lamotrigine**; **phenytoin** 200-400mg/24h PO; or **gabapentin** (p496). If drugs fail, surgery may be necessary. This may be directed at the peripheral nerve, the trigeminal ganglion or the nerve root.

Microvascular decompression:

Anomalous vessels are separated from the trigeminal root. Stereotactic gamma knife surgery can work, but length of pain relief and the time to treatment response are limiting factors.

Facial pain ΔΔ:

p60.

Headaches of subacute onset

Giant cell arteritis:

p542. *Exclude in all >50yrs old with a headache that has lasted a few weeks.* Look for tender, thickened, pulseless temporal arteries + ESR >40mm/h (↑CRP may be more sensitive). *Ask about:* Jaw claudication during eating. Prompt diagnosis and steroids avoid blindness.

Chronic headache

Tension headache:

See above.

Raised intracranial pressure:

Headache is a complaint of ~50% patients. Although variable, headaches are typically present on waking or may awaken the patient. They may not be severe, and may be worse lying down. If accompanied by other signs of ↑ICP, such as vomiting, papilloedema, epilepsy, progressive focal neurology, or mental change, admit the patient urgently for diagnostic imaging. **LP *is contra-indicated***. Any space-occupying lesion (neoplasm, abscess, subdural haematoma) may present in this way, as may benign intracranial hypertension.

Medication misuse headache:

Culprits are mixed analgesics containing codeine (self-medication), or prescribed opiates, ergotamine and triptans. It is a common reason for episodic headaches becoming daily headache. The culprit must be withdrawn, and a preventive added (eg tricyclics, valproate, gabapentin, p496).

Migraine

Migraine causes much misery and costs the UK economy >£200 million a year in lost production. Its prevalence is 8%. ♀:♂≈2:1.

Symptoms

Classically:

- Visual (or other) aura lasting 15-30min followed within 1h by unilateral, throbbing headache. *Or:*
- Isolated aura with no headache
- Episodic (often premenstrual) severe headaches, often unilateral, with nausea, vomiting ± photophobia/phonophobia but no aura; may have allodynia—all stimuli produce pain: 'I can't brush my hair, wear earrings or glasses, or shave, it's so painful'[26] —(='*common migraine*'). Signs: none. Tests: none if typical presentation.

Aura

Visual chaos (cascading, distortion, 'melting' and jumbling of print lines, dots, spots, zig-zag fortification spectra); hemianopia, hemiparesis, dysphasia, dysarthria, ataxia (basilar migraine). Mood or appetite ↑ or ↓, or ↑ sensory awareness (eg to sound) may occur hours before aura. Duration of aura is ≤ 1h, and typically before headache.

Sensory auras:

eg paraesthesiae spreading from fingers to face, or

speech auras:

(8% of auras; eg dysphasia; dysarthria; paraphasia, eg phoneme substitution).

Diagnostic criteria if no aura:

≥5 headaches lasting 4-72h with either nausea/vomiting or photophobia/phonophobia *and* ≥2 of:

- Unilateral • Pulsating
- Interferes with normal life • Worsened by routine activity, eg climbing stairs.

Pathogenesis

Cerebral oligaemia leading to the aura followed by cerebral and extracranial hyperaemia leading to the headache.[27] The underlying cause of the vascular abnormalities may be dysfunction in the sensory modulation of craniovascular afferents. Attacks are associated with changes in plasma 5HT.

Triggers—eg

CHOCOLATE or: **Ch**eese, **o**ral **c**ontraceptives, **c**affeine (or its withdrawal), alcoh**o**l, **a**nxiety, **t**ravel, or **e**xercise. In ~50%, no trigger is found, and in only a few does avoiding triggers prevent *all* attacks.

Associations:

Obesity; patent foramen ovale (catheter closure may help).[28]

Differential

Cluster or tension headache, cervical spondylosis; ↑BP; intracranial pathology, sinusitis/otitis media, caries. TIAs may mimic migraine aura. Migraine is rarely a sign of other pathology: don't look too hard for antiphospholipid syndrome, arteriovenous malformations, or microemboli (but in some they may be important).

Prophylaxis

(eg if frequency > twice a month). If one drug does not work after 3 months, try another. Most (>65%) will achieve ↓in attack frequency of 50%. Comparative trials are wanting—so select according to patient wish and SE profile.

- **Pizotifen** 0.5-1mg/8h PO; or 1-3mg PO at night (5HT antagonist). SE: drowsy, weight↑; ↑effects of alcohol; ↑glaucoma risk. Or **propranolol** 40-120mg/12h PO or **amitriptyline** 25-75mg nocte; SE: drowsiness, dry mouth, blurred vision.
- 2nd-line: **valproate** 400-600mg/12h; **NSAIDs**; **gabapentin** (p496); **topiramate**.[29] RCT[30]

Treatment

Low doses may fail as peristalsis is slow, so try *dispersible* high-dose **aspirin** 900mg/6h PO pc, or **paracetamol** 1g/6h PO 10min after metoclopramide (5mg PO, ≤15mg/d; beware extrapyramidal SEs); ***or*** **ketoprofen** 100mg stat PO.[31] Studies comparing ergotamine, NSAIDs and triptans are few.[32] In one QALY-based study, **rizatriptan** was better/cheaper than **sumatriptan** which was better/cheaper than **Cafergot**® (below).[33] Triptans are $5HT_{1B}/1D$ *agonists*, constricting cranial arteries. Rare SEs: arrhythmias or angina ± MI, even if no pre-existing risk. CI: past MI/IHD, coronary spasm, uncontrolled ↑BP, recent lithium, SSRIs, or ergot use.[1]

Ergotamine (a 5HT agonist, constricting cranial arteries) 1mg PO as headache starts, repeated at ½h, up to 3mg in a day, and 6mg in a week; or, better, as a *Cafergot® suppository* (2mg ergotamine + 100mg caffeine up to 2 in 24h; then ≥4 days without). Emphasize dangers of ergotamine (gangrene, vascular damage). CI: the Pill (OHCS p301); peripheral vascular disease/ischaemic disease; pregnancy; breast-feeding; hemiplegic migraine; Raynaud's; liver or renal impairment; BP↑.

[1] Of the oral triptans, rizatriptan is said to have quick efficacy; rizatriptan & zolmitriptan are available as rapid-dissolving wafers. Imigran Recover® may be had 'over the counter'. Almotriptan is similar to oral sumatriptan, but ?fewer SEs; 12.5mg is an effective, well-tolerated alternative if there is a poor response to sumatriptan 50mg. A poor response to one triptan does not predict a poor response to all.

Migraine questions

What is going on in migraine?

The old theory was vascular: constriction during aura, with dilatation causing pain. But MRIs during attacks show episodic cerebral oedema, dilatation of intracerebral vessels, and ↓water diffusion not respecting vascular territories, so the primary event may be neurological.[34]

Is migraine due to a hyperexcitable brain?

Magnetic studies have shown resting (interictum) hyperexcitability at least in the visual cortex, suggesting a failure of inhibitory circuits.[35] Cortical hyperexcitability may relate to imbalance between neuronal inhibition (mediated by GABA, p443) and excitation (via excitatory amino acids). Putative causes: ↓cerebral Mg^{2+} levels, mitochondrial abnormalities, dysfunctions related to ↑nitric oxide, and Ca^{2+} channelopathy.[36]

How do triptans work?

They block transmission from the trigeminal nerve to 2nd-order neurones in the trigeminal nucleus caudalis,[37] hence use in any process that activates trigeminal fibres, including migraine, cluster headache, SAH, p470.

If prophylaxis fails?

Hyperexcitability *may* be reducible by anticonvulsants lamotrigine (**SE***:* 'flu-like symptoms, drowsiness, diplopia, aggression), gabapentin (p496), topiramate (**SE***:* memory and language problems), tiagabine (**SE***:* diarrhoea, depression, concentration↓), levetiracetam (**SE***:* somnolence; amnesia; mood swings). Patients will ask about these, and we must explain that there are side-effects, and the treatment is experimental. They are also expensive.

Holistic care?

Migraine often co-exists with other chronic conditions—and the combined negative impact is immense. ▸Don't treat each disease in isolation. Rather, attempt to restore a good relationship with the self—and the recovery of the purpose of life. This is the hardest and the most rewarding task. Can these structured holistic dialogues help? Yes, definitely,[38] so don't be daunted.

For those not wanting drugs, what other/alternative therapies help?

- Some people find warm or cold packs to the head help abort attacks.
- Spinal manipulation,[39] riboflavin[40] and magnesium may have a role.
- Rebreathing into paper bag (raising P_aCO_2) may abort some attacks.[41]
- If obese, weight loss makes sense (to ↓extra-ovarian production of oestrogen and estradiol in adipose tissue—but benefit is unproven).[42]

Migraine, stroke, and the Pill *(combined oral contraception, COC)*

Incidence of migraine + Pill-related ischaemic stroke is 8 : 100,000 if aged 20; and 80 : 100,000 in those aged 40yrs. Low-dose COCs only should be used. Those with migraine with aura are known to be at especial risk, precluding use of combined Pills (but no problem with progesterone only or non-hormonal contraception). Risk is further augmented by:

- Smoking
- Age >35yrs
- BP↑
- Obesity (body mass index >30)
- Diabetes mellitus
- Hyperlipidaemia
- Family history of arteriopathy when aged <45yrs. Warn women with migraine to stop Pills at once if they develop aura or worsening migraine—see OHCS p301.

If the problem is migraine without aura in the pill-free interval consider:

- Alternative contraception method or a pill with a lower dose of the same progestogen or lowest available dose of a different progestogen.
- Tri-cycling: take the pill continuously for 3 packets (9 weeks) followed by a 7 day pill-free interval, so that the number of menstrual bleeds is reduced.
- Oestrogen supplements (below) from 3 days before menses, continuing for 7 days.

Peri-menstrual migraine

Prophylaxis: If no asthma, CCF, peptic ulcer etc, NSAID (eg mefenamic acid) at onset of menses to last day of bleeding ± transdermal oestradiol 50-100µg patches 3 days before menses, continue for 7 days. Prodigy$_{\text{guidance}}$

Pregnancy

Be optimistic: migraine often improves; if not, get help. *Prophylaxis:* stop (or go on to amitriptyline). *1st choice anti-emetic:* **cyclizine** or **promethazine**. *Analgesia:* if **paracetamol** is insufficient, try partial agonist opioids eg if attacks persist in the 2nd and 3rd trimesters (uncommon).$_{43}$ **Ibuprofen** (or **aspirin**) may be used, up to 30 weeks' gestation. Don't use aspirin if breastfeeding. Prodigy $_{\text{guidance}}$

Blackouts

History

It is vital to establish exactly what patients mean by 'blackout'. Do they mean loss of consciousness (LOC)? a fall to the ground without loss of consciousness? a clouding of vision, diplopia, or vertigo? Take a detailed history from the patient *and* a witness (see BOX).

Vasovagal (neurocardiogenic) syncope

Provoked by emotion, pain, fear or standing too long and due to reflex bradycardia ± peripheral vasodilatation. Onset is over seconds (*not* instantaneous), and is often preceded by nausea, pallor, sweating. and closing in of visual fields (pre-syncope). It cannot occur if lying down. The patient falls to the ground, being unconscious for ~2min. Incontinence of urine is rare. Brief jerking of the limbs is uncommon, but there is no tonic → clonic sequence. After an attack there is no prolonged confusion or amnesia.

Situation syncope

Cough syncope:

Weakness + LOC after a paroxysm of coughing.

Effort syncope:

Syncope on exercise; cardiac origin, eg aortic stenosis, HOCM.

Micturition syncope:

Mostly men, at night.

Carotid sinus syncope:

Carotid sinus hypersensitivity (on head-turning or shaving).

Epilepsy

presenting as blackout is most likely to be *grand mal* (LOC) or complex partial (impairment of consciousness). See p482. Attacks vary with the type of seizure, but some features suggest epilepsy as a cause of blackout: attacks when asleep or lying down; aura; identifiable precipitants, eg TV; altered breathing; cyanosis; typical movements; urinary and faecal incontinence; tongue-biting, particularly the side of the tongue, is virtually diagnostic; post-attack drowsiness or coma; amnesia; residual paralysis for <24h.

Stokes-Adams attacks

Transient arrhythmias (eg bradycardia due to complete heart block) causing ↓cardiac output and LOC. The patient falls to the ground (often with *no* warning except palpitation), pale, with a slow or absent pulse. Recovery is in seconds, the patient flushes, the pulse speeds up, and consciousness is regained. Injury is typical of these intermittent arrhythmias. A few clonic jerks may occur if an attack is prolonged. Attacks may happen several times a

day and in any posture.

Other causes

Hypoglycaemia:

Tremor, hunger, and perspiration herald light-headedness or LOC; rare in non-diabetics but see p198.

Orthostatic hypotension:

Unsteadiness or LOC on standing from lying in those with inadequate vasomotor reflexes: the elderly; autonomic neuropathy (p494); antihypertensive medication; overdiuresis; multi-system atrophy (MSA). ▸TIAs rarely cause blackouts.

Drop attacks

Sudden weakness of the legs causes the patient, usually an older woman, to fall to the ground. There is no warning, no LOC and no confusion afterwards. The condition is benign, resolving spontaneously after a number of attacks. Drop attacks also occur in hydrocephalus; these patients, however, may not be able to get up for hours.

Other causes

Anxiety:

Hyperventilation, tremor, sweating, tachycardia, paraesthesiae, light-headedness, and no LOC suggest a panic attack.

Factitious blackouts

(Münchausen's, p698).

Choking:

If a large piece of food blocks the larynx, the patient may collapse, turn blue, and be unable to speak. Do the Heimlich manoeuvre immediately to eject the food.

Examination

Cardiovascular, neurological. BP lying and standing.

Tests

Investigate unless obvious syncope. ECG;[1] 24h (or longer) ECG (arrhythmia, long Q-T, eg Romano-Ward, p82), U&E, FBC, glucose. Perhaps tilt-table tests; EEG, sleep EEG, echocardiogram, CT/MRI; HUT.[2] $P_aCO_2\downarrow$ in attacks suggests hyperventilation as the cause. ▸*While the cause is being elucidated, advise against driving*.

[1] Consider elevating V1-V3 leads from 4th to the 2nd intercostal space to reveal saddle-shaped ST elevation, a telltale sign of **Brugada syndrome** (p687)—an autosomal SCN5A channelopathy predisposing to VT.

[2] **Head-up tilt (HUT) tests** distinguish vasodepressor from cardio-inhibitory syncope. HUT is +ve if symptoms are associated with a BP drop >30mmHg (vasodepressor; consider ß-blockers to counter ↑sympathetic activity)—or bradycardia (cardio-inhibitory; consider pacing).

Taking a history of blackouts
If a series of attacks, ask a witness: During a typical attack…

- Does the patient lose consciousness?
- Does the patient injure himself?
- Does the patient move? Floppy or stiff (suggests epilepsy)? NB: not everything that twitches is epilepsy. Ask for exact details of movements.
- Is there incontinence? (irrelevant if urine, but faeces suggests epilepsy).
- Is the complexion changed? (White or red suggests arrhythmia, but may occur in temporal lobe epilepsy).
- Does the patient bite the side of his tongue? (strongly suggests epilepsy).
- What is the patient's pulse like? (abnormalities suggest a CVS cause).
- Are there associated symptoms (palpitations, chest pain, dyspnoea)?
- How long does the attack last?
- Is the patient sleepy before an attack (narcolepsy, p692).

Before the attack:

- Is there any warning?—eg typical epileptic aura or pre-syncope (above).
- In what circumstances do attacks occur? (if watching TV, it is epilepsy).

- Can the patient prevent attacks?

After the attack:

- How much does the patient remember about the attack afterwards?
- Muscle pain afterwards suggests a tonic/clonic seizure.
- Is the patient confused or sleepy (post-ictal; narcolepsy)?

Background to attacks:

Getting more frequent? Is anyone else in the family getting them? Sudden arrhythmic death[1] may leave no cardiac trace at *post mortem*, or there may be hereditary cardiomyopathy.

▸Witnesses often give conflicting accounts: the most reliable may not be the one with the most medical knowledge. He or she may know what you expect to hear, and furnish you with extra (imagined) material.

Dizziness and vertigo

Complaints of 'dizzy spells' are very common and are used by patients to describe many different sensations. The key to diagnosis is to find out exactly what the patient means by 'dizzy' and then decide whether or not this represents vertigo.

Is this vertigo?

Definition:

An illusion of movement, often rotatory, of the patient or his surroundings. In practice, straightforward 'spinning' is rare—the floor may tilt, sink, or rise or 'I veer sideways on walking as if pulled to one side by a magnet'. Vertigo is always worsened by movement.

Associated symptoms:

Difficulty walking or standing; relief on lying or sitting still; nausea; vomiting; pallor; sweating. Attacks may even cause patients to fall suddenly to the ground. Associated hearing loss or tinnitus implies labyrinth or 8th nerve involvement.

What is not vertigo:

Faintness may be described as dizziness but is often due to anxiety with associated palpitations, tremor, and sweating. Anaemia can cause light-headedness as can orthostatic hypotension or effort in an emphysematous patient. But in all of these there is no illusion of movement or typical associated symptoms. Loss of consciousness during attacks should prompt thoughts of epilepsy or syncope rather than vertigo.

Causes

Disorders of the labyrinth, vestibular nerve, vestibular nuclei, or their central connections are responsible for practically all vertigo. Only rarely are other structures implicated (BOX).

Causes of vertigo
Vestibular end-organ and vestibular nerve

- Ménière's disease
- Vestibular neuronitis (ie acute labyrinthitis)
- Benign positional vertigo (OHCS p554)
- Motion sickness
- Trauma
- Ototoxic aminoglycosides
- Zoster (ie Ramsay Hunt syndrome, OHCS p652)

Brainstem, cerebellum, cerebello-pontine angle
(Look for nystagmus and cranial nerve lesions)

- MS
- Infarction/TIA
- Haemorrhage
- Migraine (very rarely)
- Acoustic neuroma)

Cerebral cortex

- Vertiginous epilepsy

Alcohol intoxication

Labyrinthine vertigo

Benign positional vertigo

is due to canalolithiasis—mobile particles in the semicircular canal cause inappropriate endolymph flow on head movement. It is curable by Epley manoeuvres (to reposition particles, OHCS p554).

Vestibular nerve

Damage in the petrous temporal bone or cerebello-pontine angle often involves the auditory nerve, causing deafness or tinnitus. Causes: trauma and vestibular schwannomas (acoustic neuromas).

Ménière's disease:

Recurrent attacks of **vertigo** (eg lasting >20min ±nausea/vomiting), fluctuating sensorineural **hearing loss** (may become permanent), and **tinnitus** (or a sense of aural fullness) caused by endolymphatic hydrops. Drop attacks may rarely feature (no loss of consciousness or vertigo, but sudden falling to one side).

[prescription take]:

Acute attacks—bed rest and reassurance. An antihistamine (eg cinnarizine) is useful if prolonged. Consider endolymphatic sac surgery or ablation of the vestibular organ with gentamicin in very severe disease. Prophylaxis: low-salt diets and diuretics may be tried—but there is no good evidence of efficacy. There is no evidence that tinnitus or deafness is alleviated or prevented by betahistine, diuretics, trimetazidine, or lithium. prodidgy$_{+cochrane}$

Ototoxicity:

(eg from aminoglycosides) may also cause vertigo and deafness.

Acoustic neuromas

usually present with hearing loss, vertigo coming only later. With progression, ipsilateral cranial nerves V, VI, IX, and X may be affected (also ipsilateral cerebellar signs). Paradoxically, there is rarely VII nerve involvement pre-operatively. Signs of ↑ICP occur late, and indicate a large tumour.

They account for 80% of cerebello-pontine angle tumours (ΔΔ meningioma).$_{44}$ Commoner in ♀; also in neurofibromatosis (esp. NF2, p506). Not all need removing.

Acute labyrinthitis (vestibular neuronitis):

Abrupt onset of severe vertigo, nausea/vomiting ± prostration. No deafness or tinnitus. Cause: virus; vascular lesion. Severe vertigo subsides in days, complete recovery takes 3-4wks. Reassure. Sedate.

Herpes zoster:

Herpetic eruption of the external auditory meatus; facial palsy ± deafness, tinnitus, and vertigo (Ramsay Hunt syndrome).

Hearing loss ▸ See *OHCS* p550 for management

One reasonable bedside method to establish hearing loss is to whisper numbers increasingly loudly in one ear while blocking the other ear with a finger. Ask your patient to repeat the number. Make sure that failure is not from misunderstanding.

Tuning fork tests

No single test is diagnostic but tuning fork tests do give useful information (also popular in exams).

Rinne:

Use a 512-256Hz tuning fork; strike it 1/3 from its free end on your patella and hold it so that the 2 prongs and the meatus lie on the same line (air conduction, AC). Then place the vibrating stem on the mastoid for bone conduction (BC). Ask: "which is louder?"

Rinne negative:

BC > AC. This occurs with conductive deafness >20dB (or with severe sensorineural hearing loss (SNHL)—ie a false -ve Rinne: the cochlea of the other ear picks up the sound by bone conduction—use of a Barany noise box to mask the other ear during the test, prevents this).

Rinne positive:

AC > BC. Remember '**SNAC—rip**': in **s**ensorineural loss and **n**ormal ears, **a**ir **c**onduction is better—and means **Ri**nne **p**ositive.

Weber tuning fork test

With the tuning fork on the vertex, forehead or upper incisors(!), ask the patient which ear the sound is heard in. Sound localizes to the affected ear with conductive loss (>10dB loss), to the contralateral ear in SNHL, and to the midline if both ears are normal (or if bilateral sensorineural loss).

Conductive deafness

Causes: wax (remove eg by syringing with warm water after softening with olive oil drops) or otosclerosis, otitis media, glue ear (OHCS p546).

Chronic sensorineural deafness

Often due to accumulated environmental noise toxicity, ie presby(a)cusis or inherited disorders.

Sudden sensorineural deafness

▸Refer promptly. Causes: noise exposure; gentamicin or other toxin; mumps; acoustic neuroma; MS; stroke; vasculitis; TB. Do ESR; FBC; LFT; viral titres; audiologist; evoked response audiometry ± CXR; Mantoux; MRI; pANCA; lymph node & nasopharyngeal biopsy for malignancy and TB culture.

Presbyacusis

Loss of acuity for high-frequency sounds starts before 30yrs old. We do not usually notice it until hearing of speech is affected. Hearing is most affected in the presence of background noise. Hearing aids are the usual treatment.

Tinnitus (See *OHCS* p552)

This is ringing/buzzing in the ears; it is common and may cause depression ± insomnia.

Causes

Focal hyper-excitability in the auditory cortex (?the cause of common tinnitus);[45] hearing loss (20%); wax; viral; presbyacusis; noise (eg gunfire); head injury; septic otitis media; post-stapedectomy; Ménière's; head injury; anaemia; BP↑ (in up to 16%; it may not be causative).[46]

Drugs:

Aspirin; loop diuretics; aminoglycosides (eg gentamicin).

Psychological associations:

Redundancy, divorce, retirement. ♂:♀≈1:1. ▸Investigate unilateral tinnitus fully to exclude a vestibular schwannoma (acoustic neuroma, p454).

Mean age at onset:

40-50yrs.

Causes of pulsatile tinnitus:

(eg audible with stethoscope; do MRI) Carotid artery stenosis/dissection;[47] AV fistulae; glomus jugulare tumours, OHCS p552.

Treatment

Psychological support is very important (eg from a hearing therapist). Exclude serious causes; reassure that tinnitus does not mean madness or serious disease and that it often improves in time. **Cognitive therapy** helps, as does 'tinnitus coping training'. Patient support groups can help greatly.[48] **Drugs** are disappointing. Avoid tranquillizers, particularly if depressed (use tricyclic antidepressants here, eg amitriptyline[49] or nortriptyline).[50] Hypnotics at night may help. Carbamazepine is disappointing; if Ménière's disease is the cause, betahistine helps only a few. **Masking** may give relief. White noise (like an off-tuned radio) is given via a noise generator worn like a post-aural hearing aid. **Hearing aids** may help by amplifying desirable sounds. **Cochlear nerve section** can relieve disabling tinnitus in 25% (at the expense of deafness). Repetitive **focal transcranial magnetic stimulation** of the auditory cortex can help (a novel and non-standard therapy).[51]

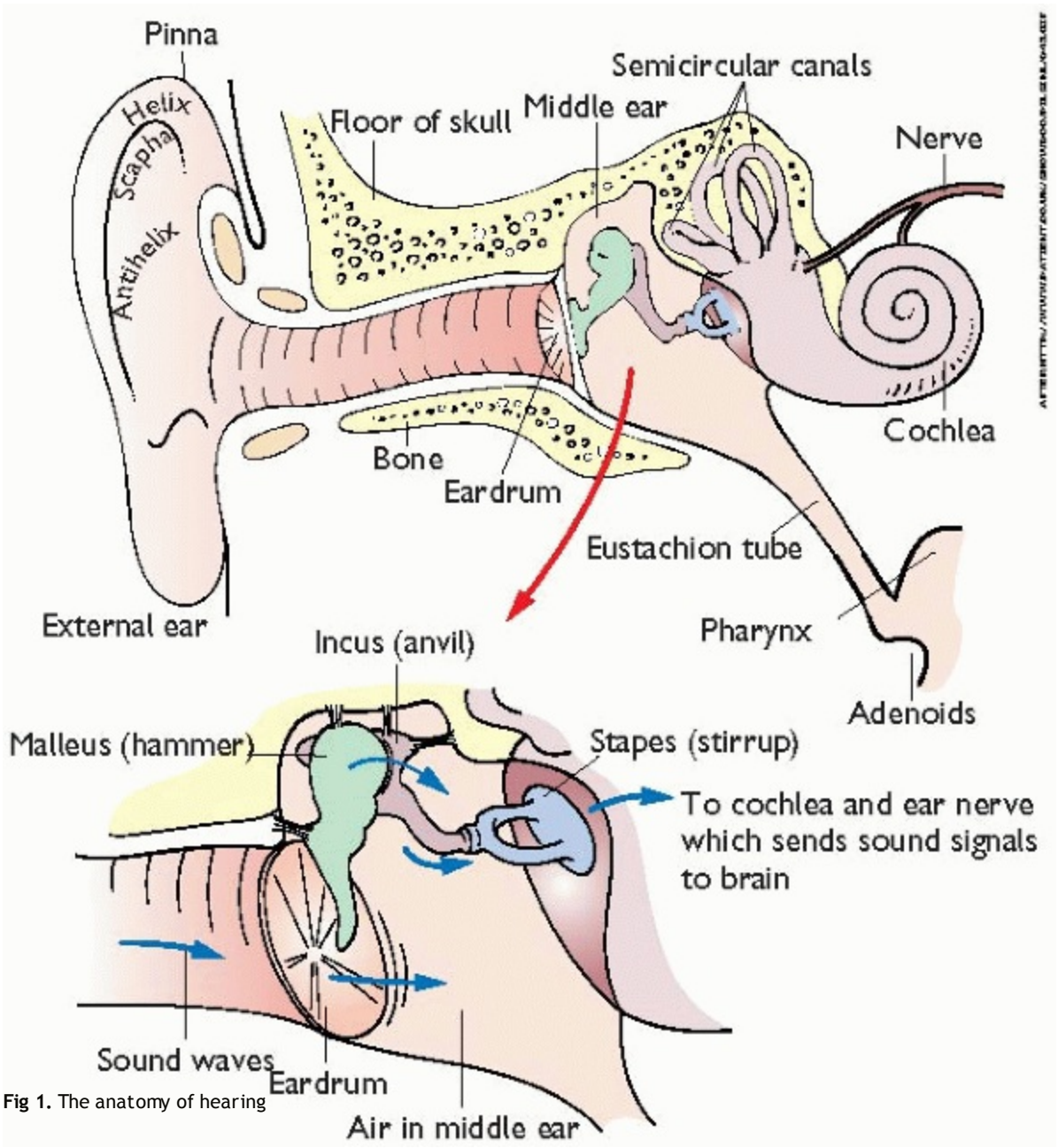


Fig 1. The anatomy of hearing

Weak legs and cord compression

Cord compression typically presents with weak legs. There are many causes of weak legs (see BOX) but only 5 cardinal questions:

1. Was the onset gradual or sudden?
2. At what rate is the weakness progressing?
3. Are the legs spastic or flaccid?
4. Is there sensory loss?[1] A sensory level usually means spinal cord disease.
5. Is there loss of sphincter control (bowels, bladder)?
6. Any signs of infection (spine tenderness, WCC↑, eg in extradural abscesses)?

Progressive weakness

Rapidly progressing cord compression is an emergency. Hours make a difference: untreated, irreversible loss of power and sensation below the lesion's level, and a neurogenic bladder and bowel may ensue.

Symptoms:

Spinal or root pain[1] may precede leg weakness and sensory loss. Arm weakness is often less severe (suggests a cervical cord lesion). Bladder (and anal) sphincter involvement is late and manifests as hesitancy, frequency, and, later, as painless retention.

Signs:

Look for a motor, reflex, and sensory level, with normal findings *above* the level of the lesion, LMN signs *at* the level (p439, especially in cervical cord compression, see p500)—and UMN signs *below* the level; remember tone and reflexes are ↓ in acute cord compression (spinal shock, OHCS p768).

Causes

Secondary malignancy (breast, lung, prostate) in the spine is commonest. Rarer: Infection (epidural abscess), cervical disc prolapse, haematoma (warfarin), intrinsic cord tumour, atlanto-axial subluxation.

ΔΔ

Transverse myelitis; MS; carcinomatous meningitis; Guillain-Barré (p694); cord vasculitis (PAN, syphilis); spinal artery thrombosis, trauma; dissecting aneurysm.

Tests

Do not delay imaging at any cost. Speed of imaging should parallel the rate of clinical progression. Spinal x-rays can be helpful, but MRI is the definitive image. Biopsy or surgical exploration may be needed to identify the nature of any mass.

Screening blood tests:

FBC, ESR, B_{12} , folate, syphilis serology, U&E, LFT, PSA. Do a CXR (primary lung malignancy, lung secondaries, TB).

Treatment

If malignancy, give dexamethasone IV 4mg/6h while considering more specific therapy, eg radiotherapy or chemotherapy ± decompressive laminectomy; which is most appropriate depends on tumour type, quality of life, and likely prognosis. Epidural abscesses must be surgically decompressed and antibiotics given.

Cauda equina and conus medullaris lesions

The big difference between these lesions and those high up in the cord is that leg weakness is flaccid and areflexic, not spastic and hyperreflexic.

Causes:

As above plus congenital lumbar disc disease; lumbosacral nerve lesions.

Clinical features:

Conus medullaris lesions show early urinary retention and constipation, back pain, sacral sensory disturbance, erectile dysfunction ± leg weakness. Cauda equina lesions feature back pain and radicular pain down the legs; asymmetrical, atrophic, areflexic paralysis of the legs; sensory loss in a root distribution —and ↓sphincter power.

Paralysed patients need especial care

Avoid pressure sores by turning. Review weight-bearing areas often. Avoid thrombosis in paralysed limbs by frequent passive movement and pressure stockings ± low molecular weight heparin (p334). Bladder care is vital; catheterization is only one option. Do not control incontinence by decreasing fluid intake (OHCS p774). Bowel evacuation may be manual or aided by suppositories. Increasing dietary fibre intake may help. Exercise of unaffected or partially paralysed limbs is important to avoid unnecessary loss of function.

Other causes of leg weakness

- ***Chronic spastic paraparesis*** **MS;** intrinsic cord tumours (astrocytomas; ependymomas; haemangioblastomas;[52] metastases, eg from melanoma, lung tumours, etc.[53]) syringomyelia; **MND** p498: subacute combined degeneration of the cord (B12 deficiency, p320); syphilis; rare non-neoplastic lesions—eg histiocytosis X; schistosomiasis; other parasites (any eosinophilia?).[54]
- ***Chronic flaccid paraparesis*** Tabes dorsalis; peripheral neuropathies (p496); myopathies (rare; arms are usually involved too, see p502).
- ***Unilateral foot drop*** **DM;** stroke; prolapsed disc; **MS**; common peroneal nerve palsy.
- ***Weak legs with no sensory loss*** **MND;** parasagittal meningioma (the rare exception to the 'rule' that weak legs mean cord or more distal problems).
- ***Absent knee jerks and extensor plantars*** eg from combined cervical and lumbar disc disease or a '**MAST**': motor neurone disease, Friedreich's **a**taxia; subacute combined degeneration of the cord (but knee jerks more often brisk); **t**aboparesis (syphilis, p419).

Specific gait disorders

(Even the best professionals have to employ extraordinary tactics simply to *describe* gaits accurately,[1] never mind *diagnose* them accurately.)

- ***Spastic:*** Stiff, circumduction of legs ± scuffing of the foot.
- ***Extrapyramidal:*** Flexed posture, shuffling feet, slow to start, postural instability. *Example*: Parkinson's disease.
- ***Apraxic:*** Pathognomonic **'glueing-to-the-floor'** on attempting walking OTM*3*[3970] or a wide-based unsteady gait with a tendency to fall. Causes: normal pressure hydrocephalus; multi-infarct states.

- ***Ataxic:*** Wide-based; falls; cannot walk heel-to-toe. May be caused by cerebellar lesions (eg **MS**; posterior fossa tumours; alcohol; phenytoin toxicity) or by proprioceptive sensory loss (eg sensory neuropathies; subacute combined degeneration of the cord). Often worse in the dark, or with eyes closed.
- ***Myopathic:*** Waddle (hip girdle weakness). Cannot climb steps.
- ***Psychogenic:*** Often a bizarre gait not conforming to any pattern of organic gait disturbance. Suspect if there is profound gait disturbance with inability even to stand, without any signs when examined on the couch ('astasia abasia')—but this may occur with midline cerebellar lesions, normal pressure hydrocephalus, and other rare tumours.[55] Video analysis reveals 6 signs of psychogenicity, seen in 97% of patients in one study:[56]

  Fluctuations in response to suggestion or distraction.

  Excessive hesitation of locomotion incompatible with CNS disease.

  'Psychogenic' Romberg test with building-up of sway amplitudes.

  Uneconomic postures wasting muscular energy.

  'Walking on ice' gait, ie small cautious steps, with ankle joints fixed.

  Sudden buckling of the knees, usually without falls.

Tests

Spinal X-rays. MRI; FBC, ESR, syphilis serology, serum B12 , U&E, LFT, PSA (prostate cancer), serum electrophoresis (myeloma); CXR (TB, Ca bronchus); LP (p756); EMG; muscle biopsy; sural nerve biopsy.

Abnormal involuntary movements (dyskinesia)

Movement disorders—ie ataxia, dystonic disorders, gait disorders (p459), Huntington disease (p694), myoclonus, parkinsonism, spasticity, tardive dyskinesia, tics and tremor—are clinically and pathologically heterogeneous and are characterized by impairment of the planning, control or execution of movement.[57]

Tremor

Note frequency, amplitude, and exacerbating factors (stress; fatigue).

Rest tremor

is tremor abolished on voluntary movement. Cause: parkinsonism (p486).

Intention tremor

is irregular, large-amplitude, and worse at the end of purposeful acts, eg pressing a remote control. It suggests cerebellar disease, eg MS, stroke.

Postural tremor

is absent at rest, present on maintained posture (arms outstretched) and may persist (but is not exaggerated) on movement. *Causes:* Benign essential tremor (autosomal dominant; helped by alcohol); thyrotoxicosis; anxiety; β agonists (eg salbutamol).

Re-emergent tremor

is a postural tremor developing after a delay of ~10sec (eg in Parkinson's).[58]

Asterixis

is a coarse, slow, non-rhythmic hand flap worse with arms outstretched and wrists extended. Cause: lapses of muscle tone in liver or renal failure. Surgery/deep brain stimulation (DBS, below) helps some tremors.[59]

Chorea, athetosis, and hemiballismus

Chorea:[1]

Non-rhythmic, jerky, purposeless movements flitting from one place to another—eg facial grimacing, raising the shoulders and flexing and extending the fingers. Causes: Huntington's or Sydenham's chorea (choreoathetoid movements; a rare complication of strep infection). The anatomical basis of chorea is uncertain but it may be the pharmacological mirror image of Parkinson's disease (L-dopa worsens chorea).

[1] Paracelsus used the term chorea to describe the jerking movements of medieval pilgrims traveling to the healing shrine of St. Vitus—reflecting the ancient Greek round dance accompanied by singing (hence chorus; choreography). He recognized 3 types: chorea arising from the imagination (chorea imaginativa), or from sexual desire (chorea lasciva)—and chorea arising from corporeal causes (chorea naturalis).

Hemiballismus:

Large-amplitude, flinging hemichorea (affects proximal muscles) contralateral to a vascular lesion of the subthalamic nucleus (often elderly diabetics). Recovers spontaneously over months.

Athetosis:

Slow, sinuous, confluent, purposeless movements (esp. digits, hands, face, tongue), often difficult to distinguish from chorea. Commonest cause is cerebral palsy (OHCS p214). Most other patterns once described as 'athetoid' may now be better characterized as one of the dystonias.

Tics

Brief, repeated, stereotyped movements which patients may suppress for a while. Tics are common in children (and usually resolve). In *Tourette's syndrome* (p692), motor and vocal tics occur. Consider psychological support, clonazepam or clonidine if tics are severe (haloperidol may help but risks tardive dyskinesia).

Myoclonus

Sudden involuntary focal or general jerks arising from cord, brainstem, or cerebral cortex, seen in metabolic problems (eg renal failure), neurodegenerative disease (eg lysosomal storage enzyme defects), CJD (p688), and myoclonic epilepsies (infantile spasms).

Benign essential myoclonus:

General myoclonus begins in childhood as muscle twitches (eg autosomal dominant and has no other consequences).

Asterixis:

Jerking of outstretched hands (metabolic flap) from loss of extensor tone.

[prescription take]:

Myoclonus may respond to valproate, clonazepam, or piracetam.

Tardive syndromes

Tardive means after *chronic* exposure to dopamine receptor blockers (eg antipsychotics, antiemetics). Tardive syndromes are a source of much distress and disability, and may be permanent, despite discontinuing all drugs.

Classification:[60]

- Tardive dyskinesia (orobuccolingual, truncal, or choreiform movements, eg vacuous chewing and grimacing movements)
- Tardive dystonia (sustained, stereotyped muscle spasms of a twisting or turning character (eg retrocollis and back arching/opisthotonic posturing
- Tardive akathisia (unpleasant inner sense of restlessness or unease ± repetitive, purposeless movements (stereotypies; eg pacing)
- Tardive myoclonus
- Tardive tourettism (p692)
- Tardive tremor (may respond to donepezil).[61]

Treating tardive dyskinesia:

Get help. Gradually withdraw neuroleptics and wait 3-6 months. If still a problem, consider tetrabenazine 12.5-50mg/8h PO.[62] Quetiapine and olanzapine are examples of atypical antipsychotics that are less likely to cause tardive syndromes.

Dystonia

Dystonia entails prolonged muscle contraction causing abnormal posture or repetitive movements due to many causes. Verbatim example of dystonic symptoms (writer's cramp, in this example): 'I cannot, for example, draw the instrument [pen, pencil] toward me in a circular motion, eg the left arc of a circle, or the letter O. If I force the move, the movements become jerky and I lose all smoothness in the character. The same thing will happen when eating and trying to use a fork…I end up moving my mouth to the fork…instead of moving my hand to my mouth—awkward."[63]

Dystonic disorders can be classified by **age of onset** (<12yrs old is childhood onset, 13-20yrs is adolescent onset, and >20yrs is adult)—or by **part of body affected**, or by **cause**. Childhood onset suggests **idiopathic generalized dystonia**, which often starts with dystonia in one leg, spreading to that side of the body over 5-10yrs. Autosomal dominant inheritance is common (gene tests often show a deletion in DTY1). Treatment is challenging; exclude Wilson's disease and dopa-responding dystonia (needs an L-dopa trial). High-dose trihexyphenidyl (=benzhexol, an anticholinergic) and deep-brain stimulation may help.[64]

Dystonia may be confined to one part of the body—ie a **focal dystonia**, eg spasmodic torticollis (head pulled to one side), blepharospasm (OHCS p460; ie involuntary contraction of orbicularis oculi), **writers cramp** (see below). Focal dystonias in adults are typically idiopathic, and they rarely generalize. They are worsened by stress; patients may develop a 'geste antagonistique' to try to resist the dystonic posturing (eg a touch of the finger to the jaw in spasmodic torticollis).[65] Effective control of focal dystonia by botulinum toxin injections into the overactive muscles (OHCS p460) is usually possible, but there may be SEs.[66]

Acute dystonia may occur in young men starting neuroleptics (head pulled back, eyes drawn upward, trismus). Use anticholinergics (benzatropine 1-2mg IV).

Writer's cramp (scrivener's palsy; graphospasm) When trying to write, the pen is driven into the paper and flow of movement is poor. "I would look at [my fingers] and tell them to do one thing, and they would do jagged things instead, I'd have full muscle control for everything—except putting a pen to a piece of paper."[67] Look for hand and forearm spasm ± dystonic arm posture ± focal tremor/myoclonus ± dominant hand muscle hypertrophy.[68]

Association: obsessive compulsive disorder.[69]

EMG:

May correlate with the chief physiological events: ↓reciprocal inhibition of wrist flexor motor neurones at rest, and ↑co-contraction of antagonist muscles of the forearm during voluntary activity.[70]

EEG:

Abnormal motor command (sensorimotor region ß rhythm).[71]

[prescription take]:

ß-blockers and valproate often fail. Breath-holding or arm cooling may work, as may botulinum and EMG biofeedback.[72]

Stroke: clinical features and investigations

Strokes result from ischaemic infarction or bleeding into part of the brain, manifest by rapid onset (over minutes) of focal CNS signs and symptoms. It is the major neurological disease of our times (1.5/1000/yr, rising with age to 10/1000/yr at 75yrs).

Causes:

- Thrombosis-*in-situ* or heart emboli (AF; endocarditis; MI—see BOX)
- Atherothromboembolism (eg from carotids)
- CNS bleeds (BP↑; trauma; aneurysm rupture)
- Failure of cerebral autoregulation of blood flow.[1]

Rare causes:

Sudden BP drop by ≳40mmHg; vasculitis (p542); venous sinus thrombosis (p472).

In young patients suspect:

Thrombophilia (p358); vasculitis; subarachnoid haemorrhage; venous-sinus thrombosis (p472); carotid artery dissection (spontaneous or from neck trauma or fibromuscular dysplasia). ▸Do not hesitate to get a neurology, cardiology, or haematology opinion.

Risk factors

BP↑, smoking, DM; heart disease (valvular, ischaemic, AF), peripheral vascular disease, past TIA, ↑PCV, carotid bruit, the Pill, lipids↑ (p682, statins ↓risk by ~17%)[73] alcoholism; clotting↑ (eg ↑plasma fibrinogen, ↓antithrombin III, p358).

Signs

Sudden onset, or a step-wise progression over hours (rarely days) is typical. In theory, focal signs relate to distribution of the affected artery (p440), but collateral supplies cloud the issue.

Cerebral hemisphere infarcts

(50%) cause: contralateral hemiplegia—initially flaccid (floppy limb, falls like a dead weight when lifted), then becomes spastic (UMN); contralateral sensory loss; homonymous hemianopia; dysphasia; visuo-spatial deficit (depending on site).

Brainstem infarction

(25%): wide range of effects which include quadriplegia, disturbances of gaze and vision, locked-in syndrome (aware, but unable to respond).

Lacunar infarcts

(25%): small infarcts around basal ganglia, internal capsule, thalamus, and pons.[2] May cause pure motor, pure sensory, mixed motor and sensory signs, or ataxia; intact cognition/consciousness.

Tests

Prompt investigation to confirm diagnosis and avoid further strokes but consider whether results will affect management. Look for:

- ***Hypertension:*** Look for retinopathy (p544) and a big heart on CXR. NB: acutely raised BP is common in early stroke. In general, don't treat (p464).
- ***Cardiac source of emboli: Atrial fibrillation (AF):*** (p116) Emboli from the left atrium may have caused the stroke. Look for a big left atrium (CXR; echo). ***Post-MI:*** Mural thrombus is best seen by echocardiography. In stroke from AF or mural thrombus do CT to exclude a haemorrhagic stroke, then start aspirin; wait before commencing full anticoagulation to avoid bleeds into infarcts. **SBE/IE:** (p136) 20% of those with endocarditis present with CNS signs due to septic emboli from valves. Treat as endocarditis; ask a cardiologist's opinion.
- ***Carotid artery stenosis:*** In carotid territory (p441) TIA/small stroke, 2 good trials RCT[74] show clear benefit of carotid surgery, so expert bodies say

that ≥80%[3] stenoses (on Doppler) merit referral for consideration of surgery in fit patients.[75]

- ***Hypoglycaemia***, ***hyperglycaemia***, and ***hyperlipidaemia***.
- ***Giant cell arteritis*** (p542) eg if ESR↑, or story of headache or tender scalp (not necessarily temporal). Give steroids promptly (p542).
- ***Syphilis:*** Look for active, untreated disease (p419).
- ***Thrombocytopenia*** and other bleeding disorders.
- ***Polycythaemia*** (p350).

Tests to exclude preventable causes of stroke

Pulse and BP	FBC, platelets	Sickling tests, eg in Blacks
CXR + CT of head	ESR	Blood glucose
ECG	U&E	Syphilis serology if relevant
Carotid Doppler	Lipids	Endocarditis tests (p136)

Then consider echocardiography, carotid angiography & clotting tests.

Cardiac causes of stroke[76]

Cardioembolic causes are the source of stroke in >30% of patients in population studies. These may recur, unless you prevent them.

▸So examine the heart with as much attention as you examine the brain.

- Nonvalvular atrial fibrillation is associated with an overall risk of stroke of 4.5% per year. Advancing age, prior stroke/TIA, diabetes and hypertension are additive risks. Ischaemic strokes in AF are often worse than ischaemic stroke with sinus rhythm. Warfarin is effective for primary and secondary prevention of ischaemic stroke, reducing ↓risk by 68%. Aspirin alone is adequate when there are few or no additional risk factors. It is safer and needs no monitoring.[77] Explain risks and benefits of warfarin, and let the patient decide, giving an evidence-based steer towards warfarin if there are additional risk factors—provided there are no contra-indications (falls, poor compliance/ concordance). If warfarin is chosen, aim for an INR of 2.5-3.5 (stroke risk is twice as much for those with an INR of 1.7 as opposed to 2). Adding aspirin to warfarin does not confer additional protection.
- External cardioversion is complicated in 1-3% by peripheral emboli: pharmacological cardioversion may carry similar risks.
- Prosthetic valves risk major emboli; anticoagulate (INR 3.5-4.5, p335).
- Acute myocardial infarct with large left ventricular wall motion abnormalities on echocardiography predispose to left ventricular thrombus. Emboli arise in 10% of these patients in the next 6-12 months; risk being reduced by two-thirds by warfarin anticoagulation.
- Paradoxical systemic emboli via the venous circulation in those with patent foramen ovale, atrial and ventricular septal defects can occur.
- Cardiac surgery, eg bypass graft, carries particular risk (0.9-5.2%).

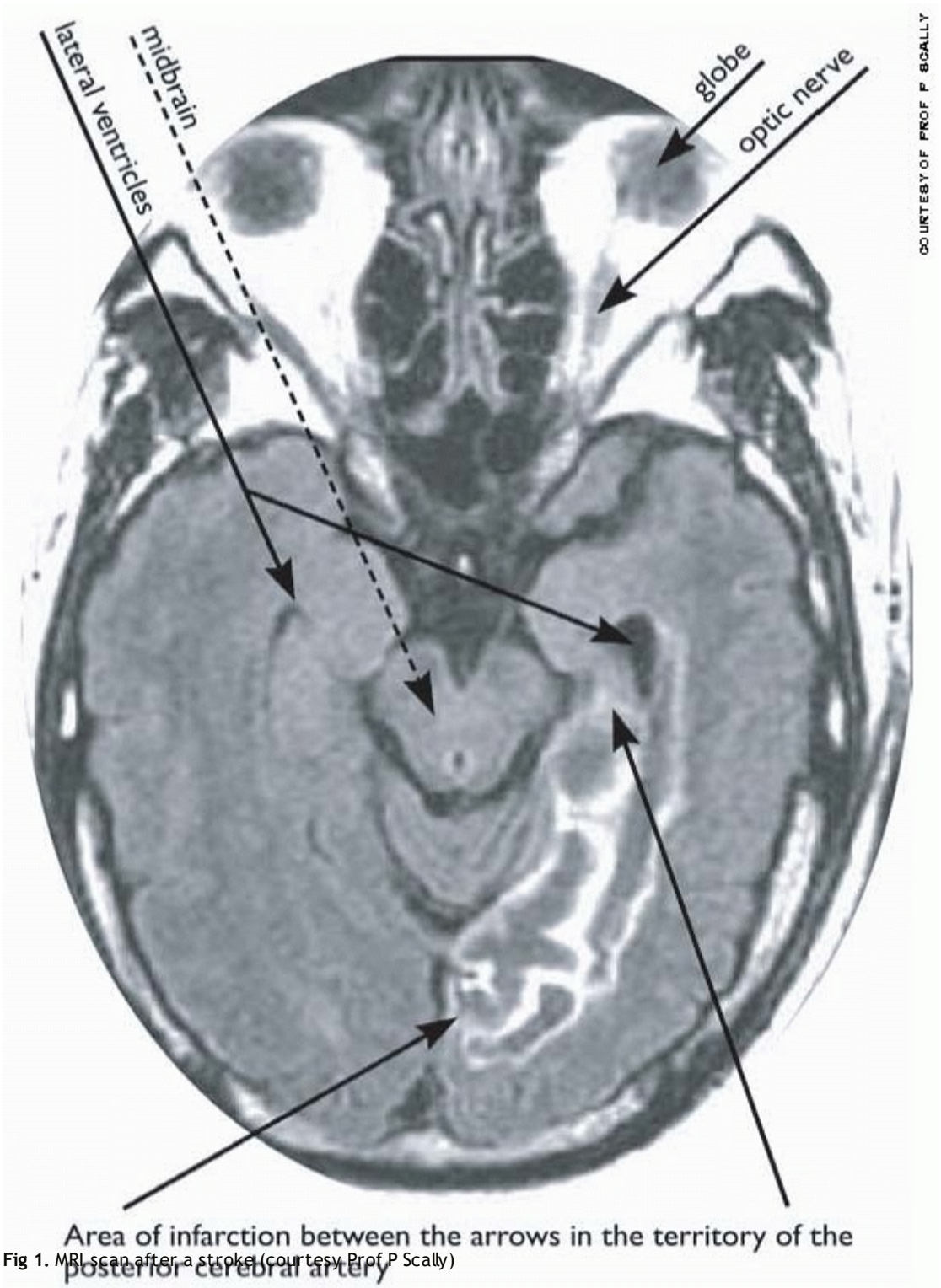


Fig 1. MRI scan after a stroke (courtesy Prof P Scally)

[1] This may explain stroke's association with morning arousal, stress, activity & winter (2006 data)

[3] '70%' or '80%' depends on perioperative stroke rate (2005 data); stenting may also be an option.

Stroke: management and prevention

Imaging

(p732) Prompt CT/MRI should now be the rule especially if:

- Unexpected deterioration after the first 24h.
- There are unusual features, or diagnosis remains unclear—eg onset slow or not known. Consider especially cerebral tumour and subdural haematoma.
- To distinguish between haemorrhage and ischaemic infarction (do scan within a few days of stroke), eg if considering later anticoagulation.
- Cerebellar stroke—cerebellar haematomas may need urgent surgery.

ΔΔ

CNS tumour; subdural bleed (p474); Todd's palsy (p704); migraine; hypoglycaemia; overdose if comatose. Ischaemic and haemorrhagic stroke are *not* reliably distinguishable clinically but pointers to haemorrhage are: meningism, severe headache, and coma within hours. Ischaemic pointers: carotid bruit, AF, past TIA.

[prescription take]

(See p462 & p466.) Explain what has happened.

▸ *Communicate fully with patient, relatives and carers* over difficult decisions, eg deciding on the kindest level of intervention taking into account quality of life, coexisting conditions, and prognosis. Admission to stroke units for nursing/physio saves lives,[78] and is a great motivator. 'Nil by mouth' if swallowing is a problem (try 1mL of water on a teaspoon first).

- Keep hydrated; don't overhydrate (cerebral oedema).
- Turn regularly and keep dry (consider catheter) to stop bed sores (**fig 1**).
- Monitor BP; but treating even very high levels may harm (unless there is encephalopathy, or aortic dissection): even a 20% fall may impair cerebral perfusion, as autoregulation is impaired.[79] NB: if on HRT—stop it.
- If cerebellar haemorrhage possible, immediate referral for evacuation may be needed (familiarize yourself with local current management).[80]

Emergency management

- ▸▸ Ensure patent airway
- ▸▸ Ensure hydration
- ▸▸ Prevent hypoxia/asphyxia
- ▸▸ Diagnose & treat fevers
- ▸▸ Treat any hyperglycaemia or hypoglycaemia
- ▸▸ Skilled nursing to prevent pressure sores (**fig 1**)

Acute antiplatelet measures:

Unless you strongly suspect CNS bleeding, give acute aspirin 300mg/24h for 2wks, then 75mg/day).[81] If CT confirms ischaemia,[82] NICE advice (2nd European stroke$_{\text{Prevention Study}}$)[83] is that dipyridamole be added (eg as Assantin Retard®, 1 bd, aspirin 25mg + dipyridamole MR 200mg/tablet). If aspirin-intolerant, add PPI, p198;[84] if aspirin-hypersensitive, substitute clopidogrel (p468).

Mortality

60,000/yr;[uk] 20% at 1 month, then ≲10%/yr. **Full recovery** ≤40%; drowsiness ≈poor prognosis. **Sequelae** Pneumonia; depression; contractures; constipation; bed sores; 'I'm a prisoner in my body'; stress in spouse (eg alcoholism), p437.

Prevention

Primary (ie before a stroke):

Control risk factors (p462: BP,[1] smoking, DM, lipids, and, possibly folate[2]); exercise helps (HDL↑; glucose tolerance↑). *Help quit smoking:* ▸p79. In middle-aged men (esp. if ↑BP), quitting ↓risk of stroke, with benefits seen in ≤5yrs. (Switching to pipes or cigars achieves little; former heavy smokers retain some excess risk.)

Lifelong anticoagulants

if rheumatic or prosthetic heart valves on left side. Consider warfarin in chronic non-rheumatic AF especially if there are risk factors for vascular disease. Prevention post-TIA (p468).

Secondary (ie preventing further strokes):

Control risk factors. Several large studies suggest considerable advantages from lowering BP and cholesterol (even if not particularly raised). Aspirin (p468) or warfarin if an embolic stroke, or in chronic AF (p130). **NB:** Combining aspirin with twice-daily modified-release dipyridamole or use of clopidogrel in place of aspirin offers additional benefit p468).

The future for ischaemic stroke[3]

Some trials suggest rapid assessment of 'brain attacks' (like 'heart attacks') and thrombolysis with alteplase (t-PA) *within 3*h *of onset of symptoms* ↓adverse outcomes by 12%.[4] CI:

- Major infarct on **CT**

- Mild deficits
- Recent surgery
- Past **CNS** haemorrhage
- Recent arterial puncture at a non-compressible site
- Anticoagulants or PTT >15s
- Platelets <100 × 109/L
- BP↑.

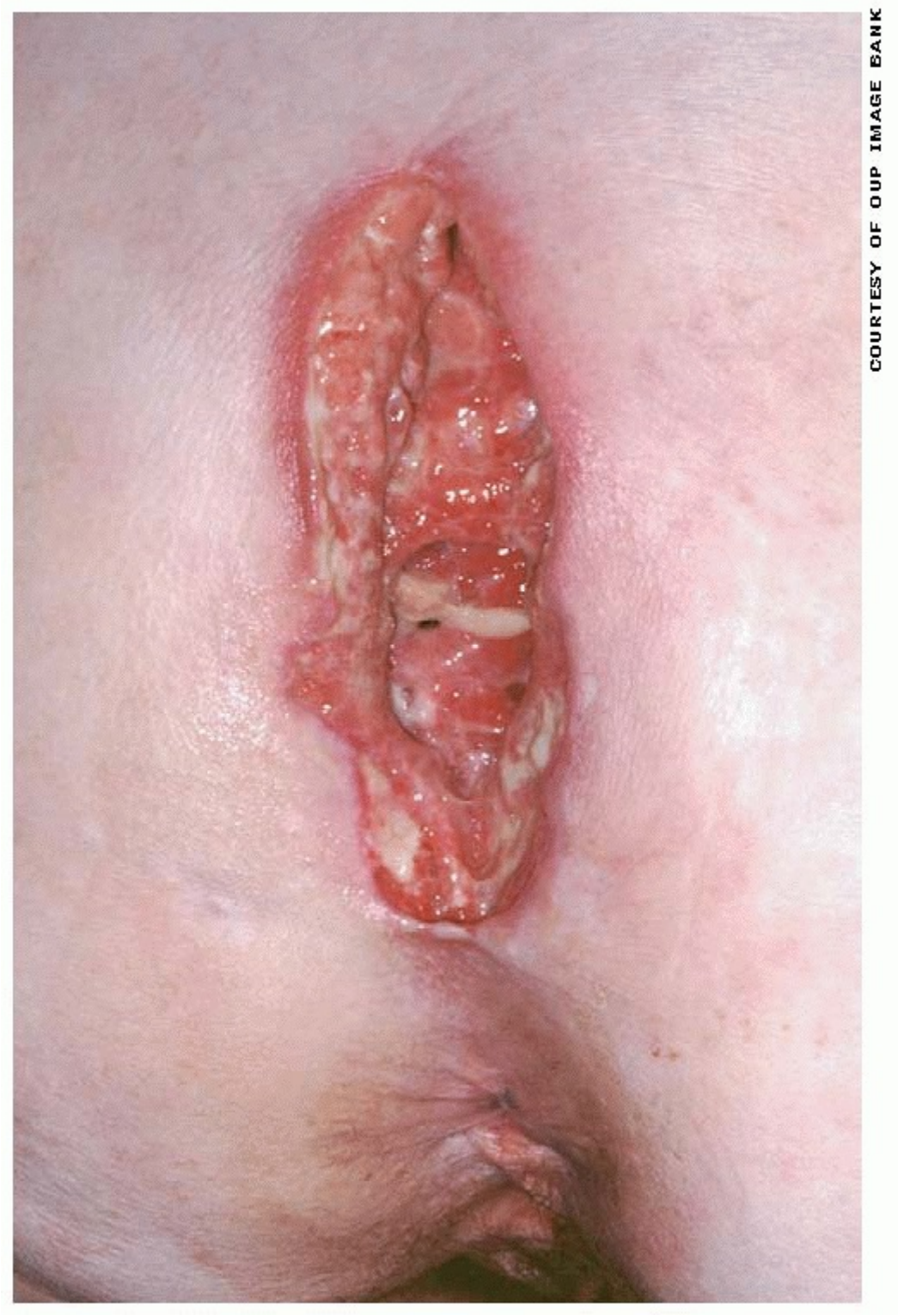


Fig 1. Sacral pressure sore after a stoke. Easy to prevent, given good nurses; so hard to treat, and so often a prelude to death.

[1] Reducing salt intake from 10g/d to 5g/day can lower systolic BP by 10mmHg, ↓stroke risk by ~1/3

[2] Folate ('good') and homocystein ('bad') have a complex link with risk of haemorrhagic stroke.

[4] Although USA doctors may be sued for *not* giving thrombolysis in stroke, Cochrane meta-analyses are unconvinced: in the most favourable trial, the placebo group had worse strokes. Despite a favourable re-analysis of the data it remains true that unreasonable data assumptions may have been made.

Rehabilitation after stroke (see p462 for acute stroke)

▸*Good care requires attention to detail*. Principles are of those of *any* chronic disease (p467) and are best realized by specialist rehab or community teams [85] (↓morbidity and institutionalization). *Special points in the early management:*

- Watch the patient swallows a small volume of water; if signs of aspiration (a cough or voice change) make *nil by mouth* for some days; use IV fluids, then semi-solids (eg jelly; avoid soups and crumbly food). Avoid early NG tube feeds (needed only in the few with established chronic swallowing problems). Speech therapists skilled in assessing swallowing difficulties are invaluable here.
- Avoid damaging patients' shoulders through careless lifting.
- Ensure good bladder and bowel care through frequent toileting. Avoid early catheterization which may prevent return to continence.
- Position the patient to minimize spasticity. Get prompt physiotherapy.
- In pseudo-emotionalism/emotional lability (sobbing unprovoked by sorrow, from failure of cortical inhibition of the limbic system), tricyclics or fluoxetine may help.
- Measure time taken to sit up, and to transfer from lying to sitting in a chair; this is a good way to monitor progress with physio/occupational therapy. [86]

Screen for depression[1]

33% are depressed, and, untreated (p13), this worsens motor function and ↑mortality (there's a known association with vascular disease). [87]

[1] Have you been bothered by **little interest or pleasure** in doing things? Have you been **feeling down**, **depressed**, or **hopeless** in the last month? If 'yes' only 4 follow-up questions—on sleep disturbance, appetite change, low self-esteem, and anhedonia—are needed to confirm depression esp if 'yes' to: 'Have your feelings in the past month caused you significant distress, or impaired your ability to function?

Tests

Asking to point to a named part of the body tests *perceptual function*.

Copying matchstick patterns tests *spatial ability*.

Dressing or drawing a clock face tests for *apraxia* (p46).

Picking out and naming easy objects from a pile tests for agnosia (acuity OK, but cannot mime use; guesses are way-out, semantically, and phonetically).

Neurorehabilitation

takes a functional approach building on what patients can do—with speech- and physiotherapy. Making it fun is an important route to motivation, eg swimming (a hemiplegic arm may be supported on a special float) and video games (which ↑recovery by aiding coordination). [88] The aim is to promote cerebral reorganization. To this end, constraint of the good arm has been found to be helpful (*constraint-induced movement therapy*). [89]

End-of-life decisions

'…And thus the native hue of resolution is sicklied o'er with the pale cast of thought' $Hamlet_{\text{act iii:i}}$—the more we think on these issues, the more we tie ourselves in knots. We intended these precepts to bisect these snares, not to reveal deep, hidden truths, but to provide a workable framework at the bedside.

- If the patient's views are known, comply with them, except perhaps where doing so entails an illegal act, or one that clearly harms others.
- No person has authority to impose his or her own views on end-of-life decisions. You cannot tell a nurse to stop feeding someone, and expect her to obey you. Consensus is the only practical way forward. Try to get the opinion of more than one relative, and more than one shift of nurses (eg at changeover time). Let everyone have their say. You may learn new and important facts about your patient, which make decisions easier—or harder.
- If consensus is impossible, recourse to the Courts is one option: but remember that judges have no special skill in this area.

Beware guidelines giving doctors special powers (such as the BMA guidelines [90]).

Doctors may be the worst decision-makers as closeness to life and death may make them tolerant of ending life—eg if the bed could be used for 'something better'. Even if *not* the case, if society thinks this, then doctors are in an untenable position. We *do* have a role, though, in facilitating consensus, and documenting it.

Success is often impossible (there are too many grey areas), but if you can stumble from one ambiguity to another without being disheartened, then that is good enough. Your patients will respect your honesty.

Assessing handicap, disability, and independence in daily life

Handicap entails inability to carry out social functions. 'A disadvantage for a given individual, resulting from an impairment or disability, that limits or prevents the fulfilment of a role.' Two people with the same ***impairment*** (eg paralysed arm) may have different ***disabilities*** (one can dress, the other cannot). Disabilities are likely to determine quality of future life. Treatment is often best aimed at reducing disability, not curing disease. For example, Velcro® fasteners in place of buttons may enable a person to dress.

A person with a severe hearing impairment may seem to you to have no disability if they can lip-read. But ask yourself (and your patients, when you get to know them) about the price they pay for rising above their disabilities. Lipreading, for example, is exhausting, requiring 100% vigilance to make sense of transitory and incomplete visual clues.

Barthel's index of activities of daily living

Bowels	0	Incontinent (or needs to be given enemas)
	1	Occasional accidents (once a week)
	2	Continent
Bladder	0	Incontinent, or catheter inserted but unable to manage it
	1	Occasional accidents (up to once per 24h)
	2	Continent (for more than seven days)
Grooming	0	Needs help with personal care: face, hair, teeth, shaving
	1	Independent (implements provided)
Toilet use	0	Dependent
	1	Needs some help but can do some things alone
	2	Independent (on and off, wiping, dressing)
Feeding	0	Unable

	1	Needs help in cutting, spreading butter, etc.
	2	Independent (food provided within reach)
Transfer	0	Unable to get from bed to commode: the vital transfer to prevent the need for 24-hour nursing care
	1	Major help needed (physical, 1-2 people), can sit
	2	Minor help needed (verbal or physical)
	3	Independent
Mobility	0	Immobile
	1	Wheelchair-independent, including corners, etc.
	2	Walks with help of one person (verbal or physical)
	3	Independent
Dressing	0	Dependent
	1	Needs help but can do about half unaided
	2	Independent (including buttons, zips, laces, etc.)

Stairs	0	Unable
	1	Needs help (verbal, physical, carrying aid)
	2	Independent up and down
Bath/shower	0	Dependent
	1	Independent (must get in and out unaided and wash self)

The aim is to establish the degree of independence from any help.

Barthel's paradox

The more we contemplate Barthel's eulogy of independence, the more we see it as a mirage reflecting a greater truth about human affairs: ▸there is no such thing as independence[1]—only **inter-dependence,** and in fostering this interdependence lies our true vocation.

Philosophy in action

[1] **No man is an Island**, intire of it selfe; every man is a peece of the Continent, a part of the maine; if a Clod bee washed away by the Sea, Europe is the lesse, as well as if a promontorie were, as well as if a Mannor of thy friends or of thine owne were. Any man's death diminishes me, because I am involved in mankinde; And therefore never send to know for whom the bell tolls: It tolls for thee. John Donne **1572-1631**;meditation XVII. What happens when we take up John Donne's offer of meditation? Some very interesting CNS events: brain activity slows, and blood is relocated to the anterior cingulate and dorsolateral prefrontal areas.

Transient ischaemic attack (TIA)

The sudden onset of focal CNS phenomena due to temporary occlusion, usually by emboli, of part of the cerebral circulation is termed a TIA if symptoms last <24h (often much shorter). Incidence: 0.4/1000/yr. 15% of 1st strokes are preceded by TIAs; they are also harbingers of MI, so… ▸▸*good management may avert disaster*. Attacks are single or many (the same or different for each TIA).

Carotid territory

(p441): Contralateral weakness/numbness; dysphasia; dysarthria; homonymous hemianopia; amaurosis fugax (one eye's vision is progressively blotted out 'like a curtain descending over my field of view').

Vertebrobasilar territory:

Hemiparesis; hemisensory loss; bilateral weakness or sensory loss; diplopia; homonymous hemianopia in cortical blindness; vertigo; deaf; tinnitus; vomiting; dysarthria; ataxia.

NB:

Global events (syncope; dizziness) are **not** typical of TIAs.

Signs of causes

Carotid bruit (p54); absence does not rule out a carotid source of emboli: tight stenoses often have *no* bruit.$_{91}$ BP ↑. Heart murmur from valve disease. ▸▸Identify and treat AF. Fundoscopy during TIAs may show retinal artery emboli.

Causes

Atherothromboembolism

from the carotid is the chief cause (may also be from heart (AF, mural thrombus post-MI, valve disease, prosthetic valve);

Hyperviscosity

(p356), eg polycythaemia, sickle-cell anaemia, WCC↑↑ (leukostasis; may need urgent chemotherapy), myeloma[92] and *vasculitis*, eg cranial arteritis, PAN, SLE, syphilis *et al* are rare causes, and perhaps shouldn't be classified as TIA.

Differential

Hypoglycaemia; migraine aura (symptoms spread and intensify over minutes, often with visual scintillations before headache); *focal epilepsy* (symptoms spread over seconds and often include twitching and jerking); hyperventilation; MS retinal bleeds; peripheral neuropathy. Rare mimics of TIA: *Malignant hypertension; hypoglycaemia;* MS; *intracranial lesions; phaeochromocytoma; somatization* (p635).

Tests

Aim to find the cause and define vascular risk: FBC, ESR, U&E, glucose, lipids, CXR, ECG, carotid Doppler ± angiography, MRI/CT (any existing infarcts?) ± cardiac echo (rarely shows cardiac cause if no suggestive signs).

Treatment

Begin after the 1st TIA: don't wait for the stroke! Control stroke risk factors (p462, eg smoking, BP, lipids, etc.) and MI (p79, risk equation, p642). *Reversible risk factors:* Hypertension (cautiously lower; aim for <140/85mmHg, p142); hyperlipidaemia (p682); help to stop smoking (p79 & OHCS p512).

- *Antiplatelet drugs:* NICE recommends low-dose aspirin if no peptic ulcer (~75mg/ *day for life*;[1] probably ↓ non-fatal strokes and MI by 25%, and vascular death by 15%) **and,** for the next 2yrs, dipyridamole (Assantin Retard® has dipyridamole MR 200mg + aspirin 25mg, so 1 tablet/12h is a good dose). Dipyridamole's effects: ↑ cAMP & ↓ thromboxane A2. *If aspirin-intolerant:* clopidogrel 75mg/day, a thienopyridine that ↓ platelet aggregation by modifying platelet ADP receptors.
- *Warfarin indications:* heart emboli, eg AF, mitral stenosis, recent big septal MI.
- Carotid endarterectomy in carotid TIA if operative risk is good[2] and ≳ 75% stenosis at the origin of the internal carotid artery.MET$_{93}$MET$_{94}$ For benefit to outweigh risk, the team's peri-operative stroke and mortality rate must be <3%.[95] Intra-operative transcranial Doppler can monitor middle cerebral artery flow. Using patches may reduce chances of restenosis. Do not stop aspirin beforehand. 50-70% stenosis may benefit from surgery only in the best hands; NNT=15.MET$_{96}$

Driving

Avoid for ≥1 month; patients in the UK should inform the DVLA if multiple attacks in short period or residual deficit.

Prognosis

The combined risk of stroke and MI is ~9%/yr; risk of stroke is 12% in year 1 and up to 10% subsequently if carotid stenosis is ≥70%. More frequent TIAs ↑ risk further. Mortality is ~3-fold that of a TIA-free matched population. In one Dutch study in 2005, 60% of patients were dead within 10 years of a TIA.[97]

▸▸When should TIA lead to *prompt* or *emergency* referral?

All patients with a suspected TIA should be referred to a specialist and seen within 7 days (ideally!). A score of ≥6 (see TABLE) strongly predicts a stroke (35.5%) in the next week, so even this difficult target may be too lax.

Aged ≥60	1 point
BP ≥140/90	1 point
Unilateral weakness	2 points
Speech disturbance without weakness	2 points

Symptoms lasting >1h	2 points
Symptoms lasting 10-59 mins	1 point

This scoring system is useful but should only be regarded as provisional: it has been formally validated only in 377 patients (from Oxfordshire; *Lancet* 2005).[98]

In assessing urgency, bear in mind Warlow's 2005 data: in stroke patients who had a preceding TIA, 17% occurred on the day of the stroke, 9% on the previous day, and 43% at some point during the 7 days before the stroke.[99] These figures should remind us to rehearse routes for referral for emergency endarterectomy— at present this is typically performed >90 days post-TIA.[100]

Subarachnoid haemorrhage (SAH)

Spontaneous bleeding into the subarachnoid space is often catastrophic. Incidence: 8/100,000/yr; typical age: 35-65. *Causes:* Rupture of saccular aneurysms (80%); arterio-venous (AV) malformations (15%). No cause is found in <15%. *Risk↑ if:* Smoking; alcohol misuse; BP↑;[1] bleeding disorders; mycotic aneurysm post-SBE; possibly lack of oestrogen (post-menopausal). ♀:♂ >1:1. Close relatives of those with SAH have a 3-5-fold ↑risk of SAH.[102]

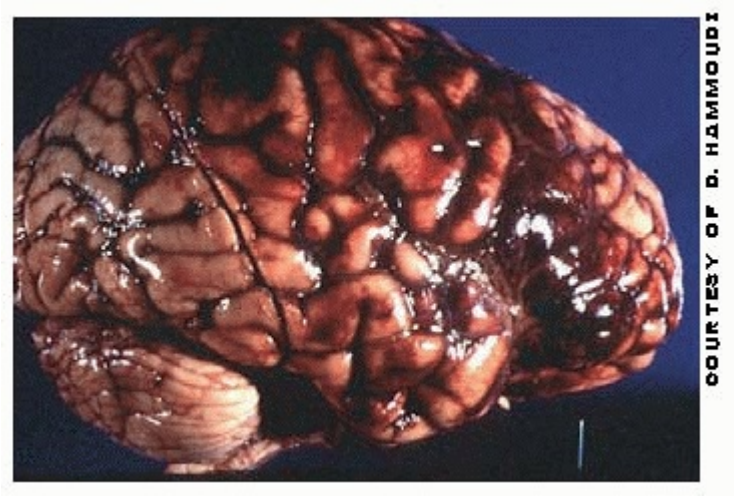


Fig 1. Middle cerebral artery SAH at the Sylvian fissure.[101]

Berry aneurysms

Common sites: junction of posterior communicating with the internal carotid or of the anterior communicating with the anterior cerebral artery or bifurcation of the middle cerebral artery (**fig 1**, p440). 15% are multiple. Some are hereditary.

Associations:

Polycystic kidneys, coarctation of the aorta, Ehlers-Danlos syndrome (hypermobile joints + ↑ skin elasticity, OHCS p642).

Symptoms

Sudden (within seconds) devastating typically occipital headache '*I thought I'd been kicked in the head*'. Vomiting, collapse (± seizures), and coma often follow. Coma/drowsiness may last for days. **Signs** Neck stiffness; Kernig's sign takes 6h to develop; retinal and subhyaloid haemorrhage. Focal neurology *at presentation* may suggest site of aneurysm (eg pupil changes indicating a IIIrd nerve palsy with a posterior communicating artery aneurysm) or intracerebral haematoma. Later deficits suggest ischaemia from vasospasm, or rebleeding, or hydrocephalus.[103]

Differential

In primary care, only 25% of those with severe, sudden 'thunderclap' headache have SAH. In 50-60%, no cause is found; the remainder have meningitis, migraine, intracerebral bleeds, or cerebral venous thrombosis. See p472.

Sentinel headache

SAH patients may earlier have experienced a sentinel headache, perhaps due to a small warning leak from the offending aneurysm (~6%), but recall-bias clouds the picture.[104] As surgery is more successful in the least symptomatic, be suspicious of any *sudden* headache especially with neck or back pain.[105]

Tests

In good hands, new CT scanners detect >90% of bleeds within the 1st 48h of SAH;[106] older scanners miss small bleeds—so if the clinical suspicion is strong and CT is -ve do an LP >12h after headache onset.[107] CSF in SAH is uniformly bloody early on and xanthochromic (yellow) after a few hours. The supernatant from spun CSF is looked at photometrically to find breakdown products of Hb. Finding bilirubin confirms SAH, showing that the LP was not a 'bloody tap' (don't rely on finding fewer CSF RBCs in each successive bottle).

Management

▸Get neurosurgical help with all cases—immediately if ↓ level of consciousness, progressive focal deficit, or cerebellar haematoma is suspected.

- Bed rest, and chart of BP, pupils, coma level (p776). ?Repeat CT if deteriorating.
- Re-examine CNS often. Prevent the need for straining with stool softeners.
- ***Surgery:*** Craniotomy and clipping aneurysms can stop rebleeds and is best in those with few or no symptoms (≤grade II). SE: intra-operative rupture; post-op epilepsy. If surgery is likely, do prompt angiography. ***Intraluminal platinum coils*** (GuglielmiMET[108]) are an alternative with less mortality (but rebleeding is a bit more common after coils than after clipping).[109][110] Intracranial stents and balloon remodelling make possible the treatment of wide-necked aneurysms. Microcatheters can now traverse tortuous vessels to treat previously unreachable lesions.[111] AV malformations and fistulae may also benefit from this procedure.
- ***Medical:*** Cautiously control *severe* hypertension; analgesia for headache; bed rest ± sedation for ~4wks. Keep hydrated (running 'dry', out of respect for ICP↑, worsens vasospasm). ***Vasospasm:*** Nimodipine (60mg/4h PO for 3wks, or 1mg/h IVI) is a Ca^{2+} antagonist that improves outcome (give to all if blood pressure allows).

Rebleeding

is a common mode of death. Rebleeding occurs in 30%, often in the 1st few days. **Vascular spasm** follows a bleed, often causing ischaemia ± permanent CNS deficit. If this happens, surgery is not helpful at the time but may be so later.

Mortality in subarachnoid haemorrhage

Grade	Signs	Mortality: %
1	None	0
II	Neck stiffness and cranial nerve palsies	11
III	Drowsiness	37
IV	Drowsy with hemiplegia	71
V	Prolonged coma	100

Almost all the mortality occurs in the 1st month. Of those who survive the 1st month, 90% survive a year or more

Unruptured aneurysms: 'the time-bomb in my head'

Usually, risks of preventive surgery outweigh any benefits, except perhaps in young patients (more years at risk, and surgery is twice as hazardous if >45yrs old)[112] who have aneurysms >7mm in diameter, especially if located at the junction of the internal carotid and the posterior communicating cerebral artery, or at the rostral basilar artery bifurcation, and especially if there is uncontrolled hypertension or a past history of bleeds.[113] Data from the 2003 International Study of Unruptured Intracranial Aneurysms (ISUIA) show that relative risks of rupture for an aneurysm 7-12mm across is 3.3; if the diameter is >12mm, the relative risk is 17 times that for aneurysms <7mm across.[114]

In other patients, bear in mind the old adage: 'if it ain't broke; don't fix it'.

Patients with a ***previous SAH*** have a high-ish risk for new aneurysm formation and enlargement of untreated aneurysms. Screening these patients might be beneficial, eg if multiple aneurysms, hypertension, or a history of smoking.[115]

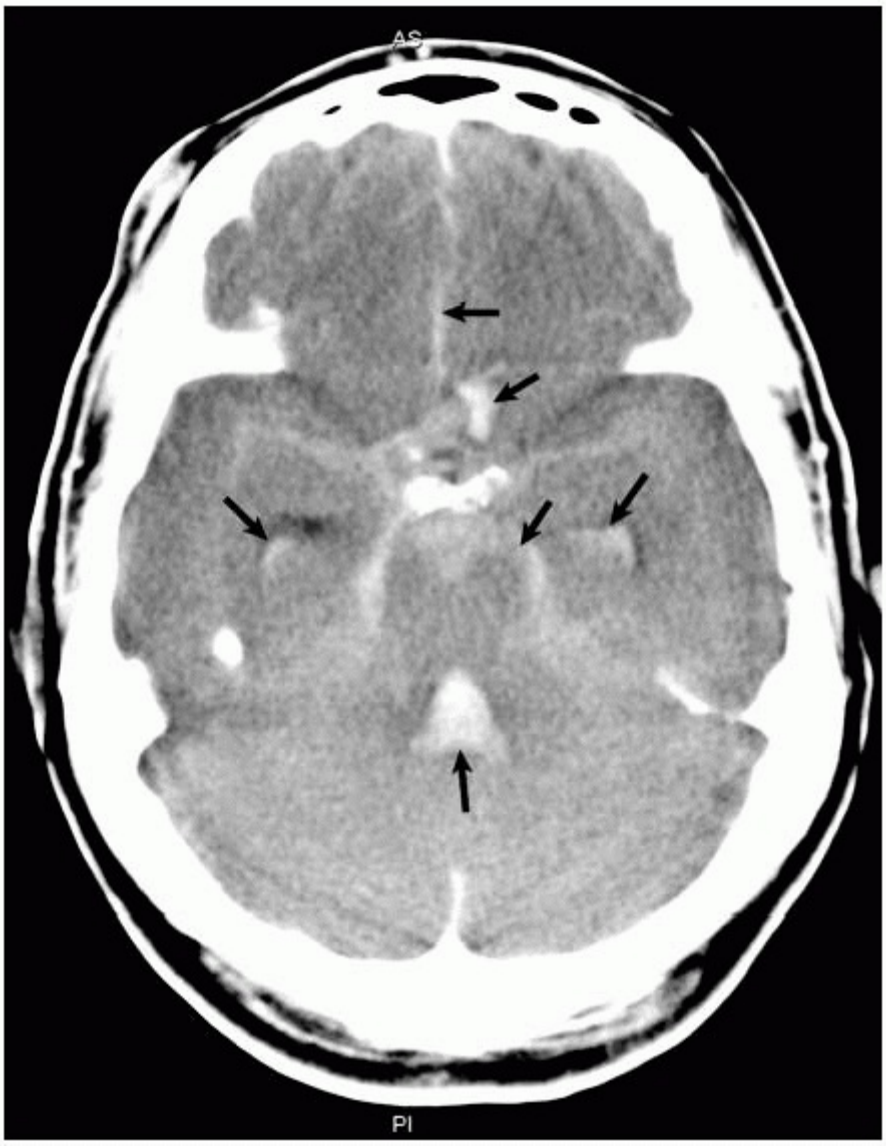


Fig 1. Blood from a ruptured aneurysm occupies the interhemispheric fissure (top arrow), a crescentic intracerebral area presumably near the aneurysm (2nd arrow), the basal cisterns, the lateral ventricles (temporal horns), and the 4th ventricle (bottom arrow).[116]

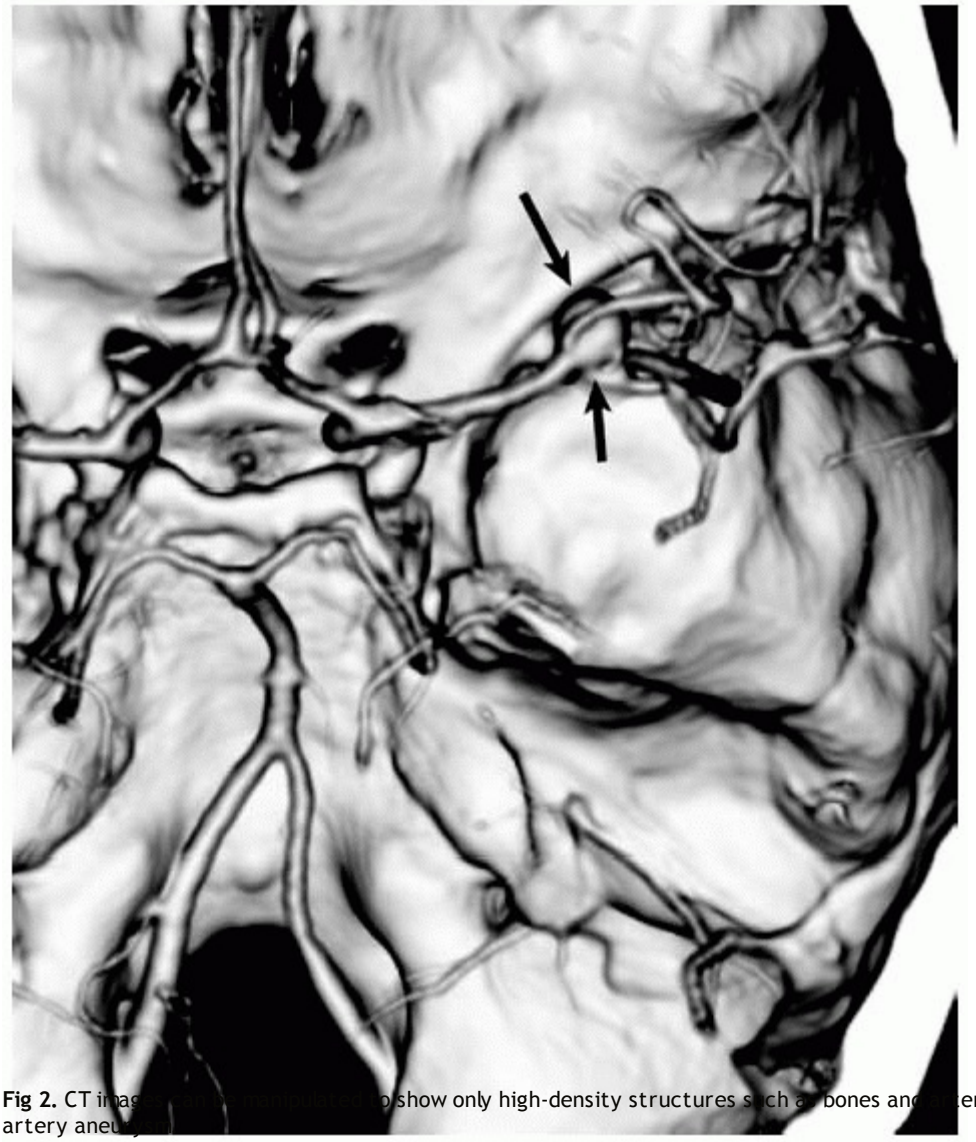


Fig 2. CT image ... manipulated to show only high-density structures such as bones and arteries containing contrast. Here is a middle cerebral artery aneu...

We thank Professor Peter Scally for these CT images and the commentaries on them.

[1] For each 20mmHg rise in systolic BP, relative risks of ischaemic stroke, intracerebral haemorrhage, and subarachnoid hemorrhage are 1.8, 2.5, and 1.6 in ♂—and 1.6, 3.1, and 2.3 in ♀, respectively.

Intracranial venous thrombosis (IVT)

Isolated sagittal sinus thrombosis

(47% of patients with IVT) ***Presentation:*** Headache, vomiting, seizures, papilloedema (one cause of benign intracranial hypertension). If venous infarction: focal signs occur, eg hemiplegia. Sagittal sinus thrombosis is usually seen with thrombosis of other sinuses, eg ***lateral sinus thrombosis*** (35%—eg headache, focal CNS signs, seizures, and papilloedema), ***cavernous sinus thrombosis*** (headache, oedematous eyelids/chemosis; proptosis; and painful eye movements/ophthalmoplegia), ***sigmoid sinus thrombosis*** (cerebellar signs, lower cranial nerve palsies), ***inferior petrosal sinus*** (V & VI cranial nerve palsies, ie Gradenigo's syndrome).

Cortical (cerebral) vein thrombosis (CVT)

may cause venous infarcts (± focal signs), encephalopathy, seizures, and headache (eg thunderclap headache,[117] a sudden, severe headache).

Signs:

Evolving speech disorders, cognition↓, vision↓; pareses.[118] It often coexists with sinus thromboses.[119] MRI may miss the diagnosis unless T2-weighted conventional gradient echo sequences are used.[120]

Causes:

Pregnancy/puerperium, oral contraceptives, head injury, dehydration, blood dyscrasias (eg mutations causing hypercoagulability), malignancies, recent LP. Galen vein (vena magna Galani) thrombosis is a rare cause of CVT and is usually associated with vascular malformation.[121] Rarer associations—see table:

Systemic diseases		Infections	Drugs
Hyperthyroidism	Hyperviscosity (p356)	Meningitis; TB	Androgens, eg
Nephrosis	Crohn's/UC (p264 & p266)	Cerebral abscess	(eg oxymetholone)[122]
Ketoacidosis[123]	Behçet's disease (p686)	Septicaemia	Antifibrinolytics, eg
Heart failure	Protein C resistance (p358)	Fungal infections	Tranexamic acid
SLE	Antiphospholipid syndrome	Otitis media	Infliximab[124]
Homocystinuria	Klippel-Trénaunay syndrome	Cerebral malaria	IV steroids in MS[125]•
Paroxysmal nocturnal haemoglobinuria		HIV with nephrosis	(methylprednisolone)

Differential diagnosis

(See subarachnoid differential diagnosis list on p470.) Thunderclap headaches also occur in dissection of a carotid or vertebral artery, as well as in benign thunderclap headache.[126]

Emergency investigation of thunderclap headache[127]

(ΔΔ: subarachnoid or pituitary bleed; CVT; idiopathic, triggered by Valsalva manoeuvre (cough, coitus).

- Check that there are no signs of meningitis (p368).
- Do emergency MRI/CT scan. If normal, do LP; measure the opening CSF pressure. If high, and headache persists, and no subarachnoid bleed, suspect cerebral vein thrombosis if predisposing factors. Get neuroimaging help. MRI angiography is best.[128] **NB:** CT may be normal early; then at ~1wk develops the delta sign, where a transversely cut sinus shows a contrast filling defect. This may also be an early sign. CSF may be normal, or show RBCs and bilirubin↑—with ↑opening pressure.

Management

Seek expert help, eg in interpreting MRI ± MRI angiography. One small randomized study shows that heparin saves lives and improves outcome.[129] This may be important even in those with haemorrhagic venous infarction. Streptokinase & other fibrinolytics has been used via selective catheterization.[130] [131]

Prognosis

Variable. Causes of death are mainly transtentorial herniation from unilateral focal mass effects or to diffuse oedema and multiple parenchymal lesions.

Independent predictors of death in one study were coma (odds ratio OR≈ 8.8), deep cortical vein thrombosis (OR≈8.5), posterior fossa lesion (OR≈6.5) right intracerebral haemorrhage (OR≈3.4), and mental disturbance (OR≈2.5).[1]

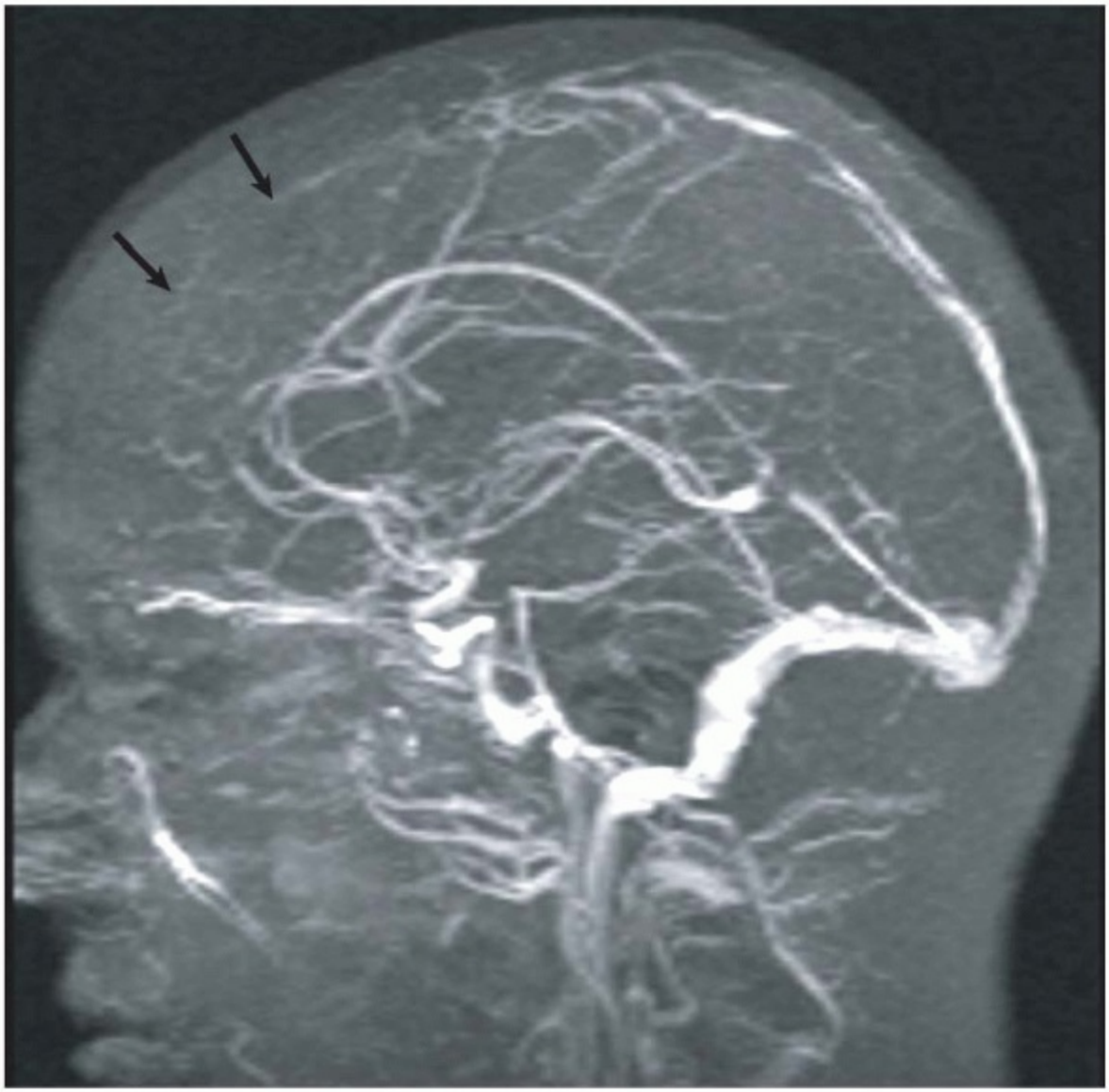


Fig 1. This magnetic resonance venogram (MRV) could look normal at first glance: the hardest thing to see in imaging is often that which is not there. Much of the superior sagittal sinus (SSS) is not demonstrated because it is filled with clot—a superior sagittal sinus thrombosis. The arrows point to where it should be seen. Posteriorly, the irregularity of the vessel indicates non-occlusive clot.

We thank Professor Peter Scally for the image and the commentary.

[1] Worsening of previous focal or new focal deficits also ↑risk of death; see *Stroke* 2005 (Jul 7th).

Subdural haemorrhage

▸Consider this very treatable condition in all whose conscious level fluctuates, and also in those having an 'evolving stroke', especially if on anticoagulants. Bleeding is from bridging veins between cortex and venous sinuses (vulnerable to deceleration injury), resulting in accumulating haematoma between dura and arachnoid. This gradually raises ICP, shifting midline structures away from the side of the clot and, if untreated, eventual tentorial herniation and coning. Most subdurals are from trauma but they can occur without (eg intracranial hypotension;[1] dural metastases).[132] *The trauma is often forgotten as it was so minor or so long ago (up to 9 months).*[132] The elderly are most susceptible, as brain shrinkage makes bridging veins vulnerable. *Other risk factors:* falls (epileptics, alcoholics); anticoagulation.

Symptoms

Fluctuating level of consciousness (seen in 35%) ± insidious physical or intellectual slowing, sleepiness, headache, personality change, and unsteadiness.

Signs

↑ICP (p812); seizures. Localizing neurological symptoms (eg unequal pupils, hemiparesis) occur late and often long after the injury (mean=63 days).

Imaging

CT/MRI shows clot ± midline shift (but beware bilateral isodense clots). Look for crescent-shaped collection of blood over 1 hemisphere. The sickle-shape differentiates subdural blood from extradural haemorrhage.

ΔΔ

Stroke, dementia, CNS masses (eg tumours, abscess, neurocysticercosis).[134]

Treatment

Irrigation/evacuation eg via burr twist drill and burr hole craniostomy can be considered 1st-line; craniotomy is 2nd-line,[135] if the clot has organized.[136] Address causes of the trauma (eg abuse; cataract *et al* causing falls, arrhythmia, etc).

[1] ***Intracranial hypotension*** (ICH) is due to CSF leaks, amenable to epidural blood patches over the leak. Suspect ICH if headaches are worse on standing. Causes: meningeal diverticula, after epidural anaesthesia; dehydration; hyperpnoea (↑tidal volume). MRI: engorged venous sinuses; meningeal enhancement; subdural fluid.

▸▸Extradural (epidural) haemorrhage

▸*Suspect this if, after head injury, conscious level falls or is slow to improve, or there is a lucid interval*. Extradural bleeds are often due to a fractured temporal or parietal bone causing laceration of the middle meningeal artery and vein, typically after trauma to a temple just lateral to the eye. Any tear in a dural venous sinus will also result in an extradural bleed. Blood accumulates between bone and dura.

Symptoms and signs

Look out for a deterioration of consciousness after any head injury that initially produced no loss of consciousness or after initial drowsiness post-injury seems to have resolved. This 'lucid interval' pattern is typical of extradural bleeds. It may last a few hours to a few days before a bleed declares itself by a deteriorating level of consciousness caused by a rising ICP. Increasingly severe headache, vomiting, confusion, and fits can follow, accompanied by a hemiparesis with brisk reflexes and an upgoing plantar. If bleeding continues, the ipsilateral pupil dilates, and coma deepens, bilateral limb weakness develops, and breathing becomes deep and irregular. Death follows a period of coma and is due to respiratory arrest. Bradycardia and raised blood pressure are late signs.

Tests

CT shows a haematoma which is often lens-shaped (biconvex; the blood forms a more rounded shape because the tough dural attachments to the skull tend to keep it more localized).[137] Skull X-ray may be normal or show fracture lines crossing the course of the middle meningeal vessels. Skull fracture after trauma greatly increases the risk of an extradural haemorrhage, and should lead to prompt CT. ▸***Lumbar puncture is contraindicated***.

Management

▸▸Stabilize and transfer promptly (with skilled medical and nursing escorts) to a neurosurgical unit for clot evacuation (± ligation of the bleeding vessel). Care of the airway in an unconscious patient, and measures to ↓ICP often mandate intubation and ventilation (+ mannitol IVI, p812).

Prognosis

Excellent if diagnosis and operation early. Poor if coma, pupil abnormalities, or decerebrate rigidity are present pre-op.

CT images

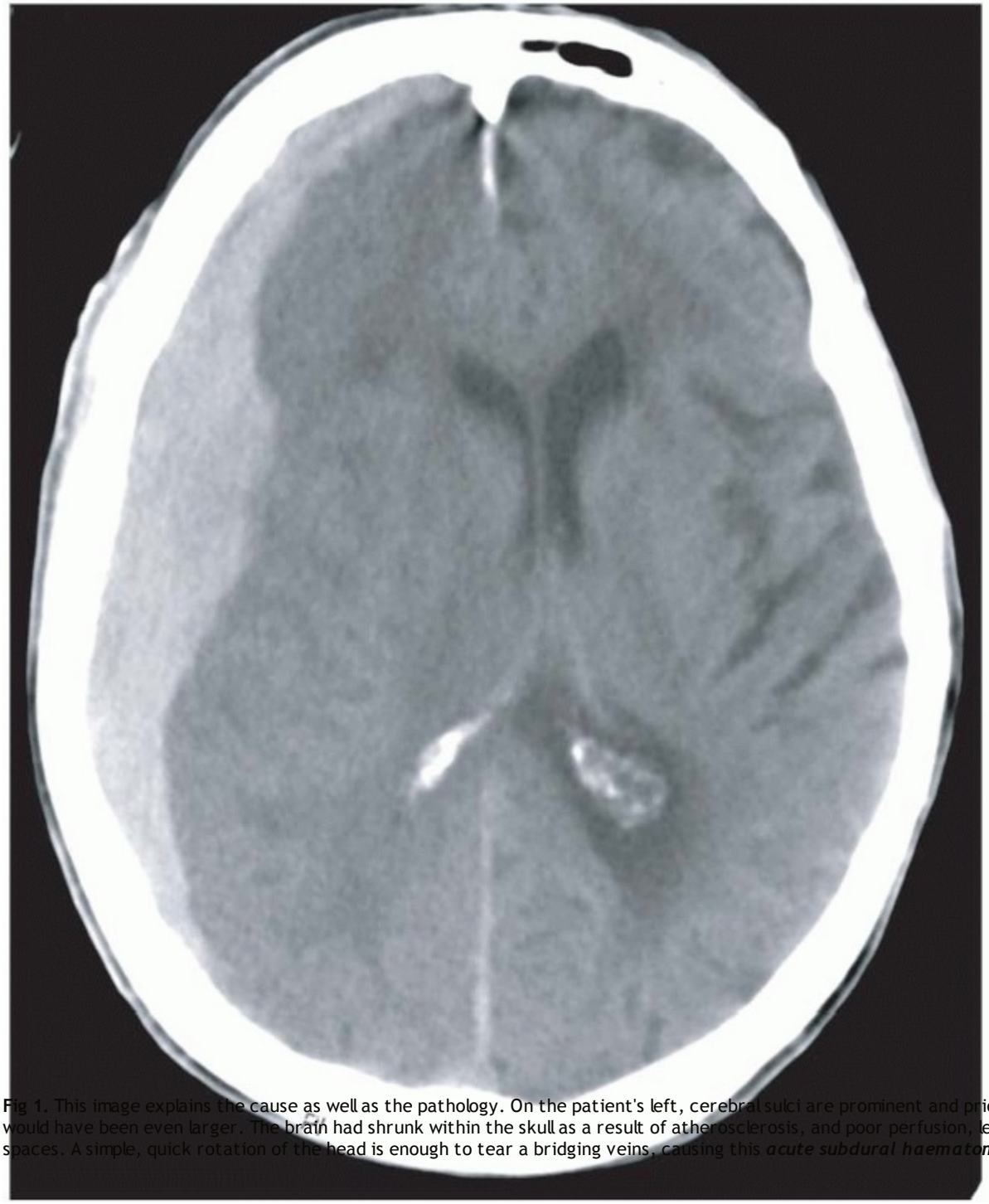


Fig 1. This image explains the cause as well as the pathology. On the patient's left, cerebral sulci are prominent and prior to this adverse event would have been even larger. The brain had shrunk within the skull as a result of atherosclerosis, and poor perfusion, leaving large subarachnoid spaces. A simple, quick rotation of the head is enough to tear a bridging veins, causing this ***acute subdural haematoma***.

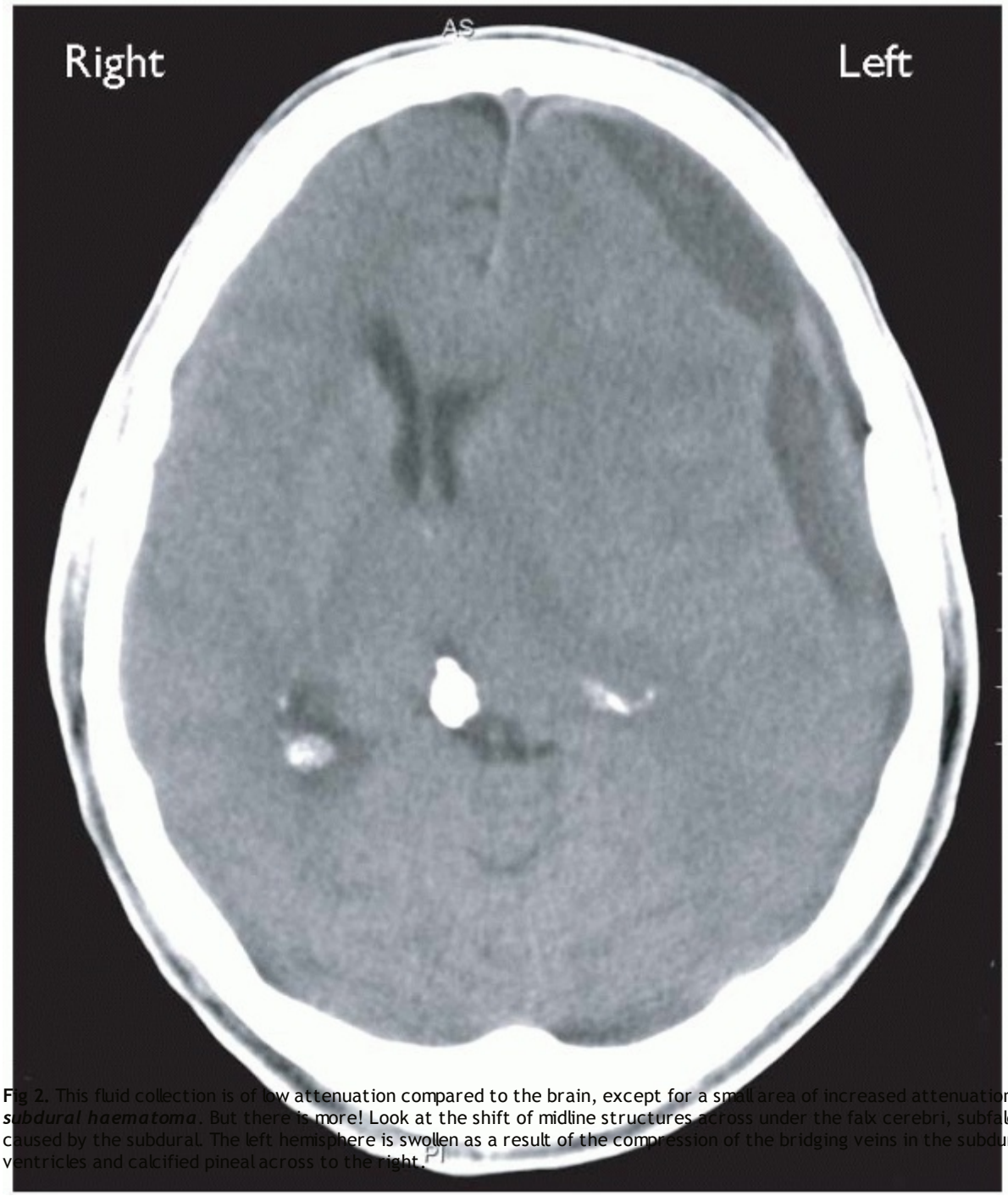


Fig 2. This fluid collection is of low attenuation compared to the brain, except for a small area of increased attenuation. It is an ***acute on chronic subdural haematoma***. But there is more! Look at the shift of midline structures across under the falx cerebri, subfalcine herniation. It is not just caused by the subdural. The left hemisphere is swollen as a result of the compression of the bridging veins in the subdural space, shifting the ventricles and calcified pineal across to the right.

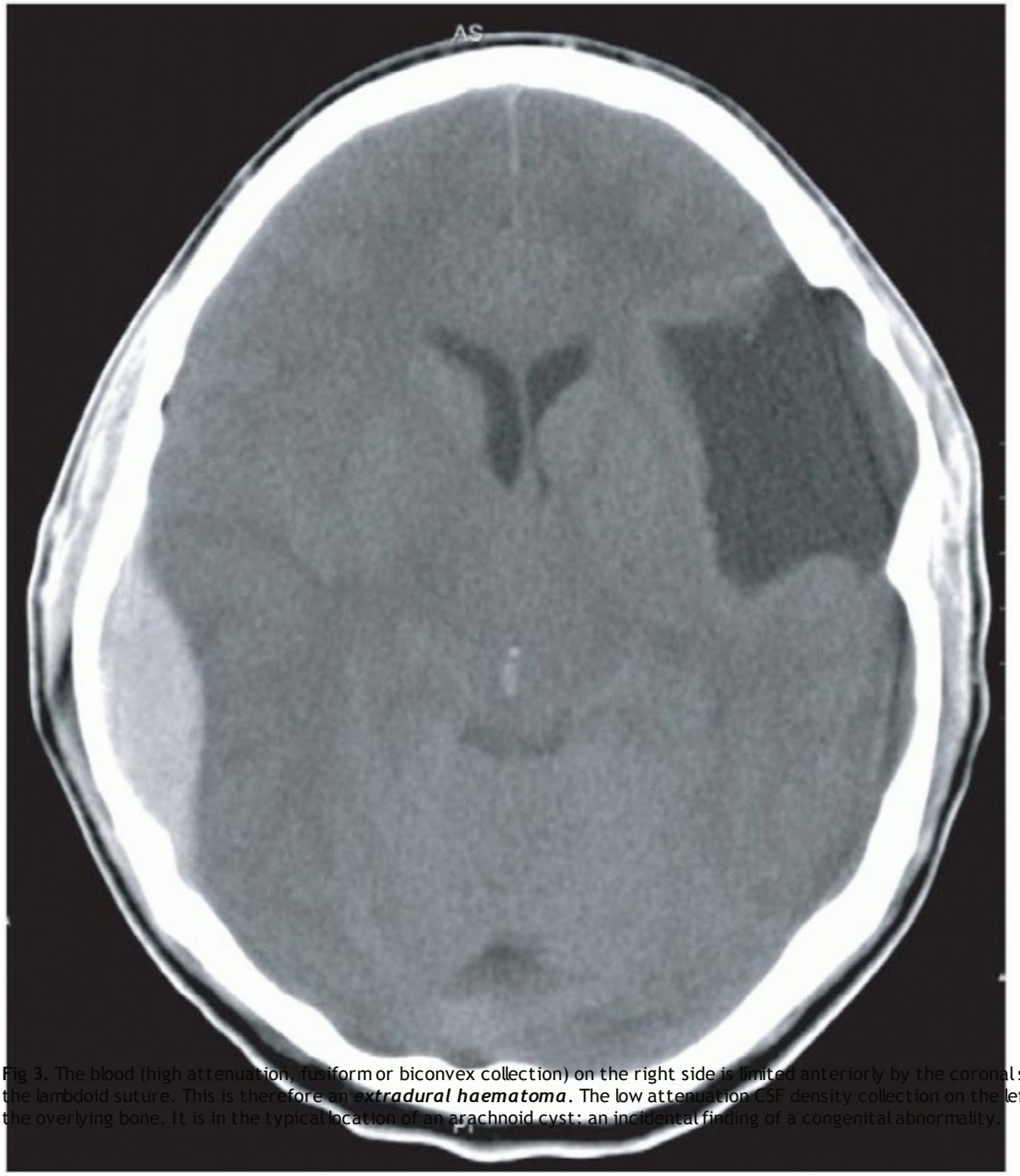


Fig 3. The blood (high attenuation, fusiform or biconvex collection) on the right side is limited anteriorly by the coronal suture and posteriorly by the lambdoid suture. This is therefore an ***extradural haematoma***. The low attenuation CSF density collection on the left is causing scalloping of the overlying bone. It is in the typical location of an arachnoid cyst: an incidental finding of a congenital abnormality.

Delirium (acute confusional state)

20% of elderly patients on medical and surgical wards have some form of delirium: consider ***any*** acute fluctuating baffling behaviour change as possible delirium. Look for organic causes (UTI, pneumonia, MI). The 8 signs of **DELIRIUM** are:

Disordered thinking: Slow, irrational, rambling, jumbled up, incoherent ideas.

Euphoria, fearful, depressed or angry: Labile mood, eg anxious then torpid.

Language impaired Speech is reduced or gabbling, repetitive and disruptive.

Illusions/delusions/hallucinations: Tactile or visual (unlike in schizophrenia)

Reversal of sleep-awake cycle: May appear drowsy or hypervigilant.

Inattention: Focusing, sustaining, or shifting attention is poor; no real dialogue.

Unaware/disorientated: Doesn't know it's evening, or his own name, or location.

Memory deficits: Often marked. (Later he may be amnesic for the episode.)

Summary:

Globally impaired cognition and impaired awareness/consciousness.

Illustration from Conrad's Heart of Darkness

'The wastes of his weary brain were haunted by shadowy images now—images of wealth and fame…Sometimes he was contemptibly childish. He desired to have kings meet him at railwaystations on his return from some ghastly Nowhere … "Close the shutter", said Kurtz suddenly "I can't bear to look at this." I did so. There was a silence. "Oh, but I will wring your heart yet!" he cried at the invisible wilderness.'[138] Impaired consciousness is difficult to describe (which is why we have to resort to Conrad— the master of multi-layered descriptions). When you talk to the patient you have the sense that he is not with you, but away with the fairies—inaccessible and lost.

Causes

(Pain and other psychological states are important co-factors.)

- Infection/contagion: pneumonia, UTI, malaria, wounds; IV lines.
- Drugs: opiates, anticonvulsants, L-dopa, sedatives, recreational, post-GA.
- Alcohol withdrawal (2-5d post-admission; raised LFTs with raised MCV; history of alcohol abuse), also drug withdrawal.
- Metabolic: hypoglycaemia, uraemia, liver failure, U&E↑↓, anaemia, malnutrition.
- Hypoxia: respiratory or cardiac failure.
- Vascular: stroke, myocardial infarction.
- Intracranial infection: encephalitis, meningitis.
- Head injury—or ↑ICP (space occupying lesions, eg tumour, subdural haematoma).
- Epilepsy: status epilepticus (see BOX), post-ictal states.
- Nutritional: thiamine, nicotinic acid, or B_{12} deficiency.

Differential

If agitated, is it **anxiety?** Check conscious level. If delusions or hallucinations, is it a **primary mental illness** (eg schizophrenia) but this is rare on the wards (esp if no past history) and delirium very is common in ill patients.

Tests

Consider U&E, FBC, ABG, blood culture, malaria films; also LP, EEG, MRI.

Management

After identifying and treating the underlying cause, aim to:

- Reduce distress and prevent accidents; encourage family to sit with the patient.
- Use the **3M** non-drug cures for agitation: **m**usic, **m**assage, and **m**uscle relaxation.
- Augment self-care. Discourage passive dependency and inappropriate napping.
- Do not use physical restraints—and remove catheters and other impedimenta.
- Hunt down hearing aids/glasses. If he's using ones from the patient next door…
- Nurse in a *moderately lit*, quiet room, ideally with the *same* staff in attendance (minimizes confusion) where the patient can be watched closely. Repeated reassurance and orientation to time and place can help.
- Minimize medication (esp. sedatives); but if disruptive, some sedation may be needed. Use a major tranquillizer—haloperidol 0.5-2mg IM/PO, p13—or chlorpromazine 50-100mg IM/PO (but not in the elderly, in whom it is liable to cause cardiac side-effects and hypotension). Wait 20min to judge effect —further doses can be given if needed. Benzodiazepines may be used for night-time sedation. **NB:** in alcohol withdrawal do *not* use chlorpromazine, use diazepam instead (p274).

Tests of consciousness, and an explanation of dissociative states

Consciousness results wherever these four entities co-exist: perception, memory, emotion, and orientation in space and time. Remorse, for example, is a blend of these four constructs. If a black box exhibited remorse no further test would be needed to establish its consciousness. Patients are often like black boxes to us: we are never quite sure what is going on inside. How do we find out? Dialogue is the first method. Patients with clouding of consciousness often engage in dialogue, but we get the feeling that they are not quite with us. A conversation may suggest clouding of consciousness —until the moment when the patient makes an ironic remark, or we subconsciously detect a twinkle in their eye, banishing the need for formal tests of consciousness.

In general, if a patient knows where they are, the time of day, and passes tests of short and long term memory we tend to think there is not a problem of consciousness—and move on to more mundane issues. This is a pity because changes in consciousness are often subtle—and we need to ask others who know the patient well if there has been any change. Thus elucidating changes in consciousness depends on triangulation between three changing and interacting centres of consciousness—our own, the patient's, and a third party. These issues are exemplified in the next two boxes—where we illustrate the concept of derealization. Here, it is sufficient to say that ***depersonalization*** and ***derealization*** are part of the ***dissociative states*** (just one example of a disorder of consciousness). Dissociation is a mechanism of the mind that separates streams of memories or thoughts from normal consciousness. These mental fragments may then resurface and peruse a life of their own. Causes: migraine, epilepsy, head injury, stress, and,

of course, prolonged sleeplessness (which is why all doctors instinctively understand this odd syndrome).

Non-convulsive status epilepticus (NCSE) as a cause of confusion

NCSE is under-diagnosed, and may manifest itself as confusion, impaired cognition/memory, odd behaviour, and dreamy derealization[139] (the external world appears unfamiliar and unreal—its objects, anchored neither in space nor time, float as in a more or less lucid dream). Other features of NCSE: aggression, psychosis ± abnormalities of eye movement, eyelid myoclonus, and odd postures. It may or may not occur in the context of classic seizures or ischaemic brain injury (eg subarachnoid haemorrhage).[140] Other causes and associations: drugs (eg antidepressants), infections (eg arboviruses; HIV; syphilis), neoplasia, dementias, sudden changes in calcium levels,[141] renal failure (eg with cephalosporin therapy or peritoneal dialysis). *Δ:* EEG evidence of rhythmical discharges (eg prolonged 3-per-second spike-wave complexes). Subsequent MRI may show focal oedema (eg in the hippocampus). **[prescription take]***:* Valproate, ethosuximide, or IV benzodiazepines may be indicated (this requires specialist evaluation).[142]

Ganser syndrome—and example of dissociative symptoms

There are absurd or approximate answers to questions ('paralogias')—plainly wrong but suggesting that the answers are unconsciously known but have been passed by or half-ignored by the current (dissociated) stream of consciousness. There is also clouding of consciousness (or hypervigilance), somatic conversion symptoms (eg inexplicable paralysis—formerly known as hysterical symptoms), hallucinations, and amnesia regarding the episode.[143] Causes/associations: head injury, Munchausen's syndrome, solitary confinement, very stressful events.[144]

When asked to spell WORLD backwards, one Ganser patient replied "EBOLG". When asked to recall the words 'honesty', 'window', and 'lace', he replied "modesty, house, shoes".[145] NB: ▸Ictal and post-ictal states may present with similarly impaired consciousness, perceptual abnormalities, and odd behaviour.

Dementia

Ameliorable causes

- T4↓; B_{12}/folate↓; thiamine↓ (eg alcohol);
- Syphilis
- Tumours (meningioma);
- Subdural haematoma
- Parkinson's (p486)
- CNS cysticercosis (p432)
- HIV (±cryptococcosis);
- Normal pressure hydrocephalus[1]
- Pellagra (p270)
- Whipple's dis. (p708)

▸Assume confusion is due to acute illness until proved otherwise (p476). Depression may mimic dementia (consider trial of therapy, p13). Dementia entails progressive deficits in several cognitive domains. The key is a good history: ask spouse, relatives, or friends about *progressively* impaired cognition/memory (autobiographical[2]; political etc.). Get *objective* evidence. Histories usually go back months or years. There is increasing forgetfulness, and normal tasks of daily living are done with increasing incompetence, eg going to buy sausages 6 times in a day, and then being baffled as to why there is a great mound of sausages in the kitchen. Sometimes the patient appears to have changed personality, eg ↑apathy, uncharacteristically rude or depressed —or with slow, repetitious speech, or literalness. For objective evidence, do tests of cognitive functioning (p47).

Epidemiology

Rare below 55yrs of age. 5-10% prevalence above 65yrs. 20% prevalence above 80yrs, and 70% of those over 100yrs.

Commonest causes

Alzheimer's disease (AD) See p480.

Vascular dementia:

~25% of all dementias. It represents the cumulative effects of many small strokes. Look for evidence of vascular pathology (BP↑; past strokes; focal CNS signs): sudden onset and stepwise deterioration is characteristic (but often difficult to recognise).

Lewy body dementia:

Characterized by Lewy bodies[3] in brainstem *and* neocortex, *fluctuating* cognitive loss, alertness; parkinsonism (p486); detailed visual hallucinations. It's the 3rd commonest dementia (15-25%) after AD and vascular causes. Older neuroleptics in these patients *often* cause neuropsychiatric SEs. Rivastigmine *may* help.MET[146]

Fronto-temporal dementia:

(Frontal and temporal atrophy without Alzheimer histology, p480). *Signs:* Behavioural/personality change; early preservation of episodic memory and spatial orientation; disinhibition; hyperorality, stereotyped behaviour, and emotional unconcern. The disinhibition is not *always* bad.[4]

Rarer causes:

Alcohol/drug abuse; pellagra (p270), Whipple's disease (p708); Huntington's (p694); CJD (p688); Parkinson's (p486); Pick's disease; HIV; cryptococcosis (p428); progressive leukencephalopathy.

Tests

FBC, ESR; U&E; Ca^{2+}; LFT; TSH; autoantibodies; folate/B_{12} (treat low-normals);[147] syphilis serology; CT/MRI (any structural pathology?). Consider EEG; CSF; functional imaging (PET; SPECT, ie single photon emission CT; cost ≈ $74,400 to $1.9 million per QALY).[148] Metabolic, genetic, and HIV tests after appropriate counselling, as indicated.

Management

Neuropsychiatric referral: are specific drugs indicated? (p480)

- Nominate a key worker; make a *care management plan*; get support from social services ± Alzheimer's Society, p481. Ensure access to benefits (p481).
- Carer stress is inevitable (p437), causing ↑morbidity *and* mortality (↑ by 45%): ameliorate this by practical steps and unswerving loyalty (p437).
- GPs have a central role in 'couple focused planning', which acknowledges that needs combine in ways which are not simply additive.[149]

▸Give any specific treatment (eg if TSH↑ or B_{12}/folate↓ or equivocal), and treat concurrent illnesses (these may contribute significantly to confusion).

The positive features of dementia (Auntie Kathleen's syndrome)

Positive features include wandering, aggression, flight of ideas, and logorrhoea:

> ***"Not for her a listless, dull-eyed wordless decline; with her it is all rush, gabble, celerity. She had always been a talker, but now her dementia unleashes torrents of speech…one train of thought switching to another without signal or pause, rattling across points and through junctions at a rate no listener can follow… Following the sense is like trying to track a particular ripple in a pelting torrent of talk."*** Alan Bennett *Untold Stories*, 87

Atypical antipsychotics may improve logorrhoea, wandering, agitation and aggression, without worsening cognition. SSRIs may help depressive symptoms, compulsions, food craving, and disinhibition in fronto-temporal dementia.[150]

Logorrhoea: when dialogue is *not* the answer

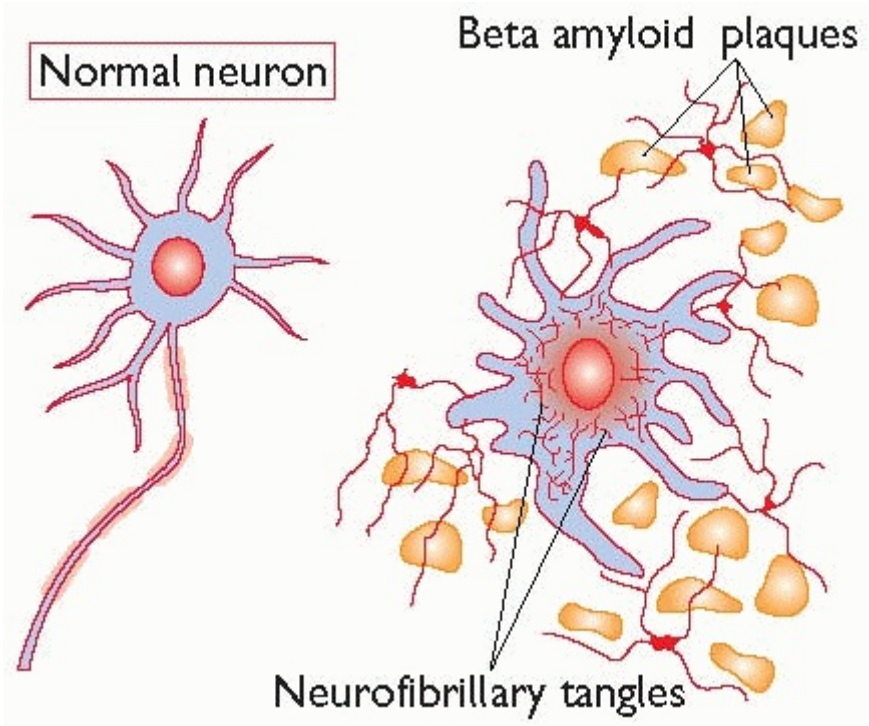


Fig 1. Amyloid plaques and neurofibrillary tangles in Alzheimer's disease. After micromedex.com.[151]

Alzheimer's disease (AD)

This leading cause of dementia is *the* big neuropsychiatric disorder of our times, dominating not just psychogeriatric wards, but the lives of countless children and spouses who have given up work, friends, and all accustomed ways of life to support relatives through the last long years. Their lives can be tormented—'*I am chained to a corpse*' (p437) or transformed, depending on how gently patients exit into their '*worlds of preoccupied emptiness*'.[152]

Mean survival:

7 years from onset.

Suspect Alzheimer's in adults with enduring,[1] acquired **deficits of visual-spatial skill** (gets lost easily), **memory**, and **cognition** (mental test scores + other neuropsychometric tests, p47). Early on there is **anosognosia**, ie lack of awareness—from the Greek *nosos* (disease) and *gnosis* (knowledge) of problems engendered by the disease, eg: missed appointments; misunderstood conversations or plots of films; mishandling of money and clerical work.[153] Onset may be from 40yrs (earlier, in Down's syndrome).

Cause:

Accumulation ß-amyloid peptide, a degradation product of amyloid precursor protein, resulting in progressive neuronal damage, neurofibrillary tangles, ↑numbers of senile plaques, and loss of the neurotransmitter acetylcholine. Neuronal loss is selective, and the hippocampus, amygdala, temporal neocortex and some subcortical nuclei, eg the nucleus basalis of Meynert are especially vulnerable (p436;2006_{data}).[154] Vascular effects are also important (see BOX).[155]

Risk factors

Defective genes on chromosomes 1, 14, 19, 21; the apoE4 variant brings forward age of onset. *Insulin resistance* (p191) *may* be important.[156]

Diagnosis

is often haphazard, as the exact form of dementia used not to matter (if B_{12} and TSH normal). This is hard to justify now that specifics are available for Alzheimer's. Brain imaging (CT; MRI; PET, p732) and neuropsychological tests help rule out fronto-temporal, Lewy body and vascular dementias. Another advantage of early diagnosis is that living will/advance directives may be made before the patient loses capacity to do this legally—the test is: can he **understand** and **retain** the information; **believe** it (no relevant delusions), and **weigh-up pros and cons**?

Presentation

Memory/cognition↓; behavioural change (eg aggression, wandering, disinhibition); hallucinations; delusions; apathy; depression; irritability; euphoria. There is no standard natural history. Cognitive impairment is progressive, but behavioural/psychotic symptoms may go after a few months or years. Towards the end, often but not invariably, patients become sedentary, taking little interest in anything. Parkinsonism (p486), wasting, mutism, incontinence ± seizures may occur.

Treatment

Evidence that **cholinesterase inhibitors** (see BOX) and **memantine** are modestly effective in treating AD is good. Cholinesterase inhibitors appear to be effective throughout the spectrum of AD, while memantine, alone or in combination with cholinesterase inhibitors, is effective in late stage disease. Memantine (see BOX) is an NMDA antagonist. (NMDA=N-methyl-D-aspartate, p443.) Manage arteriopathy (▸AD risk rises with increasing BP) so aim to normalize blood pressure.[157]

We cannot recommend one cholinesterase over another, or suggest ginkgo biloba, oestrogen (neutral, at best[158]2006_{data}), statins, or NSAIDs for prevention or treatment.[159] Vitamin E gets support from one trial; data on other antioxidants is mixed.

Prevention

Many ideas are being tested, eg cognitively stimulating hobbies, antihypertensives, statins, fish oils, ginkgo biloba, and other antioxidants—but good *replicated* randomized trials are lacking.[160] (2006_{data}) Interventions are likely to be most effective if started early, and MRI/PET *can* predict decline/dementia in the cognitively normal,[2] but this science is most uncertain. Even if we could count neurofibrillary tangles with post-mortem accuracy we could not say 'this brain is becoming demented' as there is no simple relationship between structure and function.[161]

Practical issues in managing Alzheimer's dementia

- Involve Social Services & family. UK Alzheimer's Disease Society: 0151 298 2444.
- *Exclude treatable dementias* (B_{12}, folate, syphilis serology, T4, ?HIV); *is this depression masquerading as dementia?* Antidepressant trials may be needed.
- *Meticulous* BP *control;* there is a complex interaction with AD: only 5% of AD patients have a pure form; 95% have mixed AD *and* vascular changes.[1] Optimise cerebral perfusion; it may be wrong to lower diastolic BP to ≲70mmHg.[1]
- *Treat concurrent illnesses* (many can make dementia worse). In most people, the dementia remains and will progress.
- *Avoid drugs that may ↓cognition* (neuroleptics, sedatives, tricyclics, p13).
- Arrange a well-lit, cognitively stimulating care setting. Try multisensory stimulation, eg massage, musicRCT_{162} & aromatherapy etc.RCT_{163} This can help mood, aggression, anxiety, and speech.RCT_{164} Structured conversation & exercise also help.MET_{165}
- ▸See *Living with neurological disease*, p437. In late-stage AD, gastrostomy feeding may be tried, but it is no better than oral feeding.[166] *Special help* is available for those caring for demented relatives at home, eg in the UK:
  - Laundry services for soiled linen

- Car badge giving priority parking
- Carers' groups for mutual support
- Help from occupational therapist, district nurses, and community psychiatric nurses
- Attendance allowance
- Respite care in hospital
- Council tax rebate (forms from local council office)
- Day care/lunch clubs

Oral cholinesterase inhibitors

help embedding new memories more than accessing old ones,[2] 167 and delay the need for institutional care, but not necessarily its duration. 168 Liaise with a psychogeriatrician. NICE has found it impossible to develop acceptable guidelines for their use only partly because their effects are objectively modest. One cannot say 'stop these drugs as he has only scored x on the mini-mental test score' (notoriously variable from day to day) if the wife says 'but he's brighter, more motivated'. 169 ▸Be aware that using QALYs (p12) relentlessly can make us cruel; sentiment (the alternative to QALYs) may make us useless, but *it is better to be useless than cruel*. The Scottish Intercollegiate Guidelines Network (SIGN) states that all AD patients could benefit from acetylcholinesterase inhibitors. Dose examples: **donepezil** 5mg at night (doubled after 4wks[2]);MET 170 **rivastigmine** 6mg/day;[3] **galantamine** 16mg/ day.[4] The SIGN meta-analysis did not take cost-effectiveness into account.

Antiglutamatergic treatment:

Randomized trials show that the NMDA antagonist **memantine** helps eg moderate-to-severe Alzheimer's disease.[5] Its role is still undefined (SE: hallucinations, confusion, hypertonia, hypersexuality).

▸▸IS IT BETTER TO BE USELESS OR CRUEL?

[1] In heart failure there is a ~2-fold ↑risk of getting AD; excess risk ~halves if **hypotensive**s are used. In a 2006 study of **transcranial doppler** middle cerebral artery monitoring for 1 hour, **small emboli** occurred in 40% of those with Alzheimer's compared with ~15% for controls.

[3] **Rivastigmine** is a dual acetylcholinesterase/butyrylcholinesterase (ACHE/BUCHE) inhibitor (?better than ACHE-selective inhibitors, eg donepezil & galantamine, vis-à-vis improving apathy, anxiety, depression, hallucinations & delusions (works in a wider range of dementias, eg in Parkinson's). Oncedaily dose is available. Pre-treatment orbitofrontal signs (agitation; disinhibition; odd motor activity) may predict good response to donepezil; pre-[prescription take] hallucinations predict response to rivastigmine.

[5] **Memantine** (a noncompetitive antagonist of NMDA receptors) is neuroprotective and cognitively enhances those with moderate-to-severe dementia. It can be combined with other drugs for AD.

[2] Jagust W 2006 *An Neurol*

Epilepsy: diagnosis

Epilepsy is a recurrent tendency to spontaneous, intermittent, abnormal electrical activity in part of the brain, manifest as *seizures*.[1] These may take many forms: for a given patient they tend to be stereotyped. *Convulsions* are the motor signs of electrical discharges. Many of us would have seizures in abnormal metabolic circumstances —eg Na+↓, hypoxia (reflex anoxic seizures in faints): we would not normally be said to have epilepsy. In deciding if an event is epileptic, don't pay *too* much attention to associated incontinence and abnormal movement (not everything that twitches is epilepsy): but biting the side of the tongue and slow recovery of normal mental functioning are very suggestive. Prevalence of active epilepsy is ~1%.

The patient

There may (rarely) be a *prodrome* lasting hours or days preceding the seizure. It is not part of the seizure itself: the patient or others notice a change in mood or behaviour. An *aura*, which is part of the seizure, may precede its other manifestations. The aura may be a strange feeling in the gut, or a sensation or an experience such as *déjà vu* (disturbing sense of familiarity), or strange smells or flashing lights. It implies a partial seizure (a focal event), often, but not necessarily, temporal lobe epilepsy (TLE). After a partial seizure involving the motor cortex (Jacksonian convulsion) there may be temporary weakness of the affected limb(s) (Todd's palsy). After a generalized seizure, patients may feel awful with headache, myalgia, confusion, and a sore tongue.

Diagnosis

Decide first: is this epilepsy? (p452 for ΔΔ) A detailed description from a witness of 'the fit' is vital. Try hard not to diagnose epilepsy in error—therapy has significant side-effects, the diagnosis is stigmatizing and has implications for employment, insurance, and driving. Decide next what type of seizure it is. The attack's *onset* is the key concern here: partial or generalized? If the seizure begins with focal features, it is a partial seizure, however rapidly it is generalized. Ask next: what if anything brings it on (eg flickering light (TV) or alcohol)? Can this be avoided? TV-induced seizures—almost always generalized —rarely require drugs.

Partial seizures

Features are referable to a part of one hemisphere suggesting structural disease.

- ***Elementary symptoms*** (consciousness unimpaired, eg focal motor seizures).
- ***Complex symptoms*** (consciousness impaired, eg olfactory aura preceding automatism). Usually TLE.
- ***Partial seizure with secondary generalization:*** Electrical disturbance starting focally, then spreading widely, causing a secondary generalized seizure.

Primary generalized seizures

No features referable to only one hemisphere.

- ***Absences (petit mal):*** Brief (≤10s) pauses, eg suddenly stops talking in midsentence, then carries on where left off. Presents in childhood.
- ***Tonic-clonic*** (classical *grand mal*). Sudden onset, loss of consciousness, limbs stiffen (tonic) then jerk (clonic); may have one without the other; drowsy after.
- ***Myoclonic jerk*** (eg thrown suddenly to ground, or a violently disobedient limb: a patient described it as *my flying-saucer epilepsy*, as crockery which happened to be in the hand would take off).
- ***Atonic*** (becomes flaccid) or ***Akinetic***. Note also ***infantile spasms*** (OHCS p206).

Causes

Often none is found.

Structural:

Trauma, space occupying lesions, stroke, tuberous sclerosis, SLE, PAN, sarcoid, vascular malformations.

Metabolic:

Alcohol or benzodiazepine withdrawal; glucose ↑ or ↓, P_aO_2↓ (eg in bradyarrhythmias), uraemia, Na^{2+}↑ or ↓, Ca^{2+}↓, liver disease, drugs (eg phenothiazines, tricyclics, cocaine).

Infection:

Encephalitis, syphilis, cysticercosis, HIV.

Evaluation of an adult who has just had a first-ever seizure

For status epilepticus, ▸▸see p808; here structural lesions are especially likely.

- Is it really the first? Ask the family and patient about past funny turns/odd behaviour. Déjà vu and odd episodic feelings of fear *et al* may well be relevant.
- Is it really a seizure? Convulsive syncope is problematic here; get help. Get as much history as you can from the patient and witnesses; ask yourself: *are they reliable*? In the heat of the moment many witnesses may report twitching when none in fact took place (perhaps they want to please you by seeming to be observant and they 'helpfully' fill in the gaps in reality—so, *beware*).
- Was the seizure provoked by a CNS insult, eg head injury, stroke, hypoglycaemia, alcohol, drugs (clozapine, tramadol, theophylline, baclofen); T°↑↑; U&E↑↓?
- Provoked 1st seizures are less likely to recur (3-10%, unless there is an unremovable condition, such as an infarct or glioma); if unprovoked, recurrence rates are 30-50%.[171] Provoked seizures are also called 'symptomatic'.
- Was there a possible trigger to the attack (eg strobe lighting; TV)? Triggers are different to provocations: most people would have a seizure given sufficient provocation; but most people do not have seizures however many triggers they are exposed to—so triggered seizures mean an underlying epilepsy disorder. Triggered attacks tend to recur.
- DO U&E/LFT, glucose,
- Ca^{2+}, PO^{3-}_4
- FBC; INR/PTT.
- Serum & urine alcohol and toxin screens.
- Blood levels of medications.
- Consider LP if CT shows no ↑ICP.
- Imaging: don't assume that if one CT scan is OK, there is no structural lesion. If epilepsy worsens, do MRI to find small areas of cortical dysgenesis, tumours, vascular malformations, and cavernomas (surgically correctable sporadic or multiple congenital malformations presenting with fits ± haemorrhage).[172]
- EEG is problematic (often false +ve). Don't do if the likely diagnosis is simple syncope. EEG cannot *of itself* exclude or refute epilepsy; it forms part of the context for diagnosis. It helps classification and prognosis: in 1st unprovoked seizures, unequivocal epileptiform activity on EEG helps assess risk of recurrence.[173] Only do *emergency* EEGs if nonconvulsive status is the problem, p477.
- Admission for ~24h is indicated (in <10%) for investigations and observation (eg for intractable seizures or to substantiate ideas of pseudoseizures, p484). Urgent treatment may be needed if seizures recur.
- Get prompt neurological help for diagnosis, and *individualized* counselling on employment, and possible dangers, eg swimming alone. This is a difficult area—so get help. You must give advice against driving and (in the UK) advise the patient to contact DVLA (p145). Document your discussion carefully.
- Suggest treatment eg if the risk of recurrence is high or high-ish—eg if unprovoked, or structural brain lesion, or status, or epileptiform EEG or postseizure Todd's paresis (p704). Start eg with carbamazepine if it is a focal seizure (or lamotrigine, gabapentin, topiramate) or, if generalized, valproate (or lamotrigine or topiramate).

INDIVIDUALIZED COUNSELLING IS NOT AN ANNOYING ADDITIONAL TASK YOU MUST PERFORM: IT'S THE ESSENCE OF WHAT A GOOD NEUROLOGIST IS ALL ABOUT.

Anti-epilepsy drugs (AEDs) ▸*Status:* p808; *children: OHCS p206*

▸***Involve patients in all decisions***. Compliance depends on communication and doctor-patient concordance issues (p3). Living with *active* epilepsy creates many problems (eg inability to drive, or operate machinery) and fears (eg of sudden death), and drug issues. A problem is that UK neurologists have little time to explore these issues as each could have 1500 people with epilepsy on their books. Each general practice will only have ~50 patients, but GPs may have no special interest in epilepsy. One option is a yearly visit to a GP- or hospital-based **epilepsy nurse**, to monitor drugs, address employment, leisure, and reproductive issues; and, after a few seizure-free years, to see if drugs can be carefully withdrawn (see BOX). These nurses are skilful: respect their role! For **investigating first seizures,** see p483.

Therapy

Treat with *one* drug and with *one* doctor in charge only. Slowly build up doses (over 2-3 months) until seizures are controlled, or toxic effects are manifest, or maximum drug dosage reached. Beware drug interactions (consult formulary). Most specialists would not recommend treatment after 1 fit but would start treatment after 2. ▸Discuss options with the patient. If your patient has only 1 fit every 2yrs, he or she may accept the risk (particularly if there is no need to drive or operate machinery) rather than have to take drugs every day.

Generalized:

Try **sodium valproate** as 1st-line, then **lamotrigine** (which may be more effective as well as being preferred by patients[174] —but is newer; see BOX). Also use **sodium valproate** or **ethosuximide** for absence seizures.[175]

Partial with or without secondary generalization:

Carbamazepine is 1st-line, then **sodium valproate**. Levetiracetam and topiramate are new 2nd-line agents.

Commonly used drugs

Carbamazepine:

Start with 100mg/12h PO; maximum dose: 800-1000mg/12h. A slow-release form is available, which is useful if intermittent side-effects experienced when dose peaks. Toxic effects: rash, nausea, diplopia, dizziness, fluid retention, hyponatraemia, blood dyscrasias.

Sodium valproate:

Start with 300mg/12h" PO after food; max 30mg/kg (or 2.5g) daily. The BNF suggests LFT & INR during the first 6 months of therapy (but most hepatic failure is in those <3yrs old on multi-drug regimens). Toxic effects: sedation, tremor, weight↑, hair thinning, ankle swelling, hyperammonaemia (causing encephalopathy), liver failure. Drug levels are not helpful.

Phenytoin:

Although effective and well-tried, it is not 1st line for generalized or partial epilepsy owing to toxicity: nystagmus, diplopia, tremor, dysarthria, ataxia. SEs: intellect↓, depression, poor drive, polyneuropathy, acne, coarse facial features, gum hypertrophy, blood dyscrasias. Dosage is difficult, and needs blood levels (p739).

Other drugs:

Phenobarbital; benzodiazepines; newer agents (see BOX).

Changing drugs

Indications:

On inappropriate drug; side-effects unacceptable; treatment failure; pregnancy/lactation desired.

Method:

Begin the new drug at its starting dose. At the same time, withdraw the old drug, eg over 6wks (sooner if toxicity: get help). Slowly ↑ new drug to middle of its dose range.

Enzyme-inducing AEDs & contraception

Non-enzyme inducing AEDs (valproate, gabapentin, lamotrigine, levetiracetam) have no effect on the Pill. In other AEP (eg carbamazepine, phenytoin, phenobarbital, primidone) ≥50µg of oestrogen may be needed (Norinyl-1®; ↓pill-free days from 7 to 4; use condoms too) or Depo-Provera®, dose interval is unchanged (12 weeks). The coil is suitable for emergency contraception, or levonorgestrel (1.5mg) ▸followed by 1.5mg 12h later.[176]

Pre-conception counselling & AEP

is vital ∵ teratogenicity—OHCS p2/p29. Use high dose folic acid supplements (5mg/day) preconception and during all trimesters.[177]

When it all goes wrong

Sudden unexpected death in epilepsy (SUDEP) is more common in uncontrolled epilepsy, and may be related to seizure-associated apnoea at night.[178]

Those with epilepsy have a mortality rate 3-fold that of controls. >700 epilepsy-related deaths are recorded/yr in the UK; up to 17% are SUDEPs. For help with families of those with SUDEP, contact '*Epilepsy Bereaved*', [UK]01235 772852.

Uncontrolled epilepsy and new antiepileptic drugs (AEDs)

Ask a neurologist to help. Is the diagnosis of epilepsy correct? (bear in mind non-epileptic attack disorder, below). If it *is* epilepsy, does the AED match the seizure type? Has the top dose been prescribed and taken? Has an underlying structural or metabolic abnormality been excluded? Low-grade gliomas, for example, may not show on initial MRI. Aim to use 1 drug only. If seizures are not controlled, switch to the 2nd most appropriate drug. Only consider maintenance on 2 drugs if all appropriate drugs have been tried singly at their top dose.

Newer AEDS

NICE asserts they are 2nd-line, ie if valproate and carbamazepine are contraindicated or problematic, eg: poor seizure control; fertile women; or drug interactions. They are often cost-effective (but costly, eg £100/month *vs* £12.[179]

Lamotrigine

is used as monotherapy and as an add-on for secondary generalized epilepsy (also useful in primary generalized epilepsy.) Monotherapy dose: 25mg/24h PO for 14d, ↑ to 50mg daily for a further 14d, then ↑ by up to 50-100mg every 7-14d; usual maintenance as monotherapy, 50-100mg/12h. (500mg daily may be needed.) ▸Halve monotherapy doses if already on valproate; double if on carbamazepine or phenytoin.

SE:

Rash (may be serious; typically occurs in 1st 8wks, esp if valproate co-prescribed; warn patients to see a doctor at once if rash or 'flu symptoms associated with hypersensitivity develop; do FBC; U&E; LFT; INR). Other SEs: fever; malaise; 'flu symptoms; drowsiness; LFT↑; photosensitivity; diplopia; vision↓; vomiting; aggression; tremor; agitation. Interactions (BNF): anticonvulsants (above); antimalarials; antidepressants.

Levetiracetam* & *topiramate

are powerful new AEDs for 2dary generalized fits. Levetiracetam dose: if >50kg, initially 500mg/12h PO, adjust by ≤1g every 2-4 weeks; max 1.5g/12h. SE: D&V, dyspepsia, depression, drowsiness, diplopia, WCC↓.

Gabapentin

is a weak anticonvulsant (a clearer indication is pain syndromes).

Zonisamide

is a new-generation, broad-spectrum benzisoxazole-derived glutamate inhibitor*et al* used in partial seizures (± secondary generalizations).[180]

Vigabatrin:

Only use in infantile spasms ('∴' high incidence of visual field defects).

Other new AEPs

Tiagabine and pregabalin (also used in neuropathic pain).

Non-epileptic attack disorder *(pseudo or psychogenic seizures)*

These are not infrequent: suspect this if there are uncontrollable symptoms, no learning disabilities, and CNS exam, CT, MRI, and EEG are normal.[181]

Stopping anticonvulsants

▸*Discuss risks and benefits with patients. Informed choices are vital*. Most patients are seizure-free within a few years of starting drugs. More than 50% remain so when drugs are withdrawn. After assessing risks and benefits for the individual patient (eg the need to drive), withdrawal may be tried, if the patient meets these criteria: normal CNS examination, normal IQ, normal EEG prior to withdrawal, seizure-free for >2yrs, and no juvenile myoclonic epilepsy. In one study (*N* =459), over 5yrs 52% remained seizure-free, compared with 67% continuing their medication.[182] However in another study, resuming medication did not return the patient to his/her status quo, and not all seizures could be controlled (risk factors: cognitive deficits and partial epilepsy).[183]

One way to withdraw drugs in adults is to ↓the dose by 10% every 2-4wks (for carbamazepine, lamotrigine, phenytoin, valproate, and vigabatrin) and by 10% every 4-8wks for phenobarbital, benzodiazepines, and ethosuximide.[184]

Alternative MRC regimen		Decrease every 4 weeks by:	
Phenobarbital	30mg	Valproate	200mg
Phenytoin	50mg	Primidone	125mg
Carbamazepine	100mg	Ethosuximide	250mg

Driving and jobs (p145). ***Epilepsy in pregnancy*** (OHCS p29).

Parkinson's disease (PD) and parkinsonism NICE 2006

Parkinsonism is a syndrome of *tremor*, *rigidity, bradykinesis (slowness)*, and loss of postural reflexes. *Prevalence*: 1 : 200 if >65yrs old.

- *Tremor:* 4-6Hz (cycles per sec). It is most marked at rest and coarser than cerebellar tremor. It is typically a 'pill rolling' of thumb over fingers.
- *Rigidity:* ↑Resistance to passive stretch of muscles throughout range of movement (lead-pipe); tone may be broken-up by tremor (cogwheel rigidity). Unlike in spasticity, rigidity is present equally in flexors and extensors.
- *Bradykinesis:* Slowness of movement initiation with progressive reduction in speed and amplitude of repetitive actions; also monotonous speech (± dysarthria). Expressionless face. Dribbling. Short shuffling steps with flexed trunk as if forever a step behind one's centre of gravity (*festinant gait*). Feet behave 'as if frozen to the ground'. Peristalsis↓. Blink rate↓. Fidgeting↓. Micrographia.

Parkinson's disease

is one cause of parkinsonism (due to degeneration of substantia nigra dopaminergic neurones; the pathological hallmark is Lewy bodies in this area, p478). Degeneration may be related to mitochondrial DNA dysfunction.[185] It usually starts after 50, and becomes ever more common with age.

Management:

▸***Get help***. Forge a humanizing ***therapeutic alliance*** between neurologist, physiotherapist, specialist nurse, GP, patient, and carer: see p437. ***Respite care*** is much valued by carers. Episodes of multidisciplinary ***rehabilitation*** improve mobility and morale.[186] Formal exercises regulating posture and harmonizing this with mental strength can help mobility—eg Chinese qigong.RCT[187]

- ***Assess disability*** and cognition regularly and objectively (eg time how long to walk 10 metres; can he/she dress alone, and turn over in bed?).
- ***Start drugs*** when PD seriously interferes with life (not too soon, as L-dopa's effects wear off with time; explain this to patients; let him choose); use lowest dose giving symptom relief, without bad SEs. Dopaminergic drugs (BOX), eg **L-dopa**: Start at 50mg/12h PO (with food, to avoid nausea/vomiting).[188] Increase dose to 100mg/8h, then slowly ↑ to 800mg/24h in divided doses. Give enough peripheral dopa-decarboxylase inhibitor (≥25mg/100mg L-dopa). Balance better mobility with L-dopa's SEs, eg nausea & unwanted movements (seen after ~2yrs) ± orthostatic hypotension, arrhythmias, psychosis, and compulsions (sex, gambling, food).
- Over years, drugs may get less effective with switching between times of exaggerated involuntary movement and of immobility ('***on-off***'); **slow-release L-dopa** (see BOX) aims to help this (evidence is poor); once it occurs, it may be irreversible: there is evidence that early use of dopaminergic agonists (eg **ropinirole**, see BOX) may reduce this, and allow lower doses of L-dopa.
- **Anticholinergics/antimuscarinics** (orphenadrine 50mg/8h PO; max 400mg/d) help motor symptoms. CI: Urinary retention, porphyria, angle-closure glaucoma, GI obstruction, prostatism. SE: Dry mouth, dizziness, vision↓, urinary retention, pulse↑, anxiety, confusion, excitement, hallucinations, insomnia, memory↓.
- **Modafinil** (100-200mg bd before noon; CI: BP↑) helps daytime sleepiness.MET[189]

Neuropsychiatric complications

These are seen in ~50%, and often represent the interplay of the illness and drug SEs. ***Depression*** tricyclics and SSRIs (p13) may be of help. Psychosis and dementia often complicate PD; get help, p374. Older antipsychotics worsen PD, so consider atypical antipsychotics, eg quetiapine or olanzapine. Cholinesterase inhibitors (rivastigmine; donepezil, p481) may help memory problems.

Treating drug-induced parkinsonism

It may be unwise to reduce or stop the culprit drug (eg in schizophrenia where relapse could spell catastrophe), so try adding in an antimuscarinic (eg **procyclidine** 2.5mg/8h PO).

Rare causes

Parkinsonism isn't *always* due to Parkinson's disease or neuroleptics (antiemetics; haloperidol[*et al*]), so look for **'VODKA' signs: v**ascular events elsewhere (stroke, MI) ≈ vascular causes; **o**rthostatic hypotension + atonic bladder ≈ multisystem atrophy (=MSA, p494 ≈ Shy-Drager syndrome); **d**ementia + vertical gaze paralysis ≈ supranuclear palsy (=Steele-Richardson-Olszewski syndrome); **K**ayser-Fleisher ring ≈ Wilson's disease; **a**praxic gait ≈ communicating hydrocephalus.

Drugs combining L-dopa and dopa-decarboxylase inhibitors

Trade name	L-dopa content (mg)	Benserazide (mg)	Carbidopa (mg)
Madopar 62.5®	50	12.5	

Madopar 125®	100	25	
Madopar **CR® controlled release**	100	25	
Madopar 250®	200	50	
Sinemet 62.5®*	50		12.5
Sinemet 110®*	100		10
Sinemet 275®*	250		25
Sinemet Plus®	100		25
Half Sinemet CR®	100		25
Sinemet CR®	200		50

* The proportion of carbidopa may be suboptimal.[190]

Generics:

Madopar® is co-beneldopa (1 part benserazide to 4 parts L-dopa). Sinemet ® is co-careldopa (carbidopa with L-dopa); doses are expressed as co-careldopa *x*/*y*, where *x* and *y* are strengths in mg of carbidopa and L-dopa, respectively; eg Sinemet 275® = co-careldopa 25/250 = 25mg carbidopa + 250mg L-dopa.

Dopaminergic drugs

Pergolide:

Start at 50µg/24h PO for 2d. Increase by 100-150µg every 3rd day over the next 12d. Further increases of 250µg every 3rd day may be tried. Usual dose: 1mg/8h. Tablets are 50µg (white), 250µg (green), and 1mg (pink). During titration, the dose of L-dopa may be ↓ cautiously. SE: heart valve disease/fibrosis (assess pre-[prescription take]); delusions, dyskinesia, drowsiness, dyspepsia, diplopia, dyspnoea.

Bromocriptine:

Week 1: 1.25mg at night PO with food. *Week 2:* 2.5mg at night. *Week 3:* 2.5mg/12h. *Week 4:* 2.5mg/8h. ↑ by 2.5mg/d at weekly intervals to ≤5 × 2.5mg/8h. SE: Hallucinations, BP↓, constipation, drowsiness, fibrosis.

Newer agents

Ropinirole, cabergoline & **pramipexole** (dopamine D_3 agonist) are better tolerated than L-dopa, and dosing is easier. They may be 1st-choice in younger patients to ↓risk of dyskinesias (and at any age as an adjunct to L-dopa). Claims that ropinirole ↓rate of loss of dopaminergic neurones compared with L-dopa arise from a one unreplicated PET study.[191] ***Ropinirole dose:*** eg 250µg/8h PO increased by small weekly increments to 3mg/8h if needed; tabs are 250µg, 1mg, 2mg, & 5mg. SE: drowsiness; nausea; hallucinations (17%).

Subcutaneous apomorphine

(an injectable D1 and D2 dopamine agonist) may help patients with severe on-off effects. Injections or continuous infusion may be required. Liaise with a special PD centre.[192]

NB:

the ergot-related agonists (pergolide, bromocriptine, and cabergoline) are being used less owing to pleural and cardiac valve fibrosis.

Entacapone:

This decreases peripheral L-dopa metabolism by catechol-Omethyltransferase (COMT) inhibition. It may lessen the 'off' time in those with wearing off effects. SE: red-brown urine, dyskinesia, nausea, vomiting, orthostatic hypotension, sleep disorders, hallucinations, dry mouth, Hb↓, LFT↑.[193]

Surgery for PD

• Destructive procedures interrupting overactive basal ganglia circuits (eg subthalamic nuclei) by surgical lesions or deep-brain stimulation (p460) are being tried in specialist centres in those inadequately controlled by drugs. • **Neural transplants**[1] with stem cells or dopaminergic neuroblasts from the brains aborted fetuses and **gene therapy** may be future (problematic) options. MAOI-B inhibitors, eg **selegiline**, don't delay progression but may help motor fluctuations;MET[194] they have serious SEs (postural hypotension; AF).[195]

[1] Two placebo-controlled trials were disappointing: we have yet to resolve graft survival problems. Another option is continuous infusion of glial cell line-derived neurotrophic factor into the putamen.

Multiple sclerosis (MS)

This relapsing/remitting disorder consists of plaques of demyelination (and axon loss) at sites throughout the CNS (but not peripheral nerves). Pathogenesis involves focal disruption of the blood-brain barrier and associated immune response and myelin damage—as well as axonal/neuronal neurodegenerative processes.[1][196]

Epidemiology

Commoner in temperate areas (prevalence is very variable: England ≥42/100,000; SE Scotland 200/100,000;[197] rarer in Black Africa and Asia). Lifetime UK risk: ~1 : 1000. Adult travellers take their risk with them; children acquire the risk of where they settle. ♀:♂≈2:1; mean age of onset is 30yrs.

Poor prognostic signs:

Older males; motor signs at onset; many relapses early on; many MRI lesions.

Presentation

is usually monosymptomatic: unilateral optic neuritis (pain on eye movement and rapid deterioration in central vision); numbness or tingling in the limbs; leg weakness or brainstem or cerebellar symptoms such as diplopia or ataxia. Less often there may be more than 1 symptom. Other signs: see BOX. Symptoms may worsen with heat (eg a hot bath) or exercise.

Progression/prognosis:

Early on, relapses (which can be stress induced)[198] may be followed by remission/full recovery. With time, remissions are incomplete, so disability accumulates. Steady progression of disability from the outset also occurs, while some patients experience no progressive disablement at all.

Examination

Look carefully for deficits other than the presenting problem (BOX).

Diagnosis

This is clinical, requiring demonstration of lesions disseminated in time and space, unattributable to other causes. Isolated CNS deficits are never diagnostic, but may become so if a careful history reveals previous episodes, eg unexplained blindness for a week. *The role of* MRI*:* See BOX.

Tests

None is pathognomonic. **CSF***:* up to 50 lymphocytes/mm^3, protein ≤1g/L ± oligoclonal bands of IgG on electrophoresis. Delayed visual, auditory, and somatosensory ***evoked potentials***. **MRI** is sensitive but not specific for plaque detection and may exclude other causes, eg cord compression. Correlation of MRI with clinical condition is poor. ***Antibodies to myelin oligodendrocyte glycoprotein*** (MOG) and ***myelin basic protein*** (MBP) in those with a single MS-like clinical lesion can predict time to conversion to definite MS.[199]

Treatment

Methylprednisolone

1g/24h IV/PO for 3d shortens relapses; use sparingly (≤ × 2/yr, ∵ steroid SEs, p361). It does not alter the overall prognosis.

Immuno-modulation with interferon (INF-1β; INF-1a)

Trials show that these can ↓relapses by ~30% in active relapsing-remitting MS (RRMS);[200] they also ↓lesion accumulation on MRI.MET[201] Their power to ↓disability is modest, as is their role in secondary and primary progressive (SP & PP) MS. Licensed for use by neurologists, they are expensive (eg ~£200/wk; €0.4-1.3×10^6/QALY; 20×more expensive than **azathioprine**, which may be just as good).[202] SE: flu-like symptoms, depression, abortion. CI: depression, LFT↑, pregnancy, uncontrolled epilepsy. The UK DoH, the Assocn of British Neurologists, and the drug industry are making INF more available according to agreed criteria and effectiveness monitoring.

Glatiramer

is a similar alternative. There is no good, safe preventive treatment for those with primary progressive MS.[203]

2nd-line drugs:

Alemtuzumab (Campath-1H®; T-cell killing monoclonal antibody). **Mitoxantrone** (doxorubicin analogue) ?helps in 2dry progressive MS; safety is an issue.

Palliation:

▸Help to live well with disability.

Spasticity:

Start all drugs at a low dose, and build up at weekly intervals. **Baclofen** 5-25mg/8h PO; **diazepam** 5mg/ 8-24h PO (addictive); **dantrolene** 25mg/24h (max 100mg/6h); **tizanidine** 2mg/24h PO; ↑at intervals of >3d in steps of 1mg/12h (max 9mg/6h). Intrathecal baclofen, phenol nerve block, botulinum toxin, and cannabis are less evidence-based.

Urgency/frequency:

If post-micturition residual urine >100mL teach intermittent selfcatheterization; if <100mL, try **oxybutynin** 2.5mg/8h or **tolterodine**.

Clinical features of multiple sclerosis

		• GI: swallowing disorders; constipation.
• Sensory:	dysaesthesia[1] pins and needles vibration sense↓ trigeminal neuralgia	• Diplopia; hemianopia; optic neuritis;[2] nystagmus in the abducting eye on lateral gaze.[3] Pupil defects[4] and visual defects (eg on exercise).[2]
• Motor:	spastic weakness Hyperreflexia	• Cerebellum: truncal or limb ataxia; intention tremor; scanning (ie monotonous) speech.
		• Fatigue; cognition↓; memory↓; cognition↓.
• Cord:	transverse myelitis[5] urgency; retention erectile dysfunction	• Depression (avoid ECT); mania; odd laughter, p498
		• Cranial nerve lesions; epilepsy; aphasia—all rare.

[1] In **Lhermitte's sign,** neck flexion causes 'electric shocks' in trunk/limbs also +ve in spondylosis & B_{12}↓

[2] Optic neuritis symptoms: • Acuity↓ • Phosphenes (flashes) on eye movement • Uhthoff's phenomenon (vision worsens on exercise, eating a hot meal, or in hot baths) • The **Pulfrich effect** (latencies between the eyes are unequal, causing disorientation, eg in moving traffic as straight trajectories seem curved).

[3] In internuclear ophthalmoplegia (a classic MS lesion) a lesion in the median longitudinal fasciculus causes weakness in adduction of the ipsilateral eye with nystagmus on abducting the contralateral eye.

[4] Efferent or afferent defect (p68; ie poor response to light ∴ bigger); an **Argyle Robertson**-type pupil is rarer (p70; ΔΔ: syphilis, DM, MS or sarcoidosis—lesion in or near the **Edinger-Westphal** nucleus).

[5] Loss of motor, sensory, autonomic, reflex, and sphincter function below the level of a lesion indicates transverse myelitis. **Devic's syndrome** is an MS variant of transverse myelitis with optic atrophy, p690.

Proposed McDonald criteria for diagnosing MS$_{204}$

Warning: these criteria are provisional: it is likely that they err on the side of according too much weight to MRI: ▸when in doubt, pay more attention to clinical signs.MET$_{205}$	
Clinical presentation	**Additional data needed**
2 or more attacks (relapses) with 2 or more objective clinical lesions	None; clinical evidence will do; imaging evidence desirable; must conform to MS
2 or more attacks with 1 objective clinical lesion	Typical disseminated lesions on MRI • **or** +ve CSF **and** ≥2 MRI lesions consistent with MS • **or** 2nd attack at a new site

1 attack with 2 or more objective clinical lesions	Dissemination in time, shown by • MRI **or** 2nd clinical attack
1 attack with 1 objective clinical lesion (monosymptomatic presentation)	Dissemination in space: • MRI **or** +ve CSF if ≥2 MRI lesions consistent with MS • **and** dissemination in time shown by MRI **or** 2nd clinical attack[3]
Insidious neurological progression suggestive of MS (primary progressive MS)	+ve CSF **and** dissemination in space, ie: • MRI evidence of ≥9 T2 brain lesions • **or** 2 or more cord lesions • **or** 4-8 brain and 1 cord lesion • **or** +ve visual evoked potential (VEP) with 4-8 MRI lesions • **or** +ve VEP + <4 brain lesions + 1 cord lesion **and** dissemination in time seen on MRI • **or** continued progression for ≥1yr

Attacks: These must last >1h, eg motor weakness etc., see. BOX above.

Time between attacks: 30 days. *MRI abnormality:* 3 out of 4:

- Gadolinium-enhancing **or** ≥9 T2 hyperintense lesions if no Gd-enhancing lesion

- 1 or more infratentorial lesions • **or** 1 or more juxtacortical lesions

- ≥3 periventricular lesions (1 spinal cord lesion = 1 brain lesion)

CSF: Oligoclonal IgG bands in CSF (and not serum) or ↑IgG index.

Evoked potentials: (EP) This counts if delayed but well-preserved waveform.

What provides MRI evidence of dissemination in time? A Gd-enhancing lesion demonstrated in a scan done at least 3 months following onset of clinical attack at a site different from attack, **or**

In absence of Gd-enhancing lesions at a 3-month scan, follow-up scan after an additional 3 months showing Gd-lesion or new T2 lesion.[206]

Space-occupying lesions

Signs

Features of ↑intracranial pressure, evolving focal neurology, seizures, false localizing signs, cognitive or behavioural change, local effects (eg proptosis; epistaxis).

Raised ICP

(p812): Headache (p448), vomiting, papilloedema (only in 50% of tumours), altered consciousness.

Seizures:

Seen in ≤50% of tumours. Suspect in all adult-onset seizures, especially if focal, or with a localizing aura or post-ictal weakness (Todd's palsy, p704).

Evolving focal neurology:

Depends on the site (see BOX for localizing signs). Ask first ***where*** the mass is then ***what it is***. Frontal lobe, midline, and non-dominant temporal lobe masses present late.

False localizing signs:

These are caused by ↑ICP. VI nerve palsy is commonest (p44; due to its long intracranial course).

Subtle personality change:

Irritability, lack of application to tasks, lack of initiative, socially inappropriate behaviour.

Causes

Tumour (primary or secondary), aneurysm, abscess (25% multiple); chronic subdural haematoma, granuloma p179 eg tuberculoma), cyst (eg cysticercosis).

Histology:

30% secondaries (breast, lung, melanoma). Primaries: astrocytoma, glioblastoma multiforme (case-control studies now show probably *not* associated with mobile phone use [207]2006[data]), oligodendroglioma, ependymoma (all <50% 5yr survival), primary CNS lymphoma (eg as non-infectious manifestation of HIV); cerebellar haemangioblastoma (40% 20yr survival); meningioma (♀:♂≈2:1).

ΔΔ:

Stroke, head injury, vasculitis (p542), eg SLE, syphilis, PAN, giant cell arteritis, MS, encephalitis, post-ictal (Todd's palsy, p704), metabolic, or U&E disturbance. Also colloid cyst of the 3rd ventricle and benign intracranial hypertension (see below).

Tests

CT; MRI (good for posterior fossa masses). Consider biopsy. Avoid LP (risks coning, ie cerebellar tonsils herniate through the foramen magnum).

Tumour management

Benign: Removal if possible but some may be inaccessible. *Malignant*: **Excision** of gliomas is hard as resection margins are rarely clear, but surgery does give a tissue diagnosis, it debulks pre-radiotherapy, and makes a cavity for inserting **carmustine wafers**RCT[208] (may cause serious cerebral oedema).[209] If a tumour is inaccessible but causing hydrocephalus, a **ventriculo-peritoneal shunt** can help. **Chemo-radiotherapy** is used post-op for gliomas or metastases, and as sole therapy if surgery is impossible. Oligodendroglioma with 1p/19q deletions are especially sensitive. In glioblastoma, **temozolomide** (a new alkylating agent) ↑survival (benefit is mainly if tumours have methylated methylguanine methyltransferase gene promoters and are thus unable to repair chemotherapy-induced DNA damage).[210] Prophylaxis for epilepsy is important, but often fails. Treat headache (eg **codeine** 60mg/4h PO). Cerebral oedema: **dexamethasone** 4mg/8h PO; **mannitol** if ↑ICP acutely, p812. Plan meticulous palliative treatment (p520).

Prognosis

Poor but improving in gliomas; benign tumours are curable by excision.

Third ventricle colloid cysts

These congenital cysts declare themselves in adult life with amnesia, headache (often positional), obtundation (blunted consciousness), incontinence, dim vision, bilateral paraesthesiae, weak legs, and drop attacks.

Tests:

CT scan/MRI.

Treatment:

Excision or ventriculo-peritoneal shunting.

Benign intracranial hypertension (pseudotumor cerebri)

Think of this in those presenting as if with a mass (headache, ↑ICP and papilloedema)—*when none is found*. Typical patients are obese women with blurred vision ± diplopia, VI nerve palsy, and an enlarged blind spot, if papilloedema is present (it usually is). Consciousness and cognition are preserved.

Cause:

Often unknown, or secondary to venous sinus thrombosis, or drugs, eg tetracycline, minocycline, nitrofurantoin, vitamin A, isotretinoin, danazol, and somatropin.

[prescription take]:

Weight loss, acetazolamide, loop diuretics, and prednisolone (start at ~40mg/24h PO; more SE than diuretics) *may* reverse papilloedema.[211] Consider optic nerve sheath fenestration or lumbar-peritoneal shunt if drugs fail and visual loss worsens.[212]

Prognosis:

Often self-limiting. Permanent significant visual loss in 10% (ie not so benign). CSF shunting or optic nerve sheath fenestration can help vision.[213]

Localizing signs
Temporal lobe

Remember the '**HAPPY-CLAPPY DJ**' to remind you of excessive religiosity,[214] music-induced seizures, and states of surreal happiness and out-ofbody experiences[215] which sometimes accompany temporal lobe lesions or auras in temporal lobe epilepsy. The mnemonic stands for mostly less exotic features: **h**emianopia (or upper quadrantanopia); **a**utomatisms (below); **p**sychosis (delusions ± hallucinations of smell, taste, sound, eg repeating echoes, ie palinacousis[216]); **p**recognition/persience (a sense of knowing what is about to happen); '**y**ells and falls to the floor' type of seizure[217] or **c**omplex partial seizures; **l**anguage disorders (eg dysphasia); **a**mnesia; **p**anic (or rage, or paroxysmal hypersexuality); **p**ains—eg abdominal pain (± ictal vomiting; or episodic fevers[218] or D&V[219]); **y**ou find yourself not believing your patient's bizarre story—examples are "canned music at Tesco's always makes me cry and then pass out, unless I wear an earplug in one ear"[220] or "I get orgasms when I brush my teeth" (right temporal lobe hyper- and hypo-perfusion, respectively).[221] Finally there are odd experiences such as ***déjà vu*** (everything is familiar); ***jamais vu*** (everything is alien).[222]

Automatisms are complex motor phenomena—eg oral (lip smacking; chewing; spitting; singing; kissing),[223] or genital (repeated fondling, grabbing, or scratching)[224] —or more complex and sometimes violent acts (homicide; arson).[225] Patients do not remember their automatisms after doing them.

Frontal lobe

Hemiparesis focal **motor seizures**, eg aversive seizures involving head and eyes;[226] **personality change** (indecent; indolent; indiscreet; facetious and a tendency to pun); **grasp reflex** (fingers drawn across palm are grasped) significant only if unilateral; **Broca's dysphasia**, p46, or more subtle difficulty with initiating and planning speech with intact repetition and no anomia—but loss of coherence; also general lack of drive or initiative; loss of smell unilaterally. **Concrete thinking perseveration** ± ↓verbal fluency—eg unable to switch from one line of thinking to another or to list words beginning with '***P***' (normal is ~15 in 1 min).[227] **Orbitofrontal syndrome:** Lack of empathy; disinhibition; ↓social skills; over-eating; rash actions (mania); over-familiar; unconscious imitation of postures (eg when you put your feet on the desk, or sit on the floor); '**utilization behaviour**' (whatever is provided is used, eg hand the patient spectacles, and he puts them on, hand him another pair, and this goes on his nose too, ditto for a 3rd pair).

Parietal lobe

Hemisensory loss ↓**2-point discrimination**; **astereognosis** (↓ability to recognize object in hand by touch alone); **sensory inattention**; **dysphasia** (p46); **Gerstmann's syndrome** (left-right disorientation etc, p692).

Occipital lobe

Contralateral **visual field defects** (homonymous hemianopia); hallucinations, eg **palinopsia** (persisting or recurring images, once the stimulus has left the field of view; Greek: *palin*=again). **Polyopia** is seeing multiple images.

Cerebellum

('**DASHING**') **dysdiadochokinesis**; **ataxia** (limb/truncal); **slurred speech**; **hypotonia**; **intention tremor**; **nystagmus**; **gait abnormality**. Dysdiadochokinesis is impaired *rapidly alternating* movements, eg pronation-supination. NB: If truncal ataxia is worse on eye closure, blame the dorsal columns, not cerebellum.

Cerebellopontine angle

(eg acoustic neuroma ie vestibular schwannoma) Ipsilateral **deafness**; **nystagmus**; ↓**corneal reflex**, **facial weakness (rare)**; ipsilateral **cerebellar signs** (above), **papilloedema**, **VI nerve palsy** (lateral rectus, p44).

Corpus callosum

(a rare site for lesions) Usually severe rapid **intellectual deterioration** with focal signs of adjacent lobes; signs of **loss of communication between lobes** (eg left hand unable to carry out verbal commands).

Midbrain

(eg pineal tumours or midbrain infarction) **Failure of up or down gaze**; **light/near dissociated pupil responses** (p68), with convergence globeretracting **nystagmus**[228] from co-contraction of opposing horizontal muscles, on attempted up-gaze.[229] Elicited by looking at a down-moving target.[230] video link

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Bell's palsy (idiopathic facial nerve palsy)

Bell's palsy is partly a diagnosis of exclusion, but features distinguish it from facial palsy from other causes (BOX) are:[234] abrupt onset (typically overnight or after a nap); complete unilateral facial weakness at 24 to 72h; ipsilateral numbness or pain around the ear; ↓taste (ageusia); hypersensitivity to sounds (ie hyperacusis from stapedius palsy).

Incidence

15-40/100,000/yr[235] (~1 patient/2yrs/ GP);[236] risk ↑ in pregnancy (×3) & diabetes (×5). ♀:♂≈1:1

Other symptoms of VII palsy (from any cause)

- Unilateral sagging of the mouth (it is drawn towards the normal side on smiling, producing a grimace).
- Food trapped between gum & cheek; saliva leaks out.
- Speech difficulty because of adynamic lips.[237]
- Failure of eye closure may cause a watery or dry eye, ectropion (sagging and turning-out of the lower lid), conjunctivitis, or injury from foreign bodies.

Ask the patient to

wrinkle up the forehead and close the eyes forcefully; test buccinator by whistling/blowing out the cheeks (*buccina* is Latin for trumpet). Look for other cranial neuropathies (seen in 8%, eg V, XII).[238]

Prognosis

If **incomplete paralysis** and no axonal degeneration complete recovery in a few weeks is typical. If **complete paralysis** nearly all recover too (almost fully) but ~15% have axonal degeneration and recovery starts eg after 3 months, and may be complicated by aberrant reconnections producing ***synkinesis***, eg eye blinking causes synchronous upturning of the mouth. Misconnection of parasympathetic fibres (red in **fig 1**) can produce ***crocodile tears*** (gusto-lacrimal reflex) when eating stimulates unilateral lacrimation, not salivation (intra-lacrimal gland botulinum toxin may help).[239]

Causes of facial palsy

Bell's palsy (75% of cases)

Ramsay Hunt syn: look for ear/ear-drum vesicles (herpes zoster oticus)

Lyme disease

Meningitis (eg fungal)

TB; viruses (HIV; polio)

Mycoplasma (rare)

Brainstem lesions

Stroke; tumour; MS

Cerebello-pontine angle

Acoustic neuroma (p454)

Meningioma

Systemic disease

Diabetes mellitus

Sarcoidosis[231]

Guillain-Barré syn (often gives bilateral VII palsy)

ENT and other causes

Orofacial granulomatosis

Parotid tumours

Cholesteatoma

Otitis media

Trauma to skull base

Diving (barotrauma+temporal bone pneumocele)[232]

Intracranial hypotension[233]

Tests

Electroneurography

at 2 wks predicts delayed recovery by showing axonal degeneration but doesn't influence treatment.

Serology

may show a 4-fold ↑ in antibody to varicella zoster virus.[240] **MRI + LP** to explore other diagnoses 'is only needed in atypical presentations' experts say, but this misses some Lyme disease cases.[241]

Management

If seen within 6d of onset, prednisolone (~50mg/24h PO for 5d ± 10mg/day for 5 more days)[242] may prevent weakness becoming paralysis by ↓nerve oedema.[1] Evidence for prednisolone is not universally acknowledged. NB: Many 'Bell's cases' are now thought to be due to herpes viruses, and some studies (with flaws) support antivirals (aciclovir[243] or valaciclovir[244]) + prednisolone. Noone has shown actively replicating virus, which may be why results are equivocal.[245]

- Protect the eye with dark glasses and by instilling artificial tears (eg hypromellose) if there is any evidence of drying.
- Encourage regular eyelid closure by pulling down the lid by hand.
- Use tape to close the eyes at night.
- If ectropion is severe, lateral tarsorrhaphy (partial lid-to-lid suturing) can help.

If no recovery in 1yr, plastic surgery to help lid closure and to straighten the drooping face can be tried. Botulinum toxin can augment facial symmetry,[246] and hence self-esteem (beauty ***is*** symmetry according to Greek ideals—and *Vogue*).[247]

In pregnancy, prognosis is worse if the palsy is complete (50% do badly *vs* 20% if non-pregnant). No advice on use of steroids is universally agreed.[248]

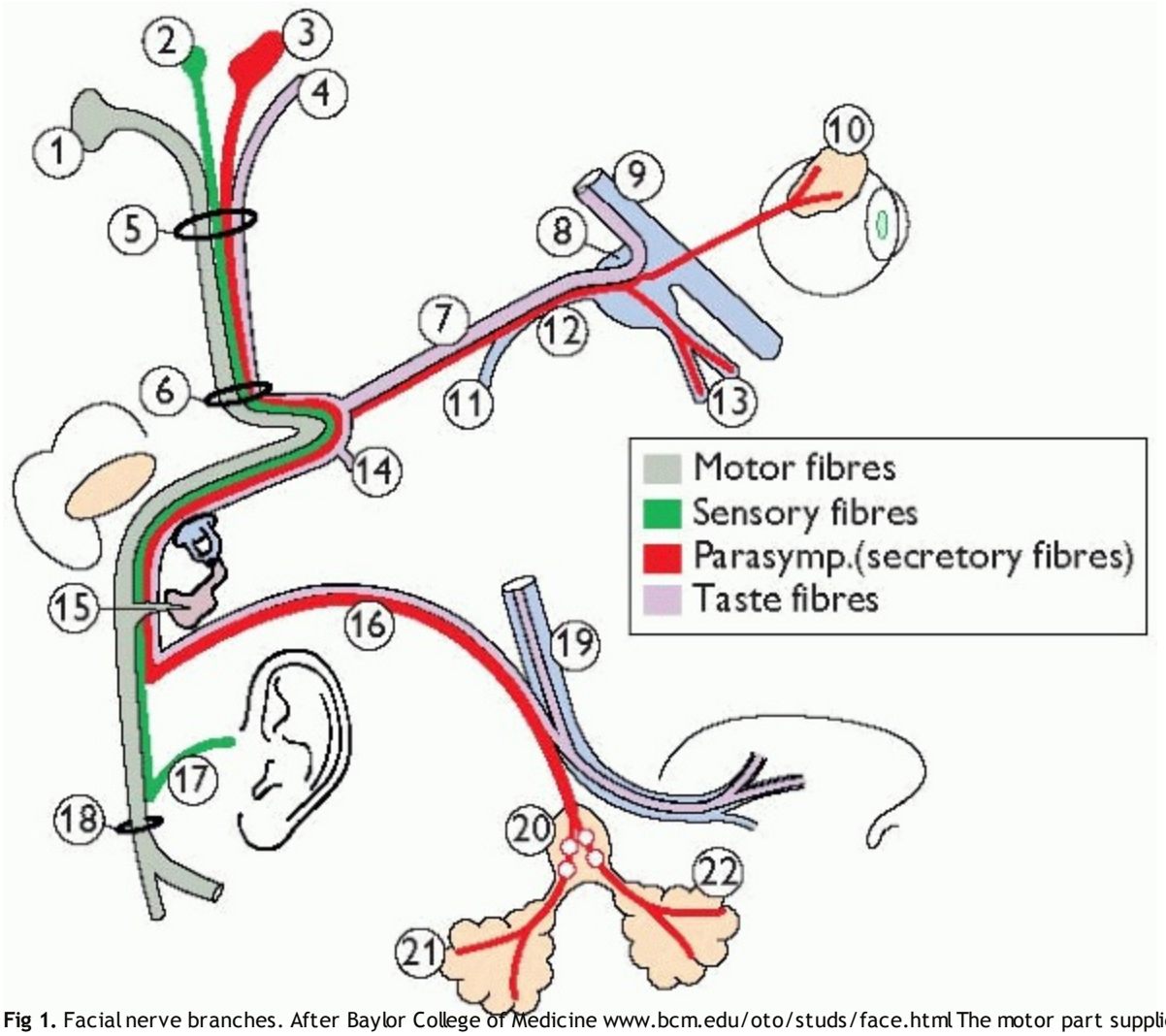


Fig 1. Facial nerve branches. After Baylor College of Medicine www.bcm.edu/oto/studs/face.html The motor part supplies moves the muscles of the face, scalp, and ears—also buccinator (puffs out the cheeks), and platysma, the stapedius, and the posterior belly of the digastricus. It also contains the sympathetic motor fibres (vasodilator) of the submaxillary and sublingual glands (via the chorda tympani nerve). The sensory part contains the fibres of taste for the anterior 2/3 of the tongue and a few somatic sensory fibres from the middle ear region.

1. Facial nerve (VII) nucleus, deep in the reticular formation of lower pons
2. Spinal nucleus of V
3. Superior salivary nucleus
4. Solitary tract
5. Porus acusticus internus
6. Meatal foramen
7. Large petrosal nerve
8. Sphenopalatine ganglion
9. Superior maxillary nerve
10. Lacrimal gland
11. Large deep petrosal nerve
12. Vidian nerve
13. Nose & palate gland nerves
14. Small petrosal nerve at geniculate ganglion 249
15. Stapedial nerve
16. Chorda tympani
17. Auricular branch
18. Stylomastoid foramen
19. Lingual nerve—visceral motor^{vii} & taste^{vii} & general sensory to tongue (V^3) 250
20. Submandibular ganglion

21. Submandibular gland

22. Sublingual gland

[1] Many neurologists give steroids 'to reduce oedema in the nerve', particularly if seen within 6d of onset. One helpful study—Shafshak T 1994 *J Laryng & Otol* **108** 940 showed that the extra benefit of steroids may be confined to those treated within 24h of onset. Spontaneous recovery is good in any case (85%). NNT=3. Older randomized studies have been inconclusive, but did not look specifically at early treatment. Older meta-analyses favour steroids (E-BM 1997 **2** 79) but not newer ones (Cochrane 2004).

Mononeuropathies

These are lesions of individual, including cranial, nerves. Trauma and entrapment are the main causes. *Others*: leprosy; DM. If ≥2 peripheral nerves are affected, the term *mononeuritis multiplex* is used (causes: 'WARDS PLC': **W**egener's (p706) , **A**IDS/ **a**myloid, **r**heumatoid, **d**iabetes mellitus, **s**arcoidosis, **P**AN, leprosy, **c**arcinomatosis).

Median nerve C6-T1

At the wrist:

(eg lacerations; carpal tunnel syndrome—see BOX) Weakness of abductor pollicis brevis and sensory loss over the radial 3½ fingers and palm. Lesions confined to the anterior interosseous nerve (neuralgic amyotrophy;[1] trauma): weakness of flexion of the distal phalanx of the thumb and index finger.

[1] Brachial plexus neuropathy (eg after an infection or an immunization into deltoid) causes pain then weakness (may involve the diaphragm). It resolves over months.

Proximal lesions

(eg at the elbow) may show combined defects.

Ulnar nerve C7-T1

Vulnerable to elbow trauma;

Signs:

Weakness/wasting of medial (ulnar side) wrist flexors; weakness/wasting of the interossei (cannot cross the fingers in the good luck sign) and medial 2 lumbricals (claw hand); hypothenar eminence wasting (∴ weak little finger abduction) and sensory loss over medial 1½ fingers and ulnar side of the hand. Flexion of 4th & 5th DIP joints is weak. Treatment: see BOX. With lesions at the wrist (digitorum profundus intact), claw hand is more marked.

Radial nerve C5-T1

This nerve opens the fist. Damaged by compression against the humerus. Test for wrist and finger drop with elbow flexed and arm pronated. Sensory loss: variable; test dorsal aspect of root of thumb.

Sciatic nerve L4-S2

Damaged by pelvic tumours or fractures to pelvis or femur. Lesions affect the hamstrings and all muscles below the knee (foot drop), with loss of sensation below the knee laterally.

Common peroneal nerve L4-S2

Often damaged as it winds round the fibular head (trauma; sitting cross-legged). ***Signs***: foot drop + weak ankle dorsiflexion/eversion, and sensory loss over dorsum of foot.

Tibial nerve S1-3

Lesions lead to an inability to stand on tiptoe (plantarflexion), invert the foot, or flex the toes. Sensory loss over the sole.

Autonomic neuropathy (sympathetic^{S} & parasympathetic^{P})

This may be isolated or part of a generalized sensory motor peripheral neuropathy.

Causes

DM; amyloid; Guillian-Barré; HIV; leprosy; SLE;$_{251}$ paraneoplastic; toxic; genetic.

Signs

Postural hypotension^{S} (faints on standing, eating, or hot bath); erectile dysfunction^{P}/ ejaculatory failure^{S} (remember '**p**oint & **s**hoot'); sweating↓^{S};

constipation/ nocturnal diarrhoea; urine retention[P]; Horner's[S] (p694); Holmes-Adie pupil[P] (p70).[252]

Autonomic function tests

Postural drop of ≳20/10mmHg is abnormal (p68).

- A variation of <10bpm with respiration is abnormal (do resting ECG).
- Bladder pressure studies (*cystometry*). •*Pupils*: Instil 0.1% epinephrine (dilates if post-ganglionic sympathetic denervation, not if normal); 2.5% cocaine (dilates if normal; not if sympathetic denervation); 2.5% methacholine (constricts if parasympathetic lesion). These are rarely used.
- Antibodies: anti-Hu & anti-nicotinic acetylcholine receptor antibodies may be +ve.

Primary autonomic failure

Occurs alone, as part of MSA[2] or with parkinsonism. Typical patient: middle-aged/elderly man. Onset: insidious (symptoms as above).

[2] **Multisystem atrophy** is parkinsonism (p486) + autonomic dysfunction + cerebellar ataxia (reflecting olivopontocerebellar atrophy) ± dystonia, rhythmic myoclonus, emotional incontinence, sleep disturbance, sleep-related movement problems, and vasomotor signs.[] [] Extra-pyramidal symptoms may precede autonomic failure. MSA may be unmasked by a sudden worsening of mild postural hypotension when presumed classical Parkinson's is treated with L-dopa. Survival: rarely >10yrs after diagnosis of MSA.

Treating postural hypotension

Compression stockings; "stand slowly". Head-up tilt of the bed at night ↑renin release, so ↓fluid loss and ↑standing BP. If post-prandial dizziness, advise eating little and often, and to ↓carbohydrate & alcohol intake. Fluidretaining drugs (fludrocortisone 0.1mg/24h PO, ↑ as needed) for severe disease.

Carpal tunnel syndrome: the commonest mononeuropathy

9 tendons and the median nerve compete for space within the wrist. Compression is common, especially in women who have narrower wrists but similar-sized tendons to men; for similar reasons, the tibial nerve may be compressed: the tarsal tunnel syndrome, causing unilateral burning sole pain, eg on walking or standing.

The patient:

Aching pain in the hand and arm (especially at night), and paraesthesiae in thumb, index, and middle fingers, all relieved by dangling the hand over the edge of the bed and shaking it. There may be sensory loss and weakness of abductor pollicis brevis ± wasting of the thenar eminence. Light touch, 2-point discrimination, and sweating may be impaired.

Associations:

Pregnancy, rheumatoid, DM, hypothyroidism, acromegaly,[253] dialysis, trauma.

Tests:

Neurophysiology helps by confirming the lesion's site and severity (and likelihood of improvement after surgery). Maximal wrist flexion for 1min (Phalen's test) may elicit symptoms (unreliable!). Tapping over the nerve at the wrist induces tingling (Tinel's test; also rather non-specific).

Treatment:

Splinting, local steroid injection (OHCS p710) ± decompression surgery; many alternative therapies are tried: meta-analyses are doubtful.[1] [254]

Managing ulnar mononeuropathies from entrapments

The ulnar nerve 'asks for trouble' in at least 5 places around the elbow, beginning proximally at the arcade of Struthers (a musculofascial band ~8cm proximal to the medial epicondyle) and ending distally where it exits the flexor carpi ulnaris muscle in the forearm.[255] Most commonly compression occurs at the epicondylar groove or at the point where the nerve passes between the 2 heads of the flexor carpi ulnaris muscle (true ***cubital tunnel syndrome***). Trauma can easily damage the nerve against its bony confines (the medial condyle of the humerus—the 'funny bone'). Normally, the ulnar nerve suffers stretch and compression forces at the elbow that are moderated by its ability to glide in its groove. When normal excursion is restricted, irritation ensues. This may cause a vicious cycle of perineural scarring, consequent loss of excursion, and progressive symptoms—without there being any antecedent trauma.

Rest and avoiding pressure on the nerve helps but if symptoms continue, night-time soft elbow splinting (to prevent flexion to >60°[256]) is warranted, eg for 6 months.[257] For chronic neuropathy associated with weakness, or if splinting fails, a variety of surgical procedures have been tried. For moderately severe neuropathies, decompressions *in situ* may help, but often fail. Medial epicondylectomies are effective in ≲50% (but many will recur). Subcutaneous nerve re-routing (transposition) may be tried. Intramuscular and submuscular transpositions are more complicated, but the latter may be preferable.[258]

Compressive ulnar neuropathies at the wrist (***Guyon's canal***—between the pisiform and hamate bones) are less common, but they can also result in disability. ***Thoracic outlet compression*** is another cause of a weak numb hand. Electromyography (EMG) helps define the anatomic site of lesions.

Polyneuropathies

Polyneuropathies are generalized disorders of peripheral nerves or cranial nerves whose distribution is usually bilaterally symmetrical and widespread often with distal muscle weakness and sensory loss ('glove & stocking anaesthesia'). They may be classified by time course (acute or chronic); by the functions disturbed (motor, sensory, autonomic, mixed); or by the underlying pathology (demyelination, axonal degeneration, or both). Guillain-Barré syndrome (p694), eg, is an acute, predominantly motor, demyelinating neuropathy, whereas chronic alcohol abuse leads to a chronic, initially sensory then mixed, axonal neuropathy.

Mostly motor	Mostly sensory
Guillain-Barré syndrome, p694	Diabetes mellitus
Lead poisoning	Uraemia
Charcot-Marie-Tooth syndrome	Leprosy

Symptoms

Sensory neuropathy:

Numbness; 'feels funny'; tingling or burning sensations eg affecting the extremities first ('glove & stocking' distribution). There may be difficulty handling small objects such as needles.

Motor neuropathy:

Often progressive (may be rapid) weakness or clumsiness of the hands; difficulty walking (falls; stumbling); respiratory difficulty. Signs are of LMN lesion: wasting and weakness most marked in the distal muscles of hands and feet (foot or wrist drop). Reflexes are reduced or absent. Involvement of the respiratory muscles may be shown by a falling vital capacity.

Cranial nerves:

Swallowing/speaking difficulty; diplopia.

Autonomic neuropathy:

See p494.

Diagnosis

The history is vital; be clear about the illness's time course; the precise nature of the symptoms; any preceding or associated events (eg *Campylobacter* D&V before Guillain-Barré syndrome; weight↓ in cancer; arthralgia from a connective tissue disease); travel; sexual infections; alcohol and drug use; family history. Pain is typical eg in neuropathy from DM or alcohol.

Examination:

Do a careful neurological examination looking for lower motor signs (weakness, wasting, reduced/absent reflexes) and sensory loss (map out for each modality). Test the autonomic system (p494) and cranial nerves (p44). Look for signs of trauma (eg finger burns) indicating ↓sensation. Scuff marks on shoes suggest foot drop. If there is nerve thickening think of leprosy or Charcot-Marie-Tooth. Examine other systems for clues to the cause, eg alcoholic liver disease.

Typical causes

Metabolic

Diabetes mellitus, Renal failure, Hypothyroidism, Hypoglycaemia, Mitochondrial disorders

Vasculitides

(p542)

Polyarteritis nodosa, Rheumatoid arthritis, Wegener's granulomatosis

Malignancy

Paraneoplastic syndromes

Polycythaemia[rubra.vera] p350

Inflammatory

Guillain-Barré synd. CIDP,[1] Sarcoidosis

Infections

HIV
Leprosy Syphilis
Lyme disease (p418),

Vitamin pathologies

Lack of B_1, B_6, B_{12} (eg alcoholic), folate *Excess* vit B_6 (>100mg/d)

Inherited syndromes

Refsum's (p702)
Charcot-Marie-Tooth, p688
Porphyria (p684)
Leukodystrophy*et al*

Toxins

Lead; arsenic

Drugs

Vincristine
Alcohol
Cisplatin
Isoniazid
Nitrofurantoin
Phenytoin
Metronidazole

Others

Paraproteinaemias
Amyloidosis (p354)

Tests

FBC, ESR, glucose, U&E, LFT, TSH, B_{12}, electrophoresis, ANCA (p539), ANA, CXR, urinalysis, and consider an LP ± specific genetic tests for inherited neuropathies (eg Charcot-Marie-Tooth, p688),[259] lead levels, and antiganglioside antibodies. Nerve conduction studies help distinguish demyelinating from axonal neuropathies.

Treatment

Treat causes. Involve **physio** & **OT** (p437). **Foot care** and **shoe choice** is important in sensory neuropathies to minimize trauma. In Guillain-Barré (p694) & CIDP,[1] IV **immunoglobulin** helps.[260] **Steroids**/immunosuppressants may help vasculitic causes. **Amitriptyline** ≥10mg PO at night may help neuropathic pain (NNT≈2; may not work in HIV neuropathy).MET[261] If this fails, try **gabapentin**[2] (NNT≈3) or **pregabalin**.[262]

Bulbar palsy

This is palsy of the tongue, muscles of chewing/swallowing, and facial muscles due to loss of function of motor nuclei in the medulla. Signs are of a LMN *lesion*; eg flaccid, fasciculating tongue (p44, like a sack of worms); jaw jerk is normal or absent, speech is quiet, hoarse, or nasal.

Causes:

MND (below); Guillain-Barré; polio; syringobulbia (p508); brainstem tumours; also as part of *central pontine myelinolysis* (CPM, in malnourished alcoholics or in rapid correction of hyponatraemia). CPM causes progressive and fatal quadriparesis, mutism, dysarthria, and bulbar palsy[263] (but recovery can occur—demonstrable by serial MRI scans).[264]

Pseudobulbar palsy

UMN *lesion* of muscles of eating, swallowing, and talking due to bilateral lesions above the midpons, eg corticobulbar tracts (MS, MND, stroke). It is commoner than bulbar palsy.

Signs:

Spastic tongue; ↑jaw jerk; Donald Duck speech; weeping unprovoked by sorrow or mood-incongruent giggling (emotional incontinence *without* mood change, ie 'hollow laugher', is also seen in dementia & head injury).[265]

Motor neurone disease (MND)

MND is caused by degeneration of neurones in motor cortex, cranial nerve nuclei, and anterior horn cells. Upper and lower motor neurones are affected but there is *no* sensory loss or sphincter disturbance, so distinguishing MND from MS and polyneuropathies. MND never affects external eye movements (III, IV, VI) distinguishing it from myasthenia (p504). Fronto-temporal dementia is seen in 10-35%.[266]

Cause:

Unknown, but as MND, like polio, affects anterior horn cells, viruses are suggested. There is no diagnostic test. 3 clinical patterns:

- ***Bulbar palsy*** See above. This accounts for about 25% of patients.
- ***Amyotrophic lateral sclerosis (ALS)*** (50%) Combined LMN wasting and UMN signs (p439) contribute to weakness. Risk↑ ~2-fold[267] in Gulf war veterans. If familial, suspect copper/zinc superoxide dismutase mutations (SOD1).[268]
- ***Progressive muscular atrophy*** (25%) Anterior horn cell lesion, affecting distal muscles before proximal. Better prognosis than ALS.

▸ Think of MND in those >40yrd old with stumbling (spastic gait, foot-drop), weak grip (door-handles are difficult), or aspiration pneumonia. Look for UMN signs: weakness; spasticity; brisk reflexes; plantars↑; and LMN signs: weakness; wasting; fasciculation of tongue, abdomen, back, thigh. Is speech or swallowing affected? Diagnosis is strongly supported by combinations of progressive UMN and LMN signs with involvement of ≥2 limbs, or a limb and bulbar muscles. Fasciculations are not enough to diagnose an LMN lesion: look for weakness too. MRI of brain and cord helps exclude structural causes; LP helps to exclude inflammatory ones, and neurophysiology can detect subclinical denervation and help exclude motor neuropathies. ***Prevalence:*** 7/10,000. ♀:♂≈3:2. ≤10% are familial.

Prognosis

MND is incurable (often fatal within 5yrs; median UK age at death is 60yrs). Prognosis is worse with bulbar-onset disease (≲1.5yrs from diagnosis).

Treatment

Due to MND's rapid course, its rarity, and its frightening nature, a multi-disciplinary approach is best:[269] neurologist; palliative nurse;[270] hospice; physio; OT; speech therapist; dietician; social services—all orchestrated by the GP. Death by choking is rare, so warmly reassure that a dignified end is the rule. mndassociation.orgtel.uk 08457 626262

- ***Antiglutamate drugs:*** Riluzole (see BOX) prolongs life by ~3 months; it is costly. It is licensed for use in MND. **Cautions:** LFT↑. Do regular LFT every month for 3 months, then every 3 months for a 9 months and annually thereafter. SE: vomiting, weakness, pulse↑, somnolence, headache, dizziness, vertigo, pain, LFT↑.
- ***Drooling:*** Propantheline 15-30mg/8h PO; amitriptyline 25-50mg/8h PO.
- ***Dysphagia:*** Blend food; would he or she like a nasogastric tube, or percutaneous catheter gastrostomy?—or would this prolong death? ***Spasticity:*** See MS (p488).
- ***Joint pains and distress:*** Analgesic ladder (p521) NSAIDS etc; then opioids.
- ***Respiratory failure (± aspiration pneumonia and sleep apnoea):*** Non-invasive ventilation at home in selected patients may give valuable palliation.

Following in the footprints of free radicals

Postmortem studies show that changes to proteins and DNA which are signs or 'footprints' of free radical damage are more pronounced in MND brains than in controls.[271] Also, cultured fibroblasts from MND brains show high sensitivity to oxidative insults. But these findings don't explain two key MND phenomena:

Why is there predilection for motor neurones? One answer may be the sheer length and complex cytoarchitecture of motor cells, with their 1 metre axons and high levels of neurofilament proteins, and low levels of Ca^{2+}-buffering proteins (thought to be protective). We note that motor cells with the shortest axons (to the eye's external muscles) are unaffected in MND; this is not true of the tongue which only requires slightly longer axons. Another answer is that it is ***not*** only motor neurones which are affected: changes are seen in other areas, and we note that specific aphasia-dementia syndromes occur in MND.[272]

Why do some* MND *brains have excess levels of glutamate? (Glutamate is the chief excitatory neurotransmitter.) This is thought to be from ↓ activity of the excitatory amino acid transporter (EAAT2), which mops up glutamate—hence the notion that MND is an 'excitotoxic' phenomenon. Motor cells have high levels of Cu/Zn superoxide dismutase (thought to protect normal motor cells from glutamate toxicity/oxidative stress). But a high level may itself be damaging, given certain genetic or acquired vulnerabilities.[273] Transgenic mice exhibiting high levels of superoxide dismutase do indeed develop an MND phenotype.

These ideas are speculative,[274] but important, perhaps, in understanding and criticizing future therapeutic options. ***Riluzole*** is an Na-channel blocker inhibiting glutamate's release. Neurotrophic factors can protect motor neurones in animal studies, but clinical trials have proved disappointing. CI : hepatic and renal impairment. Effects of free radical manipulation can be unpredictable.[275] The antioxidant **vitamin E** protects transgenic mice from developing an MND-like picture, and in at least one human trial high intake of polyunsaturated fatty acids and vitamin E was associated with a 50% decreased risk of developing ALS (these nutrients appear to act synergistically).[276]

Apoptosis is a hallmark of MND,[277] and genetically induced overexpression of proteins inhibiting cell death via apoptosis (Bcl-2) in transgenic mice can slow motor neurone degeneration.[278]

Ethical problems: beyond autonomy

Patients with MND may be ventilated, for example—and then decide that they want this intervention withdrawn.[279] In some patients, this is likely to be fatal— making these decisions difficult for everyone. Ethicists tend to speak in blackand- white prose—'do whatever promotes autonomy' and this is the *raison d'être* of assisted suicide organizations such as Dignitas[280] (increasingly popular, worldwide, even where illegal). But sometimes nature contrives something more ambiguous and poetic, in which rationality and rage,[281] and uncertainty and the forked emotions of hope and despair produce a heady internal world which the ethicist can never quite catch or tame. If this internal world is one of perpetual change and oscillating will, ideas of autonomy become incoherent. Rather than aiming to apply Kantian universal rules (p17), our role may be more to offer a well-placed hug to signal metaphysical complicity, and to stand beside our patients, come what may.

Ethics in (or out) of action

Cervical spondylosis

Cervical spondylosis with compression of the cord (myelopathy) and nerve roots is the leading cause of progressive spastic quadriparesis with sensory loss below the neck:[282] but most people with cervical spondylosis have no impairment—just degeneration of the annulus fibrosus of cervical intervertebral discs ± bony spurs which narrow the spinal canal and intervertebral foramina. As the neck flexes and extends, the cord is damaged as it is dragged over these protruding osteophytes anteriorly and indented by a thickened ligamentum flavum posteriorly.

Signs:

Limited, painful neck movement ± crepitus— be careful! Neck flexion may produce tingling down the spine—a positive Lhermitte's symptom. This does not help decide if cord or roots or both are involved.

Arm:

LMN signs at the level of the compressed cord or roots and UMN signs below. Visible atrophy of hand and forearm muscles. Sensory loss (esp. pain & T°).

Leg:

Spasticity; weakness; brisk reflexes; plantars↑↑ . Position & vibration sense↓. Examine skin sensation from below upwards to show any sensory level (eg several segments below level of cord compression).

Root compression

(radiculopathy) Pain in arms & fingers and ↓reflexes, dermatomal sensory disturbance (numbness, tingling), LMN weakness and eventual wasting of muscles innervated by the affected root.

Complaints may be of:

- Neck stiffness (unhelpful as common in anyone over 50 years old)
- Crepitus on moving neck
- Stabbing or dull arm pain (brachialgia)
- Forearm/wrist pain

Signs of cord compression:

- Spastic leg weakness
- Weak, clumsy hands
- Numbness in hands
- Weakness (often more marked in 1 leg)
- 'Heavy' weak legs
- Foot-drop/poor walking
- Incontinence/hesitancy & urgency are often late [283]

Typical motor and sensory deficits from individual root involvement	
C5/C6	Weak biceps and deltoid; ↓supinator and biceps jerks, Numb thumb
C7	Weak triceps and finger extension; ↓triceps jerks; numb middle finger

C8/T1	Weak finger flexors and small muscles of the hand; numb 5th & ring finger
C4/C5	Elbow sensation, supraspinatus.

Tests

MRI is the best localizing image. AP compression ratio is ≳30% typically induces histopathological changes in the cord (cadaver studies). Time to walk 30m helps monitor progress (valid & cheap).[284]

Differential diagnosis

MS, nerve root neurofibroma, subacute combined degeneration of the cord ($B_{12}\downarrow$).

Treatment

A firm neck collar restricts anterior-posterior movement of the neck so may relieve pain, but patients dislike them. Don't dismiss those with chronic root pain in the arm as suffering simply from 'wear and tear' spondylosis. Be optimistic: they may improve over months; if not, they *may* benefit greatly from surgical root decompression (**laminectomy, fig 2** or **laminoplasty**, **fig 3**) if there is significant MRI abnormality.[285] Consider if objective evidence of a root lesion or myelopathy, and especially if the history is short, and the neurological deficit is progressing. As a rule of thumb, opt for conservative treatment if the spinal transverse area is >70mm2, the patient is elderly, and motor conduction time is normal.RCT[286] If surgery *is* done, progression is usually halted and leg weakness may improve. Operative risk is less than with **anterior spinal fusion** (requires bone grafts with additional complications with no extra benefit).[287] **Transforaminal steroid injection** is gaining popularity on the rationale that nerve root inflammation causes radicular pain. Pain reduction can be demonstrated, but we await randomized trials.

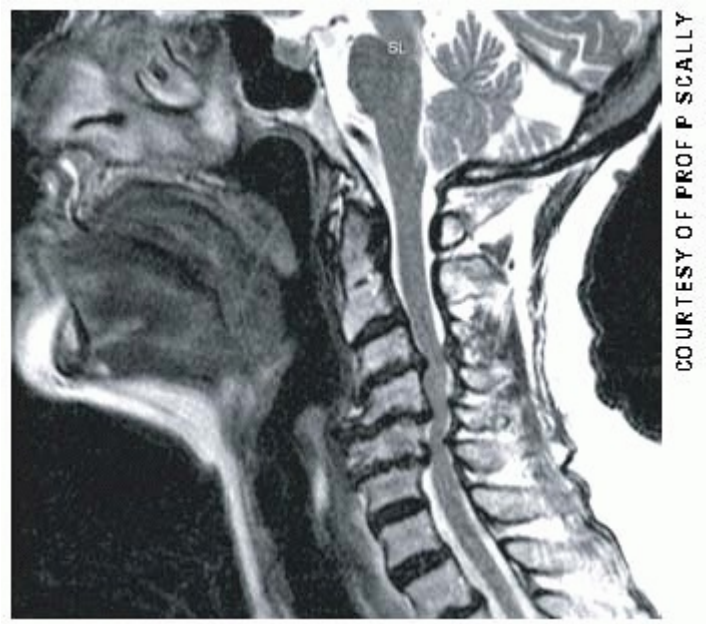


Fig 1. A T2 weighted MR image, (so CSF looks bright). The spinal cord is compressed between the osteophytes anteriorly and the ligamentum flavum posteriorly.

Rare complications

Diaphragm paralysis;[288] spinal artery syndrome mimicking angina (∵ spinal artery compression; pain & T° are lost before vibration sense).[289]

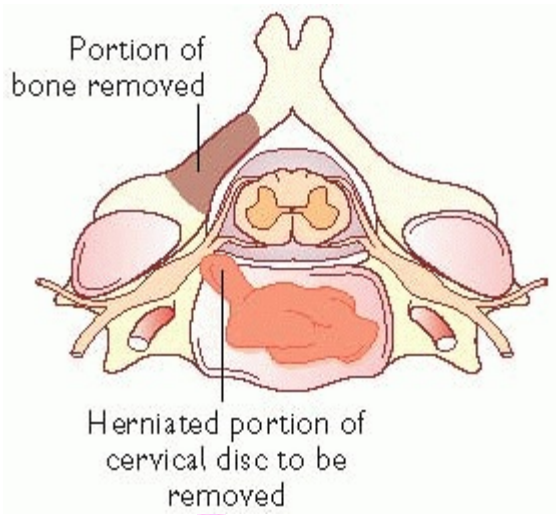


Fig 2. Laminectomy[290]

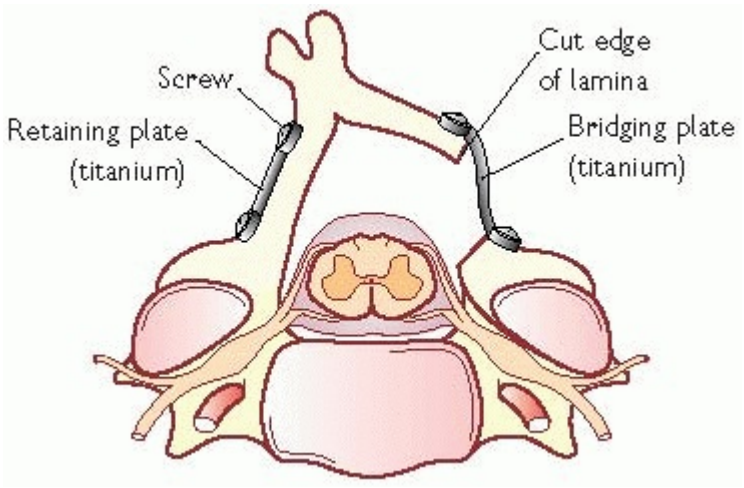


Fig 3. Laminoplasty (screws & plates)[291]

Laminectomy or laminoplasty?

Laminectomy and laminoplasty improve gait, strength, sensation, pain, and degree of myelopathy. To a roughly equal extent, but in one study of 44 consecutive patients, laminoplasty was associated with more pain reduction and fewer late complications (but there was more neck stiffness).[292] At appropriate level, the ligamentum flavum (overlies the dura) is incised and cut away with part of adjacent laminae, as necessary to expose the extradural space.[293]

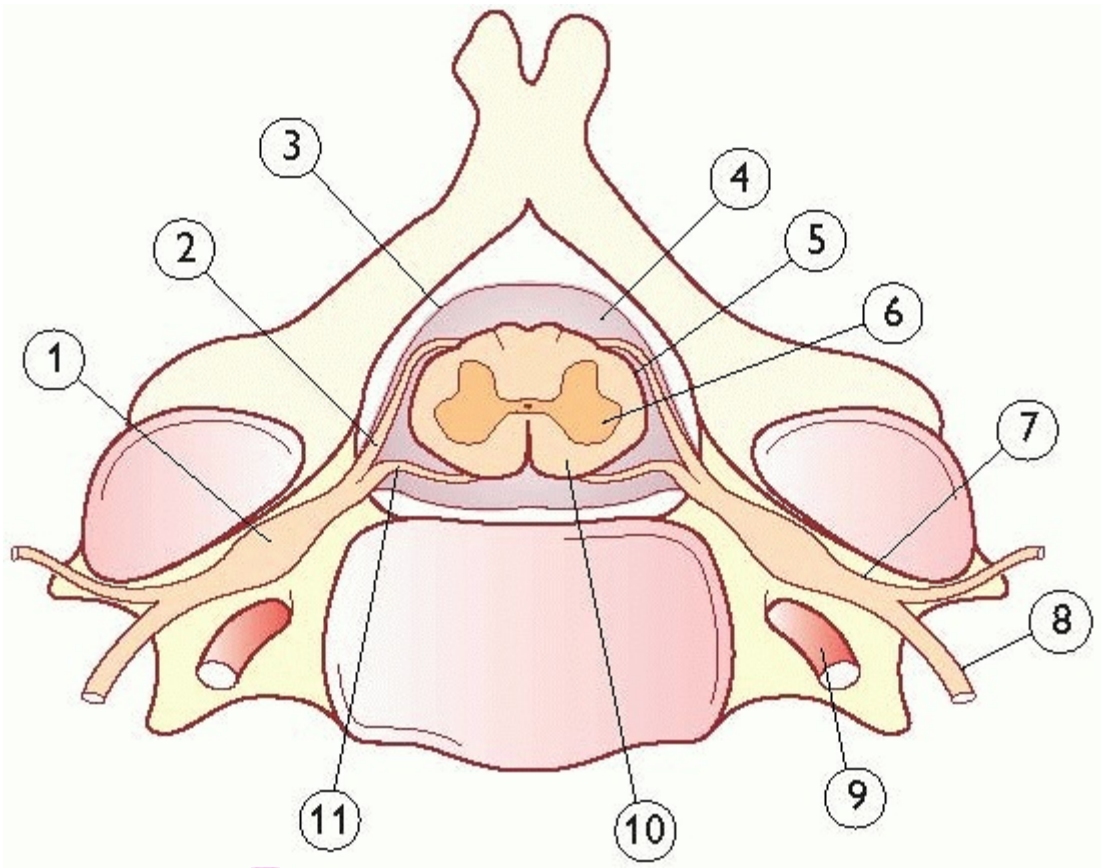


Fig 4. Cervical vertebra.[294] (After Dr Carey Carpenter)

1. Dorsal root ganglion
2. Dorsal root
3. Dura mater
4. Subarachnoid space
5. Pia mater
6. Grey matter
7. Spinal nerve
8. Ventral ramus
9. Vertebral artery in the transverse foramen
10. White matter
11. Ventral spinal nerve

Primary disorders of muscle (myopathies)

Myopathy or neuropathy?

In favour of myopathy: • Gradual onset of symmetric *proximal* weakness—difficulty combing hair & climbing stairs (but note: weakness is *distal* in myotonic dystrophy). • Neck flexion weaker than neck extension • Tendon reflexes preserved. A neuropathy is more likely if there are paraesthesiae, bladder problems or distal weakness (unless it's Guillain-Barré). Rapid onset suggests a neuropathy or a toxic, drug, or metabolic myopathy.

Excess fatigability

(weakness increases with exercise) suggests myasthenia (p504). Spontaneous ***pain*** at rest occurs in inflammatory disease as does local tenderness. Pain on exercise suggests ischaemia or metabolic myopathy (eg McArdle's disease).

Oddly firm

muscles (due to infiltrations with fat or connective tissue) suggest pseudohypertrophic muscular dystrophies. Muscle ***tumours*** are rare; common causes of ***lumps*** are herniation of muscle through fascia, haematoma, and tendon rupture.

Fasciculation

(spontaneous, irregular, brief contractions of part of a muscle) suggests anterior horn cell or root disease. Look for evidence of systemic disease.

Tests:

ESR, CK, AST & LDH may be↑. Do EMG and tests relevant to systemic causes (eg TSH ↑ or↓ p200). Many genetic disorders of muscle are detectable by DNA analysis: reserve muscle biopsy for when genetic tests are non-diagnostic.

6 types:

1. ***Muscular dystrophies*** are a group of genetic diseases with progressive degeneration and weakness of specific muscle groups. The primary abnormality may be in the muscle membrane. Secondary effects are marked variation in size of individual fibres and deposition of fat and connective tissue. The commonest is **Duchenne's muscular dystrophy** (pseudohypertrophic; sex-linked recessive— 30% from spontaneous mutation) and is (almost always) confined to boys. The Duchenne gene is on the short arm of the X chromosome (Xp23), and its product, dystrophin, is absent (or present in very low levels). Serum creatine kinase is raised >40-fold. It presents at ~4yrs old with increasingly clumsy walking, progressing to difficulty in standing and respiratory failure. Some survive beyond 20yrs. There is no specific treatment. Home ventilation is used. Genetic counselling is vital. **Fascioscapulohumeral muscular dystrophy (Landouzy -Dejerine)** is almost as common. *Inheritance:* Autosomal dominant (4q35). *Typical age of onset:* 12-14yrs. *Early symptoms:* Inability to puff out the cheeks, difficulty raising the arms above the head (eg changing light-bulbs). *Signs:* Weakness of face ('ironed out' expression), shoulders, and upper arms (often asymmetric with deltoids spared) ± foot-drop ± winging of the scapulae (due to weakness of thoracoscapular muscles)[295] ± scoliosis ± anterior axillary folds[296] ± horizontal clavicles.[297] ≲20% need a wheelchair by 40yrs old.OTM[1227]
2. ***Myotonic disorders*** cause tonic muscle spasm (myotonia); muscle histology shows long chains of central nuclei within fibres. The chief one is **dystrophia myotonica** (=DM1) a **Cl^- channelopathy**.[298] Typical onset: 25yrs with weakness (hands, legs, sternomastoids) and myotonia. Muscle wasting and weakness in the face gives a long, haggard appearance. Also: cataract; frontal baldness;♂ testis/ovary atrophy; cardiomyopathy; mild endocrine abnormalities (eg DM); and mental impairment. Most patients die in middle age of intercurrent illness. Mexiletine, phenytoin and acetazolamide may help. Genetic counselling is important. **Na^+ channelopathy** causing myotonia: paramyotonia congenita, adynamia episodica hereditaria.
3. ***Acquired myopathies of late onset*** are often part of systemic disease—eg hyperthyroidism); cancer; Cushing's; hypo- and hypercalcaemia.
4. ***Inflammatory myopathies:*** **Inclusion body myositis** is the chief example if aged >50yrs. Aggregates of Alzheimer tau proteins suggest a 'peripheral tauopathy'.[299] Signs: weakness starts with quads, finger flexors or pharyngeal muscles. Ventral extremity muscle groups are more affected than dorsal or girdle groups. Wheelchair dependency: <3%. Histology: ringed vacuoles + intranuclear inclusions. [prescription take]: nothing is consistently effective. For **polymyositis**$^{et\ al}$, see p538.
5. ***Neuromuscular junction disorders:*** **Myasthenia gravis** (p504).
6. ***Toxicity:*** Alcohol; statins; steroids; chloroquine; zidovudine; vincristine; cocaine.

Myasthenia gravis (MG)

MG is an autoimmune disease mediated by antibodies to nicotinic acetylcholine receptors (AChR), interfering with the neuromuscular transmission via depletion of working postsynaptic receptor sites. Cause: B- and T-cells are implicated.[300] [301]

Presentation

Increasing muscular fatigue. If <50yrs old, MG is commoner in women, associated with other autoimmune diseases and thymic hyperplasia. Over 50, it is commoner in men, and associated with thymic atrophy or thymic tumour. Muscle groups affected, in order: extraocular; bulbar (swallowing; chewing); face; neck; limb girdle; trunk. Look for: ptosis; diplopia; myasthenic snarl on smiling; 'peek sign'.[1] On counting to 50, the voice deteriorates. **Reflexes:** normal. Weakness is worsened by: pregnancy, K+↓, infection, overtreatment, change of climate, emotion, exercise, gentamicin, opiates, tetracycline, quinine, procainamide, ß-blockers.

Associations:

Thymic tumour; hyperthyroidism; rheumatoid arthritis; SLE.

Tests

Tensilon® test: If resuscitation facilities and atropine are to hand, prepare 2 syringes, 1 with 10mg edrophonium and 1 with 0.9% saline. Give 1st 20% of each separately IV as test dose. Ask an independent observer to comment on the effect of each; wait 30s before giving rest of each syringe. The test is +ve if edrophonium improves power in ~1min. The test may not be as dramatic as is stated. Others:

Antiacetylcholine receptor antibody: ↑ in 90% (70% in ocular-confined MG); if sero-ve look for musk antibodies (muscle specific tyrosine kinase;♀/♂≈ 15:2).[302]

Neurophysiology: Decremental muscle response to repetitive nerve stimulation ±↑ single-fibre jitter. **CT of thymus** (5mm slices).[303] NB**:** ptosis improves by >2mm after **ice application** to the (shut) affected lid for >2min: a nice, non-invasive test.[304]

Treatment

Symptom control

Anticholinesterase eg **pyridostigmine** 60-120mg PO up to 6×daily; SE: diarrhoea; colic (controllable by propantheline 15mg/8h PO; cholinergic SE: salivation↑; lacrimation; sweats; vomiting; miosis).

Immunosuppression

Prednisolone (single-dose alternate day regimen + osteoporosis prophylaxis); start at 5mg; ↑by 5mg/wk up to 1mg/kg on each treatment day; ↓dose on remission (may take months). SE: weakness (hence low starting dose); may be combined with azathioprine 2.5mg/kg/day (do FBC & LFT weekly for 8wks, then 12-weekly) or weekly methotrexate.MET$_{305}$ IV methylprednisolone has a role.

Thymectomy:

Consider if onset before 50yrs old and disease is not easily controlled by anticholinesterases. Expect remission in 25% and worthwhile benefit in a further 50%. Thymectomy is also necessary for thymomas to prevent local invasion (but MG symptoms are often unaffected).

Plasmapheresis or IV immunoglobulin

(**IVIg**) gives ~2-4wks' benefit (useful in crises$_{306}$ or pre-thymectomy, eg IVIg 0.4g/kg daily for 5 days pre-op).$_{307}$ Ventilatory ***support*** This is unlikely to be needed if vital capacity >20mL/kg.$_{308}$

Prognosis

Relapsing or slow progression. If thymoma, 5yr survival is 68%.$_{309}$

Other causes of muscle fatigability

Polymyositis; SLE; botulism; Takayasu's arteritis (fatigability of the extremities). For other myopathies, see p502.

[1] After brief opposition to gentle sustained lid closure, the lids separate ('peek') to show white sclerae.

Lambert-Eaton myasthenic syndrome (LEMS=ELMS)

This para-neoplastic (small-cell lung cancer) or autoimmune disease[2] is unlike true MG as there is: •Gait difficulty before eye signs •*Autonomic involvement* (dry mouth; constipation; impotence) •*Hyporeflexia* •*Increased* strength post-exercise •Less response to edrophonium •Antibody to the *presynaptic* membrane's voltage-gated Ca^{2+} channels (VGCC). •Electrical post-tetanic *potentiation* + >60% *increment* in post-exercise facilitation of abductor digiti quinti.$_{310}$ •Anti-P/Q VGCC antibodies are +ve in 85%.$_{311}$ **[prescription take]:** (by experts) 3,4-diaminopyridine or IV immunoglobulin.MET$_{312}$

▸Do regular CXR$_s$ as symptoms may predate the cancer by more than 4 years.

[2] 64% of those with non-tumour LEMS have a family member with autoimmune thyroid disease or DM.

Neurofibromatosis[1]

Type 1 neurofibromatosis (NF1, von Recklinghausen's disease)

Prevalence: 1 in 2500, ♀:♂≈1:1; no racial predilection. Inheritance: autosomal dominant (gene chromosome 17). Expression NF1 is variable, even within a family.

Signs

Café-au-lait spots

are flat, coffee-coloured patches of skin seen in the 1st year of life (clearest in UV light), increasing in size and number with age. Adults have ≥6, >15mm across. They do *not* predispose to skin cancer.

Freckling

typically occurs in skin-folds (axillae, groin, neck base, and submammary area♀) and is usually present by age 10.

Dermal neurofibromas

appear at puberty and are small, violaceous nodules, gelatinous in texture. They may become papillomatous. They are not painful but may itch. Numbers increase over time.

Nodular neurofibromas

arise from nerve trunks. Firm and clearly demarcated, they can give rise to paraesthesiae if pressed.

Lisch nodules

are tiny harmless regular brown/translucent mounds (hamartomas) on the iris (use a slit lamp) ≲2mm in diameter. They develop by 6yrs old in 90%. Also look

for short stature and macrocephaly.

Complications

(seen in 30%). Mild learning disability is common.

Local effects of neurofibromas:

Nerve roots—compression; gut—bleeds, obstruction; bone— cystic lesions; scoliosis pseudarthrosis. Hypertension (6%) from renal artery stenosis or phaeochromocytoma. Plexiform neurofibromas (large, subcutaneous swellings). Malignancy (5% patients with NF1): optic glioma, sarcomatous change in a neurofibroma. Epilepsy risk ↑ (slight). There is a rare association with carcinoid syndrome (p270).[314]

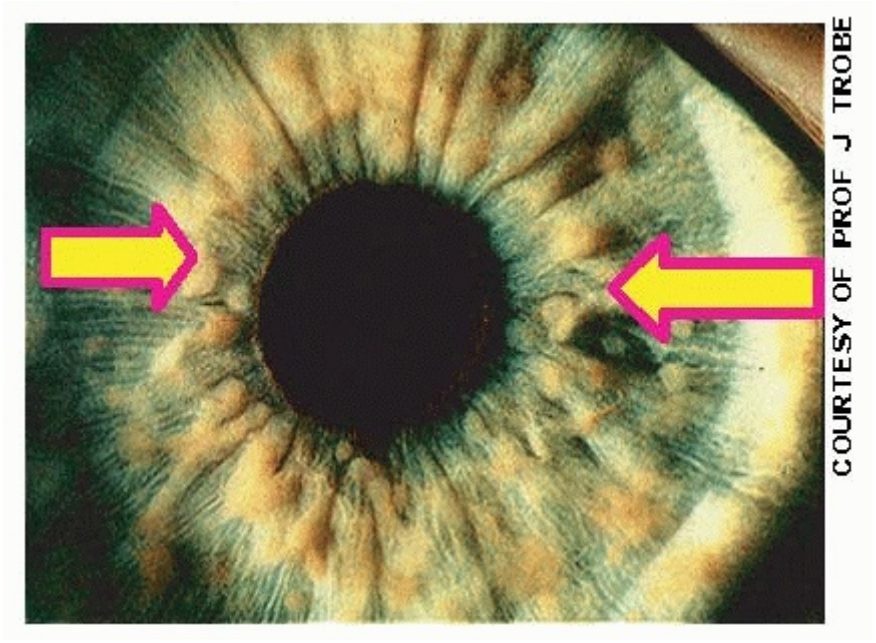


Fig 1. Many Lisch nodules (arrows) on the iris.[313]

Management

Multidisciplinary team with geneticist, neurologist, and surgeon, orchestrated by a GP. Yearly measurement of BP and cutaneous survey is advised. Dermal neurofibromas are unsightly, and catch on clothing; if troublesome, excise, but removing all lesions is unrealistic. Genetic counselling is vital (OHCS p154).

Type 2 neurofibromatosis (NF2)

Autosomal dominant inheritance. Much rarer than NF1 with a prevalence of only 1 in 35,000. The gene responsible is on chromosome 22.

Signs

Café-au-lait spots

are fewer than in NF1.

Bilateral vestibular schwannomas

(acoustic neuromas) become symptomatic in the teens or twenties when sensorineural hearing loss is the 1st sign. There may be tinnitus and vertigo. The rate of tumour growth is unpredictable and variable. The tumours are benign but cause problems by pressing on local structures and by ↑ICP.

Juvenile posterior subcapsular lenticular opacity

(a form of cataract) occurs before other manifestations and can be useful in screening those at risk.

Complications:

Schwannomas of other cranial nerves, spinal nerve roots, or nerves. Meningiomas (45% NF2; may be multiple). Glial tumours are less common. Consider NF2 in any young person presenting with one of these tumours in isolation.

Management

Hearing tests yearly from puberty with CNS MRI if abnormality is detected. A normal MRI in the late teens is helpful in assessing risk to any offspring. A clear scan at 30yrs (unless a family history of late onset) indicates that the gene has not been inherited. Treatment of vestibular schwannomas is neurosurgical and complicated by hearing loss/deterioration and facial palsy. Mean survival from diagnosis has been reported at 15yrs,[315] but with best practice this will be better.

Diagnostic criteria for neurofibromatosis

NF1 (von Recklinghausen's disease)

Diagnosis is made if 2 of the following are found:

1. ≥6 *café-au-lait* macules >5mm (prepubertal) or >15mm (post-pubertal)
2. ≥2 neurofibromas of any type or 1 plexiform
3. Freckling in the axillary or inguinal regions
4. Optic glioma
5. ≥2 Lisch nodules
6. Distinctive osseous lesion typical of NF1, eg sphenoid dysplasia
7. First degree relative with NF1 according to the above criteria

Differential:

McCune-Albright syndrome (OHCS p650), multiple lentigenes,[1] urticaria pigmentosa (OHCS p610).

NF2

Diagnosis is made if either of the following are found:

1. Bilateral vestibular schwannomas seen on MRI or CT
2. First degree relative with NF2 and either:
   a. Unilateral vestibular schwannoma
   b. One of the following:

      Neurofibroma
      Meningioma
      Glioma
      Schwannoma
      Juvenile cataract (NF2 type).

Differential:

NF1.

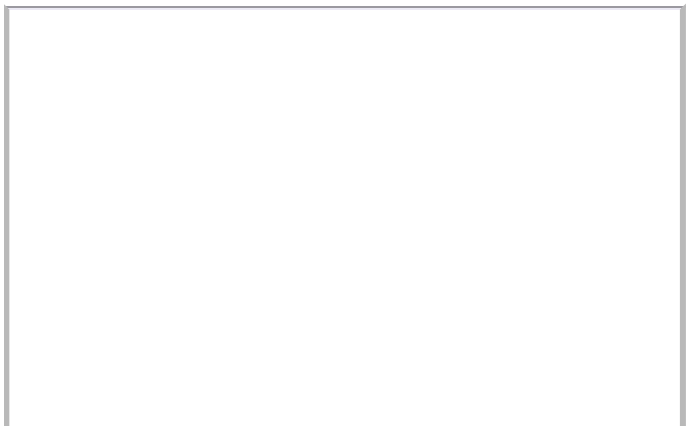
Syringomyelia

Syrinx was one of those versatile virgins of Arcadia who, on being pursued by Pan beside the river Ladon, turned herself into a reed, from which Pan made his pipes, so giving her name to various tubular structures, eg syringes, and syrinxes, which are tubular or slit-like cavities in or close to the central canal of the cervical cord. They may extend up or down. Incidence: 8/100,000/yr. See **fig 1** p689.

Cause

Typical cause: blocked csf circulation without 4th ventricular communication), with ↓flow from the basal posterior fossa to the caudal space. The chief example is Arnold-Chiari malformation (cerebellum extends through the foramen magnum; can cause communicating syringomyelia)—also basal arachnoiditis (after infection, irradiation, subarachnoid haemorrhage); basilar impression/invagination;[1] meningeal cancer; masses (cysts, rheumatoid pannus, encephalocele, tumours).

Less commonly, syrinxes develop after myelitis, cord trauma or damage from rupture of an A-V malformation,[316] or within spinal tumours ∵ fluid secreted from neoplastic cells or haemorrhage typically in an ependymoma or hemangioblastoma.



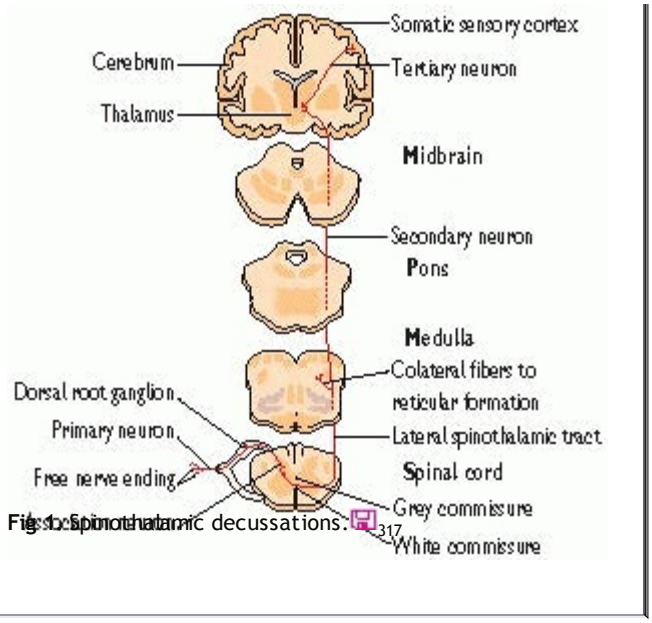


Fig 1. Spinothalamic decussations.[317]

Signs—cardinal:

Wasting/weakness of hands (± **claw-hand**—then arms, then shoulders, then respiratory muscles) + **loss of pain & T° sensation** (eg with **painless burns** with preserved light touch, vibration, and joint-position sense, ie **dissociated sensory loss**, p438, typically over trunk & arms, eg in a cape distribution (suspended sensory loss). Fibres for pain and T° are lost early as they decussate anteriorly in the cord. Anterior horn cells are similarly vulnerable.

Others:

Horner's syndrome (cervical sympathetics) & **UMN leg signs ± body asymmetry**, limb hemihypertrophy, or odomegaly/ chiromegaly (unilateral enlarged hand or foot, perhaps from release of trophic factors via anterior horn cells). **Eye movement abnormalities** (eg downbeat nystagmus, diplopia, oscillopsia,[2] and tunnel vision) are from base of brain (foramen magnum) abnormality.[318] **Charcot's (neuropathic) joints:** On losing sensation, joints are destroyed by ↑ range of movement, becoming swollen and mobile.[319] Causes: tabes dorsalis (eg knee), paraplegia (eg hips),[320] syringomyelia (shoulder; wrist),[321] leprosy, spinal osteolysis/cord atrophy (systemic sclerosis).[322]

MRI imaging

How big is the syrinx? Any base-of-brain (Chiari) malformation?

Natural history

Mean age of onset: 30yrs. Symptoms may be static for years, but then worsen fast—eg on coughing or sneezing, as rises in venous pressure causes extension eg into the brainstem (*syringobulbia*)[323] this causes nystagmus, tongue atrophy, dysphagia, pharyngeal/palatal weakness and Vth nerve sensory signs.

Surgery

Don't wait for gross deterioration to occur. Decompression at the foramen magnum may be tried in Chiari malformations, to promote free flow of CSF. preventing syrinx dilatation. Surgery may relieve pain, and slow progression.[324]

[1] The top of the odontoid process (part of C2) migrates upwards (congenitally or in rheumatoid arthritis or osteogenesis imperfecta) causing foramen magnum stenosis ± medulla oblongata compression. Consider basilar invagination if the odontoid tip is $\gtrsim$4mm above McGregor's line (drawn from the upper surface of the posterior edge of the hard palate to the most caudal point of the occipital curve).

[2] Oscillopsia (sensation of oscillation of objects viewed) in brainstem disorders not causing nystagmus is attributed to failure of vestibular-ocular reflex to compensate for head movement.

Retroviruses and neurology

HIV/AIDS

is part of the differential diagnosis of meningitis (eg fungal/TB), intracranial mass lesions (toxoplasmosis), dementia, encephalomyelitis, cord problems,[325] and peripheral nerve problems, eg mononeuritis multiplex; Guillain-Barré syndrome.

Tropical spastic paraplegia/HTLV-1

myelopathy is a progressive spastic paraplegia, with paraesthesiae, sensory loss, and disorders of micturition.

Models of brain functioning

A superficial reading of the foregoing pages might lead one to the conclusion that the structure of the adult brain is fixed, and that a circumscribed lesion

will produce reproducible, predictable results (if we remember our neuroanatomy correctly). Furthermore, if a certain phenomenon appears when part of the brain (say area a) is stimulated, and is lost when the same part of the brain is injured, we happily conclude that area a is the centre for laughter, fear, or whatever the phenomenon is. A lesion here, and you will stop laughing for ever, we might think. An area on the hard disk of our mind has been scratched. The grey cells do not regenerate themselves, so the brain carries on as before with this one defect. The more we look at the brain, the more wrong this model becomes.

If our brains were like a computer, the more tasks we did at the same time, the slower we would do any one task. In fact, our performance can improve, the more simultaneous tasks we take on. This is why music helps some of us concentrate. Experiments using functional MRI show that listening to polyphonic music recruits memory circuits, promoting attention, and aids semantic processing, target detection, and some forms of imagery.[1]

Another way in which our brains are not like a computer is that we are born with certain predispositions and expectations. Our hard disk was never blank. Just as the skin on the feet of new-born babies is thicker than other areas (as if feet were made with a pre-knowledge of walking, or somehow expecting walking), so our brains are made expecting a world of stimuli, which need making sense of by reframing sequential events in terms of cause and effect. We cannot help unconsciously imposing cause and effect relationships on events which are purely sequential. This unconscious reframing no doubt has survival value.

The model we have of brain function is important because it influences our attitude to our patients. If we are stuck with a neuroanatomical model, we will be rather pessimistic and guarded in our assessment of how patients may recover after neurological events. If we use a model which is more holistic and reality based, such as the Piaget-type model in which the brain is seen as intrinsically unstable and continually re-creating itself, we will grant our patients more possibilities.[326] Our model of the brain must encompass its ability to set goals for itself, and to be self-actuating.[327] Unstructured optimism is unwarranted, but structured optimism is to some extent a self-fulfilling prognosis. For many medical conditions, the more optimistic we are, and the more we involve our patients in their own care and its planning, the faster and better they will recover.[328] If we combine this with the observed fact that those with an optimistic turn of mind are less likely to suffer stroke,[2] we can reach the conclusion that emotional well-being predicts subsequent functional independence and survival. When this hypothesis is tested directly in a prospective way, the effect of emotional well-being is found to be direct and strong and independent of other factors such as functional status, sociodemographic variables, chronic conditions, body mass index, etc.[329]

So the conclusion is that the brain has an unknown amount of inherent plasticity, and an unknown potential for healing after injury—uninjured areas may take on new functions, and injured parts may function in new ways.[3] The great challenge of neurology is to work to maximize this potential for recovery and re-creation. This demands knowledge of your patient, as well as knowledge of neuroanatomy and neurophysiology. The point is that there is no predefined limit to what is possible.

Acknowledgements

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Title: *Oxford Handbook of Clinical Medicine, 7th Edition*

12

Oncology and Palliative Care

Communication

This forms the first step in understanding, treating, or coming to terms with cancer. A range of overwhelming feelings can surface on receiving this diagnosis, including shock, numbness, denial, panic, anger and resignation ('I knew all along…'). Some doctors instinctively turn away from 'undisciplined squads of emotions' and try to stop them taking over consultations. A more positive approach is to try to use these to benefit and motivate your patient—through listening to, and addressing, their worst fears. ▸*Include your patient in all decision-making processes*. Many patients (not just the young and well informed) will appreciate this—and the giving of information and the sharing of decisions is known to reduce treatment morbidity. So, even when this is physically exhausting (the same ground may need covering many times) it is definitely worth spending this time. A huge amount is forgotten or fails to register initially, so videos and written information are important. Be sure to question, in an open way, about use of alternative therapies which can indicate psychosocial distress and is frequently a sign of undisclosed worry of recurrence.[1][2] Ask about this and through good communication and the promotion of autonomy, your patient's fear-driven wish to try dangerous or untried therapies may be trumped by a spirit of rational optimism.

Looking after people with cancer

No rules guarantee success, but getting to know your patient, making an agreed management plan, and seeking out the right expert for each stage of treatment *all* need to be central activities in oncology. The patient will bring worries from all aspects of their family, working and social life. Communication is central to resolving these issues and the personal attributes of the doctor as a physician are key. Remember, it is never too early to start palliative care (*with* other treatments) and that *quality of life* is of the utmost importance.

Psychological support

Examples include:

- Allowing the patient to express anger, fear—or any negative feeling (anger can anaesthetize pain).
- Counselling, eg with a breast cancer nurse (mastectomy preparation).
- Biofeedback and relaxation therapy can ↓side-effects of chemotherapy.[3]
- Cognitive and behavioural therapy reduces psychological morbidity associated with cancer treatments. See OHCS p370.
- Group therapy (OHCS p376) reduces pain, mood disturbance, and the frequency of maladaptive coping strategies.
- Meta-analyses have suggested that psychological support can have some effect on improving outcome measures such as survival.[4]

Streamlining care pathways

Care pathways map patient journeys in a health system: symptoms felt→GP appointment→referral→hospital appointment →consultant clinic→imaging→1st treatment (surgery, etc). Each arrow represents a possibly fatal delay. 48h access to GPs, GP referral under a '2-week rule' (hospital must see within 2wks, inevitably making other equally or more deserving patients wait longer) and ***e***-booking (like on-line airline seat reservations) are unreliable ways of speeding up the crucial arrow pointing to 1st treatment.[5] The only way to do this is to increase capacity (beds, nurses, doctors, equipment, and theatres).

Hints on breaking bad news[6]

1. Set the environment up carefully. Choose a quiet place where you will not be disturbed. Make sure family are present if wanted. Be sure of your facts.
2. Find out what the patient already knows or surmises (often a great deal). This may change rapidly, and different perceptions may all be relevant.
3. Ascertain how much the person wants to know. You can be surprisingly direct. 'If anything were amiss, would want to know all the details?'
4. Give some warning — 'there is some bad news for us to address'. Offer small amounts of information at a time, as this can soften the impact.
5. Share information about diagnosis and treatments, Specifically list supporting people (eg nurses) and institutions (eg hospices). Ask 'Is there anything else you want me to explain?' Don't hesitate to go over the same ground repeatedly. Allow denial: don't force the pace, give them time.
6. 'Cancer' has negative connotations for many people. Address this, and explain that ~50% of cancers are cured in the developed world.[7]
7. Listen to any concerns raised; encourage the airing of feelings and empathise.
8. Prognosis questions are often hardest to answer, doctors are usually too optimistic.[8] Encourage an appropriate level of hope, refer to an expert.
9. Summarize and make a plan. Offer availability.
10. Follow through. The most important thing is to leave the patient with the strong impression that come what may, you are with them, and that this unwritten contract will not be broken.

Don't imagine that a single blueprint will do for everyone. ▸Be prepared to use *whatever* the patient gives you.[9] Closely observe both verbal and non-verbal cues. Practise in low-key interactions with patients—so when great difficulties arise, you have a better chance of helping. As humans are very complex, we all frequently fail. Don't be put off: keep trying, and recap with colleagues afterwards, so you keep learning.

Oncology and genetics

Some commoner cancer-predisposing gene mutations are given in the BOX.

Familial breast/ovarian cancer

Most breast and ovarian cancer is sporadic, but ~5% are due to germline mutation in BRCA1 (17q) or BRCA2 (13q). Both genes function as tumour suppressors. Carrying a BRCA1 mutation confers a lifetime risk of developing breast cancer of 70-80%, and ovarian cancer of 30-40%. Mutations in BRCA2 are much less likely to cause ovarian cancer, but may cause male breast cancer. Incidence of mutations varies among populations. In families with ≥3 cases of breast cancer collected by the Breast Cancer Linkage Consortium, the disease was linked to BRCA1 in 52% of families and BRCA2 in 32%. Individuals from families in which a mutation has not been detected can be given risk estimation based on number of individuals affected and age of onset of cancer. There is no consensus on efficacy of mammographic and ovarian ultrasound screening or analysis of ca125 and CEA (carcionembryonic antigen) serum markers in individuals at moderate risk.

There is debate about cost-benefits of screening and risks of radiation exposure from regular mammography. MRI assists early detection.[10] Those at high risk of breast or ovarian cancer may opt for prophylactic mastectomy and oophorectomy both of which lower, but do not remove, the risk of developing cancer derived from those sites. Drugs have an uncertain role in prevention in high-risk patients; tamoxifen is associated with unacceptable adverse side effects, anastrozole is more promising but still under trial (IBIS-II and MAP III).[11][12]

Familial colorectal cancer

~20% of those with colorectal cancer have a family history of the disease. Personal risk of colorectal cancer is proportionate to the degree of family history: the relative risk (RR) is about: ×2 for people with any family history; ×5 if 2 affected 1st degree relatives; and ×3 for an affected 1st degree relative aged <45yrs at diagnosis. On the basis of empirical risk estimation, some people may be recommended colonoscopic surveillance, but weigh against the dangers of long-term, invasive screening for at-risk individuals.

Hereditary non-polyposis colorectal cancer (HNPCC)

is a syndrome of familial aggregation of colorectal (mainly), endometrial, ovarian, gastric, upper urinary tract, small intestinal, pancreatic, and other cancers. Many HNPCC families have mutations in 1 of 5 DNA mismatch repair genes. Lifetime risk of colorectal cancer for relatives who carry a mutation is 60%, and women with a mutation have a 40% lifetime risk of endometrial cancer. Surveillance for HNPCC families is 2-yearly with colonoscopy ± gynaecological surveillance, or even prophylactic surgery. These mutations cause ~2% of all UK colorectal cancers. Suspect if: ≥3 1st-degree relatives from ≥2 generations have colorectal cancer with one <50yrs old— provided familial adenomatous polyposis has been excluded.[13]

Familial adenomatous polyposis

is due to germline mutations in the APC gene. Offspring are at 50% of risk of being a gene carrier, and gene penetrance approaches 100% for colorectal cancer by 50yrs old. ***Peutz-Jeghers' syndrome*** has a 10-20% lifetime risk of colorectal cancer, and has been shown to be due to germline mutations in STK11, a serine threonine kinase (locus: 19p14).

Familial prostate cancer

~5% of those with prostate cancer have a family history: the genetic basis is multifactorial. There is a modestly elevated life time risk of prostate cancer for male carriers of BRCA1 and BRCA2 mutations, although the molecular basis of this remains to be elucidated. Mutations in BRCA1/BRCA2 or in the genes on chromosomes 1 and X do not account for all family clusters of prostate cancer and so it is clear that other genes must be involved. In one twin study, 42% of the risk was found to be genetic.[14]

Genetic tests

can also tell if chemotherapy is likely to work: chemotherapy fails in 17% of colon cancer patients—ie those with certain mutations.[1]

Examples of cancers with a familial predisposition

Cancer/syndrome	Gene	Chromosome	
Breast and ovarian cancers	BRCA1	17q	(OPPOSITE)
	BRCA2	13q	

Hereditary non-polyposis colorectal cancer (HNPCC)	MSH2	2p	(OPPOSITE)
		MLH1	3p
	PMS2	7p	
Familial polyposis (colorectum)	APC	5q	
von Hippel-Lindau (kidney, CNS)	VHL	3p	(p207)
Carney complex	PRKAR1A	17q	(p207)
Multiple endocrine neoplasia Type I (pituitary, pancreas, thyroid)	MEN1	11q	(p207)
Multiple endocrine neoplasia Type 2	RET	10q	(p207)
Basal cell naevus syndrome (CNS, skin)	PTCH	9q	
Retinoblastoma (eye, bone)	Rb	13q	(*OHCS* p421)
Li-Fraumeni syndrome (multiple)	TP53	17p	(*OHCS* p648)
Neurofibromatosis Type I (CNS; rare)	NF1	17q	(p506)
Neurofibromatosis Type 2 (common) (meningiomas, auditory neuromas)	NF2	22	(p506)

Familial melanoma	INK4a	9p

Oncological emergencies

▸A patient who becomes acutely unwell can often be made more comfortable with simple measures, but some problems require specific treatment.

Febrile neutropenic patients

See p336.

Spinal cord compression

Requires urgent and efficient treatment to preserve neurological function. A high index of suspicion is essential.

Causes:

Typically extradural metastases. Others: extension of tumour from a vertebral body, direct extension of the tumour, or crush fracture.

Signs & symptoms:

Back pain with a root distribution, weakness and sensory loss (a level may be found), bowel and bladder dysfunction.

Tests:

Urgent MRI of the whole spine.

Management:

Dexamethasone 8-16mg IV then 4mg/6h PO. Discuss with neurosurgeon and clinical oncologist immediately.

Superior vena cava (SVC) obstruction with airway compromise

svc obstruction is not an emergency unless there is tracheal compression with *airway compromise:* usually there is time to plan optimal treatment, which is to be preferred, rather than rushing into therapy which may not be beneficial.[15]

Causes:

Typically lung cancer; rarely from causes of mediastinal enlargement (eg germ cell tumour); lymphadenopathy (lymphoma); thymus malignancy; thrombotic disorders (eg Behçet's or nephrotic syndromes); thrombus around an IV central line; hamartoma; ovarian hyperstimulation (OHCS p311); fibrotic bands (lung fibrosis after chemotherapy).

Signs & symptoms:

Dyspnoea; orthopnoea; swollen face & arm; cough; plethora/cyanosis; headache; engorged veins.

Pemberton's test:

On lifting the arms over the head for >1min, there is ↑facial plethora/cyanosis, JVP↑ (nonpulsatile), and inspiratory stridor.

Tests:

Sputum cytology, CXR, CT, venography.

Management:

Get a tissue diagnosis if possible, but bronchoscopy may be hazardous. Give **dexamethasone** 4mg/6h PO. Consider balloon **venoplasty** and SVC stenting,[16] eg prior to radical or palliative **chemo**- or **radiotherapy** (depending on tumour type).

Hypercalcaemia

Affects 10-20% of patients with cancer, and 40% of those with myeloma.

Causes:

Lytic bone metastases, production of osteoclast activating factor or PTH-like hormones by the tumour.

Symptoms:

Lethargy, anorexia, nausea, polydipsia, polyuria, constipation, dehydration, confusion, weakness. Most obvious with serum Ca^{2+} >3mmol/L.

Management:

Rehydrate with 3-4L of 0.9% saline IV over 24h. Avoid diuretics. Give **bisphosphonate** IV; consider maintenance therapy, IV or PO, p672). The best treatment is control of underlying malignancy. In resistant hypercalcaemia, consider **calcitonin**.

Raised intracranial pressure

Due to either a primary CNS tumour or metastatic disease.

Signs & symptoms:

Headache (often worse in the morning), nausea, vomiting, papilloedema, fits, focal neurological signs.

Tests:

Urgent CT is important to diagnose an expanding mass, cystic degeneration, haemorrhage within a tumour, cerebral oedema, or hydrocephalus due to tumour or blocked shunt since the management of these scenarios can be very different. **[prescription take]:** Dexamethasone 4mg/6h PO, radiotherapy, and surgery as appropriate depending on cause. **Mannitol** may be tried for symptom relief for cerebral oedema (not evidence-based).[17]

Tumour lysis syndrome

Rapid cell death on starting chemotherapy for rapidly proliferating leukaemia, lymphoma, myeloma, and some germ cell tumours can result in a rise in serum urate, K^+, and phosphate, precipitating renal failure. Prevention is with good **hydration** and **allopurinol** 24h *before* chemotherapy; dose example if renal function OK: 300mg/12h PO. If creatinine >100µmol/L: 100mg alternate days.[18] Haemodialysis may be needed in renal failure. More potent uricolytic agents: recombinant urate oxidase (**rasburicase**) 200µg/kg/d IVI for 5-7d; SE: fever; D&V; headache; rash; bronchospasm; haemolysis.[19] It may interfere with uric acid tests; see datasheet.

Inappropriate ADH secretion

p666; **febrile neutropenic regimen** p336.

Treating hypercalcaemia with bisphosphonates

Ensure adequate hydration (eg with 0.9% saline IVI). Zoledronic acid and pamidronate are 2 options.

Disodium pamidronate doses

Calcium (mmol/L; corrected)[20]	Single-dose pamidronate (mg)
<3	15-30
3-3.5	30-60
3.5-4	60-90
>4	90

Infuse slowly, eg 30mg in 300mL 0.9% saline over 3h via a largish vein. Max dose: 90mg. Response starts at ~3-5d, peaking at 1wk.

SE: 'Flu symptoms, bone pain, PO_4^{3-}↓, bone pain, myalgia, nausea, vomiting, headache, lymphocytopenia, Mg^{2+}↓, Ca^{2+}↓, seizures (rare).

Zoledronic acid

is significantly more effective in reducing serum Ca^{2+} than previously used bisphosphonates.[21] Usually, a single dose of 4mg IVI over 2h will normalize plasma Ca^{2+} within a week. A higher dose should be used if corrected Ca^{2+} is >3mmol/L. SE: 'Flu symptoms, bone pain, PO_4^{3-}↓, confusion, thirst, taste disturbance, nausea, pulse↓, WCC↓, creatinine↑.

Sodium clodronate* and *ibandronic acid

are other bisphosphonates.

Corrected calcium in mmol/L = serum Ca^{2+} *- [0.02 × serum albumin in g/L] + 0.8.*

Cancer therapy

Cancer affects 30% of the population; 20% die from it. Management requires a multidisciplinary team; communication is vital (p510). Most patients wish to have some part in decision making at the various stages of their treatment, and to be informed of their options. Patients are becoming better informed through self-help groups and access to the internet. Most patients undergo a variety of treatments during the treatment of their cancer and your job may be to orchestrate these.

Surgery

In many cases a tissue diagnosis of cancer is made with either a biopsy or formal operation to remove the primary tumour. Although it is sometimes the only treatment required in early tumours of the GI tract, soft tissue sarcomas, and gynaecological tumours, it is often the case that best results follow the combination of surgery and chemotherapy. Surgery also has a role in palliating advanced disease.

Radiotherapy

Uses ionizing radiation to kill tumour cells. See p518.

Chemotherapy

Cytotoxics should be given under expert guidance by people trained in their administration. Drugs are often given in combination with a variety of intents: *Neoadjuvant*—to shrink tumours to reduce the need for major surgery (eg mastectomy). There is also a rationale which considers early control of micrometastasis. *Primary therapy*—as the sole treatment for haematological malignancies. *Adjuvant*—to reduce the chance of relapse, eg breast and bowel cancers. *Palliative*—to provide relief from symptomatic metastatic disease and possibly to prolong survival.

Important classes of drugs include:

- Alkylating agents, eg cyclophosphamide, chlorambucil, busulfan.
- Antimetabolites, eg methotrexate, 5-fluorouracil.
- Vinca alkaloids, eg vincristine, vinblastine.
- Antitumour antibiotics, eg actinomycin D, doxorubicin.
- Others, eg etoposide, taxanes, platinum compounds. Examples of new classes: monoclonal antibodies/epidermal growth factor receptor inhibitors (gefitinit, erlotinit), EFGR. Over expression of EFGR correlates with poor prognosis in many cancers.

Side-effects depend on the types of drugs used. Nausea/vomiting are most feared by patients and are preventable or controllable in most. Alopecia can also have a profound impact on quality of life. Neutropenia is most commonly seen 10-14d after chemotherapy (but can occur within 7d for taxanes) and sepsis requires immediate attention. ▸▸See p336.

Extravasation of a chemotherapeutic agent:

Suspect if there is pain, burning or swelling at infusion site.

Management:

Stop the infusion, attempt to aspirate blood from the cannula, and then remove. Take advice. Administer steroids and consider antidotes.[1] [22] Elevate the arm and mark site affected. Review regularly and apply steroid cream. Apply cold pack (unless a vinca alkaloid, in which case a heat compress should be applied). Consider report to National Extravasation Scheme. Early liaison with plastic surgeon may be needed.

Communication

▸*Include the patient in the decision-making process*, p510.

Avoiding pointless procedures in patients with cancer

Surgery is often curative (eg for colorectal cancers), while other operations restore function, or deal with local recurrence, or reduce tumour bulk. But ambitious surgery is often pointless if the cancer has already spread beyond the organ in question. A key process in planning the right procedure

is to interest a radiologist in your problem. This may require more than scrawling a request on an x-ray form. The range of imaging available is constantly changing, and the radiologist may need detailed information to allow best use of the scans available—eg:[23]

Computer tomography (CT):

Extensive application in many cancers.

MRI:

Allows precise staging in areas occult to CT (eg marrow); see p720.

Bone scan:

Helps staging/follow-up of prostate, breast, and lung ca.

Sestamibi scan:

Localizing active disease in breast cancer and thyroid (eg if not iodine-avid). Like bone scans, it uses technetium (^{99m}Tc).

Thallium scan:

Helps localize viable tissue, eg in brain tumours.

Gallium scan:

Helps staging and follow-up in lymphoma.

Octreotide scan:

Localizes cancers with somatostatin receptors (eg pancreas, medullary thyroid, neuroblastoma, and carcinoid tumours).

Monoclonal antibodies:

(^{99m}Tc-labelled tumour antibodies). Helps staging by detecting tumour antigen, eg in lung, colon, and prostate cancer.

FDG PET:

Positron emission tomography (PET) detects high rates of aerobic metabolism, eg in lung, colon, breast, and testis. FDG = 2-[18F] fluoro- 2-deoxy-D-glucose.

MIBG scan (^{131}I):

Localizing noradrenaline production, eg phaeochromocytoma. MIBG = meta-iodobenzylguanidine.

Radiotherapy

Radiotherapy uses ionizing radiation to produce free radicals which damage DNA. Normal cells are better at repairing this damage than cancer cells, so are able to recover before the next dose (or fraction) of treatment.

Radical treatment

is given with curative intent. The total doses given range from 40-70Gy (1Gy = 100cGy = 100rads) in 15-35 daily fractions. Some regimens involve giving several smaller fractions a day with a gap of 6-8h. Combined chemoradiation is used in some sites, eg anus and oesophagus, to increase response rates.

Palliation

aims to relieve symptoms. Doses: 8-30Gy, given in 1, 2, 5, or 10 fractions. Bone pain, haemoptysis, cough, dyspnoea, and bleeding are helped in >50% of patients. *'Will this patient benefit from radiotherapy?'* is a frequently asked question.[24][25] When in doubt, ask an expert (or 2).

Early reactions

Occur during, or soon after treatment.

- Tiredness: common after radical treatments; can last weeks to months.
- Skin reactions: These vary from erythema to dry desquamation to moist desquamation to ulceration; on completing treatment, use moisturizers.
- Mucositis: all patients receiving head and neck treatment should have a dental check-up before commencing therapy. Avoid smoking, alcohol, and spicy foods. Antiseptic mouthwashes may help. Aspirin gargle and other soluble analgesics are helpful. Treat oral thrush eg with Nystatin pastilles® chewed every 6 hours.
- Nausea and vomiting: occur when stomach, liver, or brain treated. Try a dopamine serotonin antagonist 1st. If unsuccessful, try 5HT$_3$ serotonin antagonist, p438.
- Diarrhoea: usually after abdominal or pelvic treatments. Maintain good hydration. Avoid high-fibre bulking agents; try loperamide.
- Dysphagia. Thoracic treatments.
- Cystitis. Pelvic treatments. Drink plenty of fluids. NSAIDs, eg diclofenac.
- Bone marrow suppression. More likely after chemotherapy or when large areas are being treated. Usually reversible.

Late reactions

Occur months, or years after the treatment.

- CNS: somnolence, 6-12wks after brain radiotherapy. Treat with steroids. Spinal cord myelopathy—progressive weakness. MRI is needed to exclude cord compression. Brachial plexopathy—numb, weak, and painful arm after axillary radiotherapy. Reduced IQ can occur in children receiving brain irradiation if <6yrs old.

- Lung: pneumonitis may occur 6-12wks after thoracic treatment, eg with dry cough ± dyspnoea. Treatment: prednisolone 40mg reducing over 6wks.
- GI: xerostomia—reduced saliva. Treat with pilocarpine 5mg/8h or artificial saliva with meals. Care must be taken with all future dental care as healing is reduced. Benign strictures—of oesophagus or bowel. Treat with dilatation. Fistulae—need surgical intervention.
- GU: urinary frequency—small fibrosed bladder after pelvic treatments. Fertility—pelvic radiotherapy (and cytotoxics) may affect fertility, so ova or sperm storage should be considered. This is a complex area: get expert help. See BOX. In premature female menopause or reduced testosterone—replace hormones. Vaginal stenosis and dyspareunia. Impotence—can occur several years after pelvic radiotherapy.
- Others: panhypopituitarism, following radical treatment involving pituitary fossa. Children need hormones checking regularly as growth hormone may be required. Hypothyroidism—neck treatments, eg for Hodgkin's lymphoma. Cataracts. Secondary cancers, eg sarcomas usually 10 or more years later.

Fertility issues in cancer patients

Plan with patients *before* treatment.

Chemotherapy and radiotherapy often damage germ-cell spermatogonia (∴ impaired spermatogenesis ± sterility in the male), and may hasten oocyte depletion (premature menopause in women). GNRH agonists may offer some benefit to females if taken during chemotherapy. [26] As treatments become more effective and survival improves, there are more survivors in the reproductive years for whom parenting is a top priority. [27] There is nothing like the hope of creating new life to sustain patients through the difficult times of radio- and chemotherapy, so make sure this hope is well founded. [28]

Semen cryopreservation

from men and older boys with cancer must be offered before therapy. With modern fertility treatment (OHCS p293), even poor quality samples can yield successful pregnancies. [29] Another option is use of sperm from cryopreserved testicular tissue followed up with intracytoplasmic sperm injection (ICSI). If your patient is a man some years after cancer therapy who is unable to have children, refer him to a specialist. ▸*Do not write him off as infertile: t*esticular sperm extraction (TESE) with ICSI can yield normal pregnancies. [30]

Cryopreservation of embryos* and *ovarian tissue banking

are harder options in women. [31] Harvesting and storing ovarian cortical tissue from girls and young women before potentially gonadotoxic therapy is only available in some centres. [32] Success depends on the integrity of the uterus, and in some cancers this may have been badly affected by radiotherapy.

For ethical issues and the UK Human Embryology Authority, see OHCS p293.

Survival—European figures

On average, 40.5% of men and 53.6% of women survive >5yrs after a cancer diagnosis (respectively, in England, 37.1% of men and 50.8% of women). [33] These statistics are based on 1.8 million adults and 24,000 children diagnosed between 1990 and 1994 and followed to 1999. (England has probably caught up since then—see the Cancer Plan/Care Pathways, p511.) Early diagnosis, a full range of treatment options, and the money spent by nations on health care all have an impact on survival. [34]

Palliative care

This does not just apply to those with cancer but anyone in the last stages of an illness. Take time to find out exactly what is troubling a patient and approach problems holistically. Attention to detail is the key. Remember each person comes with a set of emotions, preconceptions and a family already attached. Most hospitals now have a dedicated palliative care team for help and advice.

Pain

One of the most feared sequelae of a terminal diagnosis yet largely preventable. Studies show that cancer pain especially is poorly managed in most settings [35] particularly in the elderly. No patient should live or die with unrelieved pain, aim to prevent or eliminate it.

Types:

Don't assume a cause, take a detailed history and examine to understand the aetiology. If there is nerve infiltration or local pressure damage amitryptiline may be more appropriate than opioids. Evaluate severity, nature, functional deficit and psychological state - depression occurs in up to 25% of cancer patients. [36]

Management:

Explain and plan rehabilitation goals, aim to modify the pathological process when possible, eg radiotherapy; hormones; chemotherapy; surgery. Effective analgesia is possible in 70-90% of patients [37] by adhering to 5 simple guidelines:

1. *By the mouth* - give orally wherever possible.
2. *By the clock* - at fixed intervals to give continuous relief.
3. *By the ladder* - following the WHO stepwise approach opposite.
4. *For the individual* - there are no standard doses for opiates, needs vary.
5. *With attention to detail* - inform, set times carefully, warn of side effects.

Use the WHO ladder shown opposite until pain is relieved. Monitor the response carefully, review of results and side effects is crucial to good care. Start regular laxatives and anti-emetics with strong opiates. Paracetamol PO/PR/IV at step 1 may have an opiate-sparing effect, and should be continued at

steps 2 and 3.[38] *Adjuvants* - NSAIDs, steroids, muscle relaxants, anxiolytics, anti-depressants

Morphine

- Start with oral solution 5-10mg/4h PO with an equal breakthrough dose as often as required. A double dose at bedtime can enable a good night of sleep. Patient needs will vary greatly and there is no maximum dose, aim to control symptoms with minimum side effects. Change to modified release preparations (MST 12h) once daily needs are known by totalling 24h use and dividing by 2. Give 1/6 of the total daily dose as breakthrough. Side effects (common) - drowsiness, nausea and vomiting, constipation, dry mouth. Hallucinations and myoclonic jerks are signs of toxicity and should prompt dose review. ▸*If the oral route is unavailable* try diamorphine IV/SC (see BOX for conversions), oxycodone IV/SC is a newer more potent opioid as effective as morphine, which may have fewer side effects.[39] Oxynorm is the liquid form. There are also *Fentanyl transdermal patches:* which should usually be started under specialist supervision in those already opiate-exposed for easy titration. Remove after 72h, and place a new patch at a different site. 25, 50, 75, and 100µg/h patches are made. $t_{1/2}$ ≈ 17h. See BNF.

Suppositories

for pain: try oxycodone 30mg PR (eg 30mg/8h ≈ 30mg morphine). Agitation: try diazepam 10mg/8h suppositories.

Syringe drivers

See BOX

Unfounded fears

Patients often shrink from using morphine analgesia, usually as a result of common misconceptions—that it is addictive, for the dying, signifying 'The End'. It is important to address and allay these fears. Addiction is not a problem in the palliative care setting, neither is respiratory depression with correct titration—pain stimulates the respiratory centre. Reassure that it is simply a good painkiller, used in many situations. There is evidence it has no effect on life expectancy.[40] ▸*Prescribing for morphine and other controlled drugs:* include the total quantity in both words and figures, and include the formulation (tablets, capsules, oral liquid etc). On charts rewrite medications in full if doses change and always give the amount in milligrams, especially when using liquid preparations.

In morphine-resistant pain consider adjuvants, methadone or ketamine.

The analgesic ladder[41][42] (See p560 for NNT)

Rung 1	*Non-opioid*	Aspirin; paracetamol; NSAID
Rung 2	*Weak opioid*	Codeine; dihydrocodeine; tramadol
Rung 3	*Strong opioid*	Morphine; diamorphine; hydromorphine; oxycodone; fentanyl ± adjuvant analgesics.

If one drug fails to relieve pain, move up the ladder; do not try other drugs at the same level. In new, severe pain, rung 2 may be omitted.[43]

Syringe drivers

deliver opioids, haloperidol, cyclizine and metoclopramide, levomepromazine, hyoscine, and glycopyronium amongst others, giving 24h cover using the subcutaneous route. They enable continuous administration whilst avoiding cannulation.

Opiate dose equivalents

	Daily dose, mg	4h dose, mg	Relative potency to morphine PO

Morphine PO	30	5	1×
Morphine IV	15	2.5	2×
Diamorphine IV	10	2	3×
Oxycodone PO	15	2.5	2×
Oxycodone IV	10	2	3×
Fentanyl patch	0.2	—	150×

These conversions are not exact, the table is intended only as a rough guide. The potency figures particularly can vary widely. If in doubt, use a dose below your estimate when converting between opioids and titrate up according to response.

Palliative care (further details)

Nausea and vomiting:

There are many causes to consider including chemotherapy, constipation, obstruction, drugs, severe pain, cough, squashed stomach syndrome, oral thrush, infection and uraemia.

Management:

Full history and examination, first aim to prevent, then treat the reversible with laxatives, fluconazole, analgesia and antibiotics as appropriate. Consider stopping, reducing or changing drugs or route. Anti-emetic choice should be based on mechanism and site of drug action, oral if possible, but remember alternative routes (IV/SC/IM/PR) and give regularly, monitoring response. A third will need more than one medication.[44]

▸*In chemotherapy*

vomiting is a source of much anxiety and should be prevented before the 1st dose, thus avoiding anticipatory vomiting later, dexamethasone 4mg/12h, **metoclopramide** 10mg 8h and **ondansetron** 4-8mg 8h can be effective.

Oral agents:

First line: **Cyclizine** 50mg/8h—antihistamine, central action, covers most causes; **metoclopramide** 10-20mg/8h—prokinetic, good in gastric stasis; **haloperidol** 0.5-1.5mg/12h—antipsychotic, effective in drug or metabolic induced nausea. *Others:* **Ondansetron** 4-8mg/8h—serotonin antagonist; if morphine-induced: **levomepromazine** 3-12.5mg/12h is broad spectrum but can sedate.[45]

Constipation:

Very common with opiates, better prevented than treated. Use **bisacodyl** 5mg at night or combine a stimulant with a softener (**co-danthramer** suspension 5-10mL nocte). **Movicol** sachets 2-4/12h are useful in resistance and if oral therapy fails, try **glycerol** suppositories, or an arachis oil enema.

Breathlessness:

Consider fans, air supply, and **supplementary O_2**, or **morphine**. Use of relaxation techniques and benzodiazepines can be useful. Assess for pleural or pericardial effusion. If there is significant pleural effusion, consider thoracocentesis ± pleurodesis. If there is a malignant pericardial effusion, consider pericardiocentesis (p761), pericardiectomy, pleuropericardial windows, external beam radiotherapy,[46] percutaneous balloon pericardiotomy, or pericardial instillation of immunomodulators or sclerosing bleomycin.

Coated/dry mouth:

Treat any candida, infection or other underlying cause. Simple measures such as chewing ice chips, pineapple chunks (release proteolytic enzymes) or gum should be tried, good oral hygiene with mouth washes; chorhexidine and saliva substitutes, such as Oralbalance® gel can help.

Pruritus (itching):

See p64.

Venepuncture problems:

Repeated venepuncture with the attendant risk of painful extravasation and phlebitis may be avoided by insertion of skin tunnelled catheter (eg a Hickman line)—a single or multilumen line—into a major central vein (eg subclavian or internal jugular) using a strict aseptic technique. Patients can look after their own lines at home, and give their own drugs. Problems include: infection, blockage (flush with 0.9% saline or dilute heparin, eg every week), axillary, subclavian, or superior vena cava thrombosis/obstruction, and line slippage. Even more convenient portable delivery devices are available, allowing drugs to be given at a preset time, without the patient's intervention.

The last days and weeks of life:

Once a decision has been made that a patient is entering the very final weeks of their illness, comfort should be the main concern. Think about stopping observations, unnecessary blood tests and medications (such as those for long term prophylaxis). Ensure that a decision regarding resuscitation status has been made and clearly documented; this should usually be done by a senior doctor. Syringe drivers and fluids subcutaneously are often helpful, avoiding repeated cannulation attempts. *Terminal secretions* can be eased with anticholinergics such as **glycopyrronium** 200µg SC. Relieve pain, *agitation* can be very distressing for relatives, **midazolam** 0.5-2.5mg SC can help.

Consider with the family and patient whether transfer to an alternative location or hospice may be appropriate and if going home is a priority—this can be arranged at very short notice to enable comfort during final hours.

Other agents

Other agents and procedures to know about

(alphabetically listed)

- **C(h)olestyramine** 4g/6h PO (1h after other drugs) helps itch in jaundice.
- **Fluconazole** 50md/24h PO for candida
- H_2-antagonists (eg **cimetidine** 400mg/12h PO) help gastric irritation— eg associated with gastric carcinoma.
- **Haloperidol** 0.5-5mg/24h PO helps agitation, nightmares, hallucinations, and vomiting.
- **Hyoscine hydrobromide** 0.4-0.6mg/8h SC or 0.3mg sublingual: vomiting from upper GI obstruction or noisy bronchial rattles.
- Nerve blocks may lastingly relieve pleural or other resistant pains.
- Low-residue diets may be needed for post-radiotherapy diarrhoea.
- **Metronidazole** 400mg/8h PO mitigates anaerobic odours from tumours; so do **charcoal dressings** (Actisorb®).
- **Naproxen** 250mg/8h with food: fevers caused by malignancy or bone pain from metastases (consider splinting joints if this fails).
- **Sodium chloride nebulisers** 5mL as needed, can aid persistent cough
- **Spironolactone** 100mg/12h PO + **bumetanide** 1mg/24h PO for ascites.
- Steroids: **dexamethasone**: give 8mg IV stat to relieve symptoms of superior vena cava or bronchial obstruction—or lymphangitis carcinomatosa. Tablets are 2mg (≈15mg prednisolone). 4mg/12-24h PO may stimulate appetite, or reduce ICP headache, or induce (in some patients) satisfactory sense of euphoria.

Urgent referral in possible malignancy

A variety of clinical scenarios and symptoms should alert you to the possible presence of malignancy and prompt urgent referral to the appropriate specialist. The list below is by no means exhaustive but covers the commonest presentations.[47]

Lung

• Immediate referral if there are signs of superior vena caval obstruction or stridor •Urgently with persistent haemoptysis (smokers or non-smokers over 40) • Suggestive CXR (pleural effusion, slowly resolving consolidation) • Normal CXR but high suspicion • History of asbestos exposure and recent chest pain or dyspnoea • Unexplained systemic symptoms with suspicious CXR. ▸*High risk groups:* ex- and current smokers, COPD, asbestos exposure, history of cancer.

Upper gastrointestinal

• Urgent referral should be regardless of *H. Pylori* status if there is *dyspepsia* and one of the following; chronic GI bleeding, dysphagia, progressive unintentional weight loss, persistent vomiting, iron deficiency anaemia, an epigastric mass, suspicious barium meal result. Also if: • Isolated dysphagia • Unexplained upper abdominal pain and weight loss, with or without back pain • Upper abdominal mass without dyspepsia • Obstructive jaundice • Consider in vomiting or iron deficiency anaemia with weight loss, or dyspepsia with; Barrett's oesophagus, dysplasia, atrophic gastritis or old (>20yrs ago) peptic ulcer surgery ▸*For endoscopy:* those over 55 with persistent unexplained recent onset dyspepsia.

Lower gastrointestinal

if there are equivocal symptoms and you are not anxious, it is reasonable to watch and wait. Do PR examination and FBC in all. • Over 40 with PR bleeding and bowel habit change (more loose/frequent >6 weeks) • Over 60 with PR bleed or change of bowel habit >6 weeks • Any age with a right lower abdominal mass likely to be bowel • Palpable rectal mass • Men or non-menstruating women with unexplained iron deficiency anaemia and Hb less than 11 or 10 respectively. ▸*High risk groups:* Ulcerative colitis; it is unproven whether a family history of colon cancer assists decisions in symptomatic patients.

Breast

• Discrete, hard lump with fixation • Over 30 with a discrete lump persisting after a period or presenting post-menopause • Under 30 with an enlarging lump, fixed and hard lump, or family history • Previous breast cancer with a new lump or suspicious symptoms •Unilateral eczematous skin or nipple change unresponsive to topical treatment •Recent nipple distortion • Spontaneous bloody unilateral nipple discharge • Men over 50 with a unilateral firm subareolar mass ▸consider referral if under 30 with a lump or persistent breast pain.

Gynaecology

• Examination suggestive of cervical cancer (don't wait for a smear test) • Postmenopausal bleeding in non-HRT patients or those on HRT after 6 weeks cessation • Vulval lump or bleeding • consider in persistent intermenstrual bleeding ▸*Ultrasound:* any abdominal or pelvic mass not GI or urological in origin. Do pelvic and abdominal examinations, with speculum as appropriate.

Urology

• Hard irregular prostate (refer with PSA result) • Normal prostate but raised PSA (p681) ± urinary tract symptoms • Urinary symptoms and a high PSA • Painless macroscopic haematuria at any age • Over 40 with persistent or recurrent UTI and haematuria • Over 50 with unexplained microscopic haematuria • Any abdominal mass arising from the urological tract • A swelling or mass in the body of the testis • Ulceration or mass in the penis suggestive of cancer.

Central nervous system

• Symptoms including progressive neurological deficit, new-onset seizures, headaches, mental changes, cranial nerve palsy, unilateral sensorineural deafness or a suspicion of brain tumour • Recent-onset headaches with suggestion of raised intracranial pressure eg. vomiting, drowsiness, posturerelated headache, pulse-synchronous tinnitus, or other CNS symptoms • A new and different unexplained headache of progressive severity • Suspected recent-onset seizures ▸consider in rapid progression of subacute focal deficit, unexplained cognitive impairment, or personality change with features indicative of a tumour.

Haematological p336; *Thyroid* p622.

Is the energy we expend in speeding up referrals paying off?

Possibly not. There is evidence that reducing breast cancer waits from a few months to a few weeks is helpful—but there is little evidence that a few weeks here or there make any difference in colon and other cancers.[48] There are problems with the guidelines in that patients can meet national criteria and still be deemed 'inappropriate' by the consultant, while patients not meeting the criteria can present with suspicious signs—but they will not be seen soon because these possibly less serious cases are forced to jump the queue. This is just one example of the aphorism that ***all targets distort clinical priorities***.

In one NHS trust ~66% of referrals for suspected cancer of breast, skin, and colon problems were deemed 'appropriate', and 80-100% of gynaecological, upper GI, lung, and urological cancer referrals were judged appropriate.[49]

Studies of how well dermatology cancer guidelines work conclude that the best way forward is by education regarding recognition of benign conditions.[50] It also seems likely that dialogue between local consultants and referring GPs is a key factor—and that this dialogue will become harder and less coherent as current moves for 'choose and book' and patient-choice agendas lead to referrals over ever wider geographical areas.

On the good side, establishing clear referral responsibilities forces everyone to look at what they are doing—and this has facilitated many care pathways.

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13

Rheumatological and Related Illnesses

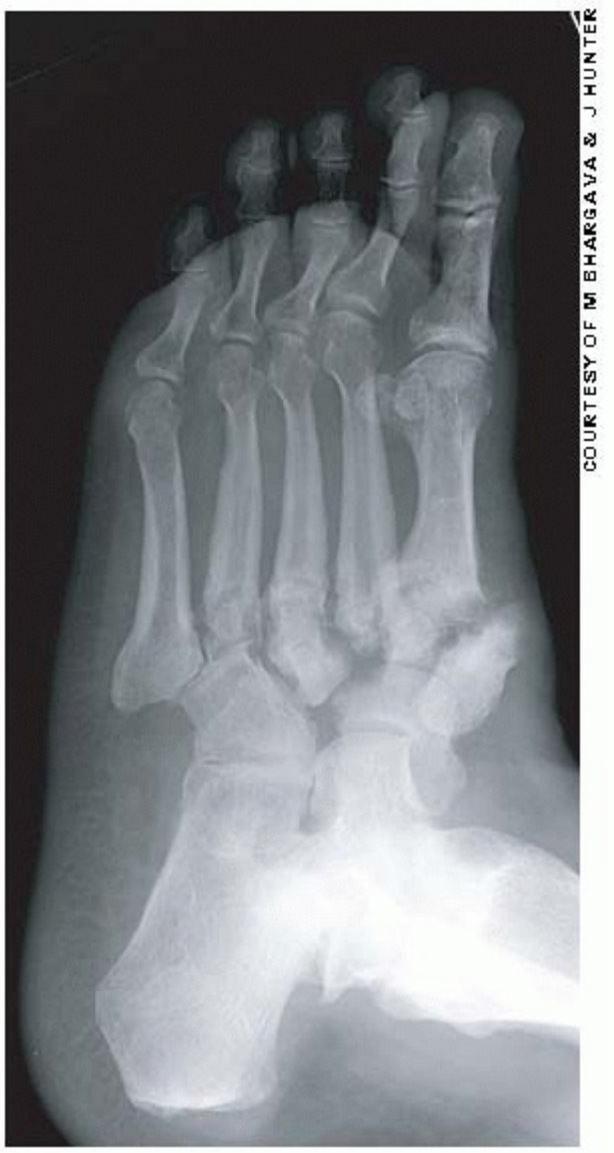


Fig 1. Oblique view of Charcot's joints in the foot[1]

Points to note in the rheumatological history

Age, occupation, origin (eg SLE is commoner in Afro-Caribbeans and Asians).

- ***Presenting symptoms***

  Joints: Pain, morning stiffness (eg RA) Pattern of distribution Swelling, loss of function

  Extra-articular: Rashes, photosensitivity (eg SLE) Raynaud's (SLE; CREST, p538; poly- and dermatomyositis) Dry eyes or mouth (Sjögren's) Red eyes (eg ank. spond., p536) Diarrhoea/urethritis (Reiter's) Nodules or nodes (RA; TB) Mouth/genital ulcers (Behçet's) Weight loss (eg TB; arthritis)

- ***Related diseases:*** eg Crohn's/UC in ankylosing spondylitis; psoriasis; gonorrhoea; Reiter'sassociated arthritis.
- ***Current & past drugs:*** Disease modifying drugs (p533), NSAIDs
- ***Family history:*** Arthritis, psoriasis, autoimmune disease.

- ***Social history:*** Functioning, eg dressing, writing, walking, domestic situation, social support, home adaptations. Smoking (may worsen RA).

Existential approaches to rheumatology patients

We like to see rheumatology patients early *before* destructive changes take place—but all too often, like François Verret[2] productions, our encounters are multimedia affairs, with conflicting lines of story and mime, ever-changing charts of painful, disjointed images, puzzling manifestations, disorganized articulations, and oblique views (**fig 1**). The diagnosis you arrive at will depend on which layer of this multimedia event you attend to. No single interpretation is universally valid, and in your attempts to lead an authentic life on the wards and in clinics you may frequently need to change your angle of approach. When in doubt (the only valid state of the thinking doctor), ask your patient what is most important. Their answers often focus on other people and their relationships—so find out how these interact with their joint symptoms.

Points to note when assessing the locomotor system

This aims to screen for most rheumatological conditions, and to assess motor disability. It is based on the GALS locomotor screen (below).[3]

Essence

Ask questions; "look, 'feel' and move" (active and passive). If a joint *feels normal* to the patient, *looks normal* to you, and has *full range of movement*, it usually *is* normal. Make sure the patient is comfortable, and obtain their consent before examination: expose the limb, including the joint above the one being examined.

3 screening questions

1. Are you free of any pain or stiffness?
2. Can you dress all right?
3. Can you manage stairs?

If 'Yes' to all 3, muscle/joint problems are unlikely. If 'No' to any, go into detail.

GALS screening examination

To be done in light underwear.

Spine:

Observe from behind: Is muscle bulk OK (buttocks, shoulders)? Is the spine straight? Symmetrical paraspinal muscles? Swellings/deformities? *Observe from the side*: Normal cervical and lumbar lordosis? Kyphosis? '*Touch your toes, please'*: Is lumbar spine flexion normal? *Observe from in front* for the rest of the examination. Ask him to: '*Tilt head towards shoulders*' (without moving the shoulders): is lateral neck flexion normal? Palpate for typical fibromyalgia tender points.[1]

Arms:

'*Try putting your hands behind head'*—tests functional shoulder movement. '*Arms straight*': Tests elbow extension. Also tests forearm supination/pronation. *Examine the hands*: See p27. Any deformity, wasting, or swellings? *Squeeze across 2nd-5th metacarpophalangeal joints*. Pain may denote joint or tendon synovitis. Repeat for metatarsophalangeal joints. '*Put index finger on thumb*'—tests pincer grip. Assess dexterity.

Legs:

Observe legs: Normal quadriceps bulk? Any swelling or deformity or length discrepancy? *Internally/externally rotate each hip in flexion.* Passively flex knee and hip to the full extent. Is movement limited? Any crepitus? *Find any knee effusion*: With patient supine, do the patella tap test. If there is fluid, consider aspirating and testing it for crystals or infection. *Observe feet*: Any deformity? Are arches high or flat? Any callosities? These may indicate an abnormal gait of some chronicity.

Gait:

'Walk over there please': Is the gait smooth? Good arm swing? Stride length OK? Normal heel strike and toe off? Can he turn quickly?

The GALS system for quickly recording your findings[4]

G (Gait) [check mark]		
	Appearance:	Movement:
A (Arms)	[check mark]	[check mark]
L (Legs)	[check mark]	[check mark]

S (Spine)	[check mark]	[check mark]

[check mark] means normal. If not normal, then put a cross with a note to explain what the exact problem is.

Range of joint movement

is noted in degrees, with anatomical position being the neutral position eg elbow flexion 0°-150° normally, with fixed flexion and limited movement, range may be 30°-90°. A valgus deformity points (deviates) away from mid-line (laterally); a varus deformity points towards.

Back pain

This is very common, and often self-limiting; but *be alert to sinister causes* ie malignancy, infection or inflammatory causes. Key points: **1** Onset: sudden (related to trauma?) or gradual? **2** Motor or sensory symptoms? **3** Is the bladder or bowel affected? **4** Is there sciatica? True sciatica radiates into the buttock, back of the thigh, and *below* the knee into the calf and ankle. This is caused by sciatic nerve irritation, and is usually due to a prolapsed disc.

Examination:

1 With the patient standing, gauge the extent and smoothness of lumbar forward/lateral flexion and extension.[1] **2** Neurological deficits: test lower limb sensation, power and reflexes (BOX)—if there is any abnormality, do a PR for perianal tone and sensation. **3** Examine for nerve root pain: this is distributed in relevant dermatomes, and is worsened by coughing or bending forward. Straight leg test is +ve if raising the leg with the knee extended causes pain below the knee, which ↑ on foot dorsiflexion. It suggests irritation to the sciatic nerve (L4, L5, S1). The main cause is lumbar disc prolapse. **4** Signs of generalized disease— malignancy? Also examine other systems (eg abdomen) as pain may be referred.

Causes

Age determines the most likely causes:

- 15-30yrs: Prolapsed disc, trauma, fractures, ankylosing spondylitis (AS; p536), spondylolisthesis (a forward shift of one vertebra over another, which is congenital or due to trauma), pregnancy.
- 30-50yrs: Degenerative spinal disease, prolapsed disc, malignancy (primary or secondary from lung, breast, prostate, thyroid or kidney Ca).
- >50yrs: Degenerative, osteoporotic vertebral collapse, Paget's, malignancy, myeloma, spinal stenosis.

Rarer:

Cauda equina tumours, spinal infection (eg discitis, usually staphylococcal, also *Proteus*; *Escherichia coli*; *S. typhi*; TB): there are often no systemic signs.

Red flags signalling to you that "*this back pain is sinister!*"[5]

- Aged <20yrs or >55yrs old
- Acute onset in elderly people
- Constant or progressive pain
- Nocturnal pain
- ↑Pain on being supine
- Morning stiffness
- Fever, night sweats, weight loss
- History of malignancy
- Thoracic back pain
- Bilateral or alternating symptoms
- Neurological disturbance
- Sphincter disturbance
- Leg claudication (spinal stenosis)
- Current or recent infection
- Immunosuppression eg, steroids/HIV
- Abdominal mass

▸*Neurosurgical emergencies*

•***Acute cauda equina compression:*** Alternating or bilateral root pain in legs, saddle anaesthesia (around anus), loss of anal tone on PR, bladder ± bowel incontinence •***Acute cord compression:*** Bilateral pain, LMN signs at level of compression, UMN and sensory loss below, sphincter disturbance.

Causes

(same for both): bony metastasis (look for missing pedicle on X-ray), large disc protrusion, myeloma, cord or paraspinal tumour, TB (p386), abscess.

ÕUrgent treatment prevents irreversible loss, eg laminectomy for disc protrusions, radiotherapy for tumours, decompression for abscesses.

Tests

are usually only needed if red flags are present: FBC, ESR & CRP (myeloma, infection, tumour), U&E, ALP (Paget's), serum/urine electrophoresis (myeloma), PSA. X-ray may show Paget's, vertebral collapse or spondylolisthesis. MRI is best for disc prolapse, cord compression, cancer, infection or inflammation (eg sacroiliitis).

[prescription take]:

If there is no serious pathology, focus on education and encouragement, as most cases are self-limiting. Analgesia (regular paracetamol ± NSAIDs ± codeine), and returning to normal activities as soon as possible is better than bed rest (which should not be advised).[6] Avoid precipitants and refer to physiotherapy if not improving. Address psycho-social issues (see BOX). Local injections, eg facet joints, may have a role. Surgical options may be considered in a small group of selected patients with intractable symptoms who fail to respond to other measures.

Yellow flags[7]

Psycho-social risk factors for developing persisting chronic pain and long-term disability have been termed ‘yellow flags’. These include:

- Belief that pain and activity are harmful.
- Sickness behaviours such as extended rest.
- Social withdrawal.
- Emotional problems such as low or negative mood, depression, anxiety, stress.
- Problems and/or dissatisfaction at work.
- Problems with claims or compensation or time off work.
- Overprotective family or lack of support.
- Inappropriate expectations of treatment eg low active participation in treatment.

Nerve root lesions

Nerve root	Pain	Weakness	Reflex change
L2	Across upper thigh	Hip flexion, adduction	Nil
L3	Across lower thigh	Hip adduction, knee extension	Knee
L4	Across knee to medial malleolus	Knee extension, foot inversion and dorsiflexion	Knee
L5	Lateral shin to dorsum of foot and big toe	Hip extension and abduction Knee flexion Foot and great toe dorsiflexion	Nil

S1	Posterior calf to lateral foot and little toe	Knee flexion Foot and toe plantar flexion Foot eversion	Ankle

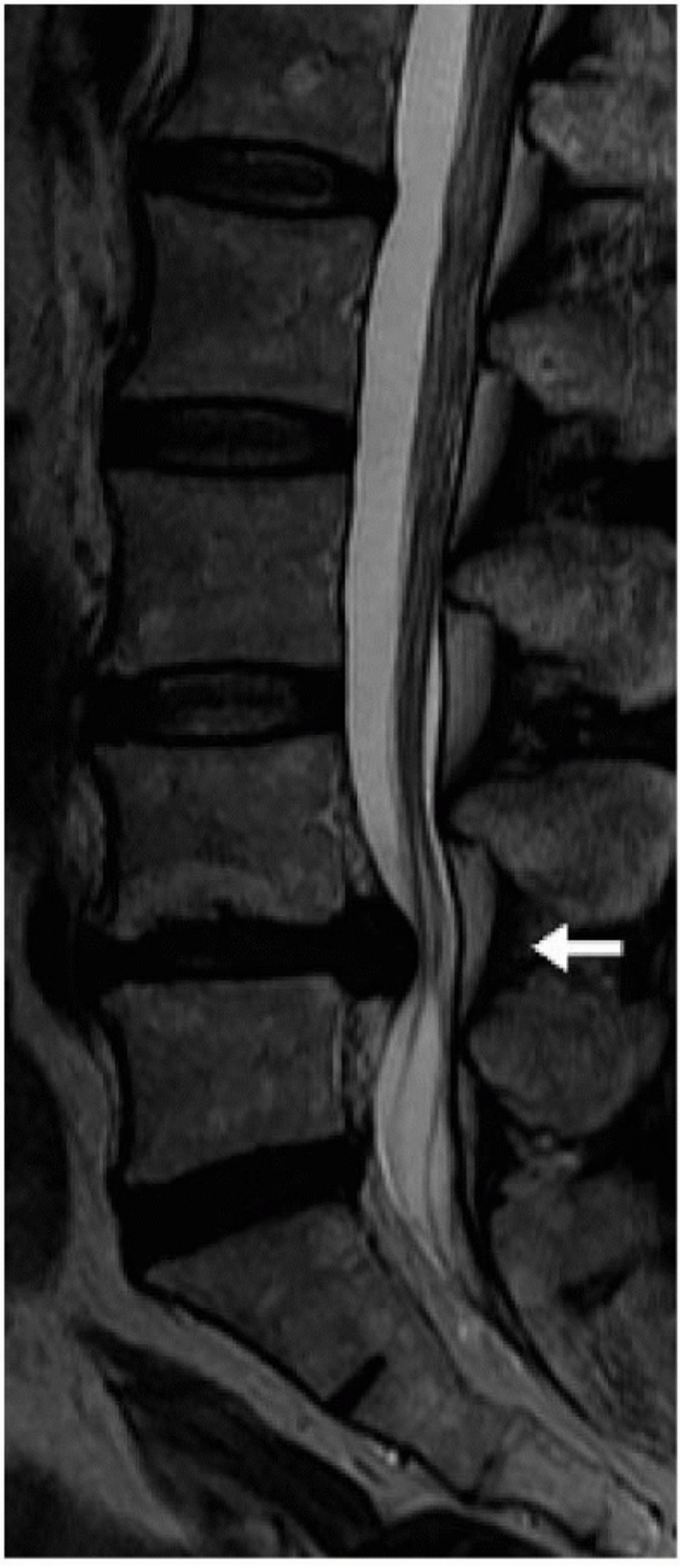


Fig 1. Sagittal T2 weighted MRI of the lumbar spine showing a herniated disc at the L4-L5 space.

Arthritis—general points

Features of inflammatory arthritis

Pain, stiffness (especially early morning >30 minutes), joint inflammation (swelling, redness, warmth) and loss of function.

Causes of inflammatory arthritis and their common presentations

Monoarthritis (1 joint)	Oligoarthritis (≤5 joints)	Polyarthritis (>5 joints)
Septic arthritis	Crystal arthritis	Rheumatoid arthritis
Crystal arthritis (gout, CPPD)	Psoriatic arthritis	Psoriatic arthritis
Osteoarthritis	Reactive arthritis	Reactive arthritis
Trauma	Ankylosing spondylitis	Osteoarthritis
(haemarthrosis)	Osteoarthritis	Systemic conditions[1]

[1] Eg: connective tissue disease (eg SLE), malignancy (eg leukaemia), endocarditis, haemochromatosis, sarcoidosis, sickle cell anaemia, familial Mediterranean fever, Behçet's, relapsing polychondritis.

Diagnosis

▸Consider septic arthritis in any acutely inflamed joint, as this may destroy a joint within 24h. All such joints should be aspirated, and if in doubt treat with antibiotics until results are known. **NB:** inflammation may be less overt if immunocompromised or if there is underlying joint disease.

Assess

Distribution of joint involvement (including spine), symmetry, disruption of joint anatomy, limitation of movement (by pain or contracture), joint effusions and peri-articular involvement (see p527 for full assessment). Look for extra-articular features: skin, nail or eye involvement; dysuria or genital ulcers; lungs, kidneys, heart, GI (eg mouth ulcers, bloody diarrhoea in Crohn's/UC) and CNS systems.

Blood tests:

Culture if septic arthritis. Do FBC, ESR, urate, U&E, CRP. Consider rheumatoid factor, antinuclear antibody, other autoantibodies (p539), and HLA B27 (p536) guided by presentation. Consider causes of reactive arthritis (p536) eg viral serology, urine chlamydia PCR, hepatitis and HIV serology if risk

factors are present.

Radiology:

Look for erosions, calcification, widening or loss of joint space, changes in underlying bone of affected joints (eg periarticular osteopenia, sclerotic areas, osteophytes). Image sacroiliac joints if considering a spondyloarthritis (there is irregularity of the lower half on XR or on MRI, which is more sensitive). Do a CXR for RA, SLE, vasculitis, TB and sarcoid. In septic arthritis, X-rays may be normal, as may ESR and CRP (if CRP ↑, expect it to fall with treatment). Other imaging (ultrasound or MRI) may be more sensitive in identifying joint inflammation or damage than XR.

Joint aspiration:

See OHCS p708. Attempt to aspirate any joint suspected of being infected. Send synovial fluid for white cell count, polarized light microscopy (for crystals, p531) and microbiology for urgent Gram stain and culture. The risk of inducing septic arthritis, using sterile precautions, is <1:10000.[8]

Treatment

is determined by the cause. If septic arthritis is suspected,[2] give good analgesia and ensure blood cultures and synovial fluid have been taken. Then start empirical IV antibiotics until sensitivities are known: flucloxacillin (in adults: ½-1g/6h slowly IV) + benzylpenicillin 1.2g/4h IV ± gentamicin (p738).[9] In infants, *Haemophilus* is common, so give cefotaxime too (50mg/kg/12h IV slowly). If HIV +ve, look for atypical mycobacteria and fungi. Ask a microbiologist how long to continue treatment (eg ²2wks IV, then 4wks PO).[10] Ask for orthopaedic advice for consideration of aspiration (arthrocentesis), lavage, and debridement, especially if there is a prosthetic joint involved.[11] This may be done by arthroscopic means (eg for knee) or open (eg for hip or shoulder, with GA; this allows biopsy—helpful for TB). Splint for ¢48h; then give physiotherapy. ▸*Ask yourself* 'how did the organism get there?' Is there immunosuppression, or a focus of infection (eg pneumonia is present in up to 50% of those with pneumococcal arthritis)?[12]

Synovial fluid in health and disease

Aspiration of synovial fluid is used primarily to look for infection or crystal (gout or CPPD crystal arthropathy, p534).

	Appearance	*Viscosity*	*wbc/mm³*	*Neutrophils*
Normal	Clear, colourless	↑	≲200	None
Osteoarthritis	Clear, straw	↑	≲1000	≲50%
Haemorrhagic[1]	Bloody, xanthochromic	Varies	≲10,000	≲50%
Acutely inflamed	Turbid, yellow	↓		
• RA			1-50000	Varies
• Crystal			5-50000	~80%

Septic	Turbid, yellow	↓	10-100000	>90%

[1] Eg seen with trauma, haemophilia or tumours.

Early treatment of rheumatoid arthritis[13]

Therapeutic strategies for the treatment of rheumatoid arthritis have changed considerably over the past decade, with emphasis shifting towards early assessment, diagnosis and therapy. This has arisen from the concept that there is a 'window of opportunity' in early disease, where using combinations of disease modifying agents ± biological agents (see p533) may alter the disease course, reduce joint damage and provide life-long benefit. Imaging techniques, such as ultrasound and MRI, can help to identify synovitis more accurately, even in joints with normal clinical examination, and have greater sensitivity in detecting bone erosions than conventional XR.[14]

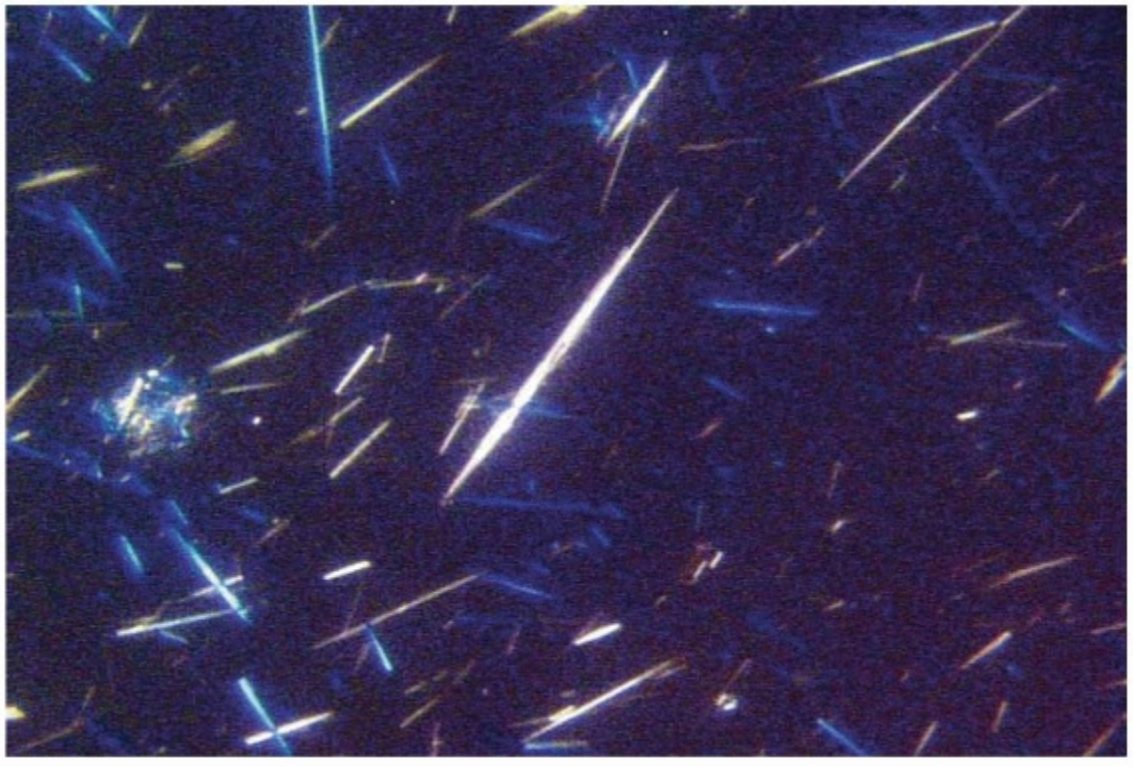


Fig 1. Needle-shaped monosodium urate crystals found in gout, displaying negative birefringence under polarised light.

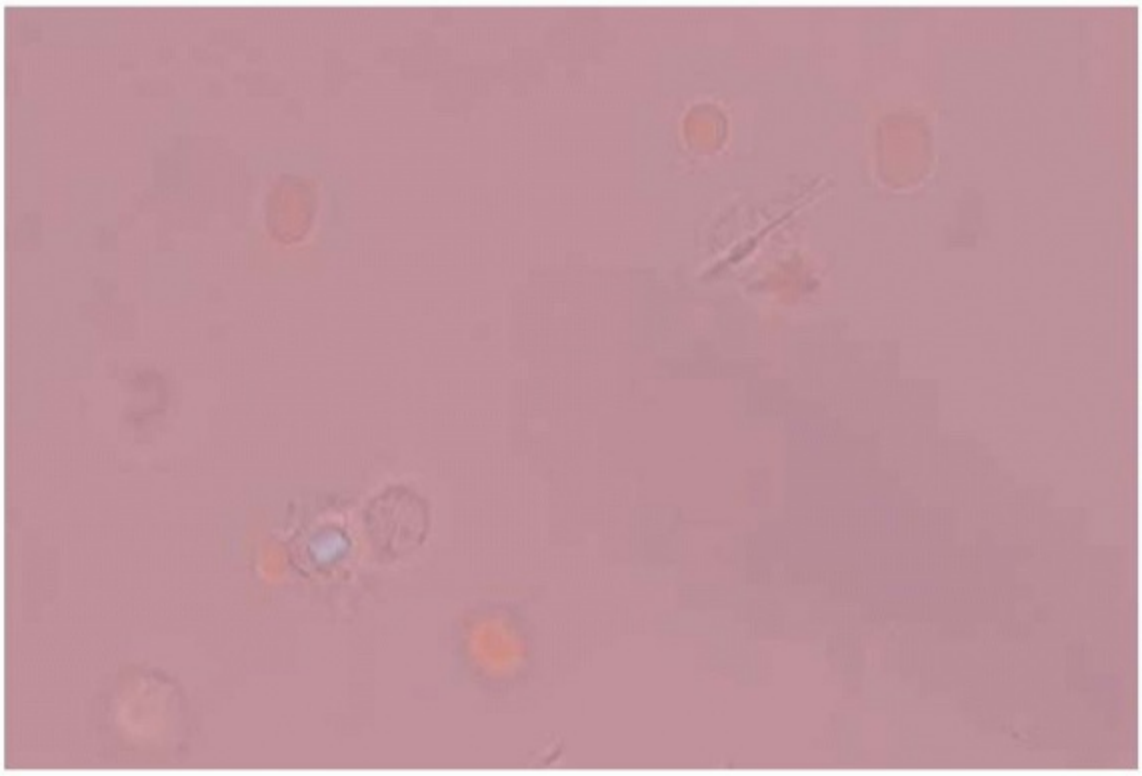


Fig 2. Calcium pyrophosphate dihydrate crystals found in pseudogout, displaying positive birefringence under polarised light.

Rheumatoid arthritis (RA)

RA is a chronic systemic inflammatory disease, characterised by a symmetrical, deforming, peripheral polyarthritis. Peak onset: 4th-5th decade. ý:û >2:1. Prevalence: ~1% (↑ in smokers). HLA DR4/DR1 linked (associated with ↑severity).

Presentation

Typically with symmetrical swollen, painful, and stiff small joints of hands and feet, worse in the morning. This can fluctuate and larger joints become involved. Less commonly presents as a sudden onset of widespread arthritis, or:

1. Recurring mono/polyarthritis of various joints (*palindromic—'was I saw!'*).[1]
2. Persistent monoarthritis (often of 1 knee, shoulder or hip).
3. Systemic illness with extra-articular symptoms eg fever, fatigue, weight loss, pericarditis, pleurisy. Minimal joint problems at first (commoner in men).
4. Polymyalgic onset—vague limb girdle aches.

Signs

Early (inflammation, no joint damage): joint swelling, esp. symmetrical MCP, PIP, wrist, metatarsal joints. Look for tenosynovitis or bursitis. Later (joint damage, deformity): ulnar deviation of the fingers and dorsal wrist subluxation. Boutonnière and swan-neck deformities of fingers or Z-deformity of thumbs occur. Hand extensor tendons may rupture. Foot changes are similar. Larger joints can be involved. Atlanto-axial joint subluxation may threaten the spinal cord.

Extra-articular

Nodules—elbows & lungs; lymphadenopathy; vasculitis; fibrosing alveolitis, obliterative bronchiolitis; pleural & pericardial effusion; Raynaud's; carpal tunnel syndrome, peripheral neuropathy; splenomegaly (in 5%; but only 1% have Felty's syndrome: RA + splenomegaly + neutropenia, p690); episcleritis, scleritis, scleromalacia, keratoconjunctivitis sicca; osteoporosis; amyloidosis (p354).

Tests

Rheumatoid factor (RhF) is +ve in ~70% (p539). A high titre is associated with severe disease, erosions and extra-articular disease. Citrullinated peptide antibodies (anti-CCP) are highly specific, but not widely available. There is often anaemia of chronic disease. Inflammation causes ↑platelets, ↑ESR, ↑CRP.

X-rays

show soft tissue swelling, juxta-articular osteopenia and ↓joint space. Later there may be bony erosions ± subluxation ± complete carpal destruction.

Diagnostic criteria

(for research) include 4 out of 7 of: Morning stiffness (>1 hour lasting >6 weeks), arthritis of ≥3 joints, arthritis of hand joints, symmetrical arthritis, rheumatoid nodules, +ve rheumatoid factor and radiographic changes.[15]

Management

▸Refer early to a rheumatologist for specialist assessment.

- Early use of DMARDs improves symptoms and long term outcomes (see BOX).
- *Steroids*: Rapidly reduce inflammation and control symptoms in the short-term. They are useful for treating acute exacerbations ("flares") of disease eg with IM depot injections of methylprednisolone 80-120mg. Intra-articular steroids also have a rapid but short-term effect (technique see OHCS p708-711). Oral steroids may control difficult symptoms—eg prednisolone 7.5mg/d PO, but long term treatment is not routinely recommended, due to their significant side effects.
- Most will need an *NSAID* to control symptoms, as paracetamol ± weak opiates are rarely effective. NSAIDs are CI in asthma or with an active peptic ulcer. One cannot predict which NSAID a patient will respond to, so different ones can be tried eg ibuprofen, diclofenac, etodolac (see p535). Patients who are >65 or who have a previous history of peptic ulcer need gastric protection eg lansoprazole 30mg/d PO.[16] NSAIDs have little effect on disease progression.
- Encourage regular exercise; physio- and occupational therapy eg for aids, splints.
- Surgery may be considered in the long-term to relieve pain, improve function, and to prevent disease complications (eg ulna stylectomy, joint replacements).
- Risk of cardiovascular and cerebrovascular disease is ↑, as atherosclerosis is accelerated in RA. Manage risk factors (p79). Smoking also ↑symptoms of RA.

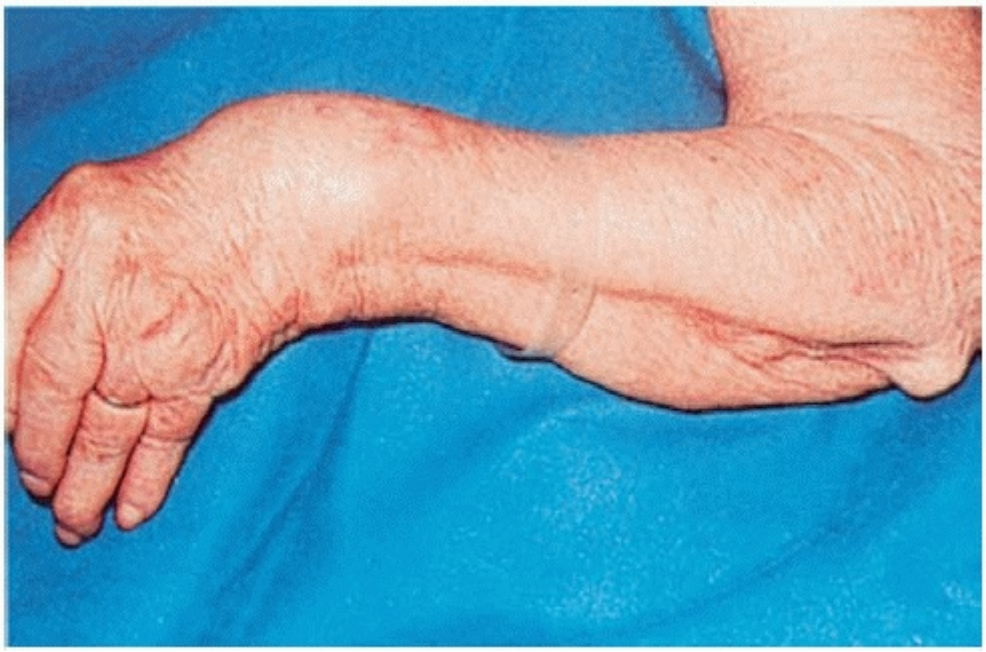


Fig 1. Rheumatoid Arthritis. Note ulna deviation of the fingers.

Influencing biological events in RA

The chief biological event is inflammation. Monocytes traffic into joints, cytokines are produced, fibroblasts and endothelial cells are activated, and tissue proliferates. Fluid is generated (effusion) and cytokines and cellular processes erode cartilage and bone. Cytokines also produce systemic effects: fatigue, accelerated atherosclerosis, and accelerated bone turnover.

Disease-modifying drugs (DMARDs)[1]

modulate the above reaction and slow or stop disease progression. Early DMARD therapy is associated with better long term prognosis. They can take up to 6-12 weeks for symptomatic benefit. Methotrexate and sulfasalazine are typical 1st line choices and may be used together. Regular blood test monitoring is required.[17]

Methotrexate

Given weekly. Avoid in liver disease, pregnancy and if alcohol consumption↑; caution if pre-existing lung disease. SE: oral ulcers, nausea, lethargy, myelosuppression, hepatotoxicity, pneumonitis (rare, but can be life-threatening). Give concurrent folic acid to ↓SE, eg 5mg/2-3 times per wk, PO.

Sulfasalazine

SE: Myelosuppression, nausea, rash, oral ulcers, ↓sperm count.

Leflunomide

may be an alternative to sulfasalazine. SE: Rash, oral ulcers, diarrhoea, ↑BP, myelosuppression, hepatotoxicity. CI: Pregnancy.

Gold

Usually by IM injection. More toxicity than methotrexate or sulfasalazine. SE: Myelosuppression, renal toxicity, rash, mouth ulcers, photosensitivity.

Penicillamine

SE: Myelosuppression, renal toxicity, loss of taste, oral ulcers, myasthenia gravis-like syndrome.

Hydroxychloroquine

Least toxic, but probably least effective. SE: Rash, retinopathy (check vision with an Amsler chart every 12 months, see p540).

Azathioprine

SE: Myelosuppression, nausea, LFT↑. See p360.

Ciclosporin

SE: Nausea, tremor, gum hypertrophy, ↑BP, renal impairment (p360).

▶Myelosuppression (bone marrow suppression) is a potentially serious SE of DMARDS which can result in pancytopenia, with ↑susceptibility to infection and overwhelming sepsis due to neutropenia.

Anti-cytokine therapy[18]

Tumour necrosis factor × (TNF×) and interleukin-1 (IL-1) are cytokines over-produced in RA synovium. TNF× blockers include ***infliximab*** (chimeric murine/human anti-TNF antibody, IV every 8wks p267), ***etanercept*** (TNF× receptor/IgFc fusion protein, SC twice weekly), and ***adalimumab*** (fully human anti-TNF monoclonal antibody, SC every 2wks). These biological agents are approved by NICE for severe active RA after failure to respond to 2 DMARDs. Clinical response can be striking, and improved outcomes have been shown. CI: Pregnancy, breast feeding, active infection, severe heart failure, demyelinating disease, previous Ca. **SE**: (Usually well tolerated): injection reaction, infections, reactivation of TB (∴ screen & consider prophylaxis), worsening of heart failure. Long-term safety is unknown (no clear evidence for ↑cancer). Neutralizing antibodies may ↓efficacy with infliximab; ANA and reversible SLE-type illness may evolve. *Anakinra*, an IL-1 inhibitor, and many more agents are being evaluated.

Osteoarthritis (OA)

OA is the commonest joint condition. ♀:♂≈3:1, usually >50yrs. It is usually primary, but may be secondary to joint disease or other conditions (eg haemochromatosis).

Signs & symptoms

In localised disease (usually knee or hip): pain on movement and crepitus, worse at end of day; background pain at rest; joint gelling—stiffness after rest up to ~30mins; joint instability. In generalised disease—with Heberden's nodes ('nodal OA'; seen mainly in post-menopausal ♀), commonly affected joints are the DIP joints, thumb carpo-metacarpal joints and the knee. There may be joint tenderness, derangement ± bony swelling (Heberden's nodes: bony lumps at DIP; Bouchard's nodes: PIP; "squared" thumb), ↓range of movement and mild synovitis.

Tests

XR shows loss of joint space, subchondral sclerosis and cysts, and marginal osteophytes (see Figure). CRP can be elevated slightly.[19]

Treatment

Do **exercises** (quadriceps exercises to ↑muscle strength and joint stability in knee OA) and keep active. Regular **paracetamol** ± **codeine** for pain. Consider NSAIDs (see BOX). **Reduce weight** if BMI >28, **walking aids**, supportive **footwear**, **physio**; **topical NSAIDs** and **capsaicin** (derived from chillies) may help. The role of hyaluronic acid injections is unclear; glucosamine & chondroitin sulfate 'failed' a 2006 NEJM trial. RCT[20] **Intra-articular steroid injections** help severe symptoms temporarily. **Joint replacement** is the best way to deal with severe OA.

Crystal arthropathies

Gout

When acute, there is severe joint redness, pain, and swelling. It often affects one joint, eg the metatarsophalangeal joint of the big toe (podagra), but can be polyarticular. Gout is associated with ↑plasma urate, and attacks are due to the deposition of monosodium urate crystals in and near joints (may be precipitated by trauma, surgery, starvation, infection or diuretics). With long-term hyperuricaemia, urate deposits (tophi) in the peripheries (pinna, tendons, joints), and renal disease (stones, interstitial nephritis) may occur.

Prevalence:

~1%. ♂:♀≈5:1.

Causes of ↑urate:

Hereditary, dietary purines, alcohol excess (esp beer), diuretics, leukaemia, cytotoxics (tumour lysis), renal impairment.

Diagnosis

depends on finding urate crystals in tissues and synovial fluid (serum urate may be normal).[21] Polarized light microscopy of synovial fluid shows *negatively birefringent* crystals. X-rays show only soft-tissue swelling in the early stages. Later, well-defined 'punched out' erosions are seen in juxta-articular bone. There is no sclerotic reaction, and joint spaces are preserved until late.

Treating acute gout:

Use a **strong NSAID** (eg indomethacin). If CI (eg peptic ulcer), use **colchicine** 0.5mg/ 8-12h,[22] or 0.5mg/2-3h PO until pain goes or D&V occurs or 6mg given. **NB:** in renal impairment, NSAIDs and colchicine are problematic. **Steroids** (oral, IM or intraarticular) may be effective.

Preventing attacks:

Avoid prolonged fasts, alcohol excess, and purine rich food.[1] Lose weight. Avoid low-dose aspirin (it ↑ serum urate). Consider reducing serum urate with long-term **allopurinol** if there are recurrent attacks, tophi or renal stones. Introduction of allopurinol may cause an attack so wait until 3wks after an acute episode, and start with regular NSAID or colchicine cover.

[1] A large prospective study (n=47150) showed an increased risk of gout with high meat (especially beef, pork or lamb) and seafood consumption, but not with consumption of purine rich vegetables or protein. A lower risk was seen with high consumption of low fat dairy products.

Allopurinol dose:

Typically 200mg/24h; max 300mg/8h. Adjust according to serum urate levels. SE: rash, fever, WCC↓. Caution in renal impairment.

Calcium pyrophosphate dihydrate (CPPD) arthropathy

Risk factors:

Old age, OA, hyperparathyroidism, haemochromatosis, hypothyroidism, $\downarrow PO4^{3-}_4$, $\downarrow Mg^{2+}$.

Acute CPPD (pseudogout):

Similar to gout, presenting as a monoarthritis. It affects different joints: knee, wrist or hip. Usually spontaneous, self-limiting, and can be provoked by illness, surgery or trauma.

Chronic CPPD:

Destructive changes like OA, but more severe. Can present as a polyarthritis (pseudo-rheumatoid).

Tests:

Polarized light microscopy of joint fluid: crystals are *weakly positively birefringent*. It is associated with chondrocalcinosis—soft-tissue calcium deposition on X-ray, eg triangular ligament in wrist, or in knee cartilage.

[prescription take]:

Analgesia, NSAIDs. If not working, try steroids (intra-articular, IM or PO) or hydroxychloroquine 200mg/d.[23]

Prescribing NSAIDs: dialogue with patients

Only prescribe NSAIDs after careful risk-benefit analysis individualized for each patient, including indication, dosage, proposed duration of therapy, and medical co-morbidity. The main serious SE are GI bleeding and renal impairment. Many patients prescribed NSAIDs do not need them all the time, so say “Take the lowest possible dose for the shortest possible time.” *Bleeding is more common in those who know less about their drugs.*[24] Explain:

- Drugs are for relief of symptoms: *on good days none may be needed.*
- Abdominal pain may be a sign of impending gut problems: stop the tablets, and come back for more advice if symptoms continue.
- Ulcers may occur with no warning: report black motions (± faints) at once.
- Don't supplement prescribed NSAIDs with ones bought over the counter (eg ibuprofen): mixing NSAIDs can increase risks 20-fold.
- Smoking and alcohol ↑NSAID risk.

When should COX-2 selective NSAIDs be considered?

Not often: perhaps **only** when an NSAID is essential **and** there is past peptic ulceration (but risk is not eliminated, and bleeds that do occur may be very serious) **if** an ordinary NSAID with PPI (proton pump inhibitors, eg omeprazole, the preferred regimen) is problematic —**or** >65yrs old (not on aspirin)—**or** needing high-dose NSAID over a long time. PPIs may also be given with COX-2 inhibitors;[25] it is not known if this works. COX-2 (cyclo-oxygenase-2) selective NSAIDs are not as safe as we had hoped. There is ↑risk of heart failure, MI & stroke.[26] This ↑risk may also apply to conventional NSAIDs.[27] So avoid if known renal failure or vascular disease (past MI/stroke). There is insufficient experience with new COX-2 selective inhibitors (etoricoxib, parecoxib, and lumiracoxib) to recommend their use as 1st-line COX-2 agents.[28]

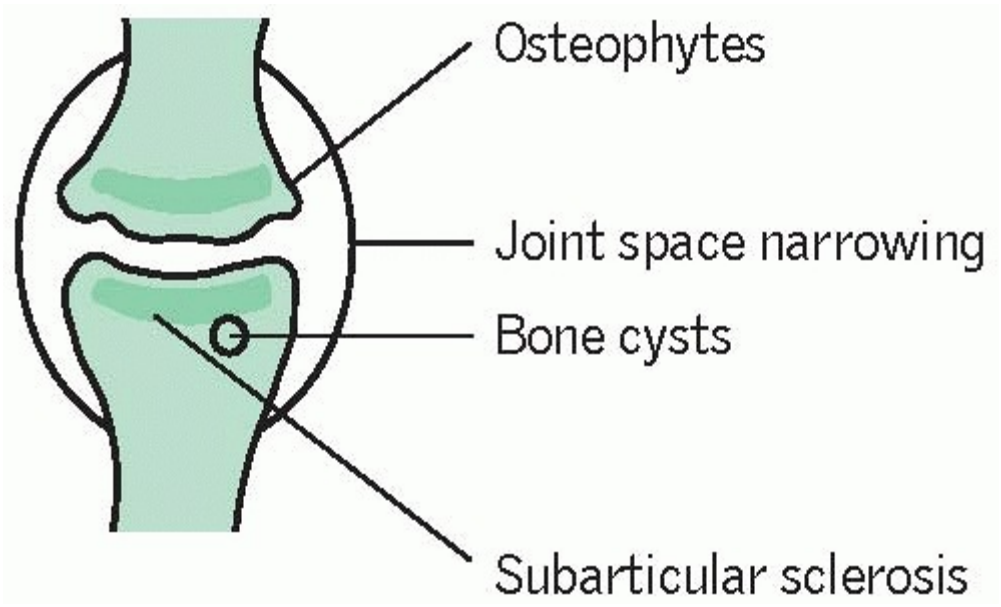


Fig 1. Imaging in osteoarthritis

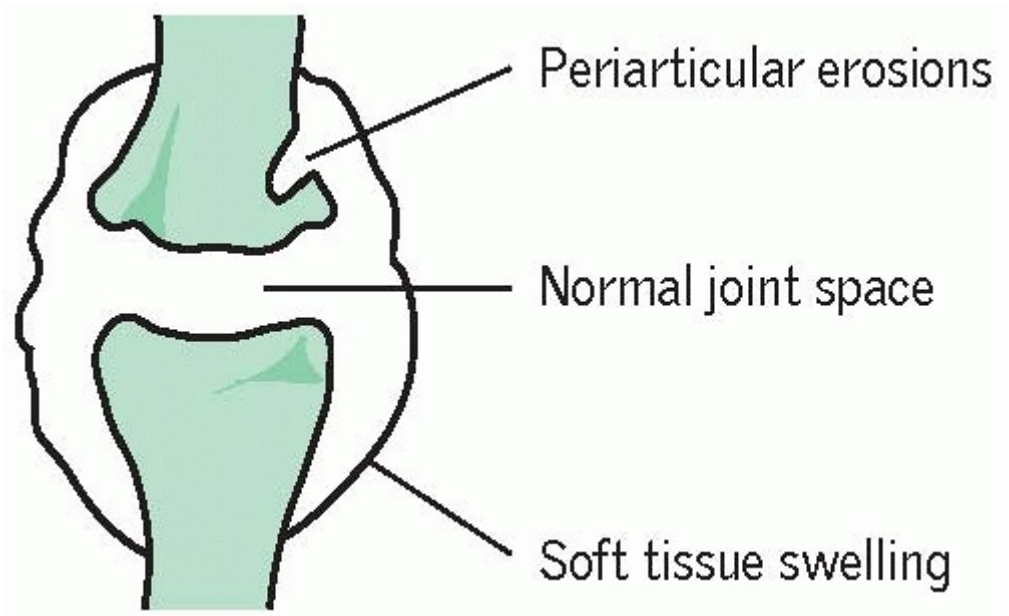


Fig 2. Imaging in gout

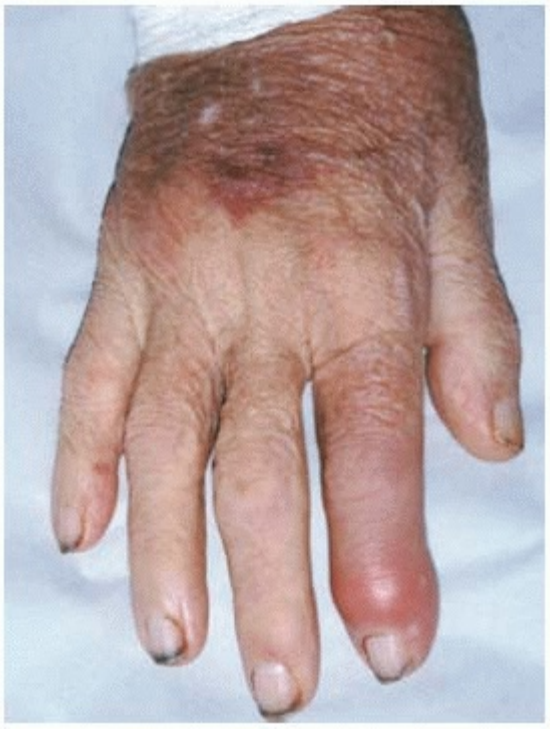


Fig 3. Acute monoarthritis in gout.

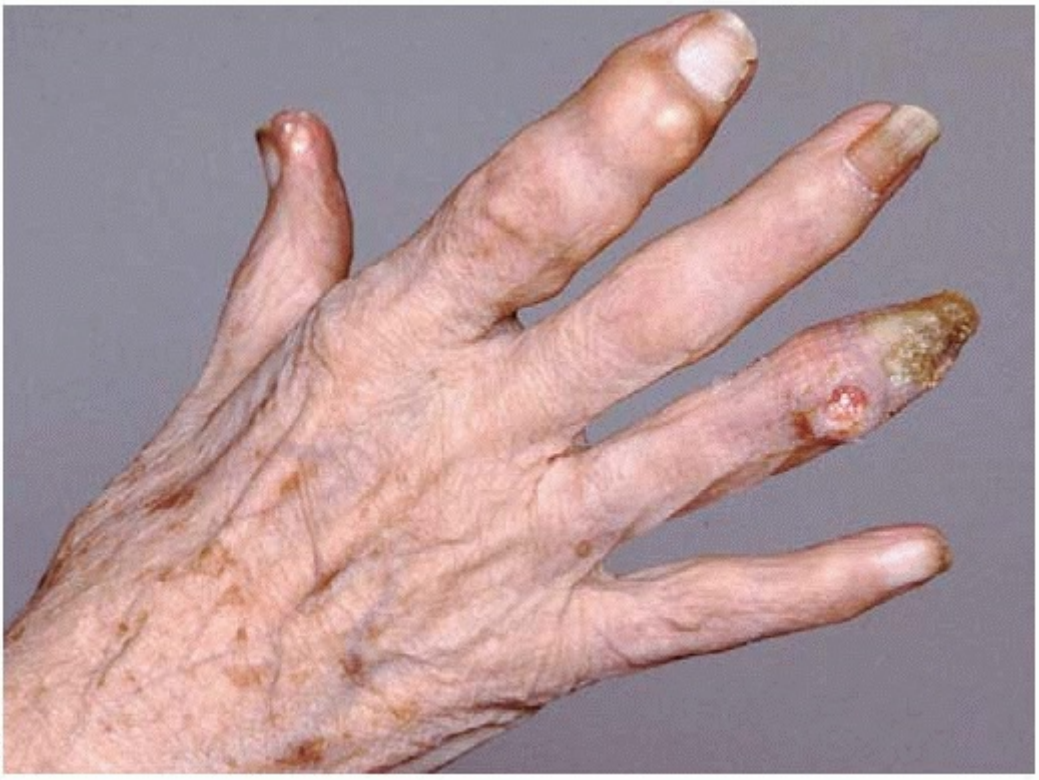


Fig 4. Ulcerated tophi in gout.

Spondyloarthritides

1 Ankylosing spondylitis (AS)

is a chronic inflammatory disease of the spine and sacroiliac joints, of unknown cause.

Prevalence:

0.25-1%. *Men present earlier*: û:ý≈6:1 at 16yrs old, and ≈ 2:1 at 30yrs old. >95% are HLA B27+ve.

Symptoms:

The typical patient is a man <30yrs old with gradual onset of low back pain, worse at night, with spinal morning stiffness relieved by exercise. Pain radiates to the sacro-iliac joints and the hips, and usually improves towards the end of the day. There is progressive loss of spinal movement (all directions)—hence ↓thoracic expansion. The disease course is variable. In a few, there is progression to kyphosis, neck hyperextension (question mark posture), and spino-cranial ankylosis (**fig 1**). Other features include enthesitis (see BOX), especially at the heel (Achilles tendon at the calcaneum and the plantar fascia), tibial and ischial tuberosity, and iliac crests; anterior mechanical chest pain due to costochondral inflammation and fatigue may feature. Acute anterior uveitis (iritis) occurs in ≈1/3 of patients, which may lead to blindness if untreated. AS is also associated with aortitis and aortic regurgitation, pulmonary apical fibrosis, amyloidosis, and other spondyloarthritides.

Tests:

Diagnosis is clinical. Sacroiliitis is the earliest feature (XR may be normal in early disease, MRI is more sensitive): look for irregularities, erosions, or sclerosis affecting the lower half of the sacroiliac joints, especially the iliac side. The spine is affected with characteristic *syndesmophytes*: bony proliferations due to enthesitis between ligaments and the vertebrae. These fuse with the above vertebral body, causing ankylosis. In later stages, calcification of ligaments with ankylosis lead to a 'bamboo spine' appearance. Also: FBC (normochromic anaemia), ↑ESR, ↑CRP, HLA-B27.

[prescription take]:

Exercise, not rest, for backache; there are intense exercise regimens to maintain posture and mobility if able to manage. If no contraindications, use NSAIDs (eg ibuprofen, diclofenac or naproxen) as symptoms are usually relieved within 48h, and they may slow radiographic progression.[29] The TNF× blockers etanercept, infliximab and adalimumab are licensed in AS but await NICE approval (p533;[30]). Local steroid injections provide temporary relief. Surgery includes hip replacement to improve pain and mobility if the hips are involved, and rarely spinal osteotomy. There is ↑risk of osteoporotic spinal fractures (bisphosphonates may prevent this).

Mortality:

Higher than expected ×1.5-4 (eg secondary amyloidosis, heart disease).

2 Enteropathic spondyloarthropathies

Associated with Crohn's/UC. Also GI bypass surgery, and possibly coeliac and Whipple's disease (p709).

3 Psoriatic arthritis

(OHCS p594) Occurs in 10-40% with psoriasis and can present before skin changes. Patterns are (1) Polyarthritis (RA like) (2) DIP joints (3) Asymmetrical oligoarthritis (4) Spinal (AS like) (5) Psoriatic mutilans (rare, severe deformity). XR: erosive changes, with 'pencil-in-cup' deformity in severe cases. Associated with nail changes in 80% (**fig 2**), synovitis (dactylitis—see BOX), acneiform rashes and palmo-plantar pustulosis. Treatments used include NSAIDs, sulfasalazine, methotrexate and ciclosporin. Anti-TNF agents are also effective.

4 Reactive arthritis

A *sterile* arthritis, typically affecting the lower limb ~1-4 weeks following urethritis (p404; *Chlamydia* or *Ureaplasma* species), or dysentery (*Campylobacter, Salmonella, Shigella,* or *Yersinia* species). It may be chronic or relapsing. Also there may be iritis, keratoderma blenorrhagica (brown, raised plaques on soles and palms), circinate balanitis (a painless serpiginous penile ulceration secondary to *Chlamydia trachomatis*), mouth ulcers, enthesitis (plantar fasciitis, Achilles tendonitis) and aortic incompetence (rare).

Reiter's syndrome

is a triad of urethritis, arthritis and conjunctivitis.

Tests:

ESR & CRP↑. Culture stool if diarrhoea, serum for serology. Consider a sexual health review. XR (or ultrasound) may show enthesitis with periosteal reaction.

[prescription take]:

Rest; splint affected joints; treat with NSAIDs or local steroid injections. Consider sulfasalazine or methotrexate. Treating the original infection may make little difference to the arthritis.

Spondyloarthritides typically hold these features in common

1. Seronegativity (rheumatoid factor -ve).
2. HLA B27 association (also in ~5% UK population, most do not have disease)
3. 'Axial arthritis': Pathology in spine (spondylo-) and sacroiliac (SI) joints.
4. Asymmetrical large-joint oligoarthritis (ie <5 joints) or monoarthritis.
5. Enthesitis: Inflammation of the site of insertion of tendon or ligament into bone, eg plantar fasciitis, Achilles tendonitis, costochondritis.
6. Dactylitis: Inflammation of an entire digit ("sausage digit"), due to soft tissue oedema, and tenosynovial and joint inflammation.

7. Extra-articular manifestations eg anterior uveitis, psoriaform rashes, oral ulcers, aortitis and aortic regurgitation, Crohn's or UC.

Spondyloarthritides show much overlap, with shared clinical features.

Juvenile idiopathic arthritis (JIA)

This is the commonest rheumatic disease of childhood, defined as a persistent arthritis lasting more than 6 weeks with an onset <16 yrs old. Recent studies have shown that most children never achieve complete remission. It is therefore important to recognise the disease and treat early, before irreversible deformity and joint damage occurs.[31]

JIA is classified into the following forms:

- Systemic arthritis (formerly Still's disease): swinging pyrexia, rash, arthritis.
- Oligoarthritis: 1-4 joints affected in first 6 months.
  - Persistent: prognosis is generally good, most are self-limiting.
  - Extended: affects other joints after 6 months, with worse prognosis.
- Polyarthritis (RhF +ve: aggressive destructive symmetrical polyarthritis)
- Polyarthritis (RhF -ve: asymmetrical, less severe than RhF +ve disease)
- Psoriatic arthritis: similar to the adult form
- Enthesitis-related arthritis: HLA-B27 linked, asymmetrical lower limb arthritis and enthesitis. There is a risk of developing acute anterior uveitis.

Patients should be referred to a specialist. Treatment is based on NSAIDs, corticosteroids and early use of disease modifying drugs (p533) such as methotrexate, sulfasalazine, leflunomide or anti-TNF agents in severe forms. Corticosteroids have the SE of growth suppression; intra-articular injections may be used to minimise this.

Fig 1. Question mark posture in ankylosing spondylitis.

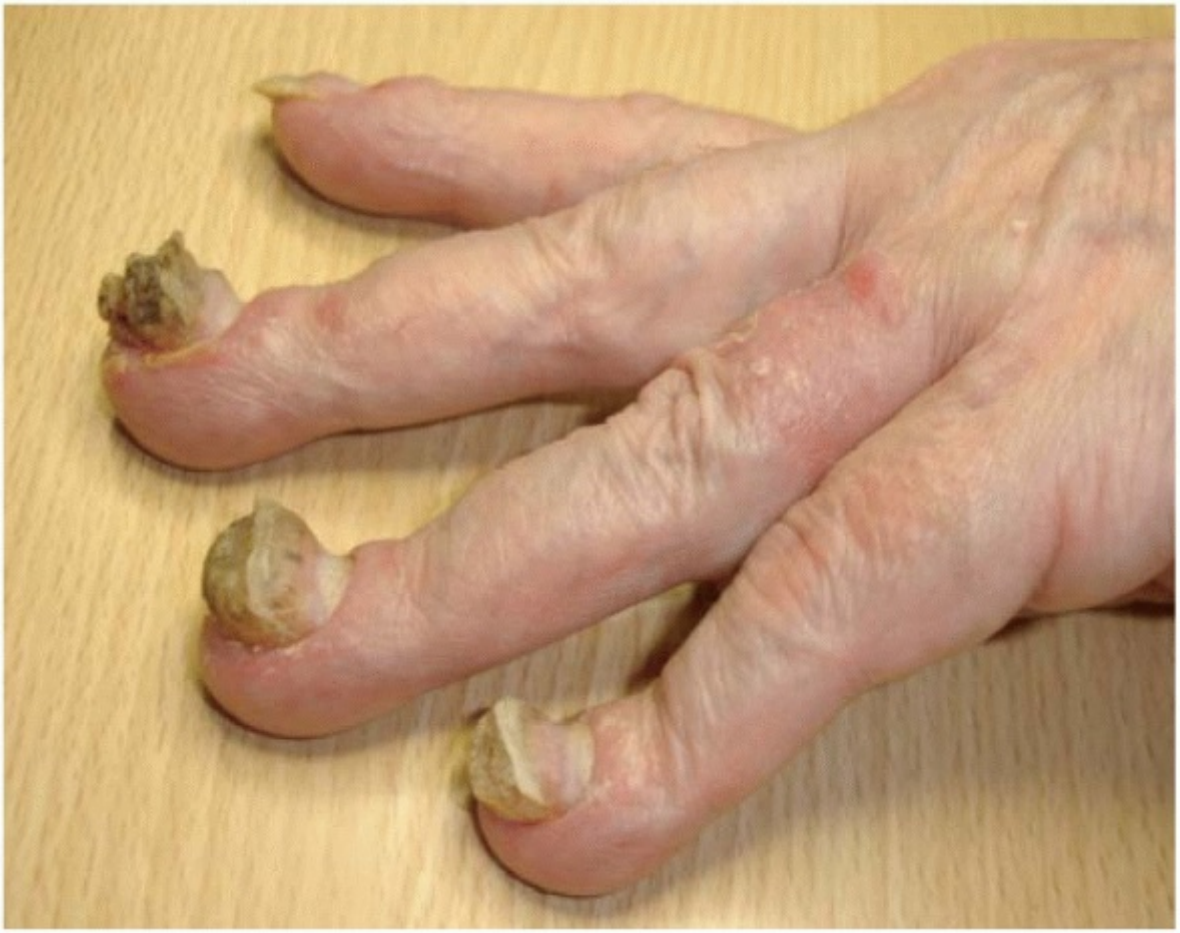


Fig 2. Nail changes in psoriasis: gross onycholysis is seen.

Autoimmune connective tissue diseases

Essence

Included under this heading are: SLE (p540), diffuse and limited systemic sclerosis, primary Sjögren's syndrome (p702), idiopathic inflammatory myopathies, mixed connective tissue disease, relapsing polychondritis, and Behçet's disease (p686). They overlap with each other, affect many organ systems, and often require immunosuppressive therapies (p360). Consider connective tissue disease in ill patients with multi-organ involvement, especially if there is no infection.

Systemic sclerosis

features scleroderma (skin fibrosis) and vascular disease:

- ***Limited systemic sclerosis:*** (of which **CREST** syndrome is part) **C**alcinosis (subcutaneous tissues), **R**aynaud's, o**e**sophageal and gut dysmotility, **S**clerodactyly, and **T**elangiectasia. Skin involvement is limited to the face, hands and feet. It is associated with anticentromere antibodies in 70-80%, and pulmonary hypertension (may be subclinical initially).
- ***Diffuse systemic sclerosis:*** 'Diffuse' skin involvement, whole body in severe cases. More profound organ fibrosis: lung, cardiac, and renal disease (p306). Antitopoisomerase-1 [scl70] antibodies are found in 40% and anti-RNA polymerase in 20%. *Prognosis:* Often poor; monitor with annual echocardiogram & spirometry.
- ***Therapy:*** Currently no cure. Immunosuppressive regimes, including IV cyclophosphamide, are used for organ involvement or progressive skin disease. Raynaud's: Hand warmers, calcium antagonists, ACE-i, A2R blockers or intermittent IV prostacyclin are used. Regular ACE-i ↓risk of renal crisis (p306).

Mixed connective tissue disease (MCTD)

combines features of systemic sclerosis, SLE and polymyositis. There is debate as to whether this is a distinct disease.[32]

Relapsing polychondritis

attacks cartilage, affecting the pinna (floppy ears), nasal septum ± larynx (hence stridor). Associations: aortic valve disease, polyarthritis and vasculitis.

[prescription take]:

Steroids and immunosuppressives.

Polymyositis and dermatomyositis

Both feature progressive symmetrical proximal muscle weakness from *striated* muscle inflammation. Muscle weakness may also cause dysphagia, dysphonia (problems with the mechanics, not the idea, of speech production, ie phonation), or respiratory weakness. There is ↑ risk of malignancy, especially in dermatomyositis.

Dermatomyositis

also features skin signs: • Macular rash (***shawl sign*** is +ve if over back & shoulders) • lilac-purple ***(heliotrope)*** rash on eyelids often with oedema • nail-fold erythema ***(dilated capillary loops)*** •roughened red papules over the knuckles, also seen on elbows, knees ***(Gottron's papules***—pathognomonic if CK↑ + muscle weakness) •subcutaneous calcifications •***Mechanic's hands:*** a painful rough skin cracking, affecting the tips and lateral aspects of the fingers.

Extra-muscular signs

in both conditions include fever, arthralgia, Raynaud's, lung (interstitial fibrosis) and myocardial involvement (myocarditis, arrhythmias).

Diagnosis

Muscle enzymes (ALT & CK) ↑ in plasma; electromyography (EMG: shows fibrillation potentials); muscle biopsy confirms the diagnosis. ***Autoantibody associations:*** anti-Mi-2, anti-Jo1—associated with a syndrome of acute onset, fever, interstitial lung fibrosis, Raynaud's, arthritis and Mechanic's hands.

Differentials

Carcinomatous myopathy, inclusion-body myositis, muscular dystrophy, endocrine/metabolic myopathy (including steroids), rhabdomyolysis, infection (eg HIV), drugs (penicillamine, colchicine, statins or chloroquine).

Management

Screen for malignancy.[1] Start prednisolone (eg 1mg/kg/24h PO). Immunosuppressives (p360) and cytotoxics are used early in resistant cases, eg azathioprine, methotrexate, cyclophosphamide or ciclosporin. Hydroxychloroquine, dapsone, thalidomide or topical tacrolimus may help with skin disease. A more aggressive form with prominent vasculitis and calcinosis occurs in children.

Plasma autoantibodies (Abs): disease associations

Always interpret in the context of clinical findings:

Rheumatological

Rheumatoid Factor (RhF): +ve in (%)

Sjögren's syndrome	≤100	Mixed connective tissue disease	50
Felty's syndrome	≤100	SLE	≤40
RA	70	Systemic sclerosis	30
Infection (endocarditis, Hepatitis)	≤50	Normal	2-10

Anti-nuclear antibody (ANA) Detected by immunofluorescence methods:

SLE	>95	RA	30

Autoimmune hepatitis	75	JIA (p299)	16
Sjögren's syndrome	68	Normal	0-2
Systemic sclerosis	64		

ANA titres are expressed according to dilutions at which antibodies can be detected ie 1:160 means antibodies can still be detected after the serum has been diluted 160 times. Titres of 1:40 or 1:80 may not be significant.

The pattern of staining may indicate the disease (although these are not specific):

- *Homogeneous* SLE
- *Speckled* Mixed connective tissue disease
- *Nucleolar* Systemic sclerosis
- *Centromere* Limited systemic sclerosis

Anti-histone Ab: Drug-induced SLE (~100%).
Anti-double stranded DNA (dsDNA): SLE (60%, more specific than ANA).
Anti-phospholipid Ab (eg anti-cardiolipin Ab): antiphospholipid syndrome, SLE.
Anti-centromere Ab: limited systemic sclerosis.
Anti-extractable nuclear antigen (ENA) antibodies (usually with +ve ANA)

- **Anti-Ro (SSA)** SLE, Sjögren's syndrome, systemic sclerosis. Associated with congenital heart block.
- **Anti-La (SSB)** Sjögren's syndrome, SLE (15%).

• **Anti-Sm**	SLE (20-30%)
• **Anti-RNP**	SLE, mixed connective tissue disease.
• **Anti Jo-1; Anti-Mi-2**	Polymyositis, dermatomyositis.
• **Anti-Scl70**	Diffuse systemic sclerosis.

GastroIntestinal

Anti-mitochondrial Ab (AMA): Primary biliary cirrhosis (PBC: >95%).

Also: autoimmune hepatitis (30%), idiopathic cirrhosis (25-30%).

Anti-smooth muscle Ab (SMA): Autoimmune hepatitis (70%), PBC (50%), idiopathic cirrhosis (25-30%).

Gastric parietal cell Ab: Pernicious anaemia (>90%), atrophic gastritis (40%).

Also: autoimmune thyroid disease (40%), 'normal' controls (10-15%).

Intrinsic factor Ab: Pernicious anaemia (50%).

α-gliadin Ab, anti-tissue transglutaminase, anti-endomysial Ab: Coeliac disease.

Endocrine

Thyroid peroxidase Ab (TPO): Hashimoto's thyroiditis (80-95%), Graves' (50-80%).

Islet cell Ab (ICA), glutamic acid decarboxylase (GAD) Ab: Type 1 DM (75%).

Renal

Glomerular basement membrane Ab (GBM): Goodpasture's syndrome.

Anti-neutrophil cytoplasmic Ab (ANCA):

- **Classical cytoplasmic (c-ANCA)**, with specificity for serine proteinase-3 (PR3 +ve). Wegener's granulomatosis (90%). Also microscopic polyangiitis (30%), PAN (11%).
- **Perinuclear (p-ANCA)**, with specificity for myeloperoxidase (MPO +ve).
  Microscopic polyangiitis (45%), Churg-Strauss, Goodpasture's.

ANCA may also be +ve in UC/Crohn's, primary sclerosing cholangitis, autoimmune hepatitis, Felty's, RA, SLE, or drugs (antithyroid, allopurinol, sulfasalazine, ciprofloxacin).

Neuromuscular

Acetylcholine receptor (ACR) Ab: Myasthenia gravis (90%).

Systemic lupus erythematosus (SLE)

SLE is a multi-systemic autoimmune disease in which autoantibodies are produced against a variety of autoantigens (eg ANA). Immunopathology results in polyclonal B-cell secretion of pathogenic autoantibodies and subsequent formation of immune complexes which deposit in sites such as the kidneys.[33] ý : û ≈ 9:1, typically women of child-bearing age.

Prevalence:

≈0.2%.

Common in:

Afro-Caribbeans, Asians, and if HLA B8, DR2 or DR3 +ve. ≈10% of relatives may be affected.

Clinical features

It is a remitting and relapsing illness. See BOX. Also: fatigue (can be disabling), pyrexia during flares, weight loss, myalgia, lymphadenopathy, alopecia, nail-fold infarcts, non-infective endocarditis (Libman-Sacks syndrome), serositis, Raynaud's (in 1/3; image p701), CNS disturbance (partly due to antiphospholipid syndrome—see below): psychosis, seizures, migraines (40%), and retinal exudates. There is an increased long-term risk of CVS disease and osteoporosis.

Immunology

>95% are ANA +ve. A high titre of antibodies directed against double-stranded DNA (dsDNA) is almost exclusive to SLE, but only ~60% of cases are +ve. 40% are Rh factor +ve. There may be false +ve syphilis serology due to anticardiolipin antibodies (see below). SLE is associated with other autoimmune conditions: Sjögren's (15-20%), autoimmune thyroid disease (5-10%).

Monitoring activity

3 best tests: (1) Double-stranded (anti-ds) DNA antibody titres. (2) Complement: C3↓, C4↓ (denotes consumption of complement, hence C3 and C4↓, and C3d and C4d↑, their degradation products). (3) ESR. Also: BP, urinalysis for blood or protein, FBC, U&E, LFT, CRP. CRP is often normal: *think of* SLE *whenever someone has a multisystem disorder and* ESR↑ *but* CRP *normal*. If CRP is raised, think instead of infection, serositis or arthritis. Skin or renal biopsies may be diagnostic.

Drug induced lupus

Causes (>50 drugs) include isoniazid, hydralazine (if >50mg/24h in slow acetylators), procainamide, chlorpromazine, minocycline, phenytoin. It is associated with antihistone antibodies in up to 100%. Skin and lung signs prevail (renal and CNS are rarely affected). The disease remits if the drug is stopped. Sulfonamides or the oral contraceptive pill may worsen idiopathic SLE.

Antiphospholipid syndrome

Occurs 'secondary' to SLE (in 20-30%) or as a primary disease (the majority). Antiphospholipid antibodies are present: anticardiolipin antibody and lupus anticoagulants. These produce features of **CLOT**: **C**oagulation defect, **L**ivedo reticularis (p542), **O**bstetric: recurrent miscarriage, **T**hrombocytopenia (↓platelets). There is a prothrombotic tendency, affecting the cerebral (stroke), renal and cardiovascular circulation.

[prescription take]:

Low dose aspirin, or warfarin if recurrent thromboses (aim INR of 2-3[34]). Seek advice in pregnancy.

Treatment

- High factor ***sun-block creams*** (OHCS p602).
- ***Hydroxychloroquine*** if joint or skin symptoms uncontrolled by NSAIDs, 200-400mg/day PO. SE: irreversible retinopathy—do baseline and annual assessment.[1]
- ***Low-dose steroids*** may be of value in chronic disease.
- ***High-dose prednisolone*** (PO/IV) is used, often with IV cyclophosphamide, for severe flares of SLE (eg haemolytic anaemia, nephritis, severe pericarditis or CNS disease). Azathioprine may be used as maintenance treatment. **NB:** immunosuppressed patients are prone to infection, which can present atypically.

Lupus nephritis:

(p306) Requires intensive immunosuppression, usually steroids + cyclophosphamide (monthly IV or daily oral doses). SE (p360): myelosuppression, nausea, alopecia, haemorrhagic cystitis, infertility (important in this patient group). Azathioprine or mycophenolate are alternatives. BP control is vital: ACE-i, α-blockers (eg doxazosin) or calcium channel blockers (eg nifedipine) are used. Renal replacement (dialysis or transplant) may be needed if disease progresses; nephritis recurs in ~50% post-transplant, but is a rare cause of graft failure.[35]

[1] Refer to ophthalmology for assessment if there is visual impairment, changes in acuity or >5 years treatment. Royal College of Ophthalmologists Guidelines 2004.

The future

A more targeted approach, such as using the B-cell depleting anti-CD20 monoclonal antibody rituximab (p346), has shown promise.[36]

Revised criteria (serial or simultaneous) for diagnosing SLE[37]

Diagnose SLE in an appropriate clinical setting if ³4 out of 11 criteria are present.

1. ***Malar rash (butterfly rash):*** Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds. Occurs in up to 1/3.
2. ***Discoid rash:*** Erythematous raised patches with adherent keratotic scales & follicular plugging ± atrophic scarring. Think of it as a 3-stage rash affecting ears, cheeks, scalp, forehead, and chest: erythema→pigmented hyperkeratotic oedematous papules→atrophic depressed lesions.
3. ***Photosensitivity:*** on exposed skin representing unusual reaction to light. Exposure to sun may also cause disease to flare, so sunblocks are advised.
4. ***Oral ulcers:*** Oral or nasopharyngeal ulceration, usually painless.
5. ***Non-erosive arthritis:*** involving ≥2 peripheral joints (tenderness, swelling, or effusion). Joint involvement is seen in 90% of patients, and may present similar to RA. A reversible deforming arthropathy may occur due to capsular laxity (Jaccoud's arthropathy). Aseptic bone necrosis may also occur.
6. ***Serositis:*** (a) **Pleuritis** (presents as pleuritic pain or dyspnoea due to pleural effusion—80% have lung function abnormalities) OR (b) **Pericarditis** (chest pain, ECG, pericardial rub or signs of pericardial effusion).
7. ***Renal disorder:*** (a) **Persistent proteinuria** >0.5g/d (or >3+ on dipstix) OR (b) **Cellular casts**—may be red cell, granular, or mixed. See p306.

8. **CNS *disorder:*** (a) **Seizures**, in the absence of causative drugs or metabolic imbalance, eg uraemia or ketoacidosis, OR (b) **Psychosis** in the absence of causative drugs/metabolic derangements, as above.
9. ***Haematological disorder:*** (a) **Haemolytic anaemia** (p322) OR (b) **Leukopenia**, ie WCC $<4\times10^9$/L on ≥2 occasions OR (c) **Lymphopenia**, ie $<1.5\times10^9$/L on ≥2 occasions OR (d) **Platelets** $<100\times10^9$/L in the absence of a drug effect.
10. ***Immunological disorder:*** (a) **Anti-dsDNA** antibody (b) **Anti-Sm** antibody OR (c) Antiphospholipid antibody +ve based on:
    - An abnormal serum level of IgG or IgM anticardiolipin antibodies,
    - Positive result for lupus anticoagulant using a standard method, or
    - False +ve syphilis serology, +ve for >6 months and confirmed by -ve *Treponema pallidum* immobilization & fluorescent treponemal antibody absorption tests.[39]
11. ***Antinuclear antibody (*ANA*):*** +ve in >95%. A useful mnemonic is '**A RASH POINT**S an **MD**'....to a possible diagnosis.[40] **A**rthritis, **R**enal disorder, **A**NA, **S**erositis, **H**aematological, **P**hotosensitivity, **O**ral ulcers, **I**mmunological disorder, **N**eurological disorder, **M**alar and **D**iscoid rash.

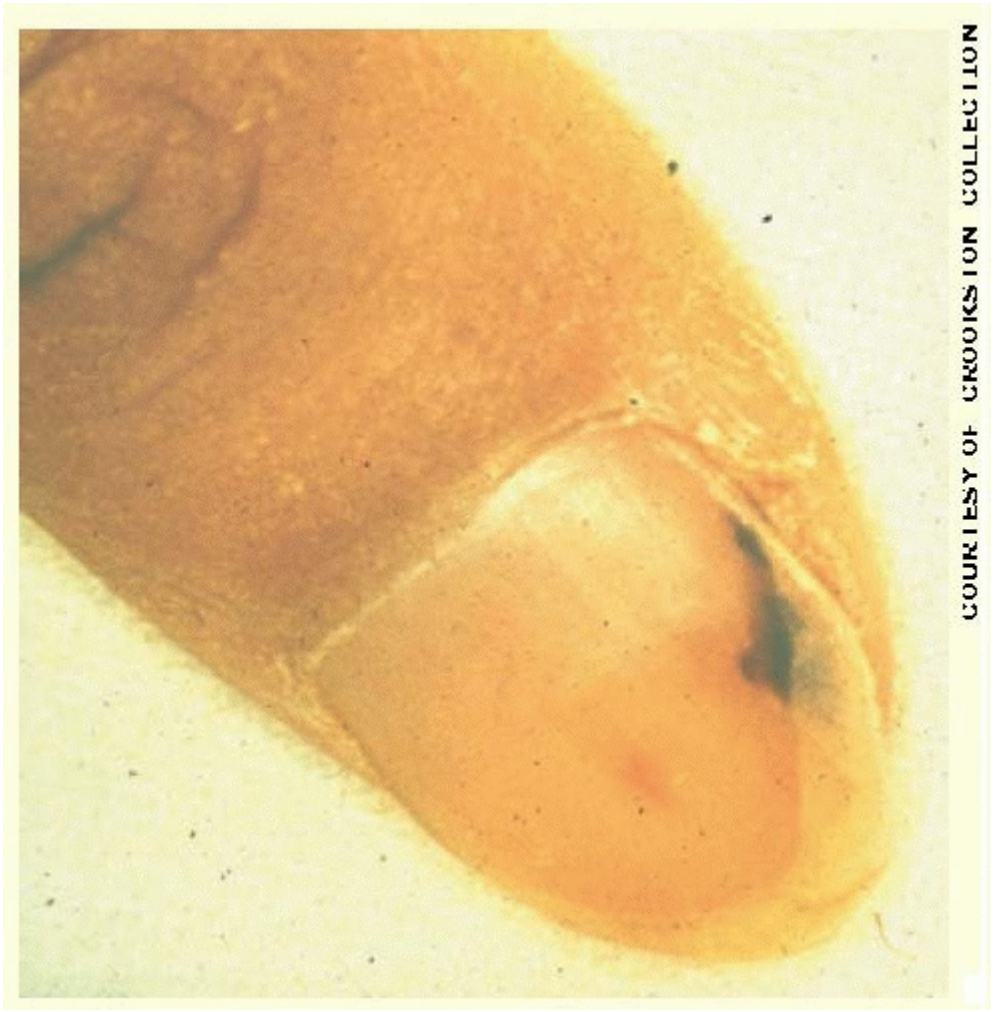


Fig 1. Nail-fold infarct. Sometimes immunological events are seen directly, as here—under the nail.[38]

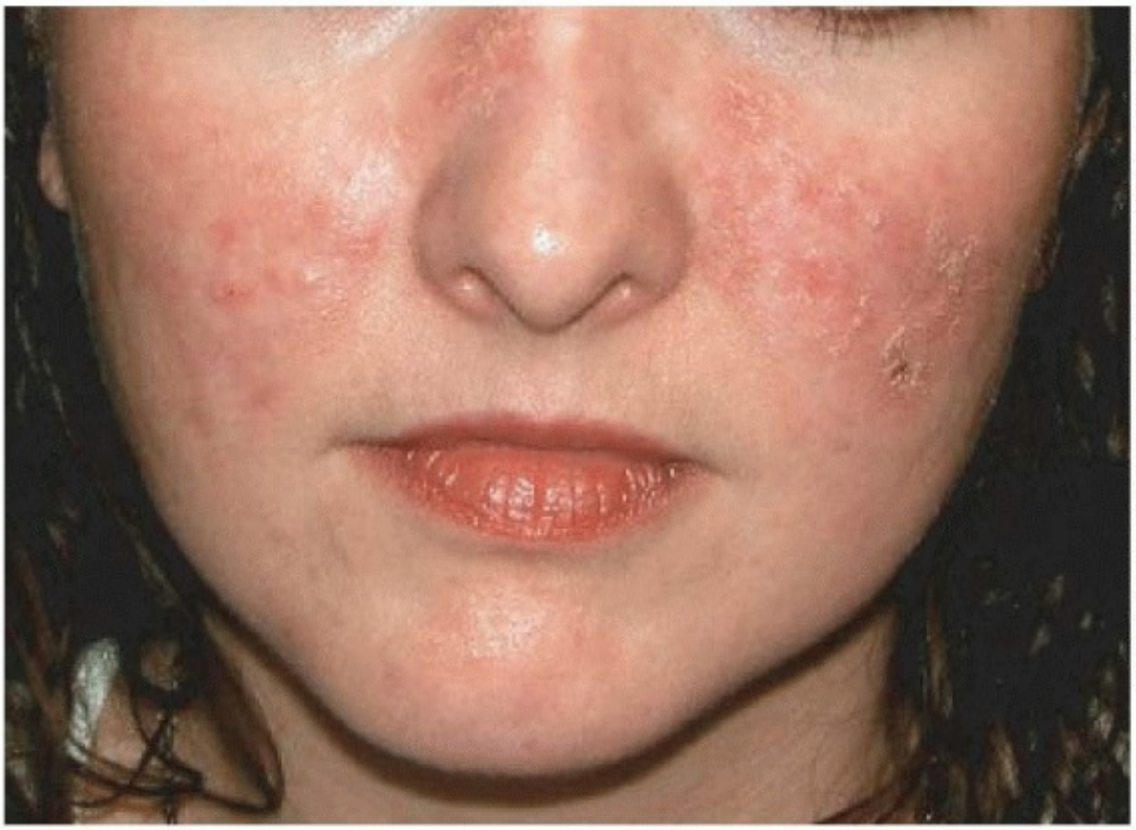


Fig 1. Malar rash; nasolabial folds spared.[41]

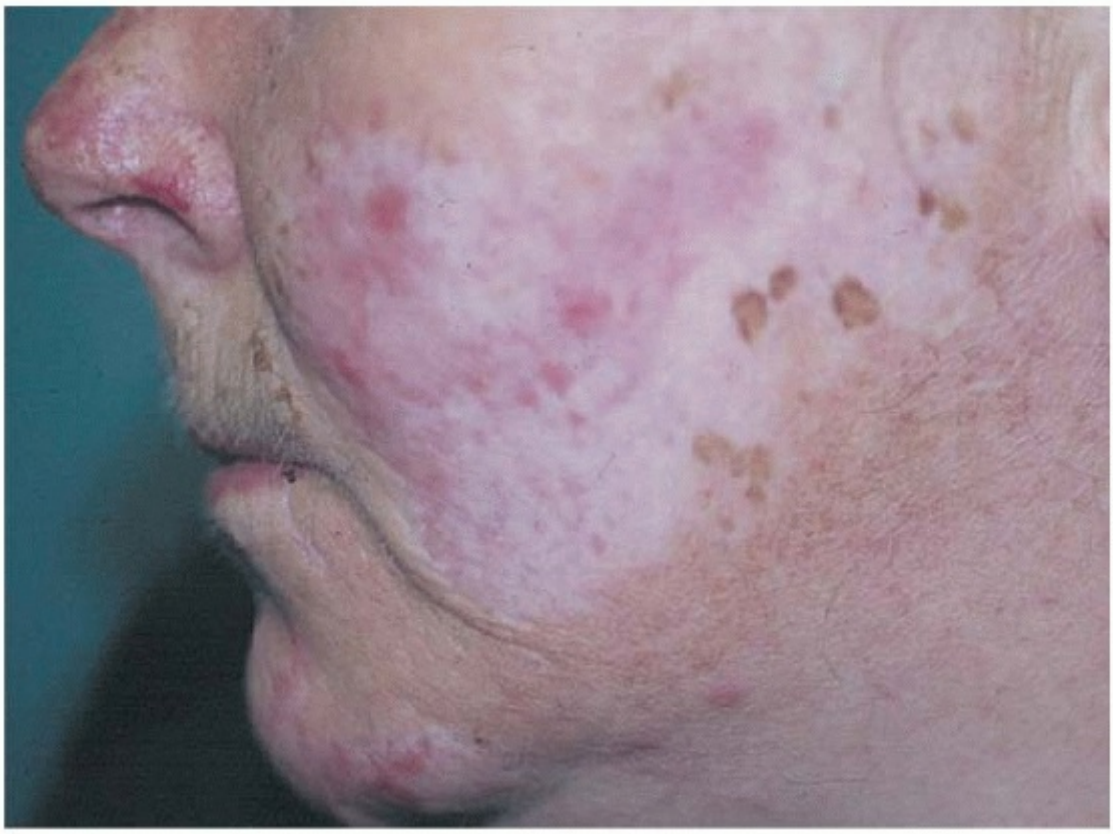


Fig 2. Discoid rash.[42]

Vasculitis

Vasculitis is defined as an inflammatory disorder of blood vessel walls and can affect vessels of any organ. They are divided according to the main size of blood vessel affected:

Large:

Giant cell arteritis, Takayasu's arteritis (p704);

Medium:

Polyarteritis nodosa (BOX), Kawasaki disease;

Small:

Subdivided into **ANCA+ve**— these are associated with glomerulonephritis: Wegener's granulomatosis (p706), microscopic polyangiitis[1], Churg-Strauss syndrome (p688); **ANCA-ve**: Henoch-Schönlein purpura (p694), cryoglobulinaemia, Goodpasture's disease (p692). Vasculitis may also be secondary to other diseases eg SLE, RA, hepatitis B and C, HIV.

▲*Consider vasculitis as a diagnosis in any unidentified multisystem disorder*. Organ damage may result from acute vasculitis, recurrent attacks, or treatment.

Features seen in many vasculitides (see also individual disease): Systemic: fever, malaise, weight↓, arthralgia, myalgia. By organ:

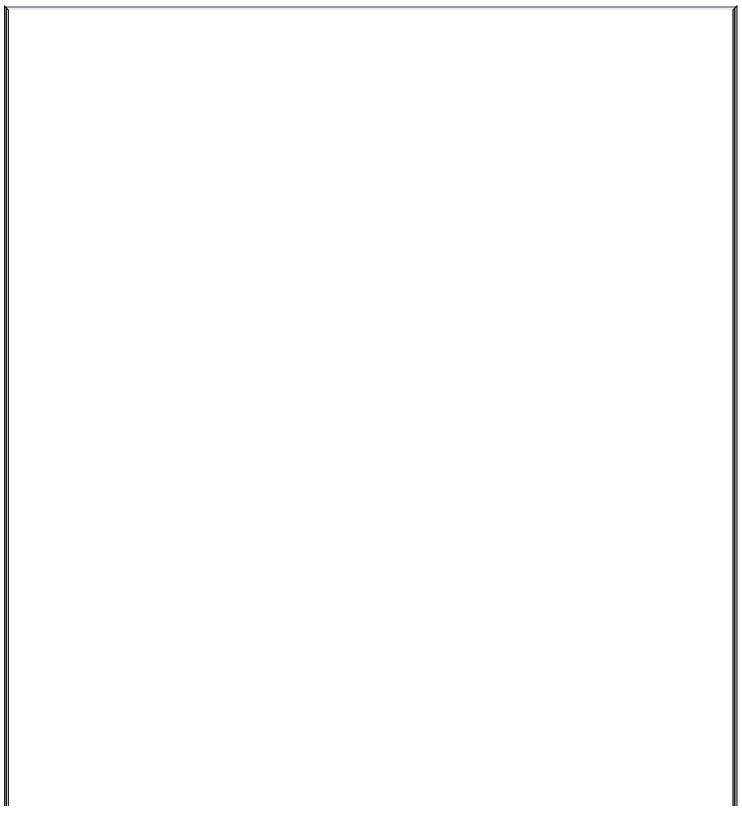
- Skin: Purpura, ulcers, livedo reticularis, nailbed infarcts, digital gangrene.
- Eyes: Episcleritis, ulcers, visual loss.
- ENT: Epistaxis, nasal crusting, stridor, deafness.
- Pulmonary: Haemoptysis, dyspnoea.
- Cardiac: Heart failure, angina/MI.
- GI: Pain, malabsorption, due to chronic ischaemia.
- Renal: BP↑, haematuria, proteinuria, casts, acute or chronic renal failure.
- Neurological:[43] Mononeuritis multiplex, sensorimotor neuropathy, stroke, fits, chorea, psychoses, confusion, cognition↓, mood↑↓.

Diagnosis:

Clinical findings, supported by histology (± angiographic findings). ESR/CRP↑. ANCA may be +ve.

[prescription take]:

Large vessel vasculitis: steroids in most cases. Medium/Small: standard therapy is steroids (10mg/kg IV) + cyclophosphamide (15mg/kg IV).[44] Azathioprine may be used as maintenance treatment.



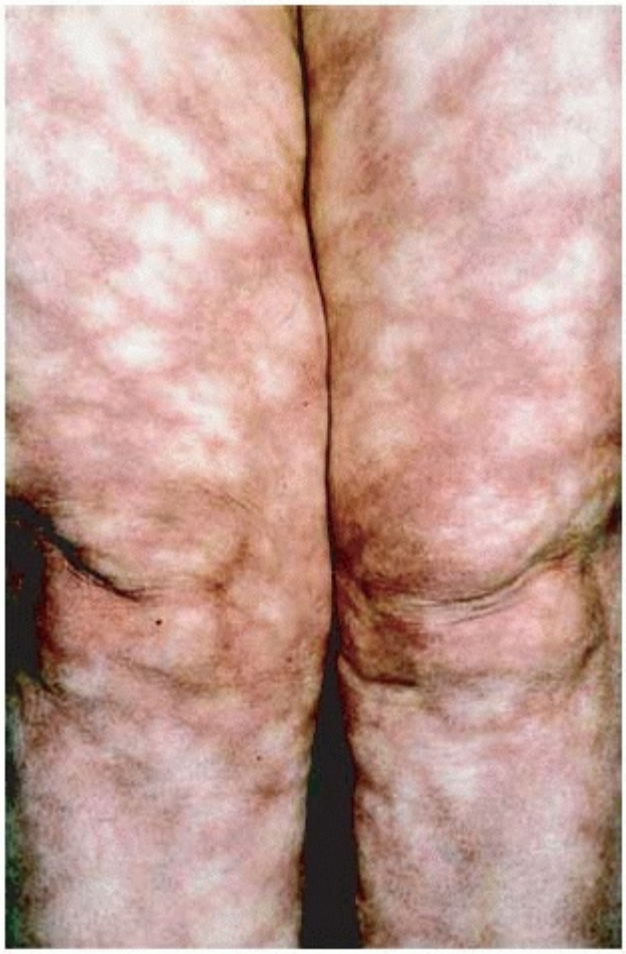


Fig 1. Livedo reticularis.[2]

Giant cell (or cranial or temporal) arteritis (GCA)

GCA is associated with polymyalgia in 25% of patients. Common in the elderly, it is rare <55yrs.

Symptoms:

Headache, temporal artery and scalp tenderness (eg on combing hair), jaw claudication, amaurosis fugax or sudden blindness in one eye. The risk is irreversible visual loss, which occurs in the 2nd eye if not treated.

Tests:

ESR and CRP↑, platelets↑, alk phos↑, Hb↓. ▸If you suspect GCA, do an ESR and start prednisolone 40-60mg/24h PO *immediately*. Some advocate higher doses (?IV) if visual symptoms (ask an ophthalmologist). Get a temporal artery biopsy within 3-4 days. Skip lesions occur, so don't be put off by a negative biopsy. **NB:** in the longer term, the main cause of death and morbidity in GCA is steroid treatment! Reduce prednisolone after 5-7d in the light of symptoms and ESR; ↑dose if symptoms recur. Give osteoporosis prophylaxis. Typical course: 2yrs, then complete remission.

Polymyalgia rheumatica (PMR)

Common in those >70yrs (rare <60yrs) with gradual onset symmetrical aching, tenderness and morning stiffness in shoulders and proximal limb muscles ± systemic features: fatigue, fever, weight↓, anorexia and depression ± mild polyarthritis, tenosynovitis, and carpal tunnel syndrome (in 10%). It overlaps with GCA. ý:û≈2:1

Tests:

CRP, plasma viscosity & ESR usually ↑; CK ↔; alk phos may be ↑.

Differentials:

Recent onset RA, polymyositis, hypothyroidism, primary muscle disease, occult malignancy or infection, osteoarthritis (esp. cervical spondylosis, shoulder OA), neck lesions, bilateral subacromial impingement (OHCS p664), spinal stenosis (OHCS p674).

[prescription take]:

Prednisolone 15mg/24h PO—expect a dramatic response within 4 days. ↓dose slowly, eg by 1mg/month (according to symptoms & ESR). Most need steroids for ≥2yrs, so prevent osteoporosis (p674).

Polyarteritis nodosa (PAN)

PAN is a necrotizing vasculitis that causes aneurysms and thrombosis in mediumsized arteries, leading to infarction in affected organs, with severe systemic symptoms. û:ý≈2:1. It may be associated with Hepatitis B, and is rare in the UK.

Signs and symptoms:

- General features: Fevers, malaise, weight↓, arthralgia.
- Skin: Urticaria, palpable purpura, infarcts, livedo reticularis,[2] nodules.
- Renal: (75%) Main cause of death. Renal cortical infarcts lead to hypertension, haematuria, proteinuria and renal failure (glomerulonephritis is not seen).
- Cardiac: (80%) Second commonest cause of death in PAN. Coronary arteritis causes consequent angina or myocardial infarction. Heart failure and pericarditis are also seen. In Kawasaki disease (childhood PAN variant, OHCS p646) coronary aneurysms occur.
- CNS: (70%) Arteritis of the vasa nervorum leads to mononeuritis multiplex or polyneuropathy. Stroke, seizures or psychoses are also seen.
- GI: (70%) Abdominal pain (any viscus may infarct), bleeding, perforation, malabsorption because of chronic ischaemia.
- GU: Orchitis—testicular pain or tenderness.

Tests:

Often WCC↑, mild eosinophilia (in 30%), anaemia, ESR↑, CRP↑. ANCA is -ve.

Diagnosis:

This is often made from clinical features with renal or mesenteric angiography. Biopsy can also be diagnostic.

Treatment:

Treat hypertension meticulously. Refer to experts. Most respond to corticosteroids and cyclophosphamide. Hepatitis B should be treated with an antiviral (lamivudine or interferon-×) after initial treatment with steroids.[45]

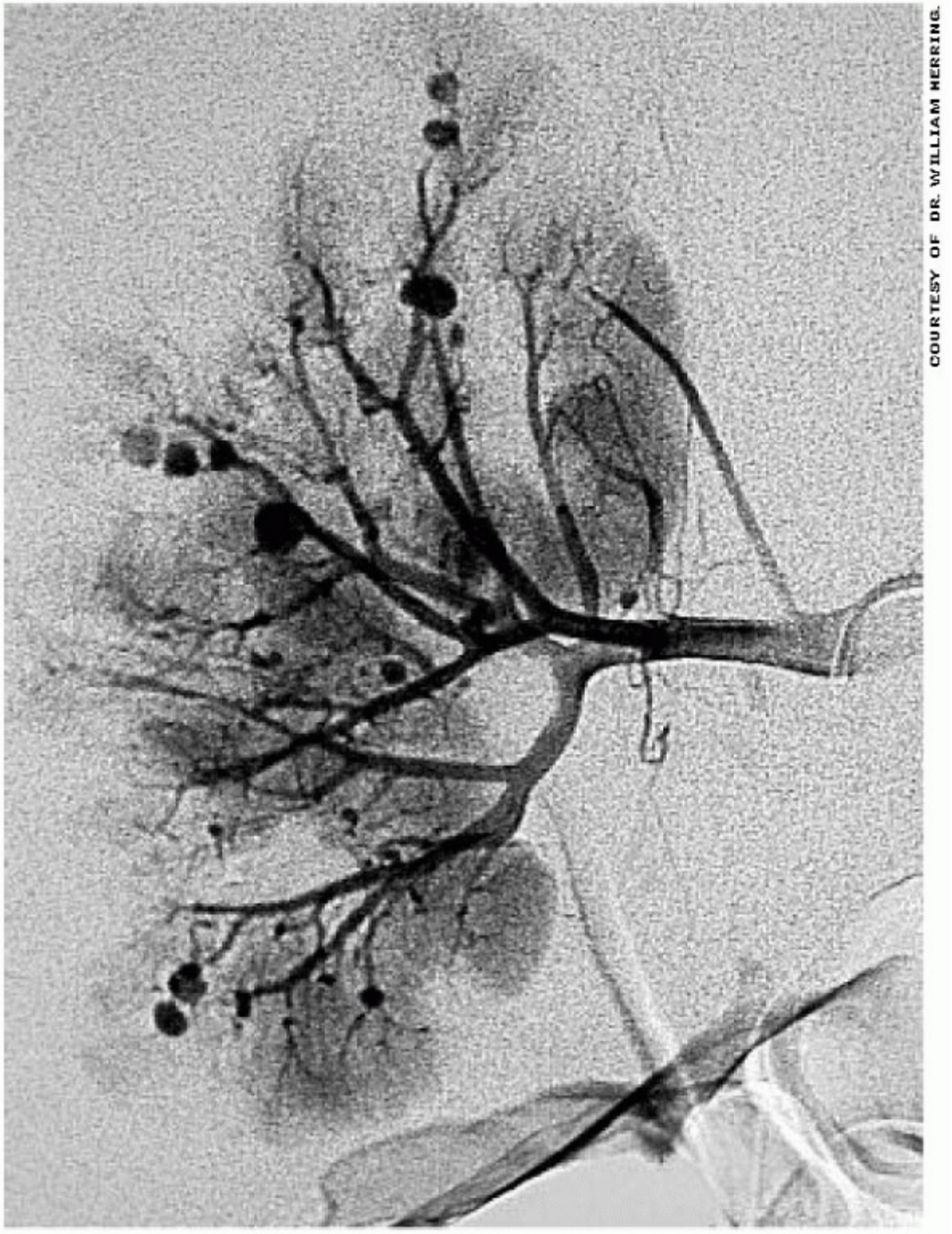


Fig 1. Angiographic appearances of the right kidney in PAN. Multiple aneurysms are present.[46]

Systemic conditions causing eye signs

The eye is host to many diseases: the more you look, the more you'll see, and the more you'll enjoy, not least because the eye is as beautiful as its signs are legion.

Granulomatous disorders

Syphilis, TB, sarcoidosis, leprosy, brucellosis, and toxoplasmosis may all inflame the eye; either front chamber (anterior uveitis/iritis) or back chamber (posterior uveitis/choroiditis). Refer to an ophthalmologist.

Connective tissue diseases

cause inflammation of the eye coat (episcleritis/scleritis). Conjunctivitis is found in Reiter's; episcleritis in PAN and SLE; uveitis in ankylosing spondylitis and Reiter's (p536). Scleritis in RA and Wegener's may damage the eye. Refer immediately if eye pain. In dermatomyositis, there is orbital oedema with

retinopathy showing cotton-wool spots (micro-infarcts).

Keratoconjunctivitis sicca

is a reduction in tear formation, tested by the Schirmer filter paper test (<5mm in 5min). It causes a gritty feeling in the eyes, and a dry mouth (xerostomia from ↓saliva production). It is found on its own (Sjögren's syndrome, p702), or with other diseases eg SLE, RA, sarcoidosis. Treatment: artificial tears/saliva (eg tears naturale, hypromellose drops, Salivaese Oral Spray®).

Vascular retinopathy

(p124) may be *arteriopathic* (arteriovenous nipping: hardened arteries nip veins where they cross) or *hypertensive*, with arteriolar vasoconstriction and leakage (hard exudates, macular oedema, haemorrhages, and papilloedema if severe). Thickened arterial walls are shiny ('silver wiring'). Narrowed arterioles lead to localized infarction of the superficial retina, seen as cotton-wool spots. Leaks from these appear as hard exudates ± macular oedema or papilloedema. The grading of hypertensive retinopathy from I to IV is considered obsolescent by some, partly because changes due to arteriopathy and those due to hypertension are confused, and also because some grades exist in normotensive, non-diabetic people.

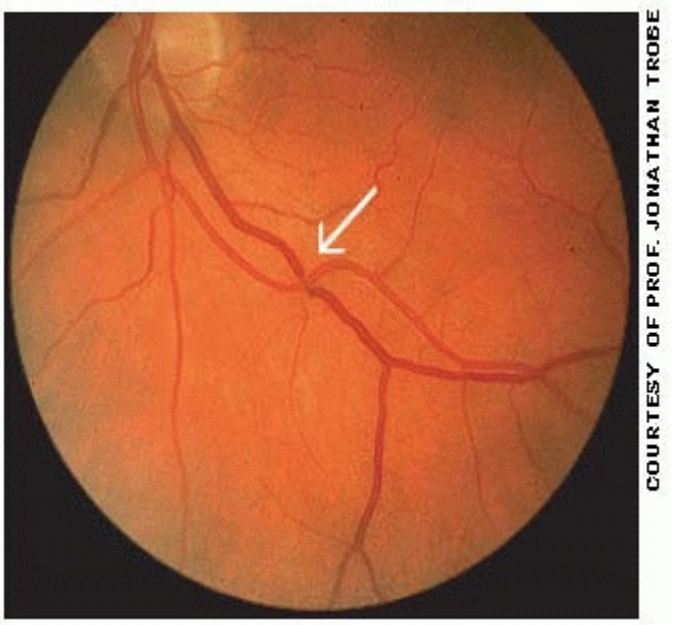


Fig 1. AV nipping.[47]

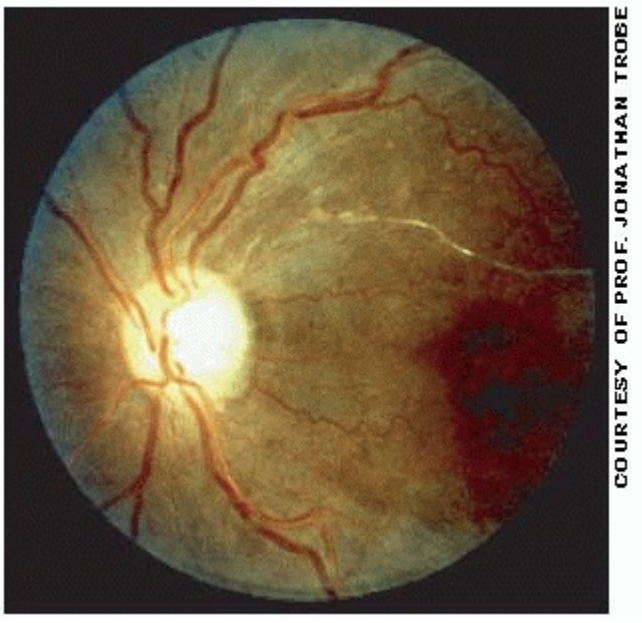


Fig 2. Silver wiring.[48]

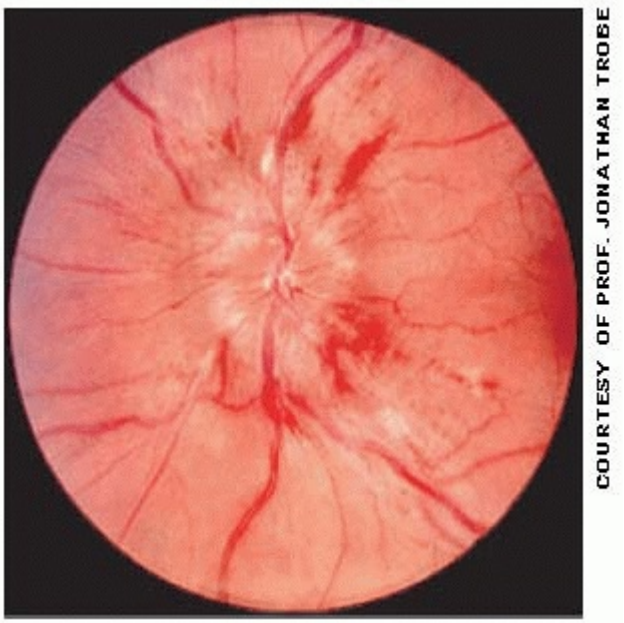


Fig 3. Papilloedema.[49]

Emboli passing through the retina produce *amaurosis fugax* (p468). *Retinal haemorrhages* occur in leukaemia; comma-shaped *conjunctival haemorrhages* and retinal *new vessel formation* may occur in sickle-cell disease; *optic atrophy* in pernicious anaemia and *Roth spots* (small retinal infarcts) in SBE/IE.

Retinal vein occlusion is caused by BP↑, age, or hyperviscosity (p356). Suspect in any acute fall in acuity. If it is the central vein, the fundus is like a stormy sunset (those angry red clouds are haemorrhages). In branch vein occlusion, changes are confined to a wedge of retina. Get expert help.

Metabolic disease

Diabetes: p190. Hyperthyroid exophthalmos: p203. Lens opacities are seen in hypoparathyroidism. Conjunctival and corneal calcification can occur in hypercalcaemia. In gout, conjunctival urate deposits may give sore eyes.

Systemic infections

Septicaemia may seed to the vitreous causing endophthalmitis. Syphilis (above) can cause iritis (+ pigmented retinopathy if congenital).

AIDS & HIV

(p396) CMV retinitis (pizza-pie fundus, p393): This may be asymptomatic but can cause sudden visual loss. If present, it implies full-blown AIDS (CD4 count $<100 \times 10^6$/L). Cotton-wool spots on their own indicate HIV retinopathy and may occur before the full HIV picture. Candidiasis of the vitreous is found in IV drug abusers and is hard to treat. Kaposi's sarcoma may affect the lids or conjunctiva.

Differential diagnosis of 'red-eye'

	Conjunctiva	Iris	Pupil	Cornea	Anterior chamber	Intraocular pressure	App
Acute glaucoma	Both ciliary and conjunctival vessels injected Entire eye is red See *OHCS*	Injected	Dilated, fixed, oval	Steamy, hazy	Very shallow	Very high	

	p430						
Anterior uveitis (Iritis)	Redness most marked around cornea Colour does not blanch on pressure (See *index* for list of causes.)	Injected	Small, irregular due to adhesions between the anterior lens and the pupil margin	Normal	Turgid	Normal	
Conjunctivitis	Conjunctival vessels injected, greatest toward fornices Blanch on pressure Mobile over sclera Purulent discharge	Normal	Normal	Normal	Normal	Normal	
Subconjunctival haemorrhage	Bright red sclera with white rim around limbus (*Causes:* BP ↑; leptospirosis; bleeding disorders; trauma: snake venom; haemorrhagic fevers.)	Normal	Normal	Normal	Normal	Normal	

After RD Judge, GD Zuidema, FT Fitzgerald *Clinical diagnosis* 5 ed, Little Brown, Boston. Images courtesy of Jonathan Trobe.[50]

Skin manifestations of systemic diseases

Erythema nodosum

Painful, blue-red, raised lesions on shin fronts (± thighs/arms). *Causes*: sarcoidosis, drugs (sulfonamides, the Pill, dapsone), streptococcal infection. *Less common*: Crohn's/UC, BCG vaccination, leptospirosis, *Mycobacterium* (TB, leprosy), *Yersinia* or various viruses and fungi. See p267.

Erythema multiforme

'Target' lesions: symmetrical ± central blister, on palms/soles, limbs, and elsewhere. Occasionally severe with fever and mucosal involvement—mouth, genital, and eye ulcers (this is the Stevens-Johnson syndrome). It is associated with a hypersensitivity reaction to drugs (barbiturates, sulfonamides) or infections (herpes, *Mycoplasma*, orf—p366). Also seen in collagen disorders. 50% of cases are idiopathic. Get expert help in severe disease.

Erythema chronicum migrans

Presents as a small papule which develops into a spreading large erythematous ring, with central fading. It lasts from 48h to 3 months. May be multiple. *Cause*: Lyme disease (p418).

Erythema marginatum

Pink coalescent rings on trunk which come and go. It is seen in rheumatic fever (or rarely other causes, eg drugs).

Pyoderma gangrenosum

Recurring nodulo-pustular ulcers, ~10cm wide, with tender red/blue overhanging necrotic edge, purulent surface, and healing with cribriform scars on leg, abdomen, or face. *Associations*: UC/Crohn's, autoimmune hepatitis, Wegener's, myeloma, neoplasia. ý:û >1:1. *Treatment*: Get help. Saline toilet, high-dose oral or topical steroids ± ciclosporin ± topical antibiotic.[51]

Vitiligo

(Fig.4) *Vitellus* is Latin for *spotted calf*: typically white patches ± hyperpigmented borders. Sunlight makes them itch. *Associations*: Autoimmunity: including Graves', Addison's, Hashimoto's, DM, alopecia areata, hypoparathyroidism; premature ovarian failure. Treat by camouflage cosmetics and sunscreens (± steroid creams ± dermabrasion). UK vitiligo society: 0800 018 2631.

Specific diseases and their skin manifestations

Diabetes mellitus

Ulcers, *necrobiosis lipoidica* (shiny area on shin with yellowish skin ± telangiectasia), *granuloma annulare* (OHCS p586), *acanthosis nigricans*.

Gluten-sensitive enteropathy (coeliac disease)

Dermatitis herpetiformis—itchy blisters, in groups on knees, elbows, and scalp. The itch (which can drive patients to suicide) responds to dapsone 25-200mg/24h PO within 48h—and this may be used as a diagnostic test. The maintenance dose may be as little as 50mg/wk. A gluten-free diet should be adhered to, but in 30% dapsone will need to be continued. SE (dose related): haemolysis (CI: anaemia; G6PD-deficiency), hepatitis, agranulocytosis (monitor FBC and LFT). There is an ↑risk of small bowel lymphoma with coeliac disease *and* dermatitis herpetiformis—so surveillance is needed.

Malabsorption

Dry pigmented skin, easy bruising, hair loss, leuconychia.

Hyperthyroidism

Pretibial myxoedema—red oedematous swellings above lateral malleoli, progressing to thickened oedema of legs and feet, *thyroid acropachy*— clubbing + subperiosteal new bone in phalanges.

Other endocrine diseases

See p188.

Neoplasia

Acanthosis nigricans: Pigmented, rough thickening of axillary, neck or groin skin with warty lesions, associated with stomach cancer. *Dermatomyositis* (p538). *Skin metastases*. *Acquired ichthyosis*: Dry scaly skin associated with lymphoma. *Thrombophlebitis migrans*: Successive crops of tender nodules affecting blood vessels throughout the body, associated with pancreatic cancer (especially body and tail tumours).

Crohn's

Perianal/vulval ulcers; erythema nodosum; pyoderma gangrenosum.

Liver disease

Palmar erythema; spider naevi; gynaecomastia; decrease in pubic hair; jaundice; bruising; scratch marks.

Dermatomyositis

Gottron's papules; shawl sign; heliotrope rash on eyelids (p538).

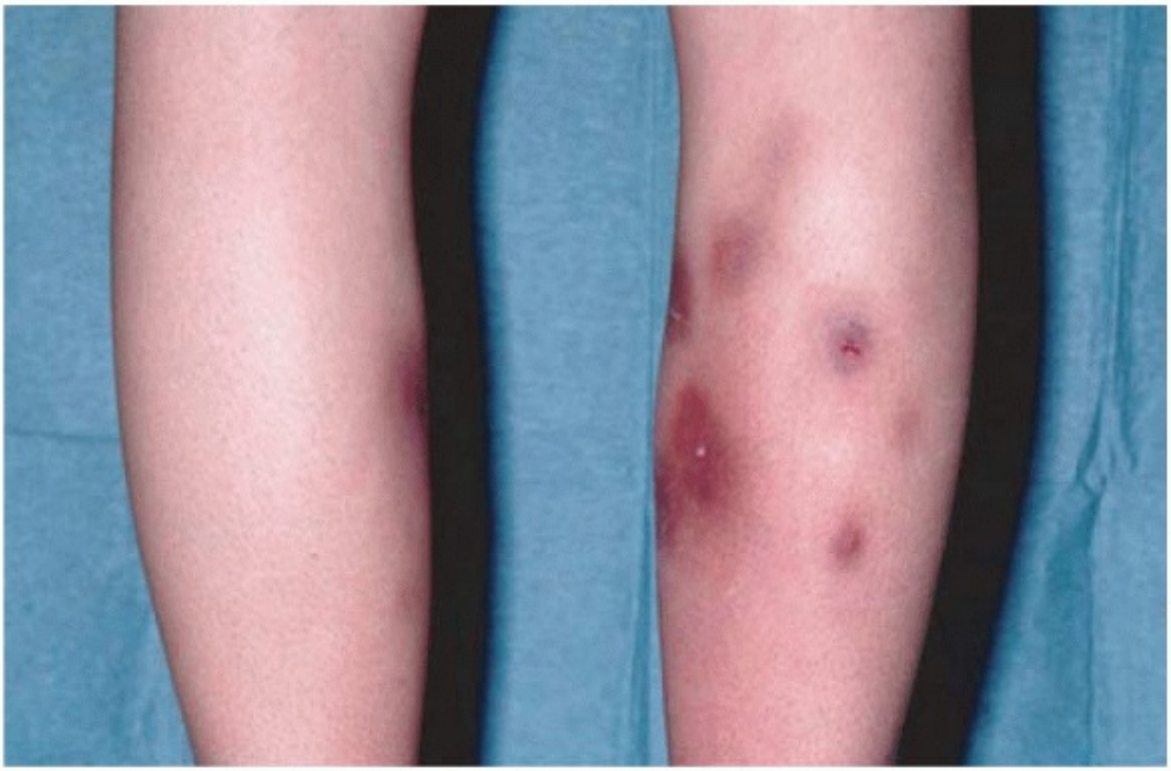


Fig 1. Erythema nodosum.

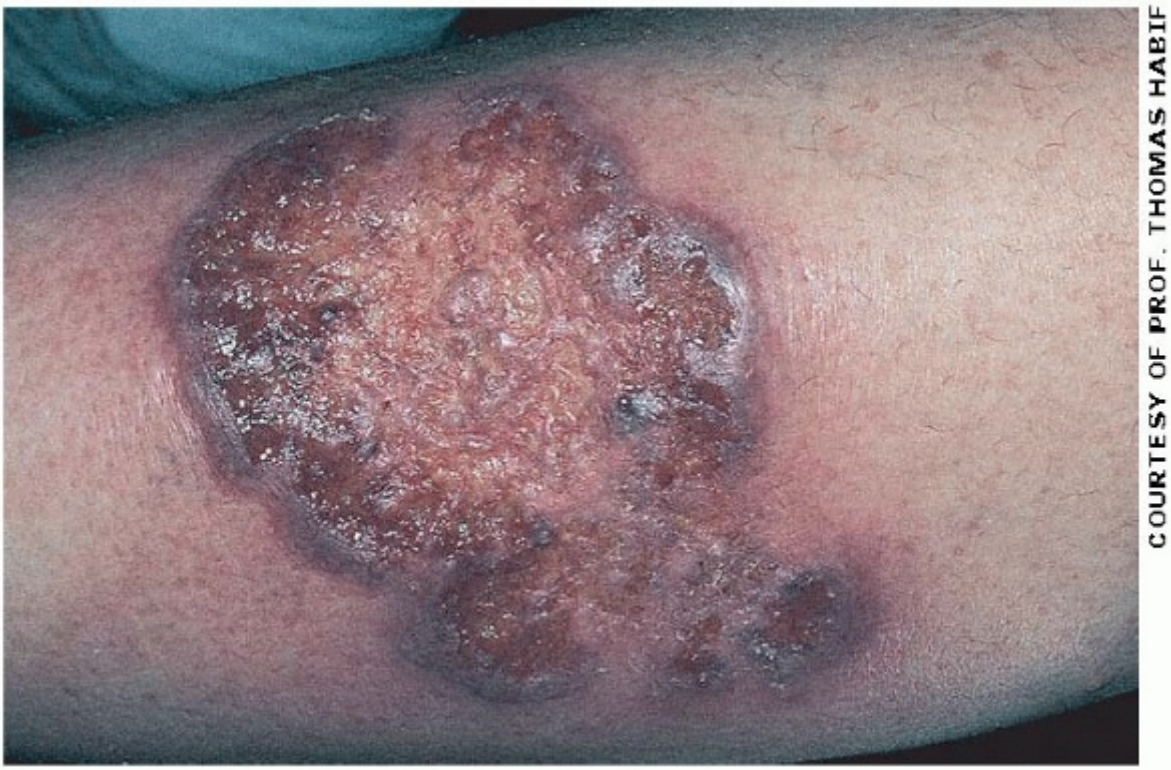


Fig 2. Pyoderma gangrenosum.[52]

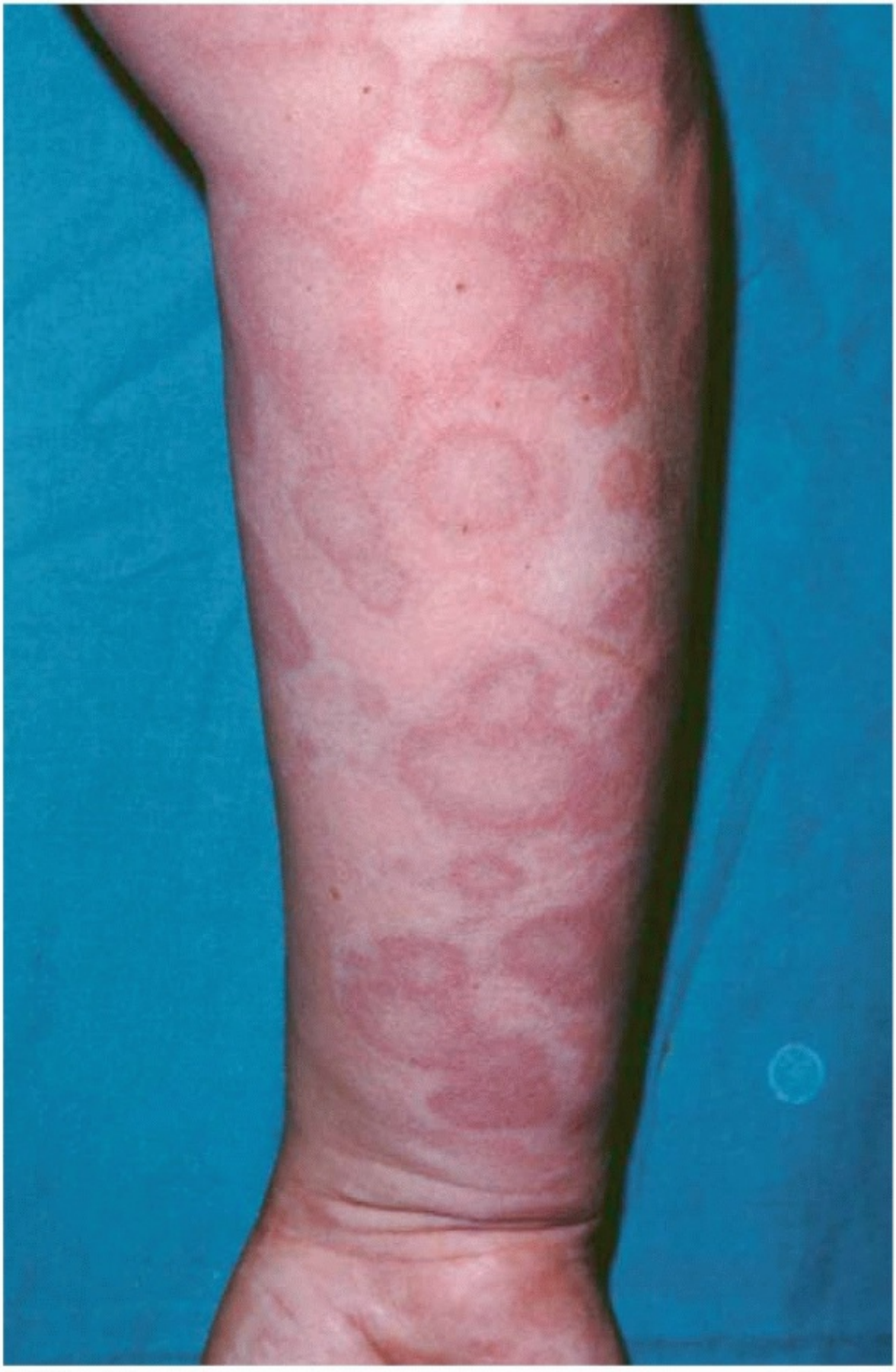


Fig 3. Erythema multiforme.

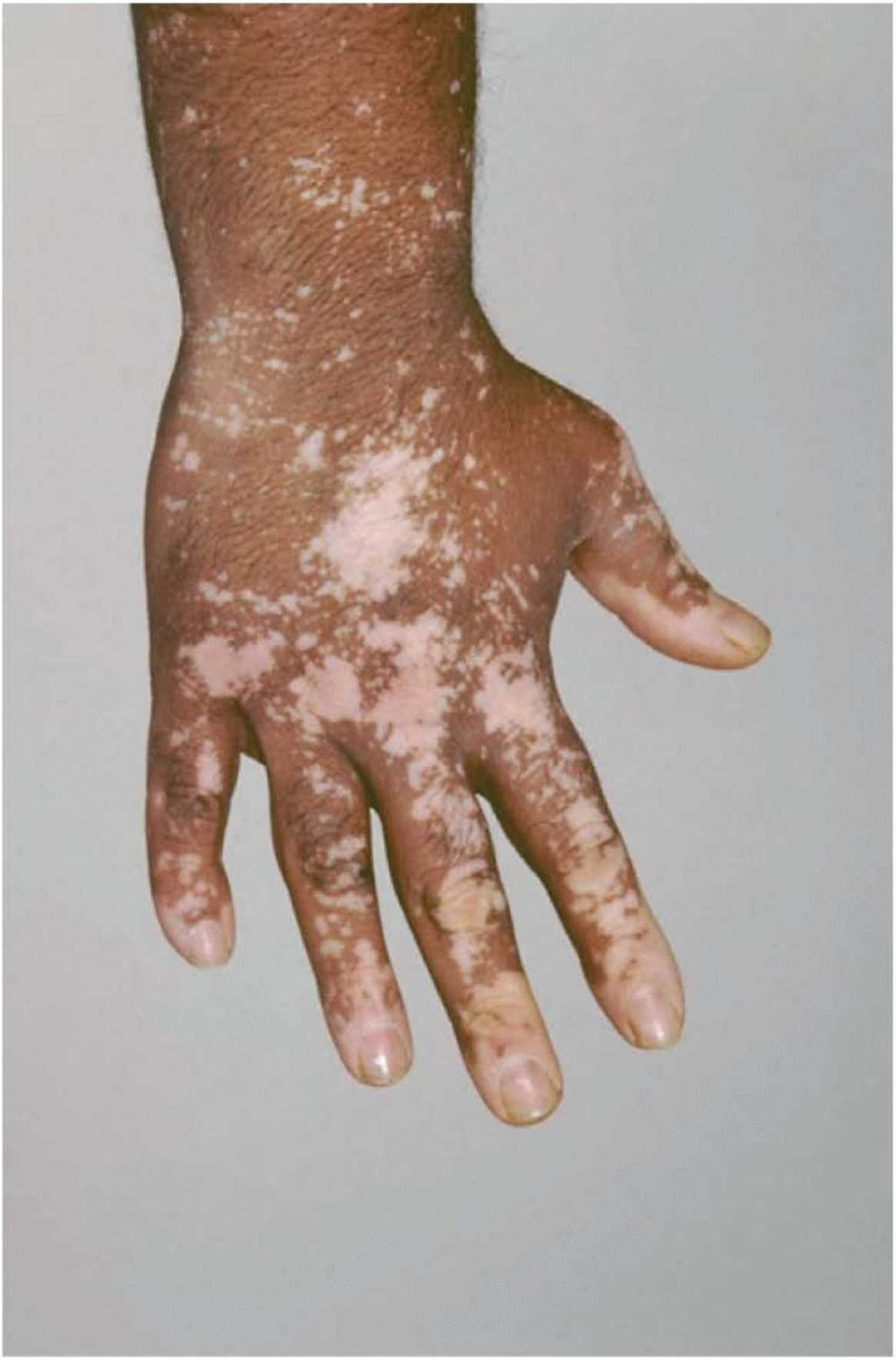


Fig 4. Vitiligo. Compare with fig 1, p417.

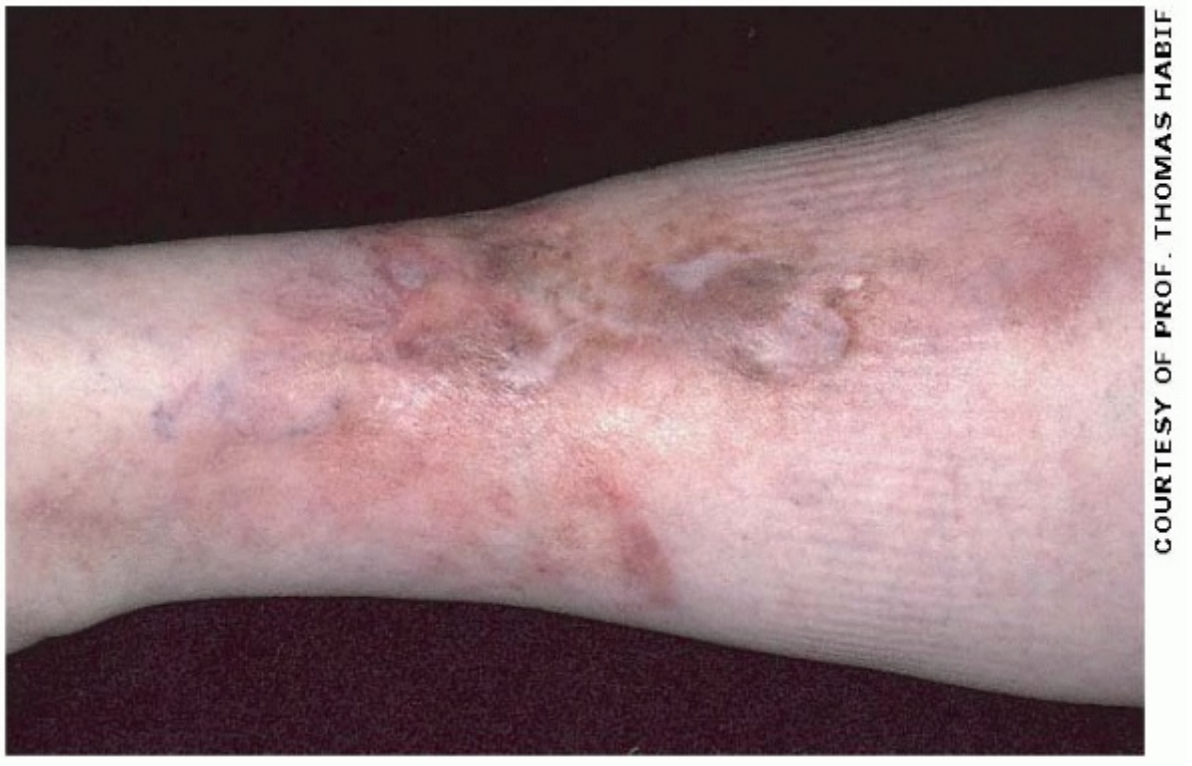


Fig 5. Necrobiosis lipoidica.[53]

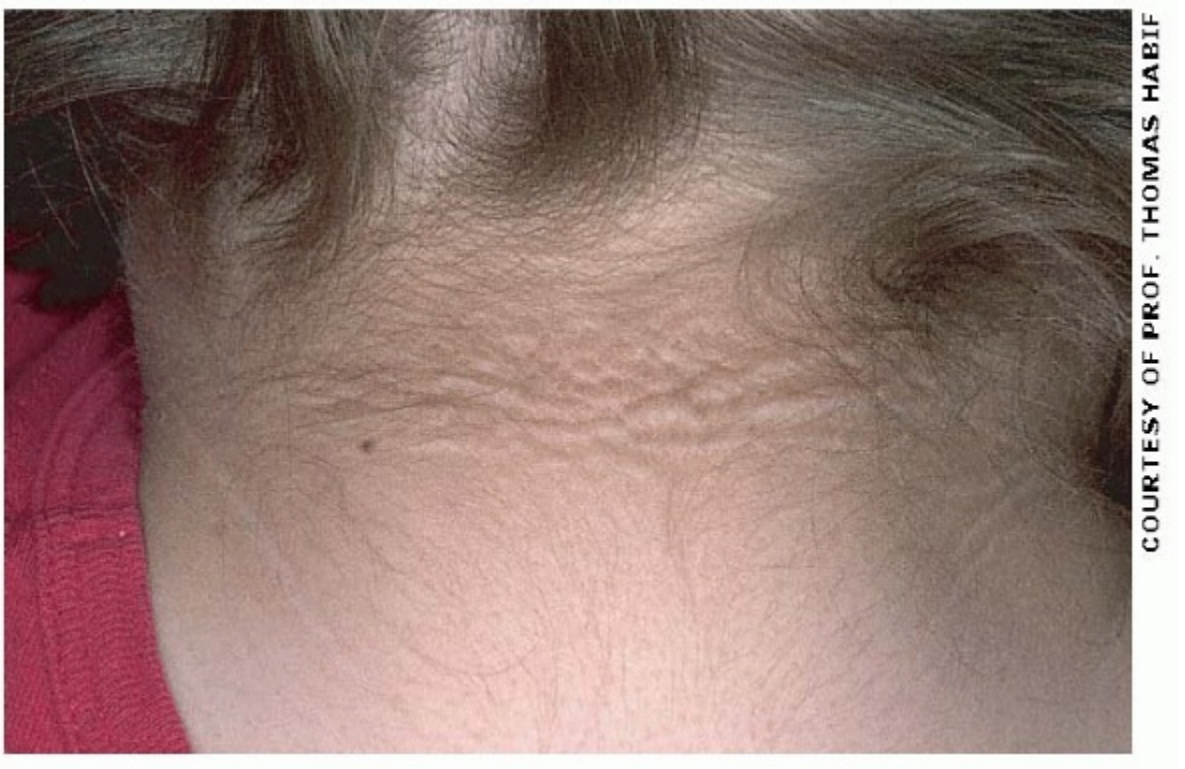


Fig 6. Acanthosis nigricans.[54]

Skin diagnoses not to be missed

Malignant tumours

1 Malignant melanoma

ý:û ≈ 1.5 : 1. UK incidence: 3500/yr, with 800 deaths/ yr (up ≥80% in last 20yrs), these metastasise early. Sunlight is a major cause, particularly in the early years. They may occur in pre-existing moles. Diagnosis can be tricky, so ▸if in doubt, refer. Refer if there are ≥3 points on the Glasgow scale (2 for major feature, 1 for minor feature), or with 1 point if suspicious.[55]

Major	Minor	Less helpful signs
•Change in size	•Inflammation, crusting, or bleeding	•Asymmetry
•Change in shape	•Sensory change	•Irregular colour
•Change in colour	•Diameter >7mm (unless growth is in the vertical plane: beware)	•Elevation
		•Irregular border

Neighbouring 'satellite' lesions may occur in melanoma. If smooth, well-demarcated and regular, it is unlikely to be a melanoma. Treatment: urgent excision. OHCS p592.

2 Squamous cell cancer

This usually presents as an ulcerated lesion, with hard, raised edges, in sun-exposed sites. They may begin in solar keratoses (below), or be found on the lips of smokers or in long-standing gravitational leg ulcers (=Marjolin's ulcer). Metastases are rare, but local destruction may be extensive.

Treatment:

Excision. **NB:** the condition may be confused with a keratoacanthoma— a fast-growing, benign, self-limiting papule plugged with keratin.

3 Basal cell carcinoma

(rodent ulcer) Typically, a pearly nodule with rolled telangiectatic edge, usually on the face on a sun-exposed site. Metastases are very rare. It slowly causes local destruction if left untreated. Lesions on the trunk can appear as red scaly plaques with a raised smooth edge. *Cause*: UV exposure.

Treatment:

Excision is best; radiotherapy may be used for larger lesions in the elderly, if surgery is to be avoided.

Pre-malignant tumours

1 Solar (actinic) keratoses

appear on sun-exposed skin as crumbly, yellow-white crusts. Malignant change to squamous cell carcinoma may occur after several years.

Treatment:

cautery, cryotherapy or twice-daily 5% 5-fluorouracil (5-FU) cream—this works by causing: erythema → vesiculation → erosion → ulceration → necrosis → healing epithelialization, leaving healthy skin unharmed. Treatment with 5-FU cream is usually for 4wks, but may be prolonged. There is no significant systemic absorption if the area treated is <500cm^2. Avoid in pregnancy. The hands should be washed after applying the cream. Alternative: diclofenac gel (3%; Solaraze®, use thinly twice-daily for ¢90d).

2 Bowen's disease

Slow-growing red scaly plaque, eg on lower legs.

Histology:

Full-thickness dysplasia (carcinoma-*in-situ*). It infrequently progresses to squamous cell cancer. Penile Bowen's disease is called Queyrat's erythroplasia.

Treatment:

Cryotherapy, topical 5-flurouracil (as above) or photodynamic therapy.

Others

- **Secondary carcinoma** The most common metastases to skin are from breast, kidney, and lung. The lesion is usually a firm nodule, most often on the scalp. See acanthosis nigricans (p546).
- **Mycosis fungoides** is a cutaneous T-cell lymphoma which is usually confined to skin. It causes itchy, red plaques. (Sézary syndrome is a variant which is also associated with erythroderma).
- **Leukoplakia** This appears as white patches (which may fissure) on oral or genital mucosa (where it may itch). Frank carcinomatous change may occur.
- **Leprosy** Suspect in any anaesthetic hypopigmented lesion (p416).
- **Syphilis** Any genital ulcer is syphilis until proved otherwise. Secondary syphilis: papular rash—including, unusually, on the palms[1] (p419).
- **Also** Kaposi's sarcoma (p694); Paget's disease of the breast (p700).

ABCDE criteria for diagnosis of melanoma
Asymmetry
Border—irregular
Colour—non-uniform
Diameter >7mm
Elevation

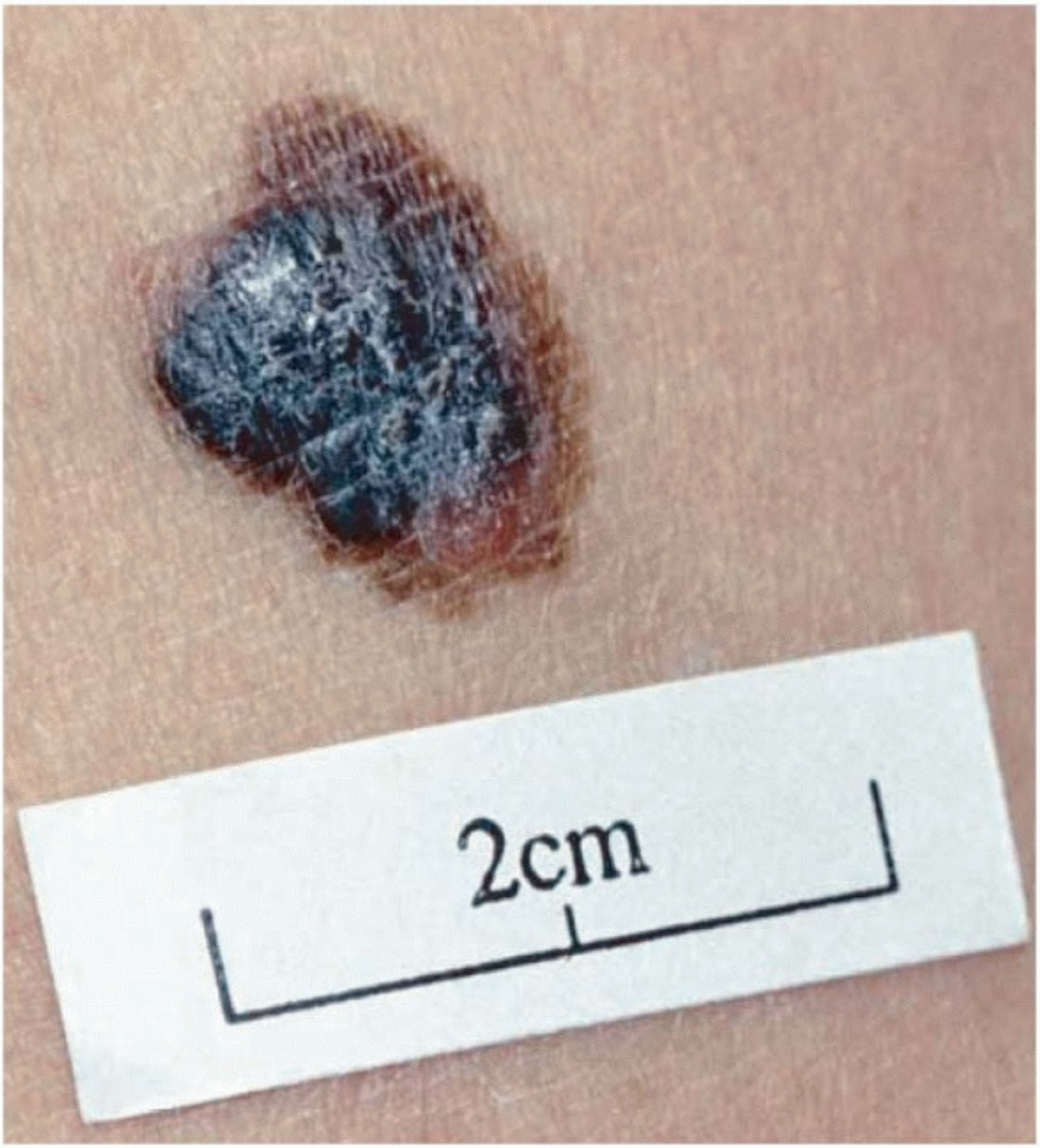


Fig 1. Melanoma

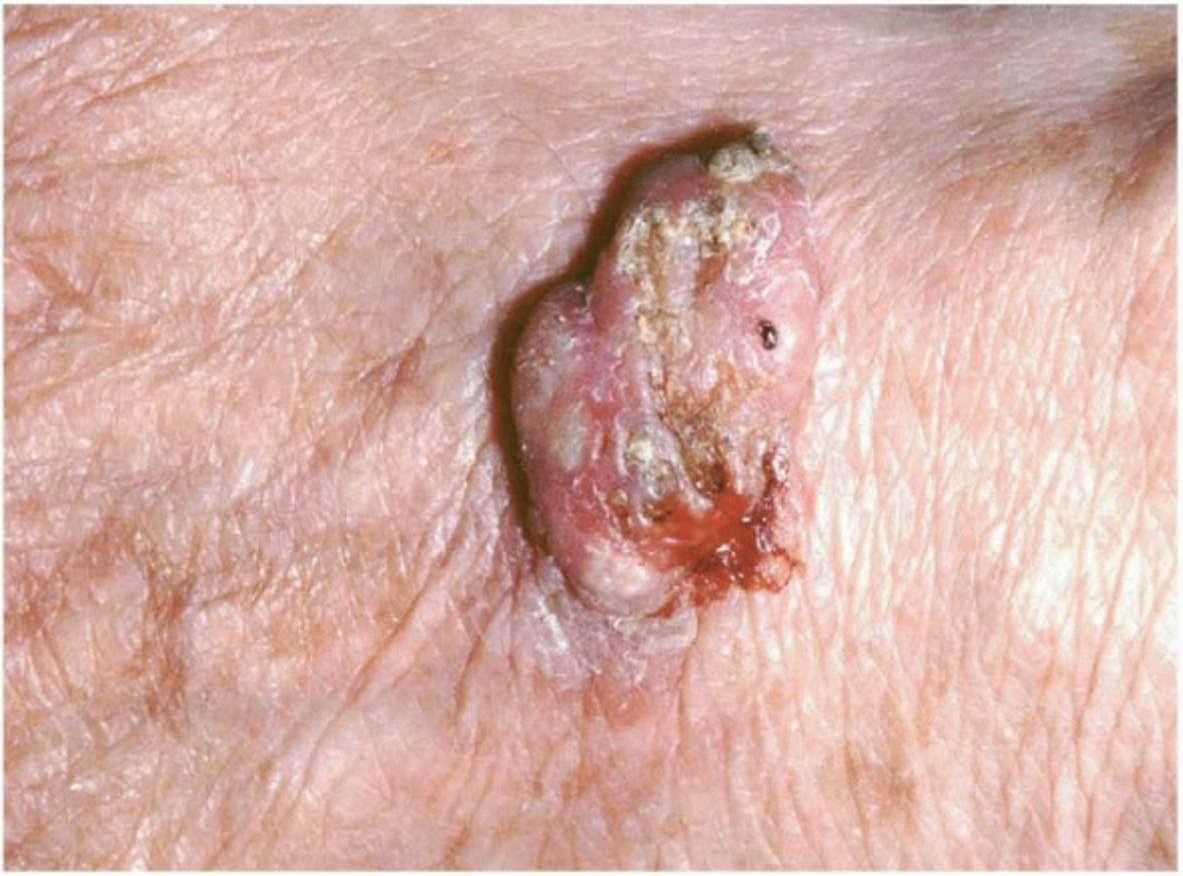


Fig 1. Squamous cell cancer

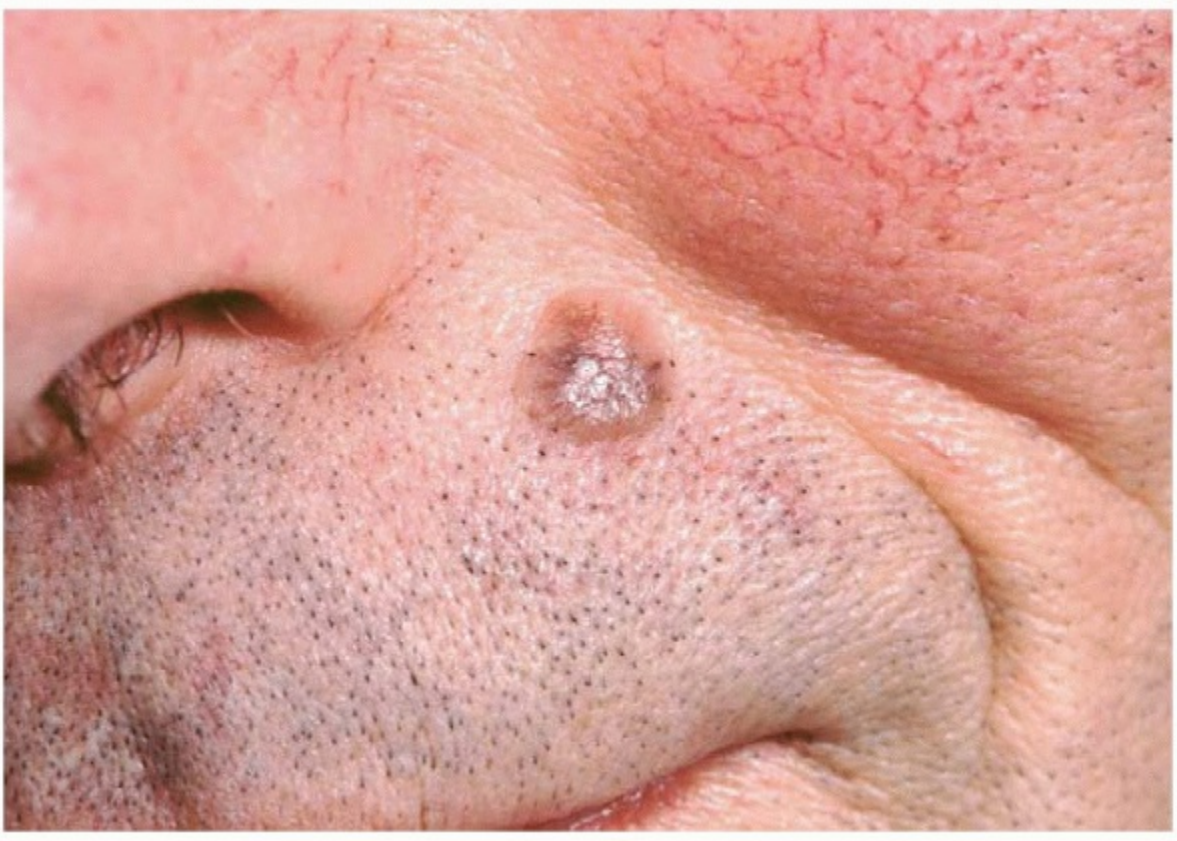


Fig 2. Basal cell carcinoma (BCC)

Acknowledgements

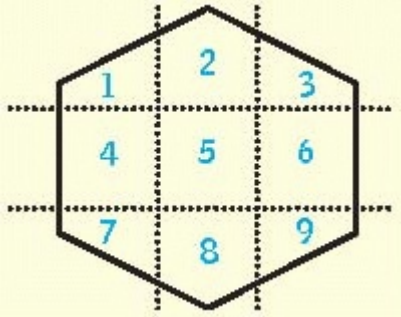
We thank Dr Andrew Brown who is our Specialist Reader for this chapter.

Editors: Longmore, Murray; Wilkinson, Ian B; Turmezei, Tom; Cheung, Chee Kay
Title: *Oxford Handbook of Clinical Medicine, 7th Edition*

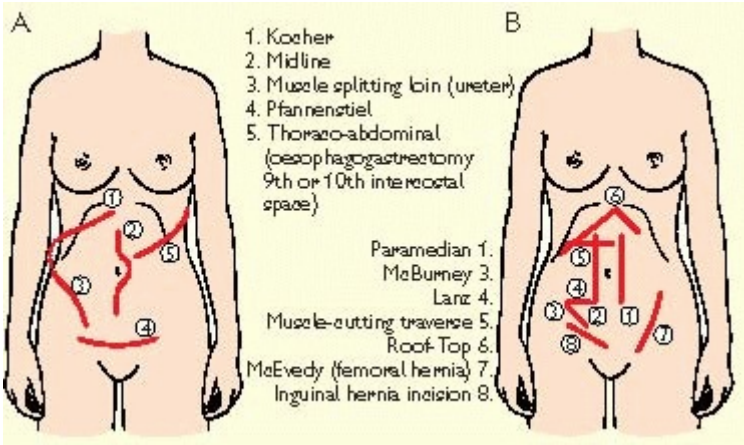
14

Surgery

The language of surgery
Abdominal areas:



Incisions:



1. Right upper quadrant (RUQ) or hypochondrium
2. Epigastrium
3. Left upper quadrant (LUQ) or hypochondrium
4. Right flank or loin
5. Peri-umbilical or central area
6. Left flank or loin
7. Right iliac fossa (RIF)
8. Suprapubic area
9. Left iliac fossa (LIF)

-ectomy	Cutting something out.
-gram	A radiological image.

-pexy	Anchoring of a structure to keep it in position.
-plasty	Surgical refashioning in order to regain good function.
-scopy	Procedure with instrumentation for looking into the body.
-stomy	An artifical union between a conduit and the outside world or another conduit (for **stoma care** see p568).
-tomy	Cutting something open to the outside world.
-tripsy	Fragementation of an object

angio-	Tube or vessel
appendic-	Appendix
chole-	Relating to gall/bile
colp-	Vagina
cyst-	Bladder/fluid-filled sac
-doch-	Ducts
enter-	Small bowel

eschar-	Burn
gastr-	Stomach
hepat-	Liver
hyster-	Uterus
lapar-	Abdomen
lith-	Stone
mast-	Breast
meso-	Mesentery
nephr-	Kidney
orchid-	Testicle
oophor-	Ovary
phren-	Diaphragm
pyloromy-	Pyloric sphincter
pyel-	Renal pelvis

proct-	Anal canal
salping-	Fallopian tube
splen-	Spleen

abscess	A cavity containing pus. For different types consult the index. Remember the aphorism: *if there is pus about, let it out*.
fistula	An abnormal connection between two epithelial surfaces. Fistulae often close spontaneously, but will not do so in the presence of malignant tissue, distal obstruction, foreign bodies, chronic inflammation, and the formation of a muco-cutaneous junction (eg stoma).
hernia	Any structure passing through another and so ending up in the wrong place.
ileus	Used in this book as a term for adynamic bowel.
sinus	A blind-ending tract, typically lined by epithelial or granulation tissue, which opens to an epithelial surface.
stent	An artificial tube placed in a biological tube to keep it open.
stoma	(p568) An artificial union between conduits or a conduit and the outside.
ulcer	(p592) An abnormal break in an epithelial surface.
volvulus	(p595, p599) Twisting of a structure around itself. Common GI sites include the sigmoid colon and caecum, and more rarely the stomach.

epi-	Upon
end-	Inside
mega-	Enlarged
pan-	Whole
para-	Alongside
per-	Going through
peri-	Around
sub-	Beneath
trans-	Across

Pre-operative care

Aims

▸To ensure that, as far as possible, any fears are addressed and the patient understands the nature, aims, and expected outcome of surgery.

- Ensure that the right patient gets the right surgery. Have the symptoms and signs changed? If so, inform the surgeon.
- Get informed consent (p554).
- Assess/balance risks of anaesthesia, and maximize fitness. Is he a smoker? Optimizing oxygenation/perfusion **before** major surgery improves outcome. [1]
- Check anaesthesia/analgesia type with anaesthetist. **Aim to allay anxiety & pain.**

Pre-op checks

Assess cardiorespiratory system, exercise tolerance, existing illnesses, drugs, and allergies. Is the neck unstable (eg arthritis complicating intubation)? Assess past history of: MI ,[1] diabetes, asthma, hypertension, rheumatic fever, epilepsy, jaundice. Assess any specific risks, eg is the patient pregnant? Is the neck/jaw immobile and teeth stable (intubation risk)? Has there been previous anaesthesia? Were there any complications (eg nausea, DVT)? ▸Is DVT/PE prophylaxis needed (p564)? ▸If for 'unilateral' surgery, mark the correct arm/leg/kidney, according to the recommendations of the UK National Patient Safety Agency.[2]

Family history

May be relevant eg in malignant hyperpyrexia (p558); dystrophia myotonica (p502); porphyria; cholinesterase problems; sickle-cell disease.

Drugs

Any drug/plaster/antiseptic allergies? ▸Inform the anaesthetist about **all** drugs even if 'over-the-counter'. For diabetes, see p576.

- *Antibiotics:* ***Tetracycline*** and ***neomycin*** may ↑neuromuscular blockade.
- *Anticoagulants:* ▸**Tell the surgeon**. Avoid epidural, spinal, and regional blocks. ***Aspirin*** should probably be continued unless there is a major risk of bleeding. Discuss stopping ***clopidogrel*** therapy with the cardiologists/neurologists.
- *Anticonvulsants:* Give as usual pre-op. Post-op, give drugs IV (or by NGT) until able to take orally. ***Valproate***: give usual dose IV. ***Phenytoin***: give IV slowly (<50mg/min; monitor ECG). IM ***phenytoin*** absorption is unreliable.
- *β-blockers:* Continue up to and including the day of surgery as this precludes a labile cardiovascular response.
- *Contraceptive steroids:* See BNF. Stop 4wks before major/leg surgery; ensure alternative contraception is used. Restart 2wks after surgery, provided mobile.
- *Digoxin:* Continue up to and including morning of surgery. Check for toxicity (ECG; plasma level); do plasma K^+ and Ca^{2+} (***suxamethonium*** can ↑K^+ and lead to ventricular arrhythmias in the fully digitalized).
- *Diuretics:* Beware hypokalaemia, dehydration. Do U&E (and bicarbonate).
- *Eye-drops:* β-blockers get absorbed; anticholinesterases ↑[***suxamethonium***].
- HRT: There may be an increased risk of DVT/PE. • *Steroids:* See p578.
- *Levodopa:* Possible arrhythmias when patient under GA.
- *Lithium:* Get expert help; it may potentiate neuromuscular blockade and cause arrhythmias. See OHCS p354.
- MAOIs: Get expert help as interactions may cause hypotensive/hypertensive crises.
- *Thyroid medication:* see p578.
- *Tricyclics:* These enhance ***adrenaline*** (epinephrine) and arrhythmias.

Preparation

▸Fast the patient; NBM for ≥2h pre-op (discuss with anaesthetist).

- Is any bowel or skin preparation needed, or prophylactic antibiotics (p556)?
- Start DVT prophylaxis as indicated, eg graduated compression stockings (not if there is peripheral arterial disease) + ***heparin*** 5000U SC 2h pre-op, then every 8-12h SC for 7d or until ambulant. Low molecular weight heparin (LMWH, p174): eg ***enoxaparin*** 20mg/d SC, increased to 40mg/d in major-risk surgery.
- Write up the pre-meds (p558); book any pre-, intra-, or post-operative x-rays or frozen sections. Book post-operative physiotherapy.
- If needed, catheterize (p750) and insert a Ryle's tube (p747) before induction. These can reduce organ bulk, making it easier to operate in the abdomen.

Pre-operative examination and tests—see NICE guidelines[3]

▸**Careful planning is the key to preventing perioperative death.**[1] A good thought exercise is to imagine yourself at the next surgical *Mortality Meeting* and ask 'If I were looking back at the pre-op period, knowing that this patient had died, would I still consider that surgery was indicated?' The UK National Confidential Enquiry into Perioperative Deaths (NCEPOD) found that 'too many' operations are performed on moribund patients.[4]

It is the anaesthetist's duty to assess suitability for anaesthesia. The ward doctor assists with a good history & examination, and can also reassure, inform, and get informed written consent (p558; ideally this should be from the surgeon herself).

Be alert to chronic lung disease, BP↑, arrhythmias, and murmurs (aortic stenosis; endocarditis prophylaxis needed?—see p136).

Tests

▸Be guided by the history and examination and local/NICE protocols.

- U&E, FBC, *and ward tests for blood glucose in most patients*. If Hb <10g/dL tell anaesthetist. Investigate/treat as appropriate. U&E are particularly important if the patient is starved, diabetic, on diuretics, a burns patient, has hepatic or renal disease, has an ileus, or is parenterally fed.

- *Crossmatching:* Examples: Group and save (G&S) for mastectomy or cholecystectomy. Crossmatch 2 units for Caesarean section; 4 units for a gastrectomy; 6 units for abdominal aortic aneurysm (AAA) surgery.
- *Specific blood tests:* LFT in jaundice, malignancy, or alcohol abuse. Amylase in acute abdominal pain. Blood glucose if diabetic (p576). Drug levels as appropriate (eg ***digoxin***, ***lithium***). Clotting studies in liver or renal disease, DIC (p336), massive blood loss, eg if on ***valproate***, ***warfarin***, or ***heparin***. HIV, HBsAg in high risk patients, after counselling. Sickle test in those from Africa, West Indies, or Mediterranean—and if origins are in malarial areas (including most of India). Thyroid function tests in those with thyroid disease.
- CXR if known cardiorespiratory disease, pathology or symptoms, possible lung metastases, or >65yrs old. Remember to check the film prior to surgery.
- ECG if >55yrs old or poor exercise tolerance, or history of myocardial ischaemia, hypertension, rheumatic fever, or other heart disease.
- *Echocardiogram* may be performed if there is a suspicion of poor LV function.
- *Lateral cervical spine x-ray* if history of rheumatoid arthritis, ankylosing spondylitis or Down's syndrome, to warn about difficult intubations.
- MRSA *screen:* Rising above the frenzied media headlines, it is still important make every effort to reduce spread of MRSA. Colonisation is **not** a contraindication to surgery, and if on balance surgery is appropriate, the case should be last on the list minimize transmission to others (with appropriate theatre protocol). Cover with appropriate antibiotic prophylaxis, eg ***vancomycin***.

Pre-op checklist:

- Blood tests (inc. group & save or crossmatch)
- IV cannula
- ECG + CXR
- Drug chart
  - Regular medications
  - Analgesia + antiemetic
  - Antibiotics
  - LMWH/***heparin***
  - Compression stockings
- Consent
- Marked site/side
- Anaesthetist informed
- Theatres informed
- Infection risk? (eg MRSA/
- HIV/HBV/HCV)
- NBM since when?

…not all will be required

American Society of Anesthesiologists (ASA) classification

Class I	Normally healthy.
Class II	Mild systemic disease.
Class III	Severe systemic disease that limits activity but is not incapacitating.
Class IV	Incapacitating systemic disease which poses a constant threat to life.
Class V	Moribund: not expected to survive 24h even with operation.

You will see a space for an ASA number on most anaesthetic charts. It is a health index **at the time of surgery**. The prefix **E** is used in emergencies.

Consent

*In which of the following situations would **you** seek 'informed written consent' from a patient?* **1** Feeling for a pulse. **2** Taking some blood. **3** Inserting a central line. **4** Removing a section of small bowel during a laparotomy for division of adhesions. **5** Orchidectomy after a failed operation for testicular torsion.

English law states that **any** intervention or treatment needs consent—ie all of the above—yet, for different reasons, we know that, for some, informed formal consent is not regularly sought! In fact, **written** consent itself is not required by law, but it does constitute 'good medical practice' in the best interests of the patient and practitioner. Sometimes actions and words can imply valid consent, eg by simply entering into conversation or holding out an arm. In these situations your actions and their consequences are understood by the patient as a product of their knowledge, previous interactions with doctors and learning through experience.[1] However, if the consequences are not clear to the patient and they have the capacity to give consent (see below & BOX), you should seek informed written consent, as this serves as a record of your conversation together.[5]

For consent to be valid:

- It can be given any time before the intervention/treatment is initiated. Earlier is better as this will give the patient time to think about the risks, benefits and alternatives—he may even bring forward questions on issues that you had not considered relevant. Think of consent as an ongoing process throughout the patient's time with you, not just the moment of signing the form.
- The proposed treatment or test must be clearly understood by the patient, taking into account the benefits, risks (including complication rates if known), additional procedures, alternative courses of action and their consequences.
- It must be given **voluntarily**. This can be difficult to evaluate—eg when live organ donation is being considered—see BOX for other difficult situations.
- The doctor who is providing treatment or undertaking the test needs to ensure that the patient has given valid consent. The act of seeking consent is ultimately the responsibility of the doctor looking after the patient, though the task may be delegated to another health professional, as long as they are suitably trained and qualified. Sometimes you may have be certified to get consent.
- The patient must have the **capacity** to give consent. UK law (case law rather than statute) implies that we are either fully competent or 'incompetent' but things are not so clear-cut, so…

When taking consent:

- Think about whether you are the right person to be obtaining consent.
- Use words the patient understands and avoid jargon and abbreviations.
- Ensure that he believes your facts and can retain 'pros' and 'cons' long enough to inform his decision. Fact sheets/diagrams for individual operations help.
- Make sure his choice is free from pressure from others, and explain that after they have signed the form he is free to choose not to have the proposed treatment (ie withdraw consent) at any time. Some patients may view the consent form as a contract from which they cannot *renege*.
- If the patient is illiterate, a witnessed mark does endorse valid consent. Similarly, if the patient is willing but physically unable to sign the consent form, then an entry into the medical notes stating so is valid.
- Remember to discuss further procedures that may become necessary during the proposed treatment. This avoids waking up to a nasty surprise (eg a missing testicle as in scenario 5 above).
- If you suspect the patient is not capable of giving consent then a formal assessment needs to be documented in the medical notes.

Consent is complex, but remember that it exists for the benefit of the patient **and** the doctor, giving you an opportunity to revisit expectations and involve the patient in his own care.

Special circumstances for consent…and who to ask

There are some areas of treatment or investigation for which it may be advisable to seek specialist advice if it is not part of your regular practice:

- Photography of a patient.
- Innovative or novel treatment.
- Living organ donation.
- Storage, use or removal of human tissue (for any length of time), as regulated under the Human Tissue Act 2004.
- The storage, loss, or use of gametes, as regulated under the Human Fertilisation and Embryology Act 1990.
- The use of patient records or tissue in research or teaching.
- In the presence of an advanced directive or living will expressly refusing a particular treatment, investigation or action.

- Consent if <16yrs—consent form 3 in NHS.[6] In the UK, those >16yrs can give valid consent. Those <16yrs can give consent for a medical decision provided they understand what it involves—the concept of *Gillick* competence.[7] It is still good practice to involve the parents in the decision. If **<18yrs and refusing life-saving surgery**, talk to the parents and your senior; the law is unclear. You may need to contact the duty judge in the High Court.
- Consent in the incapacitated (NHS consent form 4).[8] No one (parents, relatives, or even members of a healthcare team) is able to give consent on behalf of an adult in England, and the High Court may be required to give a ruling on the matters of lawfulness of a proposed procedure. Proceeding in a patient's best interest is decided by the clinician overseeing their care, although it is always good practice to involve family in the proposed course of treatment.

Who to ask if you are unsure?

Your team's senior/consultant

Your employing organisation

Legal defence organisation

National medical association

Local research ethics committee

The right to refuse treatment

Their's not to make reply,

Their's not to reason why,

Their's but to do and die.

Alfred, Lord Tennyson from *The Charge of the Light Brigade*, 1854

The rights of a patient are something of an antithesis to this military macabre of Tennyson, and it is our sacred responsibility to respect the legal and ethical rights of those we treat. We do this not only for the sake of the individual, but also for the sake of an enduring trust between the patient and doctor, remembering that is the patient's right to refuse treatment (if a fully competent adult) even when this may result in death of the patient, or even the death of an unborn child, whatever the stage of pregnancy. The only exception is in circumstances outlined by the Mental Health Act 1983.

Nil by mouth (NBM) before theatre

If in doubt about what is acceptable oral intake prior to induction for general anaesthesia (eg GI surgery), it is best to liaise with the anaesthetist concerned. However, guidelines have been published by the Royal College of Nursing to outline what is safe in the perioperative period. In **emergency surgery**, ≥6h NBM prior to theatre is best. For **adult elective surgery** in healthy patients without GI co-morbidity, water or clear fluids (eg black tea/coffee) are allowed up to 2h beforehand, with all other intake up to 6h beforehand.[9]

Prophylactic antibiotics in surgery

Prophylactic antibiotics are given to counter the risk of wound infection (p566), which occurs in ~20% of elective GI surgery (up to 60% in emergency surgery); they are also given if infection elsewhere, although unlikely, would have severe consequences (eg when prostheses are involved). They are given 15-60min prior to the procedure so that the skin concentration is maximised[10] and may be given as a single dose, 3 doses, or more depending on local guidelines and contamination at the site of surgery (see TABLE). A single dose given before surgery has been shown to be just as beneficial as more prolonged regimens in biliary surgery and colorectal surgery.[11] [12] ▸Wound infections are not necessarily trivial since sepsis may lead to haemorrhage, wound dehiscence, and initiate a fatal chain of events, so take measures to minimise the risk of wound infection:

- Time administration correctly.
- Use antibiotics which will kill anaerobes and coliforms.
- Consider use of perioperative supplemental oxygen. This is a practical method of reducing the incidence of surgical-wound infections.[13]
- Practice strictly sterile surgical technique. (Ask for a hand with scrubbing up if you are not sure—Sister will be more than pleased to help)!

Antibiotic regimens

Check for local or personal preferences. Examples:

- *Biliary surgery:* ***Cefuroxime*** 1.5g, for 1 dose IV + metronidazole (below).
- *Appendectomy:* If uncomplicated, a single dose ***cefuroxime*** 1.5g IV is effective.[14]
- *Colorectal surgery:* ***Cefuroxime*** 1.5g/8h + ***metronidazole*** 500mg/8h, 1-3 doses IV. ***Tazocin***® 4.5g/8h, 1-3 doses IV can be used if there is heavy soiling.
- *Vascular surgery:* ***Co-amoxiclav*** 1.2g IV on induction; if penicillin-allergic, ***cefuroxime*** 1.5g IV/IM + ***metronidazole*** 500mg IV. Anaerobic cover is not always necessary. MRSA is an increasing concern, and so may warrant prophylaxis.[15]

Bowel preparation in colorectal surgery

The place of bowel preparation in colorectal surgery has recently come under much scrutiny.[16] Whereas there are clear benefits when visualisation of the lumen is required (eg colonoscopy), the intended benefit for elective open procedures of minimizing post-operative infection may well be outweighed by

the complications:[17]

- Liquifying bowel contents which are spilled during surgery
- Electrolyte loss leading to hyponatraemia and seizures[18]
- A higher rate of post-operative anastomotic leakage[19]
- Perforation
- Dehydration

Usually no laxatives are needed for right-sided operations (eg right hemicolectomy); the patient is just put on a 'low-residue' diet for a few days pre-op, then clear fluids the day before. For left-sided operations and rectal operations (eg left hemicolectomy, anterior resection), laxatives and enemas may still be used. ▸If in doubt, check with the surgeon as to what preparation he prefers.

Example: 1 sachet of Picolax® (10mg ***sodium picosulfate*** + ***magnesium citrate***) on the morning before surgery and 1 sachet during the afternoon before surgery.

Sutures

Sutures (stitches) are central to the art of surgery. The trainee may face several long evenings practising knots over a pint of beer before they are allowed back to tie at the table! In their broadest sense they are absorbable or non-absorbable, synthetic or natural, and their structure may be divided into monofilament, twisted, or braided. See TABLE opposite for some examples and their uses.

Monofilament sutures are quite slippery but minimize infection and produce less reaction (natural fibres of any type produce quite a vigorous reaction). Braided sutures have plaited strands and provide secure knots, but they may allow infection to occur between their strands. Twisted sutures have 2 twisted strands and similar qualities to braided sutures. 3-0 or 4-0 (smaller) are the best sizes for skin closure.

Classification of surgical procedures and wound infection risk

Category	Description	Infection risk
Clean	Incising uninfected skin without opening a viscus	<2%
Clean-contaminated	Intraoperative breach of a viscus (but not colon)	8-10%
Contaminated	Breach of a viscus + spillage or opening of the colon	12-20%
Dirty	The site is already contaminated with pus or faeces, or from exogenous contagion eg trauma	25%

Table after *MRCS Core Modules: Essential Revision Notes*, S. Andrews, Pastest, ISBN 1901198715

Surgical drains in the post-operative period

The decision when to insert and remove drains may seem to be one of the great surgical enigmas—but there are basically 3 types to get a grip on.

1. Most are inserted to drain the area of surgery and are often put under suction or -ve pressure (Redivac® uses a 'high-vacuum'). These are removed when they stop draining. They protect against collection, haematoma and seroma formation (in breast surgery this can cause overlying skin necrosis).
2. The second type of drain is used to protect sites where leakage may occur in the post-operative period, such as bowel anastomoses. These form a tract and are removed after about 1 week.
3. The third type (eg Bellovac®) collects red blood cells from the site of the operation, which can then be autotransfused within 6h, protecting from the hazards of allotransfusion—it is used commonly in orthopaedics.

'Shortening a drain' means withdrawing it (eg by 2cm/day). This allows the tract to seal up, bit by bit.

Evidence suggests that certain types of drain are not effective and may even lead to more complications, such as when used to protect colorectal anastomoses.[20] ▸Check the individual surgeon's preference before altering a drain.

Some commonly encountered suture materials

The perfect suture material is monofilament, strong, easy to handle, holds knots well, has predictable absorption and causes minimal tissue reaction. Unfortunately no single suture fits the bill for every occasion, and so suture selection (including size) depends on a the job in hand:

Absorbable

Name	Material	Construction	Use
Monocryl®	poliglecaprone	monofilament	subcuticular skin closure
PDS®	polydioxanone	monofilament	closing abdominal wall
Vicryl®	polyglactin	braided multifilament	tying pedicles; bowel anastomosis; subcutaneous closure
Dexon®	polyglycolic acid	Braided multifilament	very similar to Vicryl®

Non-absorbable

Name	Material	Construction	Use
Ethilon®	polyamide	monofilament	closing skin wounds
Prolene®	polypropylene	monofilament	arterial anastomosis
Mersilk®^{N}	Silk	braided multifilament	securing drains

Metal	eg steel	clips or monofilament	skin wound/sternotomy closure

[N] = natural; other natural materials (eg cotton and catgut) are rarely used these days.

Timing the removal of sutures

The timing of suture removal depends on site and the general health of the patient. Face and neck sutures may be removed after 5d (earlier in children), scalp and back of neck after 5d, abdominal incisions and proximal limbs (including clips) after ~10d and those on the distal extremities after 14d. In patients with poor wound healing, eg on steroids, with malignancy, infection, cachexia (p54), the elderly, or smokers, the sutures may need 14d or longer.

Anaesthesia

Before anaesthesia, explain to the patient what will happen and where he will wake up, otherwise the recovery room or ITU will be frightening. Explain that he may feel ill on waking. The premedication aims to allay anxiety and to make the anaesthesia itself easier to conduct (see BOX). Typical regimens might include:

- *Anxiolytics:* Benzodiazepines eg ***temazepam*** 10-20mg PO. In children, ***midazolam*** 0.5mg/kg rectally 30min prior to procedure is effective.
- *Analgesics: See* p560. The patient should not be in pain prior to surgery. Opioids, local anaesthetic blocks, ***paracetamol*** and NSAIDs (beware bleeding risk) are all used. In children or anxious adults, local anaesthetic cream (eg Emla®, Ametop®) may be used on a few sites for the anaesthetist's IVI (▸they may prefer to site the cannula themselves!)
- *Antiemetics:* $5HT_3$ antagonists (eg ***ondansetron*** 4mg IV/IM) are the most effective agents; others eg ***metoclopramide*** 10mg/8h IV/IM/PO are also used—see p233.
- *Antacids:* ***Ranitidine*** 50mg IV in patients at particular risk of aspiration.
- *Antisialogues:* ***Glycopyrronium*** (200-400µg in adults, 4-8µg/kg in children; given IV/IM 30-60min before induction) is sometimes used to decrease secretions that may cause respiratory obstruction in smaller airways.
- *Antibiotics: See* p556.

Give oral premedication 1-2h before surgery (1h if IM route used).

Side-effects of anaesthetic agents

- *Hyoscine, atropine:* Anticholinergic ∴ tachycardia, urinary retention, glaucoma, sedation (especially in the elderly).
- *Opioids:* Respiratory depression, cough reflex↓, nausea & vomiting, constipation.
- *Thiopental:* (For rapid induction of anaesthesia) laryngospasm.
- *Propofol:* Respiratory depression, cardiac depression, pain on injection.
- *Volatile agents eg isoflurane:* Nausea & vomiting, cardiac depression, respiratory depression, vasodilation, hepatotoxicity (see BNF).

The complications of anaesthesia are due to loss of:

- *Pain sensation:* Urinary retention, diathermy burns, pressure necrosis, local nerve injuries (eg radial nerve palsy from arm hanging over the table edge).
- *Consciousness:* Cannot communicate 'wrong leg/kidney'. **NB:** in some patients (eg 0.15%) ***retained*** consciousness is the problem.[21] Awareness under GA sounds like a contradiction of terms, but remember that anaesthesia is a process rather than an event. Such awareness can lead to ill-defined, delayed neuroses and post-traumatic stress disorder (OHCS p347).[22]
- *Muscle power:* Corneal abrasion (∴ tape the eyes closed), no respiration, no cough (leads to pneumonia and atelectasis—partial lung collapse causing shunting ± impaired gas exchange: it starts minutes after induction, and may be related to the use of 100% O_2, supine position, surgery and age as well as to loss of power). Cannot phonate (speak) and unable to impart vital information when paralysed—eg 'I am in pain …'

Local/regional anaesthesia

If unfit/unwilling to undergo general anaesthesia, local nerve blocks (eg brachial plexus) or spinal blocks (contraindication: anticoagulation, local infection) using long-acting local anaesthetics such as ***bupivacaine*** may be indicated. See TABLE for doses and toxicity effects.

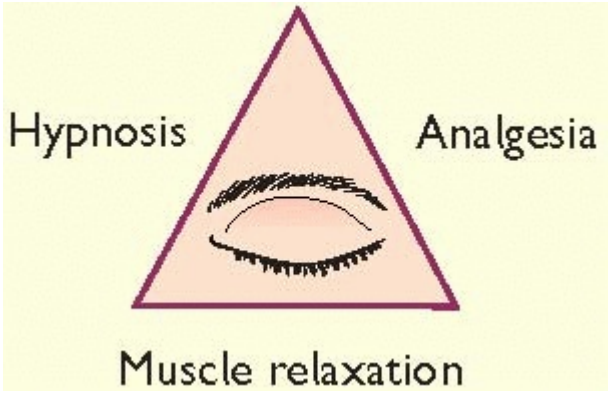
Drugs complicating anaesthesia

▸Inform anaesthetist. See p552 for lists of specific drugs, and actions to take.

Malignant hyperpyrexia

This is a rare complication, precipitated by eg ***halothane*** or ***suxamethonium***, exhibiting autosomal dominant inheritance. There is a rapid rise in temperature (>1°C every 30min); masseter spasm may also be an early sign. Complications include hypoxaemia, hypercarbia, hyperkalaemia, metabolic acidosis, and arrhythmias. ▸Get expert help immediately. Prompt treatment with ***dantrolene***,[1] cooling and supportive care can reduce mortality significantly.

Principles and practical conduct of anaesthesia



▸The general principles of anaesthesia centre on the triad of hypnosis, analgesia, and muscle relaxation.

The conduct of anaesthesia typically involves:

- *Induction:* Either intravenous (eg ***propofol*** 1.5-2.5mg/kg IV at a rate of 20-40mg every 10s; ***thiopental*** is an alternative) or, if airway obstruction or difficult IV access, gaseous (eg ***sevoflurane*** or ***nitrous oxide***, mixed in O_2).
- *Airway control:* Either using a face mask, an oropharyngeal (Guedel) airway or by intubation. The latter usually requires muscle relaxation with a depolarizing/non-depolarizing neuromuscular blocker (OHCS p622).
- *Maintenance of anaesthesia:* Either a volatile agent added to N_2O/O_2 mixture, or high-dose opiates with mechanical ventilation, or IV infusion anaesthesia (eg ***propofol*** 4-12mg/kg/h IVI).
- *End of anaesthesia:* Change inspired gases to 100% oxygen only, then discontinue any anaesthetic infusions and reverse muscle paralysis. Once spontaneously breathing, place patient in recovery position and give oxygen by face mask.

For further details, see the chapter titled *Anaesthesia* in OHCS (p612)

Local anaesthetic toxicity and maximum doses

After a few minutes conversation with an anaesthetist at work, it becomes apparent that they are masters of the drug dose by weight! It is important to remember the maximum doses for local anaesthetics, not least because we use them so frequently, but because the effects of overdose can be lethal.

Local anaesthetic toxicity starts with perioral tingling and paraesthesiae, progressing to drowsiness, seizures, coma and cardiorespiratory arrest. If suspected (the patient feels 'funny' and develops early signs) then stop administration immediately and commence ABC resuscitation as required.

Handy to remember (though it can be worked out with a pen, paper and SI units) is that a 1% concentration is equivalent to 10mg/mL. Local anaesthetics are also basic, and so do not work well in acidic environments, eg abscesses.

Agent	Total dose	Onset	Effective duration	Total dose with adrenaline*	Effective duration
Lidocaine	3mg/kg ≤200mg	Fast	½-2h	7mg/kg max 500mg	1-6h
Levobupivacaine¶	2mg/kg	Medium	2-4h	not given	—

Prilocaine[#]	6mg/kg	Fast	½-2h	6mg/kg max 400mg	1-6h

[*] ***Adrenaline*** is effective at increasing the tissue t½ of the anaesthetic and at reducing bleeding at the site of administration—very useful eg when suturing the scalp.

[¶] ***Levobupivacaine*** (Chirocaine®) is replacing racemic ***bupivacaine*** in clinical practice because it is less cardiotoxic.[23]

[#] ***Prilocaine*** can cause methaemoglobinaemia, especially in infants <6 months. This can be reversed with IV ***methylene blue***.

▸Do not use ***adrenaline*** preparations in the fingers, toes, penis or nose because of the risk of vasoconstriction of the end arteries and subsequent ischaemic necrosis.

▸**ALWAYS CHECK THE VIAL.** Adrenaline concentration should never be more than 1:80 000.

The control of pain

Humans are the most exquisite devices ever made for experiencing of pain: the richer our inner lives, the greater the varieties of pain there are for us to feel, and the more resources we have for dealing with pain. If we can connect with patients' inner lives we may make a real difference. **Never forget how painful pain is,** nor how fear magnifies pain. Try not to let these sensations, so often interposed between your patient and his recovery, be invisible to you as he bravely puts up with them.

Guidelines for success

Review and chart each pain carefully and individually.

- Identify and treat the underlying pathology wherever possible.
- Give **regular** doses rather than on an as required basis.
- Choose the best route: PO, PR, IM, epidural, SC, inhalation, or IV.
- Explanation and reassurance contribute greatly to analgesia.
- Allow the patient to be in charge. This promotes well-being, and does not lead to overuse. Patient-controlled continuous IV morphine delivery systems are useful.
- Liaise with the Acute Pain Service, if possible.

Non-narcotic (simple) analgesia

Paracetamol 0.5-1.0g/4h PO (up to 4g daily) [15mg/kg/4h IV over 1/4h in children >10kg; up to 60mg/kg/d]. Caution in liver impairment. NSAIDs, eg ***ibuprofen*** 400mg/8h PO [10mg/kg/8h in children >5kg] or ***diclofenac*** 50mg/8h PO, or 100mg PR/IM stat; these are good for musculoskeletal pain and renal or biliary colic. CI: peptic ulcer, clotting disorders, anticoagulants. Cautions: asthma, renal or hepatic impairment, pregnancy, and the elderly. ***Aspirin*** is contraindicated in children due to the risk of Reye's syndrome (OHCS p652).

Opioid drugs for severe pain

Morphine (eg 10-15mg/2-4h IV/IM) or ***diamorphine*** (5-10mg/2-4h PO, SC, or slow IV, but you may need much more) are best. **NB:** These are 'controlled' drugs. For palliative care, see p520.

Side-effects of opioids:

These include nausea (so give with an antiemetic, eg ***prochlorperazine*** 12.5mg stat IM), respiratory depression, constipation, cough suppression, urinary retention, BP↓, and sedation (do not use in hepatic failure or head injury). Dependency is rarely a problem. ***Naloxone*** (eg 100-200µg IV, followed by 100µg increments until responsive) may be needed to reverse the effects of excess opioids (p826).

How effective are standard analgesics?

Pain is subjective, but its measurement by patients is surprisingly consistent and reproducible. The table below gives 'number needed to treat' (NNT, p650), ie the number of patients who need to receive the drug for one to achieve at least 50% pain relief over 4-6h (the range is 95% confidence intervals). For an index of analgesia meta-analyses see:[24]

Codeine^{60mg}	11-48	Paracetamol^{1000mg}	3-4
Tramadol^{50mg}	6-13	Paracetamol^{1000mg}/codeine^{60mg}	2-3
Aspirin^{650mg}/codeine^{60mg}	4-7	Diclofenac^{50mg} or ibuprofen^{400mg}	2-3

Epidural analgesia

Opioids and anaesthetics are given into the epidural space by infusion or as boluses. Ask the advice of the Pain Service. SE: thought to be less as drug more localized: watch for respiratory depression; local anaesthetic-induced autonomic blockade (BP↓).

Adjuvant treatments

Eg radiotherapy for bone cancer pain; anticonvulsants, antidepressants, ***gabapentin*** or steroids for neuropathic pain, antispasmodics, eg ***hyoscine butylbromide***[1] (Buscopan® 10-20mg/8h PO/IM/IV) for intestinal, renal tract colic. If brief pain relief is needed (eg for changing dressings or exploring wounds), try inhaled ***nitrous oxide*** (with 50% O_2—as Entonox®) with an 'on demand' valve. Transcutaneous electrical nerve stimulation (TENS), local heat, local or regional anaesthesia, and neurosurgical procedures (eg excision of neuroma) may be tried but can prove disappointing. Treat conditions that exacerbate pain (eg constipation, depression, anxiety).

Why is controlling post-operative pain so important?

- Psychological reasons: Pain control is a humanitarian undertaking.
- Social reasons: Pain relief makes surgery less feared by society.
- Biological reasons: There is evidence for the following sequence: pain → autonomic activation → increased adrenergic activity → arteriolar vasoconstriction → reduced wound perfusion → decreased tissue oxygenation → delayed wound healing → serious or mortal consequences.

Who is not suitable for day-case surgery?

Over the years peri-operative care has been devolved from the inpatient setting, with better results for the patient.[1] A number of operations are performed as day-cases, commonly including varicose vein surgery, cataracts and inguinal hernia repairs. Even traditionally more demanding surgery is now being performed as day-case (eg laparoscopic cholecystectomy) and theoretically any procedure is suitable, provided the time under general anaesthetic does not exceed ~1h. The use of regional anaesthesia also helps to avoid the SE of nausea and disorientation that may accompany a general anaesthetic, thus facilitating discharge. To avoid putting the patient at unnecessary risk, it is important to identify those who are **not** suitable for day case surgery.

This may include the following:

- Severe dementia.
- Severe learning difficulties.
- Living alone (and no helpers).

- Children if supervision difficult—changes in expectation, delays and pain relief can be problematic.[25]
- BMI >32 (see p229).
- ASA category [3]III (see p553) and thus with potentially unstable co-morbidities —discuss with the anaesthetist as category III may be suitable with appropriate optimisation.
- Infection at the site of the operation.

Exclusions from local regional anaesthesia:

- Poor communication (eg deafness uncorrected by hearing aid) if co-operation is required during the anaesthetic procedure.
- Severe claustrophobia.

[1] advantages: shorter waiting lists, fewer infections, fewer days off work, and ↑patient satisfaction.

Discharging patients after day-case surgery

▸After day-case surgery, don't discharge until '**LEAP-FROG**' is established:

Lucid, not vomiting, and cough reflex established.

Easy breathing; easy urination.

Ambulant without fainting.

Pain relief + post-op drugs dispensed + given. Does he understand doses?

Follow-up arranged.

Rhythm, pulse & BP checked one last time. Is the trend satisfactory? Check no postural drop (collapsing at front doors tends to rip out your stitches).

Operation site checked and explained to patient.

GP letter sent with patient or carer; he/she *must* know what has happened.

General post-operative complications

Pyrexia

Mild pyrexia in the first 48h is typically from atelectasis (needs prompt physio, not antibiotics), tissue damage/necrosis or even from blood transfusions, but you should still have a low threshold for infection screen. See MINIBOX for where to look for infection—also check the legs for DVT (causes ↑°C). Send blood for FBC, U&E, CRP, and cultures (±LFT). Dipstick the urine. Consider MSU, CXR, and abdominal ultrasound/CT depending on clinical findings.

Looking for infection:
Check for signs of:

- Peritonism
- Chest infection
- UTI
- Wound infection
- Cannula site erythema
- Meningism
- Endocarditis

Confusion

may manifest as agitation, disorientation, and attempts to leave hospital, especially at night. Gently reassure the patient in well-lit surroundings. See p476 for a full work-up. The common causes are:

- Hypoxia (pneumonia, atelectasis, LVF, PE)
- Drugs (opiates, sedatives, and many others)
- Urinary retention
- MI or stroke
- Infection (see above)
- Alcohol withdrawal (p274)

- Liver/renal failure

Occasionally, sedation is necessary to examine the patient; consider ***midazolam*** (see p761; antidote: ***flumazenil***) or ***haloperidol*** 0.5-2mg IM. Reassure relatives that post-op confusion is common (seen in up to 40%) and reversible.

Dyspnoea or hypoxia

Any previous lung disease? Sit up and give O_2, monitoring peripheral O_2 sats by pulse oximetry (p148). Examine for evidence of:

- Pneumonia, pulmonary collapse or aspiration
- LVF (MI; fluid overload)
- Pulmonary embolism (p174);
- Pneumothorax (p174; due to CVP line, intercostal block or mechanical ventilation).

Tests

FBC; ABG; CXR; ECG. Manage according to findings.

BP↓

If severe, tilt bed head down and give O_2. Check pulse & BP yourself; compare it with pre-op values. Post-op ↓BP is often from hypovolaemia resulting from inadequate fluid input, so check fluid chart and replace losses. Monitor urine output (may need catheterization). A CVP line can help monitor fluid resuscitation (normal is 0-5cm H_2O relative to sternal angle). Hypovolaemia may also be caused by haemorrhage so review wounds and abdomen. If unstable, return to theatre for haemostasis. Beware cardiogenic and neurogenic causes and look for evidence of MI + PE. Consider sepsis and anaphylaxis.

Management:

p778.

BP↑

may be from pain, urinary retention, idiopathic hypertension (eg missed medication) or inotropic drugs. Oral cardiac medications (including antihypertensives) should be continued throughout the peri-operative period even if NBM. Treat the cause, consider increasing the regular medication, or if not absorbing orally try 50mg ***labetalol*** IV over 1 min (see p126).

Urine output↓ (oliguria)

Aim for output of >30mL/h in adults (or >½mL/kg/h). **Anuria** means a blocked or malsited catheter (see p751) and never, we hope, an impending lawsuit from both ureters tied. Flush or replace catheter. **Oliguria** is usually due to too little replacement of lost fluid. Treat by increasing fluid input.

▸Acute renal failure may follow shock, drugs, transfusion, pancreatitis or trauma.

- Review fluid chart and examine for signs of volume depletion.
- Urinary retention is also common, so examine for a palpable bladder.
- Establish normovolaemia (a CVP line may help here); you may need 1L/h IVI for 2-3h. A 250-500mL bolus of colloid (eg Gelofusin®) over 30min may also help.
- Catheterize bladder (for accurate monitoring)—see p750; check U&E.
- If intrinsic renal failure is suspected, refer to a nephrologist early.

Nausea/vomiting

Any mechanical obstruction, ileus, or emetic drugs (opiates, digoxin, anaesthetics)? Consider AXR, NGT, and an antiemetic (▸**not *metoclopramide*** because of its prokinetic property). See p233 for choice of different anti-emetics.

↓Na^+

What was the pre-op level? SIADH (p666) can be precipitated by perioperative pain, nausea, and opioids as well as chest infection. Over administration of IV fluids may exacerbate the situation. Correct slowly (p666).

Post-operative bleeding

- **Primary haemorrhage:** Ie continuous bleeding, starting during surgery. Replace blood loss. If severe, return to theatre for adequate haemostasis. Treat shock vigorously (p778).
- **Reactive haemorrhage:** Haemostasis appears secure until BP rises and bleeding starts. Replace blood and re-explore wound.
- **Secondary haemorrhage** (caused by infection) occurs 1-2 weeks post-op.

Talking about post-op complications…

When you are asked to give your thoughts on the complications of a particular operation—and this may be with an examiner or a patient—a good starting point is to divide them up accordingly:

- **From the anaesthetic:** (see p558) eg respiratory depression secondary to induction agents.
- **From surgery in general:** (see opposite and BOX above) eg wound infection, haemorrhage, neurovascular damage, DVT/PE.
- **From the specific procedure:** eg saphenous nerve damage in stripping of the long saphenous vein.

Tailor the discussion towards the individual who, eg if an arteriopath, may have a significant risk of cardiac ischaemia during hypotensive episodes whilst under the anaesthetic. For some other post-op complications, see:

- Pain (p560)
- DVT (p564 & **figs 1, 2, 3, 4** below); pulmonary embolus (p174; massive, p802)
- Wound dehiscence (p566)
- Complications in post-gastric surgery (p636)
- Other complications of specific operations (p566).

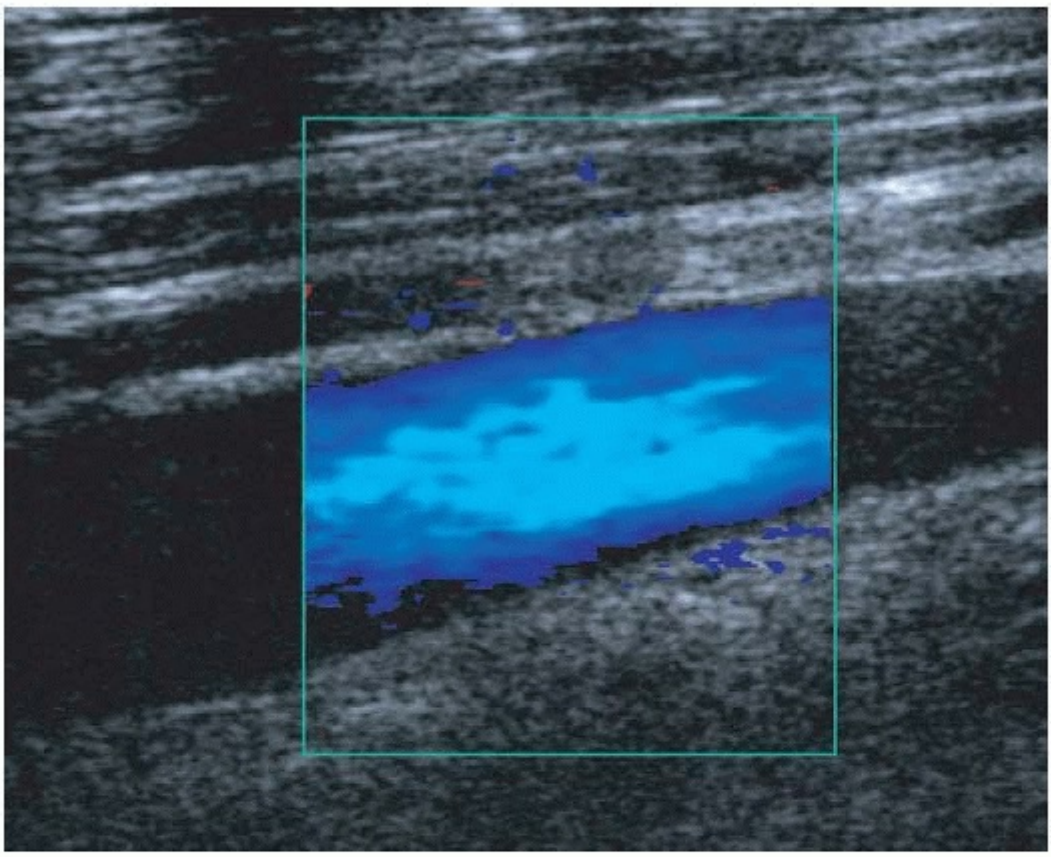


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Fig 1. A normal duplex ultrasound of the superficial femoral vein (sagittal view). Compression ultrasound is the investigation of choice in suspected DVT: an acute thrombus within a vein will not show any intraluminal echo, and its presence is confirmed by lack of compression by the ultrasound

probe (see **fig 3** below).

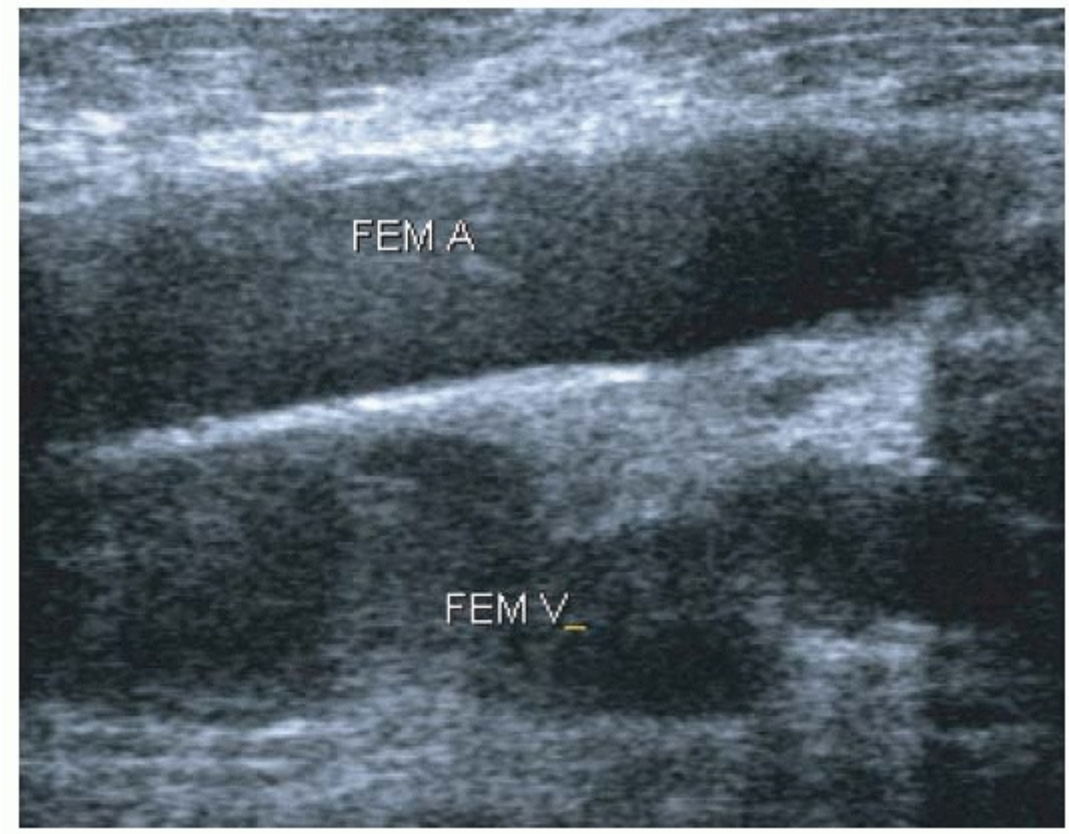


Fig 2. A sagittal view ultrasound of the femoral artery and vein. The vein (deep to the artery) has a ragged luminal edge with hyperechoic regions within the lumen. These are changes secondary to a propagating DVT.

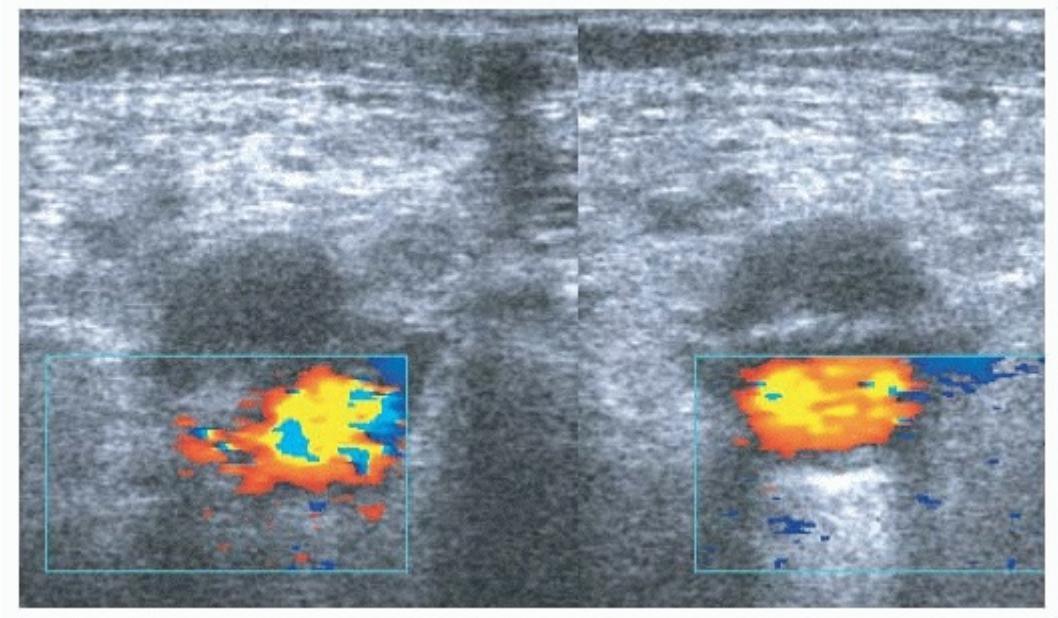


Fig 3. A duplex ultrasound showing a transverse view of the popliteal vein and artery, with (right) and without (left) compression. The vein (more superficial) is not collapsing under compression—a finding suggestive of DVT.

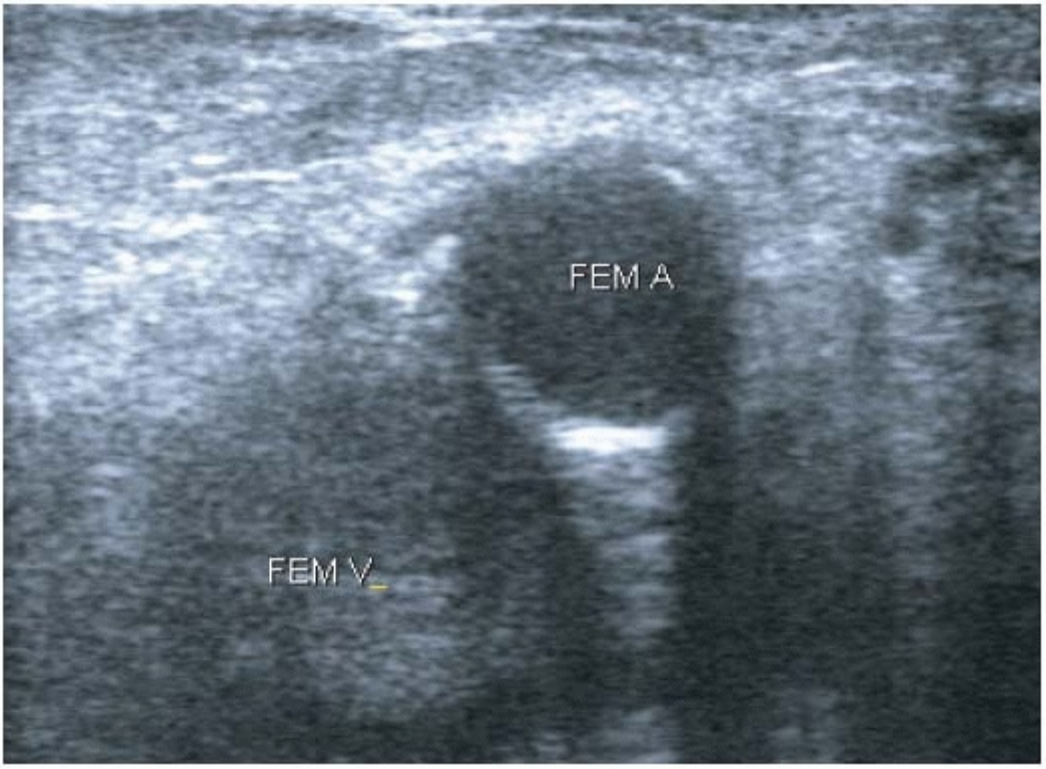


Fig 4. Ultrasound showing a transverse view of the femoral artery and vein. The lumen of the femoral vein (deep and medial to the artery) is occluded by thrombus, giving a hyperechoic signal compared to the arterial lumen.

Deep vein thrombosis (DVT) See figs, p563

DVTs occur in 25-50% of surgical patients, and many non-surgical patients. 65% of below-knee DVTs are asymptomatic; these rarely embolize to the lung.

Risk factors

Age↑, pregnancy, synthetic oestrogen, surgery (especially pelvic/ orthopaedic), past DVT, malignancy, obesity, immobility, thrombophilia (p358).

Signs

- Calf warmth/tenderness/swelling/erythema
- Mild fever
- Pitting oedema. Homans' sign (↑resistance/pain on forced foot dorsiflexion) should not be tested for as it may dislodge thrombus.

ΔΔ: Cellulitis; ruptured Baker's cyst. Both may coexist with a DVT.

Tests

D-dimer blood tests

are sensitive but not specific for DVT (also ↑ in infection, pregnancy, malignancy, and post-op).[26] A -ve result, combined with a low pretest clinical probability score (see BOX) is sufficient to exclude DVT.[27] If D-dimer↑, or the patient has a high/intermediate pretest clinical probability score, do *compression US* (**fig 3**, p563).[28] If this is -ve, a repeat US may be performed at 1wk to catch early but propagating DVTS.

Venography

is rarely necessary. Do *thrombophilia tests* (p358) **before** commencing anticoagulant therapy if there are no predisposing factors, in recurrent DVT, or if there is a family history of DVT.

Prevention

- Stop the Pill 4wks pre-op.
- Mobilize early.

- ***Heparin*** 5000U/12h SC until mobile; low molecular weight heparin (LMWH, eg ***enoxaparin*** 20mg/24h SC, ↑ to 40mg for high-risk patients, starting 2h pre-op, or ***dalteparin***) may be better (less bleeding, no monitoring needed).
- Support hosiery (CI: ischaemia).
- Intermittent pneumatic pressure, until 16h post-op.
- ***Fondaparinux*** (a factor Xa inhibitor, approved in the EU)[29] and ***ximelagatran*** may be better than LMWH.[30]

Treatment

Meta-analyses have shown LMWH (eg ***enoxaparin*** 1.5mg/kg/24h SC) to be superior to ***unfractionated heparin*** (dose guided by APTT, p334), but extensive ileofemoral thrombi may still require unfractionated heparin as such patients were excluded from the trials. Start ***warfarin*** simultaneously with LMWH as it is prothrombotic for the first 48h, stopping heparin when INR is 2-3; treat for 3 months if post-op (6 months if no cause is found; lifelong in recurrent DVT or thrombophilia).

Inferior vena caval filters

may be used in active bleeding, or when anticoagulants fails, to minimize risk of pulmonary embolus.

Post-phlebitic change

can be seen in 10-30%. Prevention with thrombolytic therapy (to reduce damage to venous valves) and graduated compression stockings have both been tried, but neither has been conclusively shown to be beneficial.[31]

Swollen legs see also p66 Treatment—see BOX

Bilateral oedema

implies systemic disease with ↑venous pressure (eg right heart failure) or ↓intravascular oncotic pressure (any cause of ↓albumin, so test the urine for protein). It is **dependent** (distributed by gravity), which is why legs are affected early, but severe oedema extends above the legs. In the bed-bound, fluid moves to the new dependent area, causing a sacral pad. The exception is the local increase in venous pressure occurring in IVC obstruction: the swelling neither extends above the legs nor redistributes.

Causes:

- Right heart failure (p120);
- Albumin ↓ (p678, eg renal or liver failure);
- Venous insufficiency: acute, eg prolonged sitting, or chronic, with haemosiderin-pigmented, itchy, eczematous skin ± ulcers;
- Vasodilators, eg ***nifedipine;***
- Pelvic mass (p52);
- Pregnancy—if BP↑ + proteinuria, diagnose pre-eclampsia (OHCS p48): find an obstetrician urgently. In all the above, both legs need not be affected to the same extent.

Unilateral oedema:

Pain ± redness implies DVT or inflammation, eg cellulitis or insect bites (any blisters?). Bone or muscle may be to blame, eg tumours; necrotizing fasciitis (p592); trauma (check for sensation, pulses and severe pain esp. on passive movement: ▸a **compartment syndrome** with ischaemic necrosis needs prompt fasciotomy). Impaired mobility suggests trauma, arthritis, or a Baker's cyst (p686). **Non-pitting oedema** is oedema you cannot indent: see p66.

Pretest clinical probability scoring for DVT: the Wells score[32]

In patients with symptoms in both legs, the more symptomatic leg is used.

Clinical features	Score
Active cancer (treatment within last 6 months or palliative)	1 point
Paralysis, paresis, or recent plaster immobilization of leg	1 point

Major surgery or recently bedridden for >3d in last 4wks	1 point
Local tenderness along distribution of deep venous system	1 point
Entire leg swollen	1 point
Calf swelling >3cm compared to asymptomatic leg (measured 10cm below tibial tuberosity)	1 point
Pitting oedema (greater in the symptomatic leg)	1 point
Collateral superficial veins (non-varicose)	1 point
Alternative diagnosis as likely or more likely than that of DVT	-2 points

Wells score:

≥3 points:

High pretest probability—treat as suspected DVT and perform compression US.

1-2 points:

Intermediate pretest probability—treat as suspected DVT and perform compression US.

≤0 points:

Low pretest probability of DVT—perform D-dimer test. If +ve then treat as suspected DVT and perform compression US. If -ve, DVT reliably excluded.

Air travel and DVT

In 1954, Homans first reported an association between air travel and venous thromboembolism. Recently, the supposed risk of DVT and sub-sequent pulmonary emboli associated with air travel (the so-called 'economy-class syndrome') has been the subject of much public scrutiny. Factors such as dehydration, immobilization, decreased oxygen tension, and prolonged pressure on the popliteal veins resulting from long periods in confined aircraft seats have all been suggested to be contributory factors. While the evidence linking air travel to an increased risk of DVT is still largely circumstantial, the following facts may help answer questions from your patients, family, and friends:

- The risk of developing a DVT from a long distance flight has been estimated at 0.01-0.04% for the general population.
- The incidence of DVT in **high risk** groups has been shown to be 4-6% for flights >10h. Prophylaxis with one dose of LMWH **may** be justified.[33]
- There is an increased risk of pulmonary embolus associated with long distance air travel.[34]
- Compression stockings may decrease the risk of DVT, though they may also cause superficial thrombophlebitis.
- The role of prophylactic ***aspirin*** is still unclear and under investigation.
- Measures to minimize risk of DVT include leg exercises, increased water intake, and refraining from alcohol or caffeine during the flight.

9 questions to ask those with swollen legs

1. Is it **both** legs?
2. Is she pregnant?
3. Is she mobile?
4. Any trauma?
5. Any pitting?
6. Past diseases/on drugs?
7. Any pain?
8. Any skin changes?
9. Any oedema elsewhere?

Treatment of leg oedema

Treat the cause. Giving diuretics to everyone is not an answer. Ameliorate dependent oedema by elevating the legs (ankles higher than hips—do not just use foot stools); raise the foot of the bed. Graduated support stockings may help (CI: ischaemia).[35]

Specific post-operative complications

Laparotomy

In the elderly, or the malnourished, the wound may break down from a few days to a few weeks post-op, eg if infection or haematoma is present, or this is major surgery in a patient already compromised, eg by cancer, or this is a 2nd laparotomy. The warning sign of wound dehiscence (incidence ≈3.5%) is a pink serous discharge. Always assume that the defect involves the whole of the wound. Serious wound dehiscence may lead to a 'burst abdomen' with evisceration of bowel (mortality 15-30%). If you are on the ward when this happens, put the guts back into the abdomen, place a sterile dressing over the wound, give IV antibiotics (eg **cefuroxime** + **metronidazole)** and call your senior. Allay anxiety, give parenteral pain control, set up an IVI, and return patient to theatre. *Incisional hernia* is a common problem (20%), repairable by mesh insertion.[36]

Biliary surgery

After exploration of the common bile duct (CBD), a T-tube is usually left in the bile duct draining freely to the exterior. A T-tube cholangiogram is done at 8-10d and if there are no retained stones, the tube may be pulled out.

Retained stones may be removed by ERCP (p728), further surgery, or instillation of stone-dissolving agents (via T-tube). If there is distal obstruction in the CBD, fistula formation may occur with a chronic leakage of bile. Other complications of biliary surgery are CBD stricture; cholangitis; bleeding into the biliary tree (haemobilia) which may lead to biliary colic, jaundice, and haematemesis; pancreatitis; leak of bile causing biliary peritonitis. If jaundiced, it is important to maintain a good urine output as there is a danger of hepatorenal syndrome (p251). See TABLE for ***laparoscopic cholecystectomy***.

Thyroid surgery

(also see p622) Recurrent (± superior) laryngeal nerve palsy (→hoarseness) can occur permanently in 0.5% and transiently in 1.5%[37] —warn the patient that **their voice will be different** for a few days post-op because of intubation and local oedema. **NB:** Pre-operative fibreoptic laryngoscopy should be performed to exclude pre-existing vocal cord dysfunction); hypoparathyroidism (p206), causing hypocalcaemia (p670) that is permanent in 2.5%; hypothyroidism in the long term; thyroid storm (p816); tracheal obstruction due to haematoma in the wound may occur: ▸▸relieve by immediate removal of stitches or clips using the cutter/remover that should remain at the beside; may require urgent surgery.

Mastectomy

Arm lymphoedema in up to 20% of those undergoing axillary node sampling or dissection—see BOX;[38] skin necrosis.

Arterial surgery

Bleeding; thrombosis; embolism; graft infection; MI; AV fistula formation.

Complications of aortic surgery:

Gut ischaemia; renal failure; respiratory distress; aorto-enteric fistula; trauma to ureters or anterior spinal artery (leading to paraplegia); distal trash from dislodged thrombus.

Colonic surgery

Sepsis; ileus; fistulae; anastomotic leak (10% for anterior resection);[39] obstruction from adhesions (BOX); haemorrhage; trauma to ureters or spleen.

Small bowel surgery

Short gut syndrome (best defined **functionally**, though anatomically $\lesssim$250cm in the adult) may result from substantial resections of small bowel. Diarrhoea and malabsorption (particularly of fats) lead to a number of metabolic abnormalities including deficiency in vitamins A, D, E, K, & B_{12}, hyperoxaluria (causing renal stones), and bile salt depletion (causing gallstones).[40]

Tracheostomy

Stenosis; mediastinitis; surgical emphysema.

Splenectomy

Acute gastric dilatation (a serious consequence of not using a NGT, or to check that the one in place is working); thrombocytosis; sepsis. ▸Lifetime sepsis risk is partly preventable with pre-op vaccines—ie *Haemophilus* type B, meningococcal, & pneumococcal (p381 & p152) and prophylactic penicillin (p357).

Genitourinary surgery

Septicaemia (from instrumentation in the presence of infected urine)—consider a stat dose of ***gentamicin***; urinoma—rupture of a ureter or renal pelvis leading to a mass of extravasated urine.

Gastrectomy

See p636.

Prostatectomy

p603.

Haemorrhoidectomy

p626.

Adhesions—legacy of the laparotomy, bane of the surgeon

When re-operating on the abdomen, the struggle against adhesions tests the farthest and darkest boundaries of patience of the abdominal surgeon and the assistant. The skill and persistence required to gently and atraumatically tease apart these fibrous bands that restrict access and vision makes any progression, no matter how slight, cause for subdued celebration. Perseverance is the name of this game—also known as *adhesiolysis*.

Any surgical procedure that breaches the abdominal or pelvic cavities can predispose to the formation of adhesions, which are found in up to 90% of those with previous abdominal surgery, hence why we do not rush to operate on small bowel obstruction: the operation predisposes to yet more adhesions. Handling of the serosal surface of the bowel causes inflammation, which over the period of weeks to years can lead to the formation of fibrous bands that tether the bowel to itself or adjacent structures—though adhesions can also form secondary to infection, radiation injury and inflammatory processes such as Crohn's disease. Their main sequelae are intestinal obstruction (the cause in ~60% of cases—see p598) and chronic abdominal or pelvic pain. Studies have shown that adhesiolysis may help relieve chronic pain, though for a small proportion of patients the pain never improves or even worsens after directed intervention.[1]

As far as prevention is concerned, the best approach is to avoid operating, though there is evidence to suggest that laparoscopy compared to laparotomy reduces the rate of local adhesions,[42] and that there may be a role for the insertion of synthetic films to prevent adhesions to the anterior abdominal wall.[43]

Lymphatic drainage of the breast

Risk of lymphoedema increases with the level of axillary dissection:

- **Level 1** dissection remains inferior to pectoralis minor
- **Level 2** goes behind pectoralis minor
- **Level 3** goes superior to pectoralis minor (rarely done).

The higher the dissection, the greater the risk of interference with lymphatic drainage of the arm and ∴ of lymphoedema.

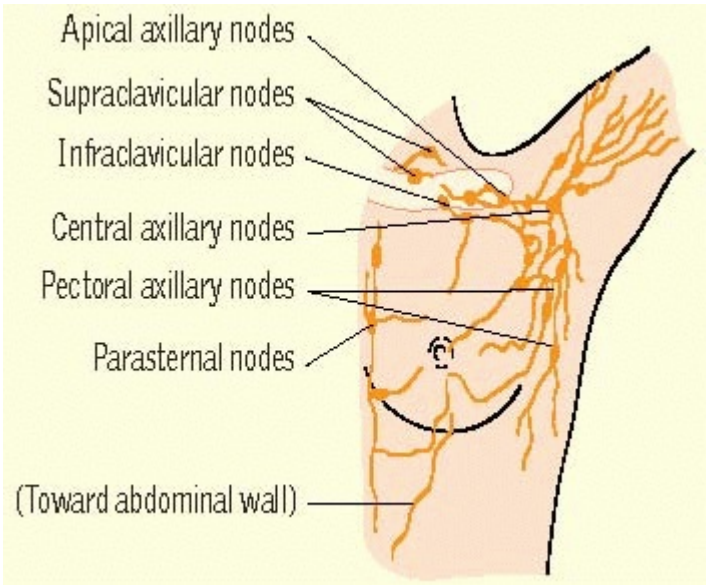


Image after RCSI website

The complications of laparoscopic cholecystectomy

Complications that should be discussed include:	Risk
Conversion to open procedure	5%
CBD injury[1]	0.32%
Bile leak	0.2%
Post-operative haemorrhage	0.1%
Intra-abdominal abscess	0.07%
Mortality secondary to operative injury	0.04%

These complication rates are taken from one study that reviewed 39,238 cases.[44]

NB: Total operative mortality may be nearer 0.1%

[1] The nasty long-term sequela of this is permanent CBD stricture and a life of misery along with it. CBD damage rate during laparoscopic surgery is twice that of open surgery.

Stoma care

A stoma (Greek στομα=mouth) is an artificial union made between 2 conduits (eg a choledochojejunostomy) or, more commonly, between a conduit and the outside— eg a colostomy, in which faeces are made to pass through a hole in the abdominal wall into an adherent plastic bag, ideally as 1-2 formed motions/day.

The physical and psychological aspects of stoma care must not be undervalued. Be alert to any vicious cycle in which a skin reaction leads to leakage → fear of going out into the world → fear of eating → poor skin nutrition → further skin reactions → further leakage → more depression. These cycles can be circumvented by the *stoma nurse*, who is **the** expert in fitting secure, odourless devices.[45] Ensure patients have her phone number for use before and after surgery. Her visits are more useful than any doctor's in explaining what is going to happen, what the stoma will be like, and in troubleshooting post-op problems. ▸**Early direct self-referral prevents problems.** Without her, a patient may reject his colostomy, never attend to it, or even become

suicidal.

Colostomies

Pre-op, confirm that he is unsuited to one of the newer colostomy avoiding operations (see below). Are they suitable for a laparoscopic operation?[46]

- *Loop colostomy:* A loop of colon is exteriorized, opened, and sewn to the skin. A rod under the loop prevents retraction and may be removed after 7d. This can be a defunctioning stoma (below), though faeces may pass beyond the loop. It is often temporary, and more prone to complications than end colostomies.
- *End colostomy:* The bowel is divided; the proximal end brought out as a stoma; the distal end may be:
  1. **resected**, eg abdominoperineal resection;
  2. **closed** & left in the abdomen (Hartman's procedure);
  3. **exteriorized**, forming a 'mucous fistula'.
- *Double-barrelled (Paul-Mikulicz) colostomy:* The colon is brought out as a double-barrel. It may be closed using an enterotome. See **figs 1** & **3**.

Incidence:

50,000 colostomies/yr[UK]. Most manage their colostomies well. The cost for appliances is ~£1300/yr (allowing for a bag-use rate of 1-3/d). If there is an allergic-type reaction to the adhesive or other part of the device, a change of device may be all that is needed. Contact the local specialist nurse. Avoid most creams which can be troublesome if of an oily nature; Comfeel® is an exception.

Ileostomies

protrude from the skin and emit fluid motions which contain active enzymes (so skin needs protecting). End ileostomy usually follows proctocolectomy, typically for UC; loop ileostomies can also be formed. See **fig 2**.

Defunctioning stomas

(eg loop colostomy/ileostomy) are used to relieve distal obstruction or to protect distal anastomoses. Although they do not reduce leakage rates, they probably minimise the severity of leakage when it does occur.[47]

The alternatives to colostomy

Total anorectal reconstruction uses gracilis muscle disconnected distally and wound around the anus and induced to contract by a pulse generator implanted in the abdomen, with bowel action triggered by a hand-held radiofrequency controller. It is still rather experimental, but patients will ask about it. Warn them that it is not without complications and that normal-quality continence will not be achieved because of lack of sensation of the arrival of stools.[48] **Posterior sagittal anorectoplasty (PSARP)** is also possible.

There is some evidence from non-randomized trials that sphincter-saving operations are not associated with poorer disease-free survival compared with abdominoperineal resection in those with rectal carcinoma near the anal verge.[49]

Urostomies

are fashioned after total cystectomy, bringing urine from the ureters to the abdominal wall via an **ileal conduit** that is usually incontinent. Formation of a catherizable valvular mechanism may retain continence. Advances in urological surgery have seen an increase in continence-saving procedures such as orthotopic neobladder reconstruction.[50]

Complications of stomas

▸Liaise with the stoma nurse, starting pre-operatively.

Early:

- Haemorrhage at stoma site
- Stoma ischaemia—colour progresses from dusky grey to black
- High output (can lead to $K^+\downarrow$)—consider ***loperamide*** ± ***codeine*** to thicken the output
- Obstruction secondary to adhesions (see p567)
- Stoma retraction.

Delayed:

- Obstruction (failure at operation to close lateral space around stoma)
- Dermatitis around stoma site (worse with ileostomy)
- Stoma prolapse
- Parastomal hernia (risk increases with time)[51]
- Fistulae (p551)
- Psychological problems.

Choosing a stoma site[1]

When choosing the site for a stoma, avoid:

- Bony prominences (eg anterior superior iliac spine, costal margins)
- The umbilicus
- Old wounds/scars—there may be adhesions beneath
- Skin folds and creases
- The waistline.

The site should be assessed pre-operatively by the stoma nurse, with the patient both lying and standing.

When placing the first bag at the end of the operation, think about whether the patient will be sitting up or mobile (direct bag towards feet) or whether they will be recumbent for a period (direct bag towards the flank). This will help the person looking after the bag in their task—which may not be the patient if they are too unwell.

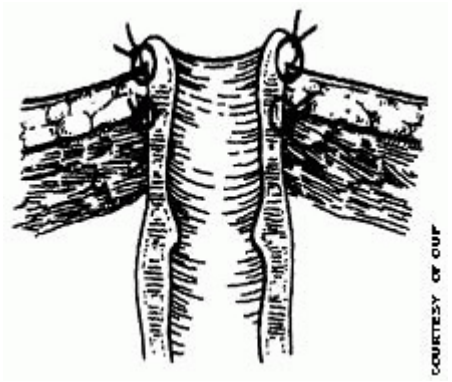


Fig 1. Colostomy

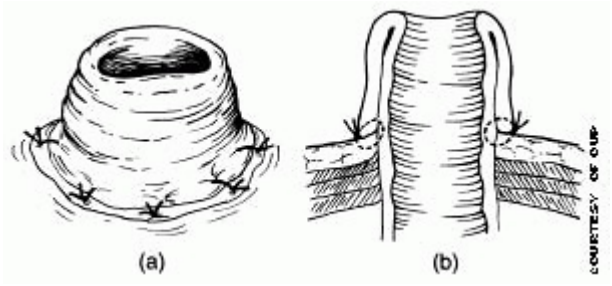


Fig 2. Ileostomy

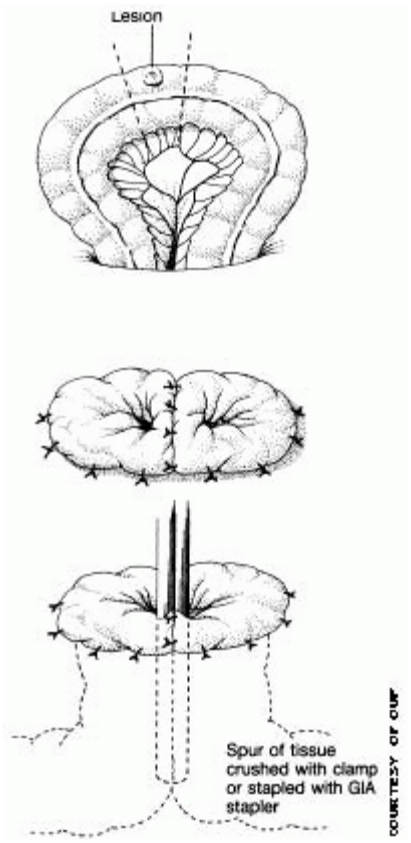


Fig 3. Paul-Mikulicz stoma

Blood transfusion and blood products

▸Blood should only be given if strictly necessary.

- **Know and use** local procedures to ensure that the right blood gets to the right patient at the right time. See p553 for quantities to request.
- Take blood for crossmatching from only 1 patient at a time. Label immediately. This minimizes risk of wrong labelling of samples.
- When giving blood, monitor TPR and BP every ½h.
- Do not use giving sets which have contained dextrose or Gelofusine®.

Group-and-save (G&S) requests

Find out your local guidelines for elective surgery. Having crossmatched blood to hand may not be needed if a blood sample is already in the lab, with group determined, with any atypical antibodies (ie G&S).

Products

Whole blood:

(rarely used) Indications: exchange transfusion; grave exsanguination—use crossmatched blood if possible, but if not, use 'universal donor' group **O Rh-ve** blood, changing to crossmatched blood as soon as possible. ▸Blood >2d old has no effective platelets.

Red cells:

(packed to make haematocrit ~70%) Use to correct anaemia or blood loss. 1U ↑Hb by 1-1.5g/dL. In anaemia, transfuse until Hb ~8g/dL.

Platelets:

(p348) Not usually needed if not bleeding or count is >20 × 10^9/L. 1U should ↑platelet count by >20 × 10^9/L. Failure to do so suggests refractoriness—discuss with haematologist. If surgery is planned, get advice if <100 × 10^9/L.

Fresh frozen plasma (FFP):

Use to correct clotting defects: eg DIC (p336); warfarin overdosage where **vitamin K** would be too slow; liver disease; thrombotic thrombocytopenic purpura (p300). It is expensive and carries all the risks of blood transfusion. Do not use as a simple volume expander. ***Human albumin solution*** is produced

as 4.5% or 20% protein solution and is for use as protein replacement. 20% albumin can be used temporarily in the hypoproteinaemic patient (eg liver disease; nephrosis) who is fluid overloaded, without giving an excessive salt load. Also used as replacement in abdominal paracentesis (p753).

Others

Cryoprecipitate (a source of fibrinogen); coagulation concentrates (self-injected in haemophilia); immunoglobulin (***anti-D***, OHCS p9).

Complications of transfusion

[52] ▸**Management of acute reactions: see BOX.**

- ***Early (within 24h):*** Acute haemolytic reactions (eg ABO or Rhesus incompatibility); anaphylaxis; bacterial contamination; febrile reactions (eg from HLA antibodies); allergic reactions (eg itch, urticaria, mild fever); fluid overload; transfusion-related acute lung injury (TRALI)—basically ARDS due to antileucocyte antibodies in donor plasma.
- ***Delayed (after 24h):*** Infections (eg viruses: hepatitis B/C, HIV; bacteria; protozoa; prions); iron overload (treatable with ***desferrioxamine***); graft-versus-host disease; post-transfusion purpura—potentially lethal fall in platelet count 5- 7d post-transfusion requiring specialist treatment with IV immunoglobulin and platelet transfusions.

Massive blood transfusion

This is defined as replacement of an individual's entire blood volume (>10U) within 24h. Complications: platelets↓; Ca^{2+} ↓; clotting factors↓; K^{+}↑; hypothermia.

Transfusing patients with heart failure

If Hb ≤5g/dL with heart failure, transfusion with packed red cells is vital to restore Hb to safe level, eg 6-8g/dL, but must be done with great care. Give each unit over 4h with ***furosemide*** (eg 40mg slow IV/PO; don't mix with blood) with alternate units. Check for ↑JVP and basal lung crackles; consider CVP line. If CCF gets worse, and immediate transfusion is vital, try a 2-3U exchange transfusion, removing blood at same rate as transfused.

Autologous transfusion

There is a role for patients having their own blood stored pre-op for later use. ***Erythropoietin*** (***EPO***,p294) can increase the yield of autologous blood in normal people. Intraoperative cell salvage with retransfusion is also being used more often, especially in cardiac, vascular and emergency surgery.[53] Costanalysis shows that it may be worthwhile on an economic basis alone.[54]

Transfusion reactions

All UK blood products are now leucocyte-depleted (white cells <5×10^{6}/L) so as to reduce the incidence of complications such as alloimmunisation to HLA class I antigens and febrile transfusion reactions.

Acute haemolytic reaction (eg ABO incompatibility) Agitation, T°↑ (rapid onset), ↓BP, flushing, abdominal/chest pain, oozing venepuncture sites, DIC.	**STOP** transfusion. Check identity and name on unit; tell haematologist; send unit + FBC, U&E, clotting, cultures, & urine (haemoglobinuria) to lab. Keep IV line open with 0.9% saline. Treat DIC (p336).
Anaphylaxis Bronchospasm, cyanosis, ↓BP, soft tissue swelling.	**SLOW** or **STOP** the transfusion. Maintain airway and give oxygen. Contact anaesthetist. ▸▸See p780.
Bacterial contamination T°↑ (rapid onset), ↓BP, and rigors.	**STOP** the transfusion. Check identity against name on unit; tell haematologist and send unit + FBC, U&E, clotting, cultures & urine to lab. Start broad-spectrum antibiotics.
TRALI (See OPPOSITE) Dyspnoea, cough;	**STOP** the transfusion. Give 100% O2. Treat as ARDS: ▸▸see p170. Donor should be removed from donor

CXR 'white out'	panel.
Non-haemolytic febrile transfusion reaction Shivering and fever usually ½-1h after starting transfusion.	**SLOW** or **STOP** the transfusion. Give an antipyretic, eg ***paracetamol*** 1g. Monitor closely. If recurrent, use leucocyte-depleted blood or WBC filter.
Allergic reactions Urticaria and itch.	**SLOW** or **STOP** the transfusion; ***chlorphenamine*** 10mg slow IV/IM. Monitor closely.
Fluid overload Dyspnoea, hypoxia, tachycardia, ↑JVP & basal crepitations.	**SLOW** or **STOP** the transfusion. Give oxygen and a diuretic, eg ***furosemide*** 40mg IV initially. Consider CVP line+exchange transfusion.

Blood transfusion and Jehovah's witnesses

These patients are likely to refuse even vital transfusions on religious grounds.[1] These views must be respected, but complex issues arise if the patient is a child, or (perhaps) an adult who lives a sheltered life, and may not be able to give, or withhold consent in an informed way—see p554. When in doubt, apply to the Court. Judges tend to take a narrow view on this, acting as if any immediate benefit to life must trump putative benefits in any life hereafter.[2] How can refusal be informed, it might be argued, if only the physical (and not the metaphysical) consequences of transfusion can be foreseen?

Even if metaphysical considerations are put to one side, it is a question whether giving a transfusion against consent could amount to a degrading act or torture, against which the European Convention on Human Rights gives absolute, inalienable protection. ▸Some patients may not want to forsake their principles but would not mind too much being told what to do, thereby not being the means of their child's destruction, while being true to their beliefs. It is possible to hold two incompatible beliefs at the same time.[1]

[1] Accepting transfusion implies **self-expulsion** from the church, but it is no longer a **'disfellowshipping event'** with active expulsion. This tenet is based on (among others) the biblical verse "*no soul of you shall eat blood*" (Leviticus 17:12).

Nutritional support in hospital

▸Over 25% of hospital inpatients may be malnourished. Hospitals can become so focused on curing disease that they ignore the foundations of good health—malnourished patients recover more slowly and experience more complications.[1]

Why are so many hospital patients malnourished?

1. Increased nutritional requirements (eg sepsis, burns, surgery).
2. Increased nutritional losses (eg malabsorption, output from stoma).
3. Decreased intake (eg dysphagia, sedation, coma).
4. Effect of treatment (eg nausea, diarrhoea).
5. Enforced starvation (eg prolonged periods nil by mouth).
6. Missing meals through being whisked off, eg for investigations.
7. Difficulty with feeding (eg lost dentures; no one available to give enough help).
8. Unappetizing food: 'They feed me stuff I wouldn't give my cat'.

Identifying the malnourished patient

- ***History:*** Recent weight↓ (>20%, accounting for fluid balance); recent reduced intake; diet change (eg recent change in consistency of food); nausea, vomiting, pain, diarrhoea which might have led to reduced intake.

- ***Examination:*** Examine for state of hydration (p664): dehydration can go hand-in-hand with malnutrition, and overhydration can mask the appearance of malnutrition. Evidence of malnutrition: skin hanging off muscles (eg over biceps); no fat between fold of skin; hair rough and wiry; pressure sores; sores at corner of mouth. Calculate the body mass index (p229); BMI <20kg/m^2 suggests malnourishment. Anthropomorphic indices, eg mid arm circumference, can also be used.
- ***Investigations:*** Generally unhelpful. Low albumin suggestive, but is affected by many things other than nutrition. ↑Albumin can be helpful in monitoring recovery.

Prevention of malnutrition

Assess nutrition state and weight on admission, and eg weekly thereafter. Identify those at risk (see above). Ensure that meals are uninterrupted, when possible. Provide appetizing food to the patient when he wants to eat it. If patient requires nutritional support, seek help from dietician.

Calorie and nutritional requirements

See TABLE.

Approximate energy contents

See TABLE.

Enteral nutrition

(ie nutrition given into gastrointestinal tract) If at all possible, give nutrition by mouth. An all-fluid diet can meet requirements (but get advice from dietician). If danger of choking or aspiration (eg after stroke), consider semi-solid diet before abandoning food by mouth. Post-op enteral nutrition has been shown to benefit patients (eg after surgery for gut perforation).[55]

Tube feeding:

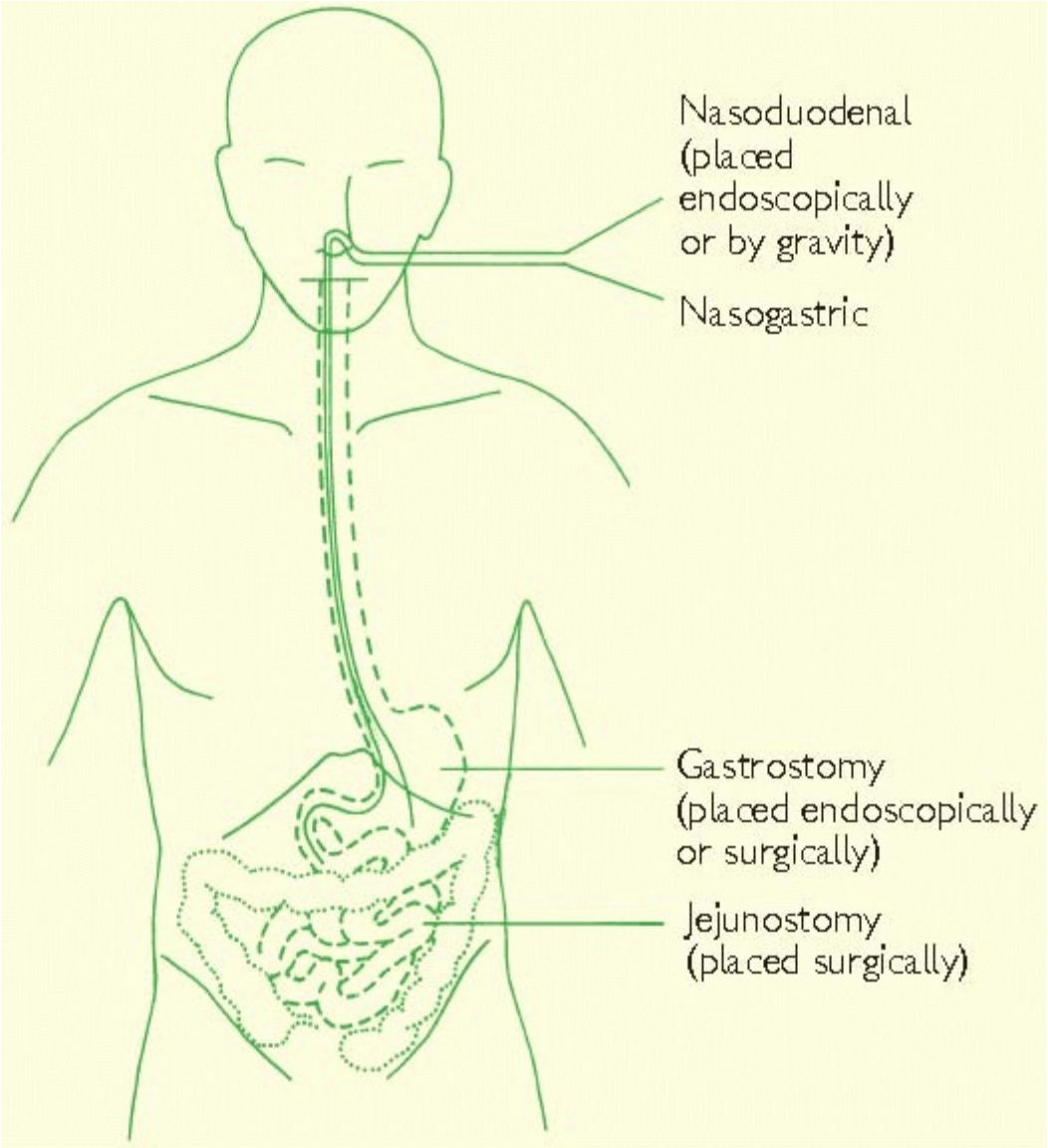
This is giving liquid nutrition *via* a tube, eg placed endoscopically, radiologically, or surgically (directly into stomach, ie gastrostomy)—see BOX. Use nutritionally complete, commercially prepared feeds. Standard feeds (eg Nutrison standard®, Osmolite®) normally contain ~1kCal/mL and 4-6g protein per 100mL. Most people's requirements are met with 2L/24h. Specialist advice from dietician is essential. Nausea and vomiting is less of a problem if feed given continuously with pump, but may have disadvantages compared with intermittent nutrition.

Guidelines for success

- Use fine-bore (9 Fr) nasogastric feeding tube when possible.
- Check position of nasogastric tube (pH testing, listening for *borborygmi*) or nasoduodenal tube (X-ray) before starting feeding.
- Build up feeds gradually to avoid diarrhoea and distension.
- Weigh weekly, check blood glucose and plasma electrolytes (including phosphate, zinc, and magnesium, if previously malnourished).
- Treat underlying conditions vigorously—eg sepsis may impede +ve nitrogen balance.

▸ Close liaison with a dietician is essential.

Enteral tube feeding



Daily energy and nutritional requirements

Substance	Requirement (/kg/d)	Notes
Energy	20-40kCal	Normal adult requirements will be 2000-2500kCal/d; even catabolic patients rarely require >2500kCal/d. Very high calorie diets (eg >4000kCal/d) can lead to a fatty liver.
	84-168kJ	Multiply kCal by a factor of 4.2.
Nitrogen	0.2-0.4g	6.25g of enteral protein gives 1g of nitrogen. Considering nitrogen balance is important because although catabolism is inevitable, replenishment is vital.

Protein	0.5g	Contains 5kCal/g.
Fat	3g	Contains 10kCal/g.
Carbohydrate	2g	Contains 4kCal/g.
Water	30-35ml	+500ml/d for each °C of pyrexia.
Na/K/Cl	1.0mmol each	Electrolytes need to be considered, even if not on IVI.

Parenteral (intravenous) nutrition

Do not undertake parenteral feeding lightly: it has risks. Specialist advice is vital. It should only be considered if the patient is likely to become malnourished without it—this normally means that the gastrointestinal tract is not functioning (eg bowel obstruction), and is unlikely to function for at least 7d. Parenteral feeding may supplement other forms of nutrition (eg in short bowel syndrome or active Crohn's disease, when nutrition cannot be sufficiently absorbed in the gut) or it can be used alone (total parenteral nutrition—TPN). ▸Even if there is GI disease, studies show that enteral nutrition is safer, cheaper, and at least as efficacious as parenteral nutrition in the perioperative period.[1] 56

Administration

Nutrition is normally given through a central venous line as this usually lasts longer than if given into a peripheral vein. A peripherally inserted central catheter (PICC line) is another option, though they can be trickier to insert and may have a higher rate of thrombophlebitis. 57 Insert under strict sterile conditions and check position on x-ray—**figs 1** & **2**.

Requirements

There are many different regimens for parenteral feeding. Most provide 2000kCal and 10-14g nitrogen in 2-3L; this usually meets a patient's daily requirements (see TABLE, p573). ~50% of calories are provided by fat and ~50% by carbohydrate. Regimens comprise vitamins, minerals, trace elements, and electrolytes; these will normally be included by the pharmacist.

Complications[2]

- ***Sepsis*** (Eg *Staphylococcus epidermidis* and *Staphylococcus aureus; Candida; Pseudomonas;* infective endocarditis.) Look for spiking pyrexia and examine wound at tube insertion point. Take line **and** peripheral cultures. If central venous line-related sepsis is suspected, the safest course of action is always to remove the line. Do not attempt to salvage a line when *S. aureus* or *Candida* infection has been identified. Antimicrobial-impregnated central lines decrease the incidence of line-related infections. 58
- ***Thrombosis*** Central vein thrombosis may occur, resulting in pulmonary embolus or superior vena caval obstruction (p514). ***Heparin*** in the nutrient solution may be useful for prophylaxis in high-risk patients, though there is little clear-cut evidence in adult studies.
- *Metabolic imbalance* Electrolyte abnormalities—see BOX; deranged plasma glucose; hyperlipidaemia; deficiency syndromes (TABLE, p273); acid-base disturbance (eg hypercapnia from excessive CO_2 production).
- *Mechanical:* Pneumothorax; embolism of IV line tip.

Guidelines for success

- ▸Liaise closely with line insertion team, nutrition team and pharmacist.
- Meticulous sterility. Do not use central venous lines for uses other than nutrition. Remove the line if you suspect infection. Culture its tip.
- Review fluid balance at least twice daily, and requirements for energy and electrolytes daily.
- Check weight, fluid balance, and urine glucose daily throughout period of parenteral nutrition. Check plasma glucose, creatinine and electrolytes

(including calcium and phosphate), and FBC daily until stable and then 3 times a week. Check LFT and lipid clearance three times a week until stable and then weekly. Check zinc and magnesium weekly throughout.

- Do not rush. Achieve the maintenance regimen in small steps.
- Treat underlying conditions vigorously—eg sepsis may impede +ve nitrogen balance.

Refeeding syndrome

This is a life-threatening metabolic complication of refeeding *via* any route after a prolonged period of starvation.[59] As the body turns to fat and protein metabolism in the starved state, there is a drop in the level of circulating insulin (because of the paucity of dietary carbohydrates). The catabolic state also depletes intracellular stores of phosphate, although serum levels may remain normal (0.85-1.45mmol/L). When refeeding begins, level of insulin rises in response to the carbohydrate load, and one of the consequences is to increase cellular uptake of phosphate.

A hypophosphataemic state (<0.50mmol/L) normally develops within 4d and is mostly responsible for the features of '**refeeding syndrome**' which include: rhabdomyolysis; red and white cell dysfunction; respiratory insufficiency; arrhythmias; cardiogenic shock; seizures; sudden death.

Prevention

requires at-risk patients to be identified, assessed and monitored closely during the period of refeeding (glucose, lipids, and electrolytes—sodium, potassium, phosphate, calcium, magnesium, and zinc). Close involvement of a nutritionist is required.

Treatment

is of the complicating features and includes parenteral phosphate administration (eg 18mmol/d) in addition to oral supplementation.[60]

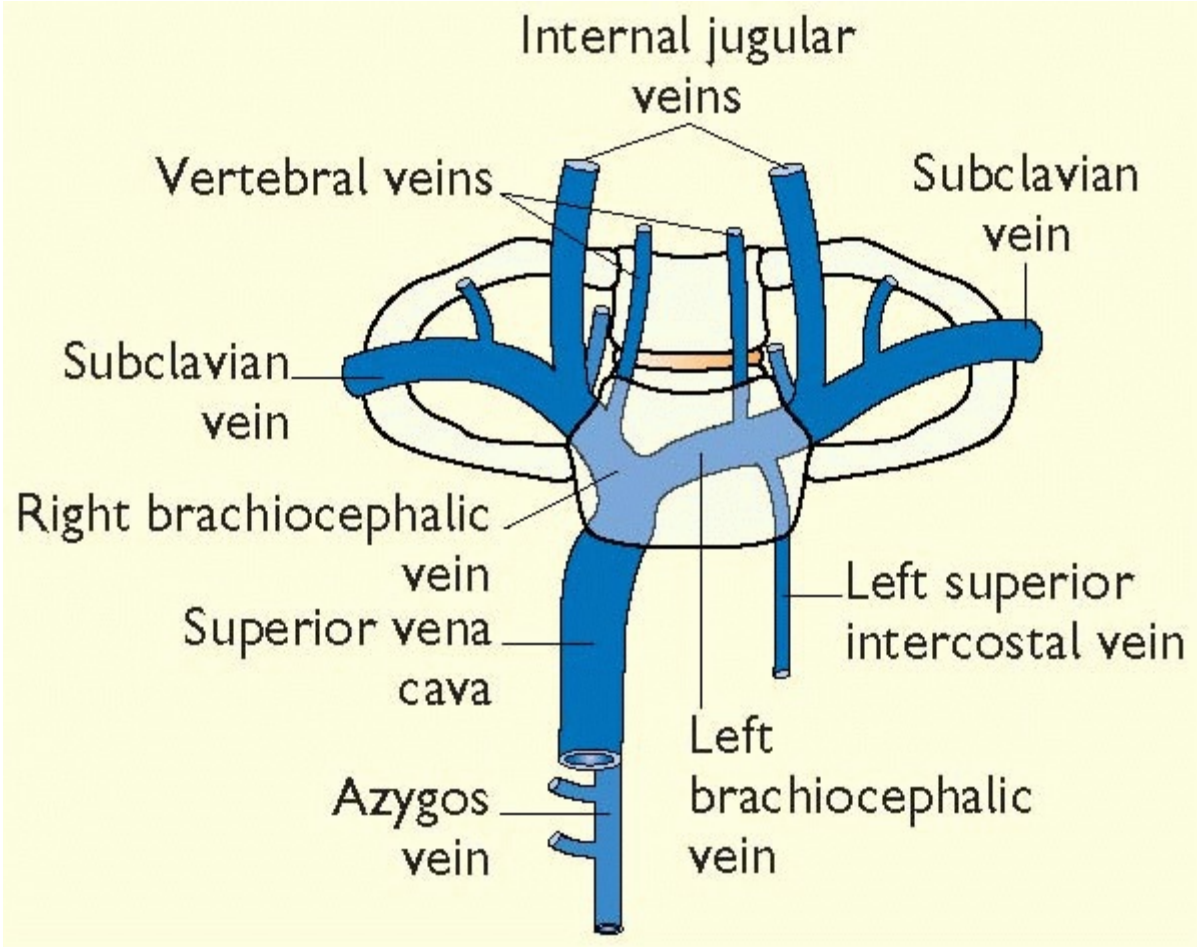
At risk with:

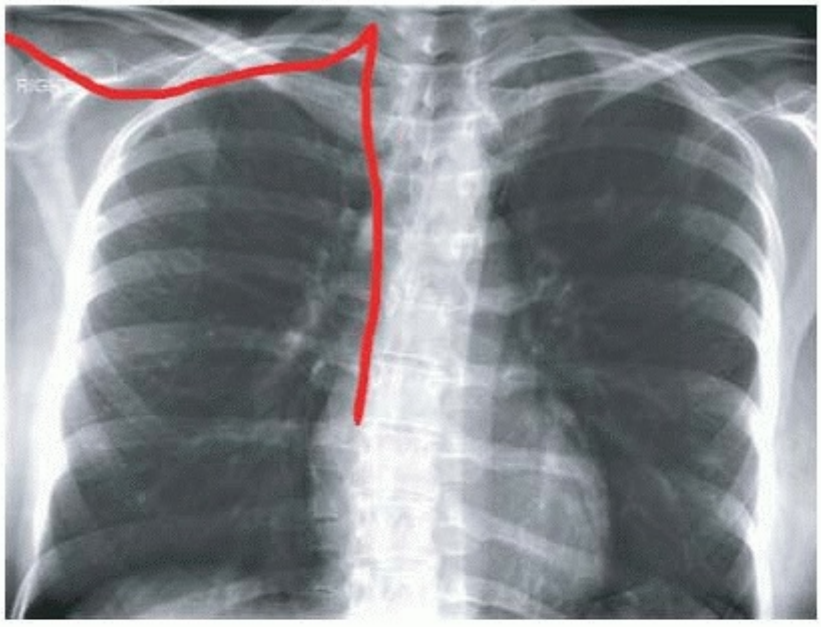
- Malignancy
- Anorexia nervosa
- Alcoholism
- GI surgery
- Starvation

The venous system at the thoracic outlet

When trying to judge the position of a central venous line tip on CXR (see **figs 1** & **2**) it helps to know the anatomical landmarks of the venous system. The subclavian veins join the internal jugular veins behind the sternoclavicular joints to form the brachio-cephalic veins. These come together behind the right 1st sternocostal joint to form the superior vena cava (SVC), which runs from this point to the right 3rd sternocostal joint. The right atrium starts here.

After RCSI website





BOTH IMAGES COURTESY OF ADDENBROOKE'S HOSPITAL NHS TRUST

Fig 1. This is a CXR showing a correctly placed peripherally inserted central catheter (PICC) (red highlight). The catheter is placed under strict sterile conditions via the ante-cubital fossa, through the cephalic and subclavian veins, down into the SVC (compare with BOX above).

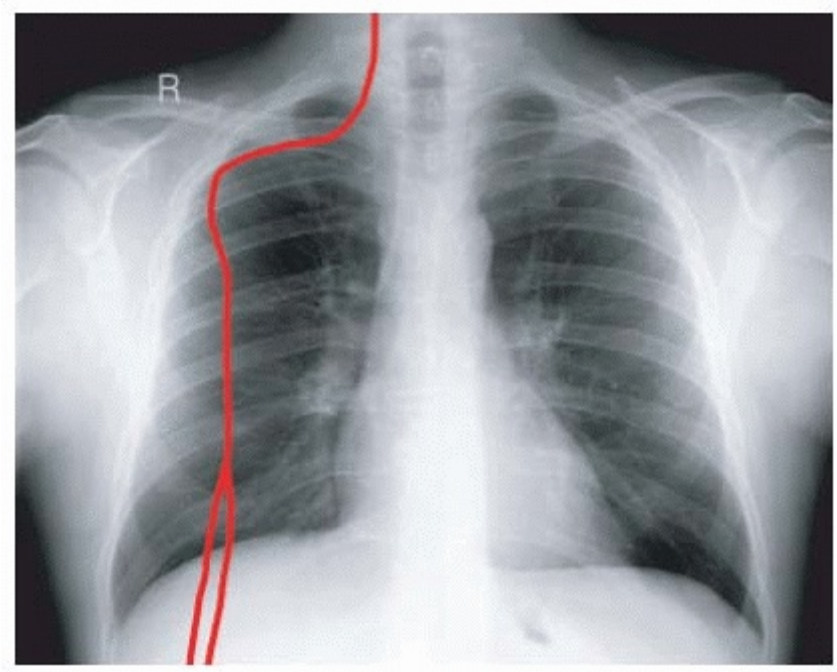


Fig 2. This is a CXR showing a malpositioned right subclavian central venous line (red highlight). Rather than passing inferiorly into the SVC and the right atrium, the catheter has passed up the right internal jugular vein towards the head (compare with BOX above). ▸This line needs removal followed by re-insertion of a new line: see p762 for the technique.

Diabetic patients undergoing surgery

Insulin-dependent diabetes mellitus (eg Type 1 diabetes mellitus)

- Patients are often well informed about their diabetes; involve them fully when managing their diabetic care.
- Stress or intercurrent illness increases basal insulin needs (see p190).
- Always try to put the patient first on the list (surgery, endoscopy, bronchoscopy, etc.). Inform the surgeon and anaesthetist early.
- Stop all long-acting insulin the night before. Get IV access before you need it urgently. If surgery is in the morning, stop all SC morning insulin. If surgery is in the afternoon, have the usual short-acting insulin in the morning at breakfast. No medium- or long-acting insulin. It may be feasible to continue ***glargine*** (p193) as baseline therapy throughout the peri-operative period though there have been no large studies into this.[61]
- Check blood glucose hourly. Aim for 7-11mmol/L during surgery.
- Check U&E pre-op. Start an IVI of 1L of 5% dextrose with 20mmol KCl/8h. Dextrose saline can be given if Na^+ low, but do not give only saline; dextrose may need constant infusion to maintain blood glucose.
- Start an infusion pump with 50U short-acting insulin (eg Actrapid®) in 50mL 0.9% saline. Give according to a sliding scale (see TABLE) adjusted in the light of blood glucose.
- Post-op, continue IV insulin + dextrose until patient tolerating food. Check fingerprick glucose every 2h. Switch to usual SC regimen around a meal.

Practical hints:

- Some centres prefer to control blood sugar with a glucose-potassium-insulin (GKI) infusion—see BOX.
- If the patient is having minor surgery (ie will not be NBM for >6h) and will definitely be able to eat post-op, IV insulin may not be necessary. Some advocate giving the patient a small glucose drink early on the morning of surgery, and delaying their morning insulin dose and breakfast until after the procedure.
- If in doubt, check with the anaesthetist and liaise with a diabetes specialist nurse.

Non-insulin-dependent diabetes mellitus (≈Type 2 diabetes)

- These patients are usually controlled on oral hypoglycaemics (p192). If diabetes poorly controlled (eg fasting glucose >10mmol/L), treat as for type 1 diabetes.
- Do not give long-acting sulphonylureas (eg ***glibenclamide***) on the morning of surgery, as they can cause prolonged hypoglycaemia on fasting.
- Beware lactic acidosis in patients on biguanides (eg ***metformin***), especially if using IV contrast agents and/or renal function poor (creatinine >150μmol/L).
- If the patient can eat post-operatively, simply omit tablets on the morning of surgery and give post-op with a meal.
- If the patient is having major surgery with restrictions to eating post-op, check fasting glucose on the morning of surgery and start IV or SC insulin given according to sliding scale. Post-op, consult the diabetic team as the patient may need a phase of insulin to supplement their oral hypoglycaemics.

Diet-controlled diabetes

Usually no problem, though patient may briefly be insulin dependent post-op. Monitor fingerprick glucose before meals and bedtime. Avoid giving 5% dextrose IVI as a fluid replacement as blood glucose will rise.

Peri-operative morbidity and mortality

Diabetes mellitus is classed as in intermediate risk factor for increased perioperative cardiovascular risk by the American Heart Association, so screen for the presence of asymptomatic cardiac and renal disease (p553) and be aware of possible 'silent' myocardial ischaemia.[62]

One retrospective study on those undergoing major vascular surgery showed that although long term survival was poorer for patients with diabetes, perioperative cardiovascular morbidity and mortality were only increased in the presence of congestive heart failure and haemodialysis—ie **not** diabetes alone.[63]

An example of an IV sliding scale

Fingerprick glucose	IV soluble insulin[1]	Alternative SC insulin[2]
<2 ▸▸See p816	None-50% glucose IV + Hypostop® PO	
2-5	No insulin	No insulin
5-10	1U/h	2U/h (rough guide only)
10-15	2U/h	5U/h
15-20	3U/h	7U/h
>20	6U/h-get urgent diabetic review	

NB: this is a guide only: individual scales may vary between institutions

[1] Check glucose hourly and adjust insulin accordingly.

[2] ▸Only use SC route if IV route is problematic as it is associated with much variability; check finger prick glucose every 2-4h if NBM, or pre-meals if using SC insulin to supplement other hypoglycaemics.

GKI infusions (glucose, K+ & insulin)

▸A problem when giving IV insulin and IV dextrose simultaneously through separate intravenous lines is that if one cannula becomes blocked, the patient may become hypo- or hyperglycaemic. If the glucose and insulin are given through the same cannula, however, and the 3-way converter becomes blocked, the syringe driver may retrogradely fill the infusion set with insulin. When the cannula is subsequently resited and the infusion restarted, the patient will receive this large accumulated dose of insulin. This has caused lethal hypoglycaemia, so some centres now use GKI infusions instead of sliding scales.

- A 500mL bag of 5 or 10% dextrose ± KCl is given over 6h, with a short-acting insulin (eg Actrapid®) added according to blood glucose:[64]

Blood glucose (mmol/L)	Insulin dose (units/bag)	Serum K^+ (mmol/L)	KCl to be added (mmol/bag)
<4	None	<3	20
4-6	5	3-5	10
6-10	10	>5	None
10-20	15		
>20	20		

- Check blood glucose every 3h. If levels too high or low, start a new 500mL bag of 5% dextrose with the correct insulin dose.
- Check U&E daily.

GKI infusions are useful when close monitoring of blood glucose is not possible, but are not be suitable in poorly controlled diabetes. If the patient is under a fluid restriction then it is possible to halve the bag volume and double the dextrose concentration (eg 250 mL of 10-20% dextrose), dosing the insulin per bag just as before. If the patient is ***hyponatraemic*** then a concomitant infusion of 0.9% saline should be considered.

NB: regimens vary and sometimes more insulin will be required; eg if shocked, severely ill, or if on steroids or sympathomimetics, 2-4 times as much insulin may be needed. See BNF section 6.1.

Jaundiced patients undergoing surgery

Patients with obstructive jaundice are particularly prone to developing renal failure after surgery, perhaps from the toxic effect of bilirubin and any concomitant sepsis (see hepatorenal syndrome—p251). In practice this means that good urine output must be maintained in such patients around the time of surgery.

Pre-operative preparation

Avoid ***morphine*** in the premedication.

- Give antibiotic prophylaxis (p556) and treat sepsis to ↓ risk of endotoxaemia.[65]
- Insert IV line and give 1L of 0.9% saline over ½-1h following pre-med (unless the patient has heart failure), to produce a moderate diuresis peri-operatively. A loop diuretic (eg ***furosemide***) may be needed to ensure diuresis. Pre-op mannitol is no longer routine in jaundiced patients—it may even be deleterious.[66]
- Insert a urinary catheter.
- A 'renal' dose ***dopamine*** (2-5µg/kg/min) IVI **may** be indicated. See[67] but also [68]
- Remember there may be side-effects from any central line used, and from the drug:
  - Sepsis (immune dysfunction)
  - Arrhythmias
  - Gut + myocardial perfusion↓
  - Diuresis when hypovolaemic
  - Catabolism↑
  - Gastric motility decreased
  - Pulmonary hypertension
  - Impaired hypoxic ventilatory responses[69]
- Check clotting and consider giving prophylactic ***vit K*** (p330), even if normal.

During surgery

- Measure urine output hourly and give 0.9% saline IV to match the urine output.

For 48h after surgery

- Measure urine output every 2h; measure U&E daily.
- Give 0.9% saline at rate to match urine output and fluid lost eg through NGT; give 2L of dextrose-saline every 24h.
- Consider ***furosemide*** if urine output is poor despite adequate hydration.
- Give 20mmol of K+/L of fluid after 24h post-op if urine output good.

Surgery in those on steroids

Patients on steroid therapy need extra cover to cope with the stress of surgery— their endogenous adrenal hormone levels will be suppressed, even for a period after cessation of a course of treatment. The amount of extra cover needed depends on the extent of the surgery and the pre-op dose of steroids. For routine surgery, aim to reduce the dose of steroid as much as possible. Consider steroid cover for anyone who has had high-dose glucocorticoid therapy in the last year.

Major surgery:

Typically give ***hydrocortisone*** 50-100mg IV with the pre-med and then every 6-8h IV/IM for 3d, then wean to previous medication.

Minor surgery:

Prepare as for major surgery except that ***hydrocortisone*** is given for 24h only.

The major risk with adrenal insufficiency is hypotension, so if this is encountered without an obvious cause, it may be worthwhile giving a STAT dose of 50mg ***hydrocortisone*** IV. See BNF section 6.3 for steroid dose equivalences.

Surgery in those on anticoagulants

▸Contact your lab, and inform the surgeon and anaesthetist. ***Very minor surgery*** has been undertaken without stopping ***warfarin*** (do INR within 24h: it

may be safe to proceed if <3.5).[70] In ***major surgery***, drugs may be stopped for 2-5d pre-op. Risks and benefits are individual to each patient, so exact rules are impossible. Discuss these issues when arranging consent. ***Vitamin K*** (eg 10mg IV) ± **FFP** may be needed in emergency surgery. **▸Monitor clotting meticulously.**

One elective option is conversion to ***heparin*** (stop 6h prior to surgery, and monitor APTT perioperatively): unfractionated heparin's short $t_{½}$ allows swift reversal with ***protamine*** (p334).[71] When rewarfarinizing, don't stop heparin cover until the INR is therapeutic, as warfarin is prothrombotic in the early stages.

The bleeding tendency effects of ***aspirin*** are reversed by 5d after stopping, but check with local policy to see if cessation is required.[72] The alteration of antiplatelet agents (and NSAIDs) is a complex business and is best discussed with an expert.[73]

Thyroid disease and surgery

Thyroid surgery for hyperthyroidism

If severe, give ***carbimazole*** until euthyroid (p202). Arrange operation date and 10-14d before this, start aqueous iodine oral solution (Lugol's solution), 0.1-0.3mL/8h PO well diluted with milk or water. Continue until surgery.

Mild hyperthyroidism

Start ***propranolol*** 80mg/8h PO and Lugol's solution as above at the 1st consultation. Stop Lugol's solution on the day of surgery but continue ***propranolol*** for 5d post-op.

▸▸Thyrotoxic storm

A rare but potentially fatal consequence of thyroid surgery (mortality 50%). See p817.

Non-thyroid surgery

Thyroxine has a long $t_{½}$ (~7d) so omitting a dose while nil by mouth will not have any major effects.

Surgery in the obese

It has long been believed that obesity increases the risk of post-operative complications.[1] Indeed, 50 years ago obesity was considered a contraindication to elective surgery.

One study has suggested, however, that obesity in itself may not be a risk factor for most complications.[74] Overall incidence of complications after elective general surgery did not differ significantly between obese and non-obese patients, though only 1.7% of the 6336 patients in the trial had a BMI >40kg/m^2. The only post-operative complication found to have an increased incidence in the obese was wound infection after open surgery. Overall it would seem that the practice of forcing patients to lose weight prior to elective general surgery may be inappropriate.

Surgery for obesity

Bariatric surgery has become very successful at weight reduction **and** symptom resolution (eg sleep apnoea), especially in the extremely obese.[MET][75] Common procedures include Roux-en-Y gastric bypass, stomach stapling, and laparoscopic banding.

Complications:

Dumping syndrome, wound infection, hernias, malabsorption, diarrhoea, and a mortality of ~0.5% (at experienced centres).

One prospective study on the effects of laparoscopic banding showed that at one year the mean **excess** weight loss was 45.7%, with improvement of quality of life.[76] Whether or not the weight remains off in the long-term is yet to be firmly established.

[1] Obesity has been shown to increase risks of cardiac and spinal surgery.

The acute abdomen

Someone who becomes acutely ill and in whom symptoms and signs are chiefly related to the abdomen has an acute abdomen. Prompt laparotomy is sometimes essential: **repeated examination is the key to making the decision.**

Clinical syndromes that usually require laparotomy:

1. ***Rupture of an organ*** (Spleen, aorta, ectopic pregnancy) Shock is a leading sign— see TABLE for assessment of blood loss. Abdominal swelling may be seen. Any history of trauma: blunt trauma → spleen; penetrating trauma → liver. **Delayed** rupture of the spleen may occur weeks after trauma. Peritonism may be mild.
2. ***Peritonitis*** (Perforation of peptic ulcer, diverticulum, appendix, bowel, or gall bladder) Signs: prostration, shock, lying still, +ve cough test (p40), tenderness (± rebound/percussion pain, p70), board-like abdominal rigidity, guarding, and no bowel sounds. Erect CXR may show gas under the diaphragm (**fig 1**). **NB:** Acute pancreatitis (p582) causes these signs, but does **not** require a laparotomy so don't be caught out and **▸ALWAYS CHECK SERUM AMYLASE.**

Syndromes that may not require a laparotomy:

1. ***Local peritonitis:*** Eg diverticulitis, cholecystitis, salpingitis, and appendicitis (the latter **will** need surgery). If abscess formation is suspected (swelling, swinging fever, and WCC↑) do ultrasound or CT. Drainage can be percutaneous (ultrasound or CT-guided), or by laparotomy. Look for 'a sentinel loop' on plain AXR (p717).
2. ***Colic*** is a regularly waxing and waning pain, caused by muscular spasm in a hollow viscus, eg gut, ureter, salpinx, uterus bile duct, or gall bladder (in the latter pain is often dull and constant). Colic, unlike peritonitis, causes restlessness and the patient may well be pacing around when you go to see him!

Obstruction of the bowel

See p598.

Tests

U&E; FBC; amylase; LFT; CRP; ABG (is there mesenteric ischaemia?); urinalysis. Laparoscopy may avert open surgery. CT can be helpful provided it is readily available and causes no delay; ultrasound is becoming more popular and may identify perforation or free fluid immediately, but appropriate performer training is important.

Pre-op care

▸Don't rush to theatre. **Anaesthesia compounds shock**, so resuscitate properly first (p779) unless blood is being lost faster than it can be replaced, eg in ruptured ectopic pregnancy, (OHCS p262), leaking aneurysm (p586) or trauma.

Plan:
Put to bed—then:

- Treat shock (p778)
- Crossmatch, eg 2U or just group and save
- Blood culture; then…
- Antibiotics[1]
- Relieve pain (p560)
- IVI (0.9% saline)
- Plain abdominal film
- CXR if peritonitic or >50yrs
- ECG if >50yrs
- Consent
- NBM for 2h pre-op

The medical acute abdomen

Irritable bowel syndrome (p268) is the chief cause, so always ask about episodes of pain associated with loose stools, relieved by defecation, bloating, and urgency (but **not** blood—this may be UC). Other causes:

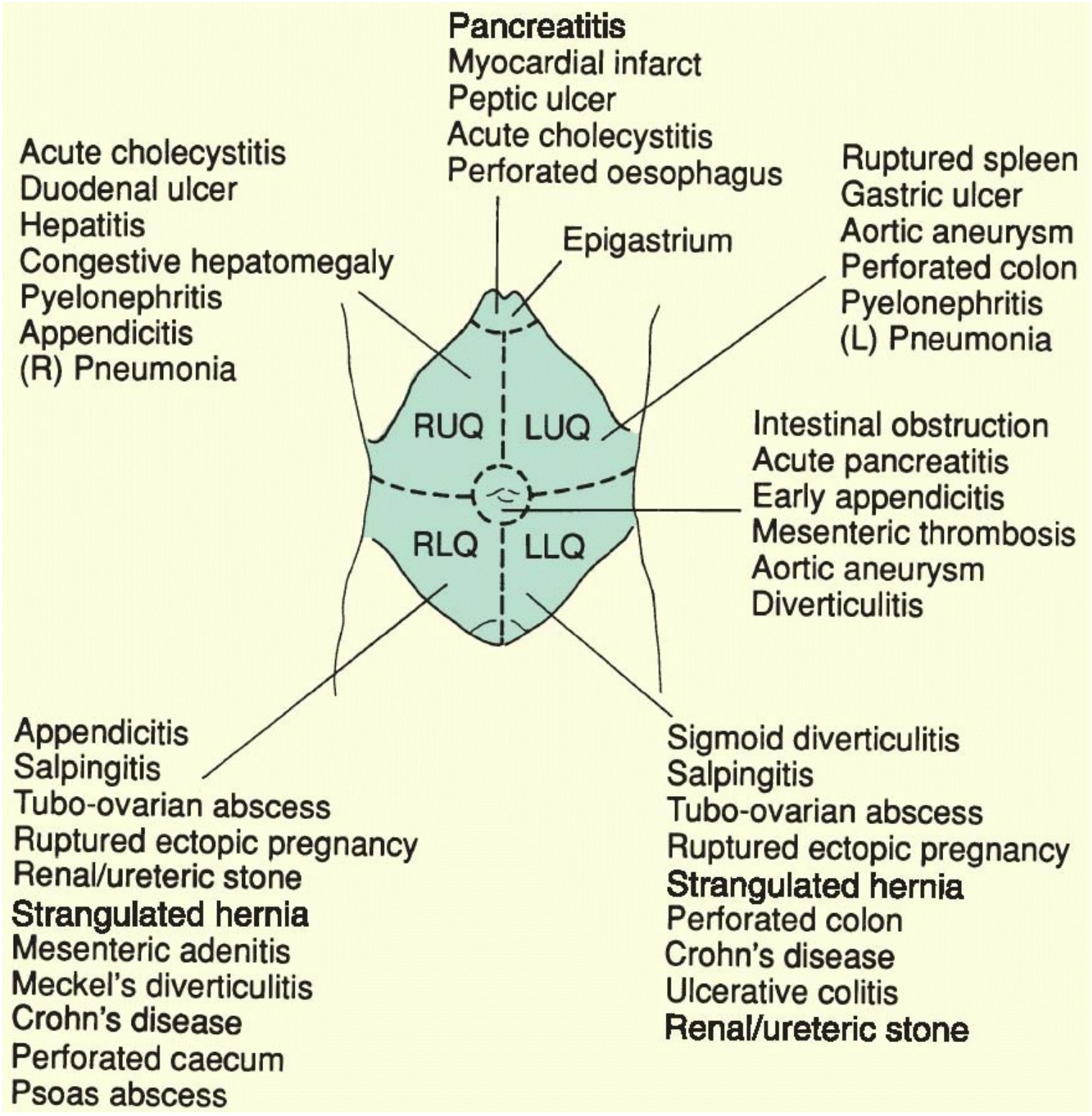
▸▸Myocardial infarction	Pneumonia (p152)	Sickle-cell crisis (p326)
Gastroenteritis or UTI	Thyroid storm (p816)	Phaeochromocytoma (p818)
Diabetes mellitus (p190)	Zoster (p388)	Malaria (p382)
Bornholm disease (p55)	Tuberculosis (p386)	Typhoid fever (p414)
Pneumococcal peritonitis	Porphyria (p684)	Cholera (p414)
Henoch-Schönlein (p694)	Narcotic addiction	*Yersinia enterocolitica* (p411)

Tabes dorsalis (p419) PAN (p543) Lead colic

Hidden diagnoses

▸▸Mesenteric ischaemia (p594), ▸▸acute pancreatitis (p584) and ▸▸a leaking AAA (p586) are the *Unterseebooten* of the acute abdomen— unsuspected, undetectable unless carefully looked for, and underestimatedly deadly. They may have non-specific symptoms and signs that are surprisingly mild, so always think of them when assessing the acute abdomen and hopefully you will 'spot' them! ▸Finally: **ALWAYS EXCLUDE PREGNANCY IN FEMALES.**

Causes of abdominal pain



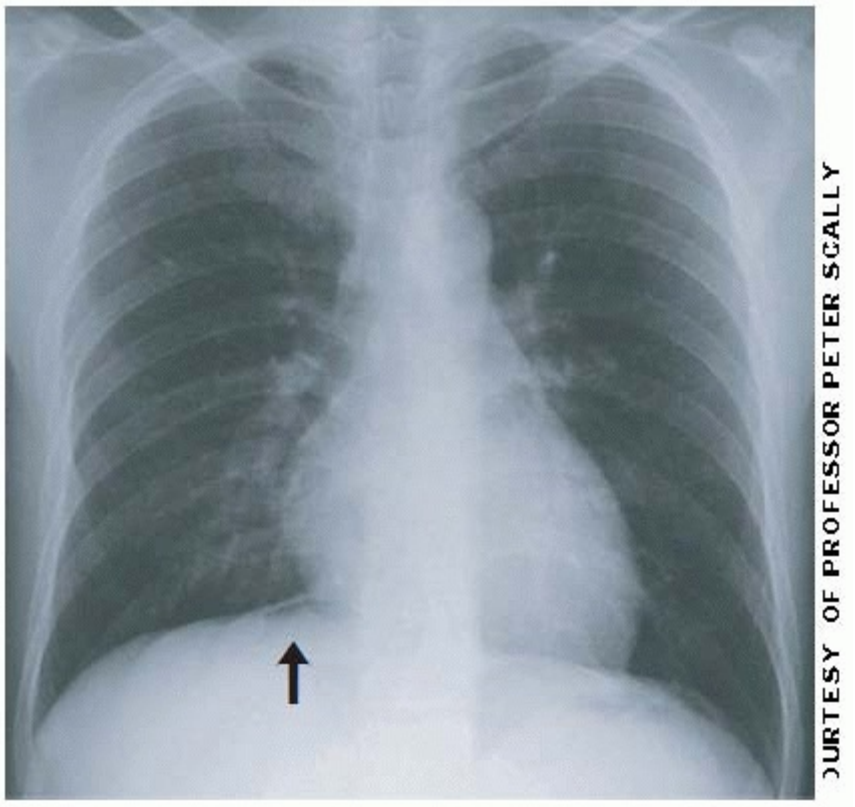


Fig 1. Erect CXR showing a sliver of air beneath the right hemidiaphragm (arrow), indicating presence of a pneumoperitoneum. ***Causes:***

- Perforation of the bowel (visible only in 75%)
- Gas-forming infection eg *Clostridium perfringens*
- Iatrogenic eg open or laparoscopic surgery[1]
- *Per vaginam* (water ski-ing; prolonged intercourse)
- Interposition of bowel between liver & diaphragm

Assessing hypovolaemia from blood loss

The most likely cause of shock in a surgical patient is hypovolaemia (but don't forget the other causes—p778). The most important physiological parameters for the assessment of shock assess target organ perfusion rather than the direct measurement of BP and pulse, which may be 'normal' in one individual and yet totally abnormal for another. The most perfused organs in a normal state are the kidney, brain, and skin, so check **urine output**, **GCS** and **capillary refill** (CR).

Of course, BP, pulse, and respirations are still **vital** signs, but the message here is: ▸treat suspected shock rather than wait for BP to fall. When there is any blood loss (eg a trauma situation), assess the status of the following:

Parameter	Class I	Class II	Class III	Class IV
Blood loss	>750mL >15%	750-1500mL 15-30%	1500-2000mL 30-40%	>2000mL >40%

Pulse	<100bpm	>100bpm	>120bpm	>140bpm
BP	↔	↔	↓	↓
Pulse pressure	↔ or ↑	↓	↓	↓
Respirations	14-20/min	20-30/min	30-40/min	>35/min
Urine output	>30mL/h	20-30mL/h	5-15mL/h	Negligible
Mental state	Slightly anxious	Mildly anxious	Confused →	Lethargic
Fluid to give	Crystalloid	Crystalloid	Crystalloid + blood	
Assumes a body mass of 70kg and a circulating blood volume of 5L.				

[1] Gas under the diaphragm can be still detected on CXR up to 10 days post-op.

Acute appendicitis

This is the most common surgical emergency (lifetime incidence = 6%).

Pathogenesis

Gut organisms invade the appendix wall after lumen obstruction by lymphoid hyperplasia, faecolith, or filarial worms—or there may be impaired ability to prevent invasion, brought about by improved hygiene (so less exposure to gut pathogens). This 'hygiene hypothesis' explains the rise in appendicitis rates in the early 1900s and its later decline (as pathogen exposure dwindles further).

Symptoms

Classically periumbilical pain that moves to the RIF (see BOX). Anorexia is an important feature and vomiting is rarely prominent—pain normally precedes vomiting in the surgical abdomen. Constipation is usual. Diarrhoea may occur.

Special tests:

Rovsing's sign (pain more in the RIF than the LIF when the LIF is pressed). In women, do a vaginal examination: does she have salpingitis (+ve cervical excitation, OHCS p286)? CT (if diagnosis unclear: reduces -ve appendicectomy rate, but may cause fatal delay).[77] See BOX for evaluation of the ***Alvarado score***.

General signs

- Tachycardia
- Fever 37.5-38.5°C
- Furred tongue
- Lying still
- Foetor ± flushing
- Coughing hurts (p40)
- Shallow breaths

Signs in the RIF

- Guarding (p60)
- Rebound + percussion tenderness (p70)
- PR painful on right

Variations in the clinical picture

- The infant with watery diarrhoea and vomiting.
- The boy with vague abdominal pain who will not eat his favourite food.
- The shocked, confused octogenarian who is not in pain.

Hints

▸Don't rely on tests, eg WCC; CRP; urinoscopy; CT (may cause fatal delay).

- If the child is anxious, use his hand to press his belly—see also p601 for tips.
- Check for recent viral illnesses and lymphadenopathy—mesenteric adenitis?
- Don't **start** palpating in the RIF as this may make it difficult to illicit pain elsewhere.
- Do not ignore right-sided tenderness on rectal examination: it may be the only sign.
- Expect your diagnosis to be wrong half the time. This means that those who seem not to have appendicitis should be re-examined often.

Treatment

Prompt ***appendicectomy***. Stump inversion at operation remains a topic of debate.[78] but also [79]

Antibiotics:

Metronidazole 500mg/8h + ***cefuroxime*** 1.5g/8h, 1 to 3 doses IV starting 1h pre-op, reduces wound infections. Give a longer course if perforated.

Laparoscopy:

Useful because of its diagnostic and therapeutic advantages (when performed by an experienced surgeon), especially in women and the obese. It is not recommended in cases suspected of gangrenous perforation because the rate of abscess formation may be higher.[80]

△△

- Ectopic pregnancy

▸▸Do a pregnancy test!

- Mesenteric adenitis
- Cystitis
- Cholecystitis
- Diverticulitis
- Salpingitis/PID
- Dysmenorrhoea
- Crohn's disease

- Perforated ulcer
- Food poisoning
- Meckel's diverticulum

Complications

- ***Perforation*** (does not appear to cause later infertility in girls).[81] In children perforation is commoner with decreasing age: this reflects diagnostic difficulty.[82]
- *Appendix mass* May result when an inflamed appendix becomes covered with omentum. US/CT may help with the diagnosis. Some advocate early surgery, but initial management is usually conservative—NBM and antibiotics (eg ***cefuroxime*** 1.5g/8h IV and ***metronidazole*** 500mg/8h IV). Mark out the size of the mass and proceed to drainage if the mass develops into an abscess (see below). If the mass resolves, some perform an **interval** (ie delayed) **appendicectomy**. Exclude a colonic tumour (laparotomy or colonoscopy), which can present as early as the 4th decade.
- ***Appendix abscess*** May result if an appendix mass fails to resolve. Signs include enlargement of the mass or if the patient gets more toxic (pain↑; °C↑; pulse↑; WCC↑). ***Treatment*** usually involves drainage, either surgical or percutaneous (under US/CT-guidance). Antibiotics alone may bring resolution.

Explaining the pattern of abdominal pain in appendicitis

The classic pattern in acute appendicitis is early periumbilical pain that then migrates to rest in the RIF. But why does this pattern occur?

The chief aspect to consider is the difference in innervation between the visceral and parietal peritoneal layers. A viscus and its visceral peritoneum have no somatic innervation, so the brain attributes the visceral (splanchnic) signals to a physical location whose dermatome corresponds to the same entry level in the spinal cord. Importantly, there is no laterality to the visceral unmyelinated C-fibre pain signals, which enter the cord bilaterally and at multiple levels. Division of the gut according to embryological origin is the important determinant here:

Gut	Division points	Somatic referral	Arterial supply
Fore	Proximal to 2nd part of duodenum	Upper abdomen	Coeliac axis
Mid	Above to 2/3 along transverse colon	Middle abdomen	Superior mesenteric
Hind	Distal to above	Lower abdomen	Inferior mesenteric

Early inflammation irritates the structure and walls of the appendix, so a colicky pain is referred to the mid-abdomen—classically periumbilical. As the inflammation progresses and irritates the parietal peritoneum (especially on examination!) the somatic, lateralized pain settles at McBurney's point, 2/3 of the way along from the umbilicus to the right anterior superior iliac spine.

These principles also help us understand patterns of *referred pain*. In pneumonia, the T9 dermatome is shared by the lung and the abdomen. Also, irritation of the underside of the diaphragm (sensory innervation is from above through the phrenic nerve, C3-5) by an inflamed gallbladder or a subphrenic abscess refers pain to the right shoulder: dermatomes C3-5!

Appendicitis in pregnancy

Appendicitis occurs in ~1/1000 pregnancies. It is not commoner, but mortality is higher, especially from 20wks gestation. Perforation is commoner (15-20%), and increases fetal mortality from ~1.5% (for simple appendicitis) to ~30%. As pregnancy progresses, the appendix migrates, so pain is often less well localized, and signs of peritonism less obvious. ▸Prompt assessment is vital; laparotomy should be performed by an experienced surgeon (OHCS p38).

The Alvarado score—what does it add up to?

The diagnosis of appendicitis has always been a clinical challenge. In 1986, Alvarado published a scoring system that was designed to identify those with suspected appendicitis who needed an operation.[83] The principle was to minimise the number of -ve operations without missing messy perforated disease, which holds a much worse prognosis. The scoring system was:

Feature	Score	Feature	Score
Migration of pain	1	Rebound pain	1
Nausea/vomiting	1	Temperature >37.3°C	1
Anorexia	1	WCC >10× 10^9/L	2
RIF tenderness	2	Neutrophil count ≥75%	1
Total score: if ≤4 = diagnosis unlikely; 5-6 = observe; ≥7 = operation required.			

However, the score alone has proven inadequate for diagnosis on account of poor sensitivity.[84] One study combined the scoring system with US imaging to see if this improved diagnostic yield, but the results showed that, apart from reduced time to operation, it was no better than independent clinical judgement.[85]

So where does that leave us? The scoring system clearly incorporates important features of appendicitis, but its application remains hindered by variable group demographics (eg it is more accurate in children and men) and the lack of an appropriate balance between specificity and sensitivity for a threshold score.[86] The ambiguity is in where to draw this line, but at lease knowing the score may help—and forces us to get a full-data set of variables.

Acute pancreatitis

This unpredictable disease (mortality ~12%) is managed on the surgical wards, but because surgery is often not involved, it is easy to think that there is no acute problem: **there is**—due to self-perpetuating pancreatic inflammation (and of other retroperitoneal tissues). Litres of extracellular fluid are trapped in the gut, peritoneum, and retroperitoneum. There may be rapid progression from a phase of mild oedema to necrotizing pancreatitis. In fulminating cases, the pancreas is replaced by black fluid. Contributory factors to demise include protease-induced activation of complement, kinin, and the fibrinolytic and coagulation cascades. Evidence is accumulating that oxidant stress is important,[88] and congenital abnormality (eg *pancreas divisum* or an annular pancreas) is known to predispose to pancreatitis.[89]

Causes '**GET SMASHED**':
Gallstones(38%)
Ethanol(35%)
Trauma(1.5%)
Steroids
Mumps
Autoimmune (PAN)
Scorpion venom
Hyperlipidaemia, hypothermia, ↑Ca^{2+}
ERCP(5%) and emboli
Drugs[87]

also pregnancy or no cause found(10-30%)

Symptoms

Gradual or sudden severe **epigastric** or **central abdominal pain** (radiating to the back); vomiting is prominent. Sitting forward may relieve pain.

Signs

may be mild in serious disease! Tachycardia, fever, jaundice, shock, ileus, rigid abdomen ± local/generalized tenderness and periumbilical discolouration (Cullen's sign) or in the flanks (Grey Turner's sign).

Tests

Raised serum ***amylase*** (>1000U/mL); cholecystitis, mesenteric infarction, and GI perforation can cause lesser rises (usually). It is excreted renally so renal failure will ↑ levels. ▸**Amylase may be normal even in severe pancreatitis** (levels starts to fall within the 1st 24-48h). Serum ***lipase*** is more sensitive and specific for pancreatitis, and may eventually replace amylase measurement.[90] **ABG** to monitor oxygenation and acid-base status. AXR: No psoas shadow (retroperitoneal fluid↑), 'sentinel loop' of proximal jejunum (solitary air-filled dilatation). ***Erect*** **CXR** helps exclude other causes (eg perforation). **CT** to assess severity—**MRI** may be even better.[91] ***US*** (if gallstones + AST↑). **ERCP** if LFT worsen (may mean duct obstruction).

Management

Get expert help. Nil by mouth and likely to need an NGT (p747).

1. Set up IVI and **give lots of 0.9% saline**, to counter third space sequestration, until vital signs are satisfactory and urine flows stays at >30mL/h. Insert a urinary catheter and consider CVP monitoring. Think about nutrition early on (p572).
2. Analgesia: ***pethidine*** 75-100mg/4h IM, or ***morphine*** (may cause Oddi's sphincter to contract more,[92] but it is a better analgesic and not contraindicated).[93]
3. Hourly pulse, BP, and urine output; daily FBC, U&E, Ca2+, glucose, amylase, ABG.
4. If worsening, take to ITU. O_2 if P_aO_2↓. In suspected abscess formation or pancreatic necrosis (on contrast-enhanced CT), consider parenteral nutrition ± laparotomy & debridement. Antibiotics may help in specific severe disease.[94]
5. ERCP + gallstone removal may be needed if there is progressive jaundice.
6. Repeat imaging (usually CT) is performed in order to monitor progress.

▲▲: Any acute abdomen (p580), myocardial infarct.

Prognosis

See BOX.

Early complications:

Shock, ARDS (p170), renal failure (▸**give lots of fluid!**), DIC, sepsis, Ca^{2+}↓, (10mL of 10% ***calcium gluconate*** IV slowly is, rarely, needed; ***albumin*** replacement has also been tried), glucose↑ (transient; 5% need insulin).

Late complications

(>1wk) ***Pancreatic necrosis*** & ***pseudocyst*** (fluid in lesser sac, **fig 1**), with T°↑, a mass ± persistent ↑amylase/LFT; it may resolve or need drainage, externally, or into stomach (eg laparoscopically). ***Abscesses*** need draining. ***Bleeding*** from elastase eroding a major vessel (eg splenic artery); embolization may be life-saving. ***Thrombosis*** may occur in the splenic/gastroduodenal arteries, or in the colic branches of the superior mesenteric artery, causing bowel necrosis. ***Fistulae*** normally close spontaneously. If purely pancreatic they do not irritate the skin. Some patients suffer ***recurrent oedematous pancreatitis*** so often that near-total pancreatectomy is contemplated. ▸It can all be a miserable course.

Modified Glasgow criteria for predicting severity of pancreatitis

▸3 or more positive factors detected within 48h of onset suggest severe pancreatitis, and should prompt transfer to ITU/HDU. Mnemonic: **PANCREAS.**[95]

COURTESY OF MR ETIENNE MOORE FRCS

P_aO_2	<8kPa
Age	>55yrs

Neutrophils:	WBC >15 x 10^9/L
Calcium	<2mmol/L
Renal function:	Urea >16mmol/L
Enzymes	LDH >600iu/L; AST >200iu/L
Albumin	<32g/L (serum)
Sugar	blood glucose >10mmol/L

These criteria have been validated for pancreatitis caused by gallstones and alcohol; Ranson's criteria are valid for alcohol-induced pancreatitis, and can only be fully applied after 48h, which does have its disadvantages.

Other methods of severity assessment:

Severity can be assessed with the help of CT.[1] CRP can also be a helpful marker.[96]

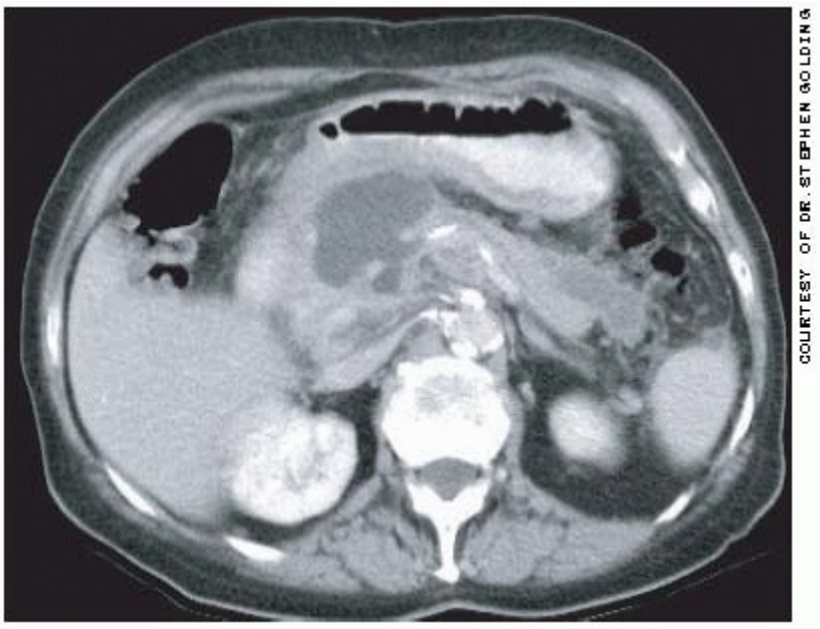


Fig 1. Axial CT of the abdomen (with IV and PO contrast media) showing a pancreatic pseudocyst occupying the lesser sac of the abdomen posterior the stomach. It is called a 'pseudocyst' because it is not a true cyst, rather a collection of fluid in the lesser sac. It develops at [2]6wks. The cyst fluid is of low attenuation compared to the stomach contents because it has not been enhanced by the contrast media.

Aneurysms and dissections of arteries

The definition of an arterial aneurysm is dilatation to >150% of the original diameter; remember that this is an ongoing process. ***True*** aneurysms are abnormal dilatations of arteries. ***False*** aneurysms (pseudoaneurysms) are collections of blood around a vessel wall (eg after trauma) that communicate with the vessel lumen. Aneurysms may be fusiform or sac-like (eg circle of Willis Berry aneurysms; p471, **fig 2**) and on palpation (be gentle!) they are **expansile** (it expands and contracts: swellings that are pulsatile just transmit the pulse, eg nodes overlying arteries).

Common sites

Aorta, iliac, femoral & popliteal arteries. Pathophysiology: see BOX.

Complications

Rupture; thrombosis; embolism; pressure on other structures.

Ruptured abdominal aortic aneurysm (AAA)

Death rates/year from ruptured AAAs rise with age: 125/million in those aged 55-59; 2728/million if over 85yrs.

Symptoms & signs:

Intermittent or continuous abdominal pain (radiates to back, iliac fossae, or groins—▸don't dismiss this as renal colic), collapse, an **expansile** abdominal mass, and shock. If in doubt, assume a ruptured aneurysm.

Management:

▸▸Summon a vascular surgeon and an experienced anaesthetist. Warn theatre. Put up 2 large IVIs. Treat shock with ORh-ve blood (if desperate), but keep systolic BP ≤100mmHg (but note: **raised** BP is common early on). Do an ECG, and take blood for amylase, Hb, crossmatch (10-40U may eventually be needed). Take the patient straight to theatre. Do not waste time doing x-rays: fatal delay may result, though CT can be helpful in a stable patient with an uncertain diagnosis. Catheterize the bladder. Give prophylactic antibiotics eg ***cefuroxime*** 1.5g + ***metronidazole*** 500mg IV. Surgery involves clamping the aorta above the leak, and inserting a Dacron® graft (eg 'tube graft' or, if significant iliac aneurysm also, a 'trouser graft' with each 'leg' attached to an iliac artery). Mortality— treated: 41% and improving; untreated: 100%.[97]

Unruptured AAA

Prevalence: 3% of those >50yrs. Often symptomless, they **may** cause abdominal/back pain, and **may** be discovered incidentally on abdominal examination (see BOX). The UK Small Aneurysm Trial suggested that aneurysms <5.5cm across might safely be monitored by regular examination and ultrasound/CT,[98] though endovascular repair for these may be better than surveillance.[99] Risk of rupture below this size is <1%/yr, compared with ~25%/yr for aneurysms >6cm across. Aneurysms larger than this, rapidly expanding (>1cm/yr) or symptomatic should be considered for elective surgery. It should be noted that ~75% of aneurysms monitored in this way will eventually need repair. Elective operative mortality is ~5% and complications include spinal or mesenteric ischaemia and distal trash from dislodged thrombus debris.[100] Studies show that age >80yrs is **not** a reason to decline surgery.

Stenting

Big operations can sometimes be avoided by inserting an endovascular stent via the femoral artery. When successfully positioned, such stents can lead to a shorter hospital stay and fewer transfusions than with conventional surgery, but see **fig 1** and its footnote.

Thoracic aortic dissection

Blood splits the aortic media with sudden tearing chest pain (± radiation to back). As the dissection unfolds, branches of the aorta occlude sequentially leading to hemiplegia (carotid artery), unequal arm pulses and BP or acute limb ischaemia, paraplegia (anterior spinal artery), and anuria (renal arteries). Aortic incompetence and inferior MI may develop if dissection moves proximally. ***Type A*** dissections involve the ascending aorta, irrespective of site of the tear, whilst if the ascending aorta is not involved it is called ***type B***. **▸▸All patients with type A thoracic dissection should be considered for surgery: get urgent cardiothoracic advice.**

Management:

• Crossmatch 10U blood; ECG & CXR (expanded mediastinum is rare). • CT/MRI or transoesophageal echocardiography (TOE).[101] Take to ITU; hypotensives: keep systolic at ~100-110mmHg: ***labetalol*** (p126) or ***esmolol*** (p112; $t_{½}$ is ultra-short) by IVI is helpful here. Acute operative mortality: <25%.

The pathophysiology of aneurysmal disease

Atheromatous degeneration is the main contributor to the formation of true arterial aneurysms. Other risk factors include connective tissue disorders (eg Marfan's, Ehlers-Danlos), and infection (mycotic aneurysms, eg SBE/IE; tertiary syphilis). For AAAs, degenerative processes leading to **cystic medial necrosis** include:

- Immune responses
- Biomechanical wall stress
- Shifts in the balance of remodelling causing proteolytic degradation of aortic wall connective tissue, eg from ↑matrix metalloprotease activity
- Inflammation: increased lymphocyte and macrophage infiltration
- Molecular genetics: eg extracellular matrix protein degradation.

Remember the cardiovascular risk factors:

- Smoking
- Family history
- Diabetes mellitus
- Hypertension
- Hyperlipidaemia

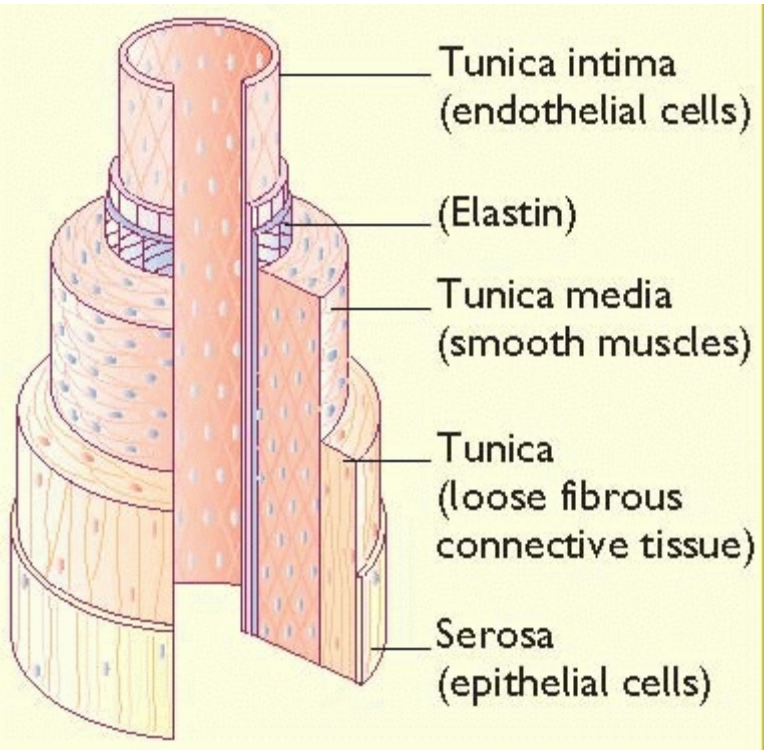


IMAGE AFTER FOX S.I., HUMAN PHYSIOLOGY 4TH EDITION, BROWN

Population screening for AAAs

A number of studies have looked at the screening of asymptomatic patients in 'at-risk' groups for AAAs. A multi-centre study showed that ultrasound screening of 65-74yr old men decreases mortality related to AAAs. Cost per life-year gained was £28,400 after 4yrs, and is expected to drop to a quarter of this figure after 10yrs.[102] A Danish study in 64-73yrs old men showed that the number needed to screen with ultrasound to save one life was 352.[103]

One aspect of screening for AAA that is easily overlooked is the ~5% elective operative mortality. This makes informed consent (the Rees' rules, OHCS p486), a key issue in developing ultrasound-based screening of 'healthy' people.

Other than screening, AAAs are picked up in a number of ways:

- Symptomatic with abdominal pain
- Incidentally on physical examination (though may miss 1/3of AAAs)
- Incidentally on radiological examination (especially ultrasound)
- An abdominal mass noticed by the patient
- Symptomatic distal shedding of mural thrombus

▸▸ Rupture: see OPPOSITE.

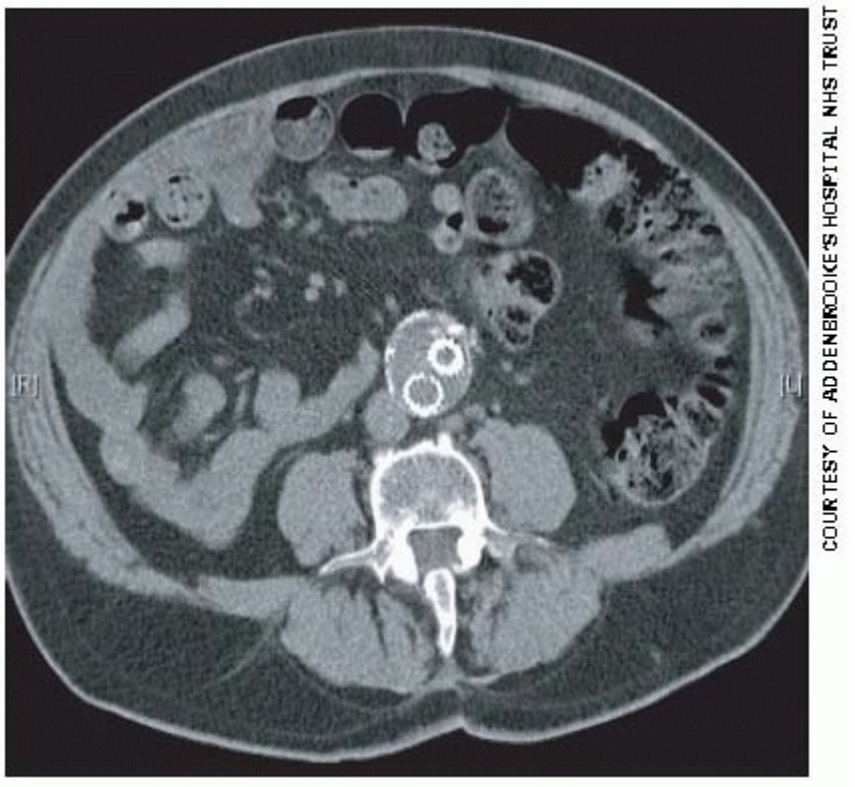


Fig 1. Axial CT of the abdomen showing position of an endovascular stent in the aorta, anterior to the vertebral column. The 'trousers' of the stent are seen within the calcified wall of the aorta. Although less invasive, many are unsuited to this method, owing to the anatomy of their aneurysms. Lifelong monitoring is needed: stents may leak and the aneurysm progress.[104] Safety and efficacy of endovascular stenting may not be better than open repair.[1]

Diverticular disease

A GI **diverticulum** is an outpouching of the gut wall. **Diverticulosis** means that diverticula are present, and **diverticular disease** implies they are symptomatic. **Diverticulitis** refers to inflammation of a diverticulum. Although diverticula may be congenital or acquired and can occur in any part of the gut, by far the most important type are acquired colonic diverticula, to which this page refers.

Pathology

Most occur in the sigmoid colon with 95% of complications at this site, but right-sided and massive single diverticula can occur. Lack of dietary fibre is thought to lead to high intraluminal pressures which force the mucosa to herniate through the muscle layers of the gut at weak points adjacent to penetrating vessels. 30% of Westerners have diverticulosis by 60 years of age.

Diagnosis

PR *examination* (may reveal a pelvic abscess, or colorectal cancer, the chief competing diagnosis); ***sigmoidoscopy***; ***barium enema***; ***colonoscopy*** (**fig 5**, p249); **CT** may be more useful than ***ultrasound***, and ***plain films*** may only be useful in showing vesical fistulae (air in the bladder).

Complications of diverticulosis

There may be altered bowel habit ± left-sided colic relieved by defecation; nausea and flatulence. A high-fibre diet (wholemeal bread, fruit and vegetables) may be tried. Antispasmodics, eg ***mebeverine*** 135mg/8h PO may help. Surgical resection is occasionally resorted to. Others:

1. ***Diverticulitis***—with features above + pyrexia, WCC↑, CRP/ESR↑, a tender colon, ± localized or generalized peritonism. Treatment: analgesia, NBM, IV fluids, and antibiotics: see BOX. ▸Beware diverticulitis in immunocompromised patients (eg on steroids) who often have few symptoms, and may present late.
2. ▸▸***Perforation*** There is ileus, peritonitis ± shock. Mortality: 40%. Manage as for an acute abdomen. At laparotomy a Hartman's procedure may be performed (temporary colostomy + partial colectomy). It is possible to do colonic lavage via the appendix stump, then immediate primary anastomosis

(so avoiding repeat surgery to close the colostomy). Neither is yet proven to be better.[105]

3. *Haemorrhage* is usually sudden and painless. It is a common cause of big rectal bleeds. ▸See BOX. Bleeding usually stops with bed rest. Transfusion may be needed. Embolization or colonic resection may be necessary after locating bleeding points by angiography or colonoscopy (here diathermy ± local ***adrenaline*** injections may obviate the need for surgery).
4. ***Fistulae*** Enterocolic, colovaginal, or colovesical (pneumaturia ± intractible UTIs). Treatment is surgical, eg colonic resection.
5. ***Abscesses*** eg with swinging fever, leucocytosis, and localizing signs eg boggy rectal mass (pelvic abscess—drain rectally). If no localizing signs, remember the aphorism: *pus somewhere, pus nowhere = pus under the diaphragm*. A subphrenic abscess is a horrible way to die, so do an urgent ultrasound. Antibiotics ± ultrasound-guided drainage may be needed.
6. ***Post-infective strictures*** may form in the sigmoid colon.

Angiodysplasia

Angiodysplasia refers to submucosal arteriovenous malformations that typically present as fresh PR bleeding in the elderly. The underlying cause is unknown.

Pathology:

70-90% of lesions occur in the right colon, though angiodysplasia can affect anywhere in the GI tract.

Diagnosis:

PR examination, barium enema, colonoscopy (**fig 4**, p248) may exclude competing diagnoses; ^{99m}Tc radionuclide labelled red cell imaging (p725) is useful for identifying lesions during active bleeding (if >0.1mL/min). Mesenteric angiography is very helpful in diagnosing angiodysplasia (shows early filling at the site of the lesion, then extravasation), and allows therapeutic embolization during active bleeding—it detects bleeding >1mL/min. CT angiography offers a non-invasive alternative.

Treatment options:

Embolization, endoscopic laser electrocoagulation, resection.

Managing diverticulitis[106]
Initial management

- Mild attacks can be treated at home with bowel rest (fluids only) + ***co-amoxiclav*** (p368, or ***metronidazole*** 400mg/8h PO, or ***ciprofloxacin***).
- If oral fluids cannot be tolerated or pain cannot be controlled, admit to hospital for analgesia, NBM, IV fluids and antibiotics eg ***cefuroxime*** 1.5g/8h IV with ***metronidazole*** 500mg/8h IV/PR, until the results of cultures are available. Most settle on this regimen but there may be abscess formation (necessitating drainage) or perforation—see OPPOSITE for management.

Imaging:

Ultrasound can detect perforation, free fluid, and collections, though CT with contrast is probably more accurate, especially in complicated disease. If a contrast enema is performed, then water-soluble contrast should be used (see p734). ▸In an acute attack colonoscopy should not be done.[107]

Surgery:

The need for surgery is reflected by the degree of infective complications:

Stage 1	Small confined pericolonic abscesses	**Surgery rarely needed**
Stage 2	Larger abscesses	**May resolve without surgery**
Stage 3	Generalized suppurative peritonitis	**Surgery required**
Stage 4	Faecal peritonitis	**Surgery required**

- For severe or recurrent diverticulitis ~20% will require surgery.
- Elective sigmoid resection after medical management as a 1-stage open procedure has been performed (also laparoscopically),[108] although interestingly no evidence currently exists to support elective surgery after ≥2 acute attacks of diverticulitis.[109]
- For emergency colonic resection see OPPOSITE.

Rectal bleeding—an acute management plan

The causes of rectal bleeding are covered elsewhere (MINIBOX). Here let's make an **acute management plan** for this common surgical event:

▸▸ ABC resuscitation, if necessary.

▸▸ History and examination.

▸▸ Blood tests: FBC, U&E, LFT, clotting, amylase (always thinking of pancreatitis), CRP, group & save serum—await Hb result before cross-matching unless unstable and bleeding.

▸▸ Imaging May only need plain AXR, but if there are signs of perforation (eg sepsis, peritonism) or if there is cardiorespiratory co-morbidity, then request an erect CXR. See OPPOSITE for more imaging options (under **angiodysplasia**).

▸▸ Fluid management Insert 2 cannulae (³18G) into the ante-cubital fossae. Insert a urinary catheter if there is a suspicion of haemodynamic compromise —there is no absolute indication, but remember that you are weighing up the risks and benefits. Give crystalloid as replacement and maintenance IVI. Transfusion is rarely needed in the acute setting.

▸▸ Antibiotics may occasionally be required if there is evidence of sepsis or perforation, eg ***cefuroxime*** 1.5g/8h IV + ***metronidazole*** 500mg/8h IV.

▸▸ PPI Consider ***omeprazole*** 40mg/d IV—around 15% are UGI bleeds (p244).

▸▸ Keep bed-bound The patient may feel the need to get out of bed to pass stool, but this could be another large bleed, resulting in collapse if they try to walk.

▸Don't allow them to mobilise and inform the nursing staff of this.

▸▸ Start a stool chart to monitor volume and frequency of motions. Send a sample for MC+S (3 if known to have compromising co-morbidity such as IBD).

▸▸ Diet Keep on clear fluids so that they can have something, yet the colon will be clear for colonoscopy (which is of little value until bleeding has stopped).

▸▸ Surgery The main indication for this is unremitting, massive bleeding.

Typical causes

- Diverticulitis, p588
- Colorectal cancer, p612
- Haemorrhoids, p628
- Crohn's, UC, P264
- Perianal disease, p626
- Angiodysplasia, p588
- Rarities—trauma, also:
  - ischaemic colitis, p594
  - radiation proctitis
  - aorto-enteric fistula

Gallstones

Bile contains cholesterol, bile pigments (from broken down Hb), and phospholipids. If the concentrations of these vary, different kinds of stones may be formed.[110]

Pigment stones:

Small, friable, and irregular. Causes: haemolysis.

Cholesterol stones:

Large, often solitary. Causes: ♀, age, obesity.

Mixed stones:

Faceted (calcium salts, pigment, and cholesterol).

Gallstone prevalence:

8% of those over 40yrs. 90% remain asymptomatic. Risk factors for stones becoming symptomatic: smoking; parity. Stones may cause: acute or chronic cholecystitis, biliary colic, pancreatitis (p584), or obstructive jaundice (p242).

Acute cholecystitis

follows stone or sludge impaction in the neck of the gall bladder (GB), which may cause continuous epigastric or RUQ pain (referred to the right shoulder—see p583), vomiting, fever, local peritonism, or a GB mass. The main difference from biliary colic is the inflammatory component (local peritonism, fever, WCC↑). If the stone moves to the common bile duct (CBD), obstructive jaundice and cholangitis may occur—see BOX for complications. **Murphy's sign**: Lay 2 fingers over the RUQ. Ask the patient to breathe in. This causes pain and arrest of inspiration as an inflamed GB impinges on your fingers. It is only +ve if the same test in the LUQ does not cause pain.

Tests:

WCC↑, ultrasound (a thick-walled, shrunken GB, pericholecystic fluid, stones, CBD—dilated if >6mm), HIDA cholescintigraphy (useful if diagnosis uncertain after US). Plain AXR only shows ~10% of gallstones; it may identify a 'porcelain' GB.[111]

Treatment:

NBM, pain relief, IVI, and antibiotics (eg ***cefuroxime*** 1.5g/8h IV). In suitable candidates, do cholecystectomy (laparoscopic if no question of GB perforation) within 72h; mortality: <1%. If delayed, relapse occurs in 18% and may be associated with more complications, so early surgery is generally recommended.[112] Otherwise, operate after 6-12wks. If elderly or high-risk/unsuitable for surgery, consider percutaneous cholecystostomy; cholecystectomy can still be performed at a later date. Cholecystostomy is also the preferred treatment for acalculous cholecystitis, though removal can be done.[113]

Chronic cholecystitis

Stones cause chronic inflammation ± colic. Vague abdominal discomfort, distension, nausea, flatulence, and fat intolerance may also be caused by reflux, ulcers, irritable bowel syndrome, relapsing pancreatitis, or tumour (stomach, pancreas, colon, GB). US is used to image stones and to assess CBD diameter. MRCP (p729) is increasingly used to check for CBD stones. P_x: Cholecystectomy. If US shows a dilated CBD with stones, ERCP (p728) + sphincterotomy for stone removal, usually before surgery. No comparative trials favour lithotripsy.

Biliary colic

occurs when gallstones become symptomatic with cystic duct obstruction or by passing into the CBD—it is part of the spectrum of gallstone disease—giving RUQ pain (radiates → back) ± jaundice. P_x: Pain control: ***morphine*** (see p584) ~ 5-10mg/4h IM + antiemetic. Elective cholecystectomy. ΔΔ: Hard as the above may overlap. Urinalysis, CXR, and ECG help exclude other diseases.

Other presentations:

- ***Obstructive jaundice with* CBD *stones***—if LFT worsening, ERCP with sphincterotomy ± biliary trawl, then cholecystectomy may be needed, or open surgery with CBD exploration. If CBD stones are suspected pre-operatively, then intraoperative fluoroscopic cholangiography can be done, though they can now be successfully identified with pre-operative MRCP, p734.[114]
- ***Cholangitis*** (bile duct infection) causing RUQ pain, jaundice, and rigors. Treat with eg ***cefuroxime*** 1.5g/8h IV and ***metronidazole*** 500mg/8h IV/PR.
- ***Gallstone ileus:*** A stone perforates the GB, entering the duodenum; it may then obstruct the terminal ileum. X-ray: air in CBD (=pneumatobilia), small bowel fluid levels, and a stone. Duodenal obstruction is rarer (Bouveret's syndrome).[115]
- ***Pancreatitis*** (p584)
- ***Empyema:*** The obstructed GB fills with pus.
- ***Silent stones:*** Some advise elective surgery. Dissolution of cholesterol stones by oral ***ursodeoxycholic acid*** is expensive, and often causes diarrhoea.

Complications of gallstones
In the gall bladder:

- Biliary colic
- Acute and chronic cholecystitis
- Empyema
- Mucocoele
- Carcinoma

In the bile ducts:

- Obstructive jaundice
- Pancreatitis
- Cholangitis

In the gut:

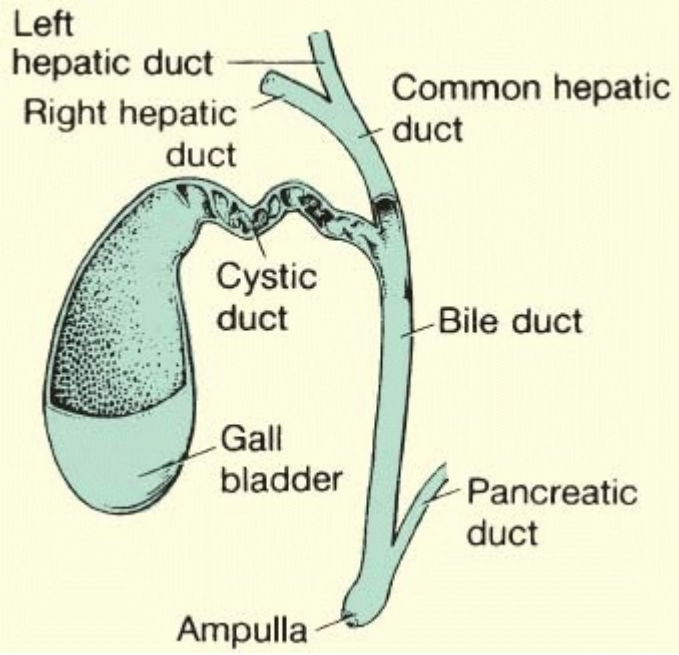
- Gallstone ileus

Diseases having biliary complications

Causes of cholecystitis and biliary symptoms, other than gallstones, are rare, eg:

- Infections:
  - Typhoid
  - Cryptosporidiosis, p380
  - Brucellosis
  - Opisthorchiasis
  - Ascariasis
- Complications of parenteral nutrition
- Polyarteritis nodosa (p543)
- Hormonal: release of cholecystokinin
- Structural abnormality of the cystic duct
- High pressure sphincter of Oddi.

The anatomy of the gallbladder and extrahepatic biliary tree



COURTESY OF CUNNINGHAM'S *MANUAL OF PRACTICAL ANATOMY* VOL 2 138

Is it possible to perform double-blind RCTs in surgery?

In 2005 a double-blinded randomized controlled trial (RCT) looked at the differences between open and laparoscopic cholecystectomy.**RCT**[116] This raises issues on both the place and validity of double-blinded RCTs in surgery.

Overcoming established treatments always has difficulties, as when faced with either surgery or a non-operative management, everyone's preference would be to avoid surgery (with the complications of pain, scarring, etc.), especially if there is equipoise about which treatment is superior. Operations are also technically complex, and the skill required to perform them well has to be learned. The negative influence of the learning curve for a new treatment must be considered and this may take time to overcome (p641). Furthermore, controlling the bias introduced by interperformer and patient variance is impossible (both in the trial and the 'real world'), not least because each patient is different. There are also inherent difficulties in double-blinding surgical treatment, though the imaginative extents to which researchers will go are admirable. 'Sham' surgery remains an contentious issue.[117]

Incidentally, the trial showed that laparoscopic patients were discharged sooner, albeit on the same 2nd day of the stay, with no other major differences.

Gangrene and necrotizing fasciitis

Definitions

Gangrene is death of tissue from poor vascular supply and is a sign of critical ischaemia (see p596). Tissues are black and may slough.

Wet gangrene

is tissue death and infection occurring together (p707, **fig 1**).

Dry gangrene

means no infection.

Pregangrene

is a term used to describe tissue that is on the brink of gangrene. Note a line of demarcation between living and dead tissue.[1]

Management

Take cultures; look out for group A ß-haemolytic streptococci—a cause of Fournier's (male genitalia) or Meleney's gangrene (post-operative ulceration), both a form of rapidly progressive necrotizing fasciitis or myositis. Other pathogens can be involved, eg *S. aureus*. ▸**In any atypical cellulitis, get prompt surgical help.** Radical debridement (eg preserving a skin flap) ± amputation is needed, always covered by antibiotics, including eg 5 days of ***benzylpenicillin*** 600mg/6h IV starting 1h pre-op, to prevent gas gangrene (± ***clindamycin*** 0.6-1.2g/6h IV/IM). Get the help of a plastic surgeon. Remember to consider mycobacteria in any necrotizing infection.[118]

Gas gangrene

is a *Clostridium perfringens* myositis. Risk factors: diabetes; trauma; malignancy. Toxaemia, delirium, and haemolytic jaundice occur early. There is oedema, crepitus from surgical emphysema and bubbly brown pus. Treatment: Remove all dead tissue (eg amputation); ***benzylpenicillin***; ***hyperbaric O_2***, ***clindamycin*** & ***metronidazole*** have a role.[119]

Skin ulcers see also *OHCS*, p604

Ulcers are abnormal breaks in an epithelial surface. Leg ulcers affect ~2% in developed countries.

Causes:

see MINIBOX—there may be multiple causes. For leg ulcers, venous disease accounts for 70%, mixed arterial and venous disease for 15% and arterial disease alone for 2%. For pressure sores, see **fig 1**, p465.

History

Ask about number, pain, trauma. Go over co-morbidities—eg varicose veins, peripheral arterial disease, diabetes, vasculitis etc. Is the history long or short? Is the patient taking steroids? Is the patient a bit odd? (remember self-induced ulcers: *dermatitis artefacta*). Has a biopsy been taken?

Examination

Note features such as site, number, surface area, depth, edge, base, discharge, lymphadenopathy, sensation, and healing. See BOX. If in the legs, note features of venous insufficiency or arterial disease and if possible, apply a BP cuff to perform ankle—brachial pressure index (ABPI).

Tests

Skin and ulcer biopsy may be necessary—eg to assess for vasculitis (will need immunohistopathology) or malignant change in an established ulcer (Marjolin's ulcer). If ulceration is the first presentation of a suspected systemic disorder then further screening tests will be required accordingly.

Management

Managing ulcers is often difficult and expensive. Treat the cause(s) and focus on prevention. Optimize nutrition. Are there adverse risk factors (drug addiction, or risk factors for arteriopathy, eg smoking etc)? Get expert nursing care. Consider referral to community nurse, varicose leg ulcer clinic: 'Charing-cross' 4-layer compression bandaging may help (only if arterial pulses OK: ABPI should be > 0.8) and is better than standard bandages. Treating ulcers with systemic antibiotics rarely helps, though topical agents such as ***silver sulfadiazine*** and ***gentamicin*** may be effective.[120]

Causes

- Venous disease
- Arterial disease
  - Large vessel
  - Small vessel
- Neuropathy
- Diabetes
  - Neuropathic, arterial or both

- Lymphoedema
- Vasculitis
- Malignancy (p548)
- Infection
  - TB, syphilis
- Trauma (pressure)
- Pyoderma gangrenosum
- Drugs

Features of skin ulceration to note on examination

Site

Above the medial malleolus is the favourite place for ***gravitational ulcers*** (mostly related to superficial venous disease, but may reflect venous hypertension via damage to the valves of the deep venous system, eg 2° to DVT). Venous hypertension leads to the development of superficial varicosities and skin changes (***lipodermatosclerosis*** = induration, pigmentation, and inflammation of the skin). Minimal trauma to the leg leads to ulceration which often takes many months to heal. Ulcers on the sacrum or greater trochanter, or heel suggest ***pressure sores*** (OHCS p605), particularly if the patient is bed-bound with suboptimal nutrition.

Temperature

The ulcer and surrounding tissues are cold in an ischaemic ulcer. If the skin is warm and well perfused then local factors are more likely.

Surface area

Draw a map of the area to quantify and time any healing (a wound >4weeks old is a chronic ulcer as distinguished from an acute wound).

Shape

Oval, circular (cigarette burns), serpiginous (*granuloma inguinale*, p404); unusual morphology can be secondary to myocbacterial infection, eg cutaneous tuberculosis or scrofuloderma (*tuberculosis colliquativa cutis*, where an infected lymph node ulcerates through to the skin).[121]

Edge

Eroded ≈ active and spreading; shelved/sloping ≈ healing; punched-out ≈ syphilis or ischaemic; rolled/everted ≈ malignant; undermined ≈ TB.

Base

Any muscle, bone, or tendon destruction (malignancy; pressure sores; ischaemia)? There may be a grey-yellow slough, beneath which is a pale pink base. **Slough** is a mixture of fibrin, cell breakdown products, serous exudate, leucocytes and bacteria—it need not imply infection, and can be part of the normal wound healing process. **Granulation tissue** is a deep pink gel-like matrix contained within a fibrous collagen network and is evidence of a healing wound.

Depth

If not uncomfortable for the patient (eg in neuropathic ulceration) a probe can be used gauge how deep the ulceration extends.

Discharge

Culture before starting any antibiotics (which usually don't work). A watery discharge is said to favour TB; bleeding can ≈ malignancy.

Associated lymphadenopathy

suggests infection or malignancy.

Sensation

Decreased sensation around the ulcer implies neuropathy.

Position in phases of extension/healing

Healing is heralded by granulation, scar formation, and epithelialization. Inflamed margins ≈ extension.

Mesenteric ischaemia

▸AF with abdominal pain should always prompt thoughts of mesenteric ischaemia.

Acute mesenteric ischaemia[122]

almost always involves the small bowel and may follow superior mesenteric artery (SMA) thrombosis or embolism, mesenteric vein thrombosis, or non-occlusive disease (see MINIBOX). Arterial thrombosis is becoming the commonest cause of acute ischaemia as embolism becomes rarer. Venous thrombosis is more common in younger patients with hypercoagulable states and tends to affect smaller lengths of bowel. Non-occlusive ischaemia occurs in low flow states and usually reflects poor cardiac output, though there may be other factors such as recent cardiac surgery or renal failure.[123] Presentation is **a classical clinical triad:**

▸Acute severe abdominal pain; no abdominal signs; rapid hypovolaemia → shock. Pain tends to be constant and central, or around the right iliac fossa. The degree of illness is often far out of proportion with clinical signs.

Acute ischaemia

- Arterial
  - Thrombotic(35%)
  - Embolic(35%)

- Non-occlusive(20%)
- Venous(5%)
- Other
  - Trauma
  - Vasculitis (p542)
  - Radiotherapy
  - Strangulation eg volvulus or hernia

Chronic ischaemia

- Usually a combination of a low flow state with atherosclerosis. Classified as either small or large bowel.

- ***Tests:*** There may be Hb↑ (due to plasma loss), WCC↑, modestly raised plasma amylase, and a persistent metabolic acidosis. Early on the abdominal x-ray shows a 'gasless' abdomen. Arteriography (**fig 1**) helps but many diagnoses are made at laparotomy with the finding of nasty necrotic bowel on opening up. CT/MR angiography may provide a non-invasive alternative to simple arteriography.[124]
- ***Treatment:*** The main life-threatening complications secondary to acute mesenteric ischaemia are **1** septic peritonitis and **2** progression of a systemic inflammatory response syndrome (SIRS) into a multi-organ dysfunction syndrome (MODS), that is mediated by bacterial translocation across the dying gut wall. Resuscitation with fluid replacement, antibiotics (***gentamicin*** + ***metronidazole***, p371) and, usually, ***heparin*** are required. If arteriography is performed, thrombolytics may be infused locally via the catheter. At surgery dead bowel must be removed. Revascularization may be attempted on potentially viable bowel but it is a difficult process and often needs a second laparotomy.
- ***Prognosis:*** Poor for arterial thrombosis and non-occlusive disease (<40% survive), though not so bad for venous and embolic ischaemia.[125]

Chronic small bowel ischaemia

This presents quite a different picture to acute ischaemia, with severe, colicky post-prandial abdominal pain ('gut claudication') with PR bleeding ± ↓weight (food hurts) and malabsorption. It is difficult to diagnose but, following angiography, surgery may be helpful. Angioplasty is an appropriate treatment if the bowel is viable.

Chronic colonic ischaemia

This usually follows low flow in the inferior mesenteric artery (IMA) territory.

Presentation:

Lower left-sided abdominal pain and bloody diarrhoea. There may be pyrexia, tachycardia, PR bleeding, and a leucocytosis. Usually this 'ischaemic colitis' resolves, but it may progress to gangrenous ischaemic colitis with the development of peritonitis and hypovolaemic shock.

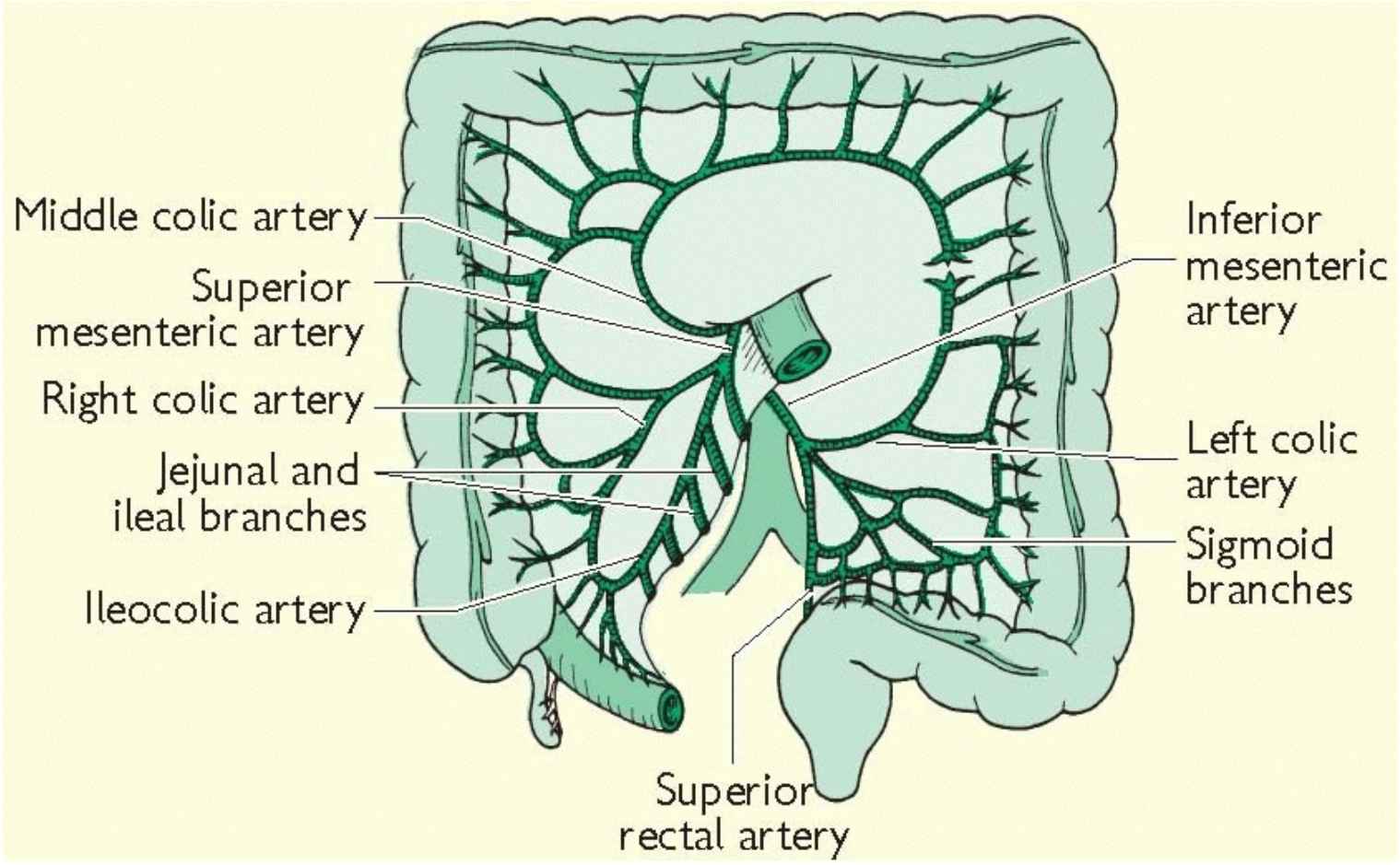
Tests:

Barium enema may show 'thumb-printing' indentation of the barium due to submucosal swelling. MR angiography is being used increasingly.[126]

Treatment:

This is usually conservative with fluid replacement and antibiotics. Most recover but strictures are common. Percutaneous transluminal angioplasty and endovascular stent insertion are alternatives to revascularization surgery that show good results with lower mortality.[127] Gangrenous ischaemic colitis requires prompt resuscitation followed by resection of the affected bowel and stoma formation.

The arterial supply to the colon



There are two **potential watershed areas** in the arterial supply of the colon. The first is at the splenic flexure where the SMA and the IMA circulations meet as the 'Marginal artery of Drummond'— it has also been called Griffith's point. The significance of good blood flow at this point to ensure adequate colonic supply after surgical ligation of the IMA has long been a point of debate.[128] The 2nd contentious watershed area is at the origin of the superior rectal artery—also known as Sudeck's point (**fig 1**). When ligated, flow to the rectum is maintained by the sigmoidal branches that arise from the left colic artery.[129] Remember that the arterial supply to the gut does have a large number of anatomical variations.

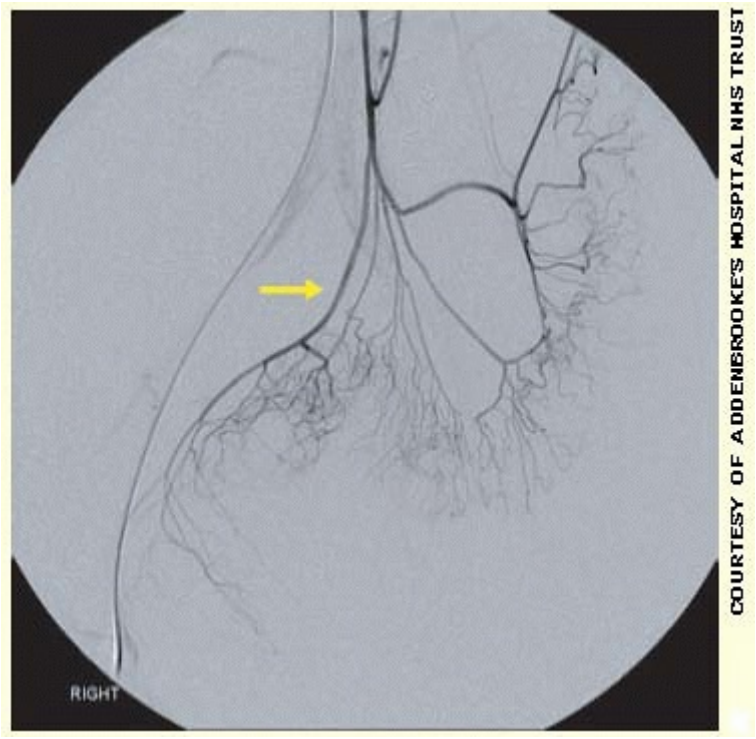


Fig 1. Digital subtraction angiogram (DSA) of the IMA and the superior rectal artery (arrow).

IMAGE REPRODUCED WITH KIND PERMISSION FROM *CLINICAL ANATOMY*, H. ELLIS, BLACKWELL

Volvulus of the stomach

If the stomach twists, the classical triad of gastro-oesophageal obstruction may occur: vomiting (then non-productive retching), pain, and failed attempts to pass an NG tube. Regurgitation of saliva also occurs. Dysphagia and noisy gastric peristalsis (relieved by lying down) may occur in chronic volvulus.

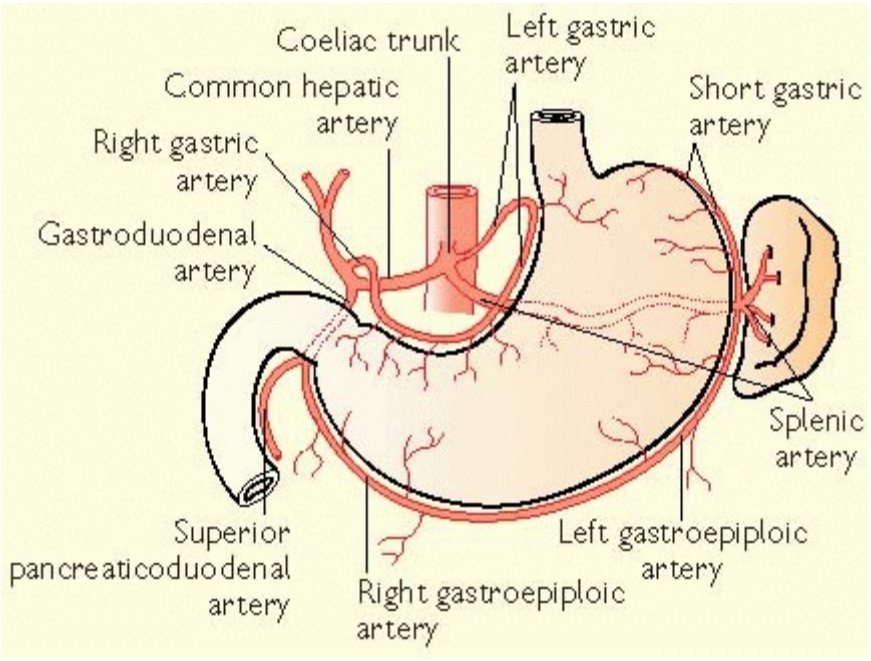


IMAGE AFTER RCSI WEBSITE.

Risk factors

Congenital:

Paraoesophageal hernia; congenital bands; bowel malformations; pyloric stenosis.

Acquired:

Gastric/oesophageal surgery.

Tests

Look for gastric dilatation and a double fluid level on erect films.

Treatment

If acutely unwell (obstruction, peritonism, necrosis) arrange prompt resuscitation and laparotomy. In organoaxial volvulus, rotation is typically 180° left to right, about a line joining the relatively fixed pylorus and oesophagus. Mesenteroaxial rotation is at right angles to this line (and is from right to left). Laparoscopic management may be possible.[130]

Limb ischaemia ▸▸Acute ischaemia—See EMERGENCY BOX.

Chronic ischaemia

This is 'always' due to atherosclerosis (fibromuscular dysplasia and vasculitis are very rare). Its chief feature is intermittent claudication.

Symptoms

Cramping pain is felt in the calf, thigh, or buttock after walking for a fairly fixed distance (the **claudication distance**). **Ulceration, gangrene** (p592), and foot pain **at rest**—eg burning pain at night relieved by hanging legs over side of bed—are the cardinal features of ***critical ischaemia***. Buttock claudication ± impotence imply Leriche's syndrome (p696). Young, heavy smokers are at risk from Buerger's disease (thromboangiitis obliterans, p688).[131]

Signs:

Absent pulses; cold, white leg(s); atrophic skin; punched out ulcers (often painful); postural/dependent colour change; a vascular (Buerger's) angle[1] of <20° and capillary **filling** time >15s are found in severe ischaemia.

Tests:

Exclude DM, arteritis (ESR/CRP). Do FBC (anaemia, infection); U&E (renal disease); lipids (dyslipidaemia); syphilis serology; ECG (cardiac ischaemia). Check platelets, clotting and U&E (problems with IV contrast exacerbated by renal disease) and do group & save if planning arteriography.

Ankle-brachial pressure index (ABPI):

Normal ≳ 1. Claudication ≈ 0.9-0.6. Rest pain ≈ 0.3-0.6. Impending gangrene ≲ 0.3 or ankle systolic pressure <50mmHg. Beware falsely high measurements from the incompressible vessels found in severe atherosclerosis, DM and chronic renal failure. Do ***contrast arteriography***, ***digital subtraction arteriography (DSA***, fig 2*)* or ***colour duplex imaging*** to assess the extent and location of stenoses and the quality of distal vessels ('*run off*'). Remember to stop ***metformin*** before angiography to avoid metabolic acidosis. ***MR angiography*** has a developing role (p721).[132] If only distal obliterative disease is seen, and little proximal atheroma, suspect arteritis, previous embolus, or DM.

Management

More conservative measures are undervalued—ie quit smoking, ↓weight, exercise programmes.**RCT**[133] ~ 1/3 of claudicants improve with exercise, 1/3 remain the same, and 1/3 deteriorate. Results may be better with a supervised exercise programme.**RCT**[134] The mainstay of treatment is energetic risk factor reduction: encourage cessation of smoking, and treat diabetes, hypertension (avoid Òblockers) and dyslipidaemia. Antiplatelet agents have a role (usually ***aspirin)***.

Percutaneous transluminal angioplasty

is good for short stenoses in big arteries (a balloon is inflated in the narrowed segment). Stents maintain artery patency after angioplasty, and are beneficial for iliac artery disease.

Surgical reconstruction

If atheromatous disease is extensive but distal run off is good (ie distal arteries filled by collateral vessels), he may be a candidate for arterial reconstruction by a bypass graft. Procedures include above knee femoral-popliteal bypass, femoral-femoral crossover and aorto-bifemoral bypass grafts. Vein grafts are often used but prosthetic grafts (eg polytetrafluoroethylene, PTFE) are an option.[135] ***Aspirin*** helps prosthetic grafts to remain patent; ***warfarin*** may be better after vein grafts and in high-risk patients.**RCT**[136]

Sympathectomy

(chemical or surgical) may help relieve rest pain if revascularization is impossible. It may not be wise in diabetic patients with neuropathy.

Amputation

may relieve intractable pain and death from sepsis and gangrene. The decision to amputate must be made by the patient, usually against a background of failed alternative strategies. The level of amputation must be high enough to ensure healing of the stump. Above knee amputation (AKA) tends to heal better, but has worse rehabilitation potential, whereas the reverse is true of below knee amputation (BKA). Having to perform the above knee procedure can also be the herald of a much poorer overall prognosis—the 5 year survival for AKA in one retrospective study was 22.5% compared to 37.8% for BKA.[137] Rehabilitation should be started early with a view to limb fitting. ***Gabapentin*** (regimen on p496) can be used to treat the gruelling post-operative complication of phantom limb pain.**RCT**[138] It may be more effective if started prior to surgery.

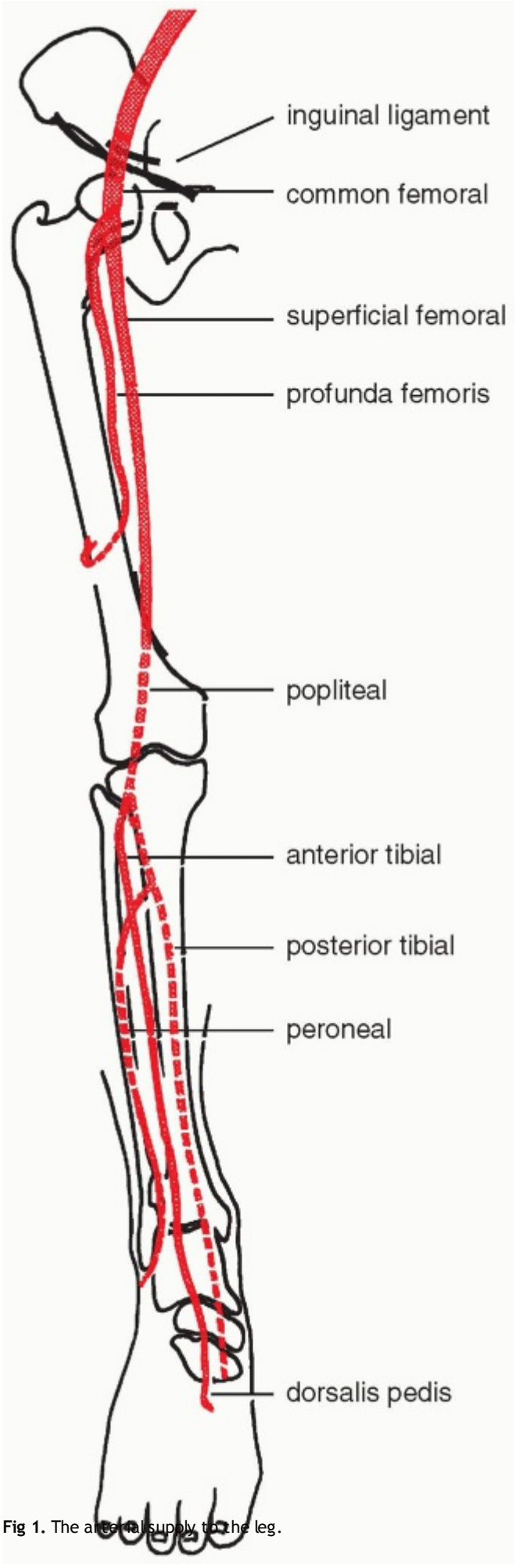


Fig 1. The arterial supply to the leg.

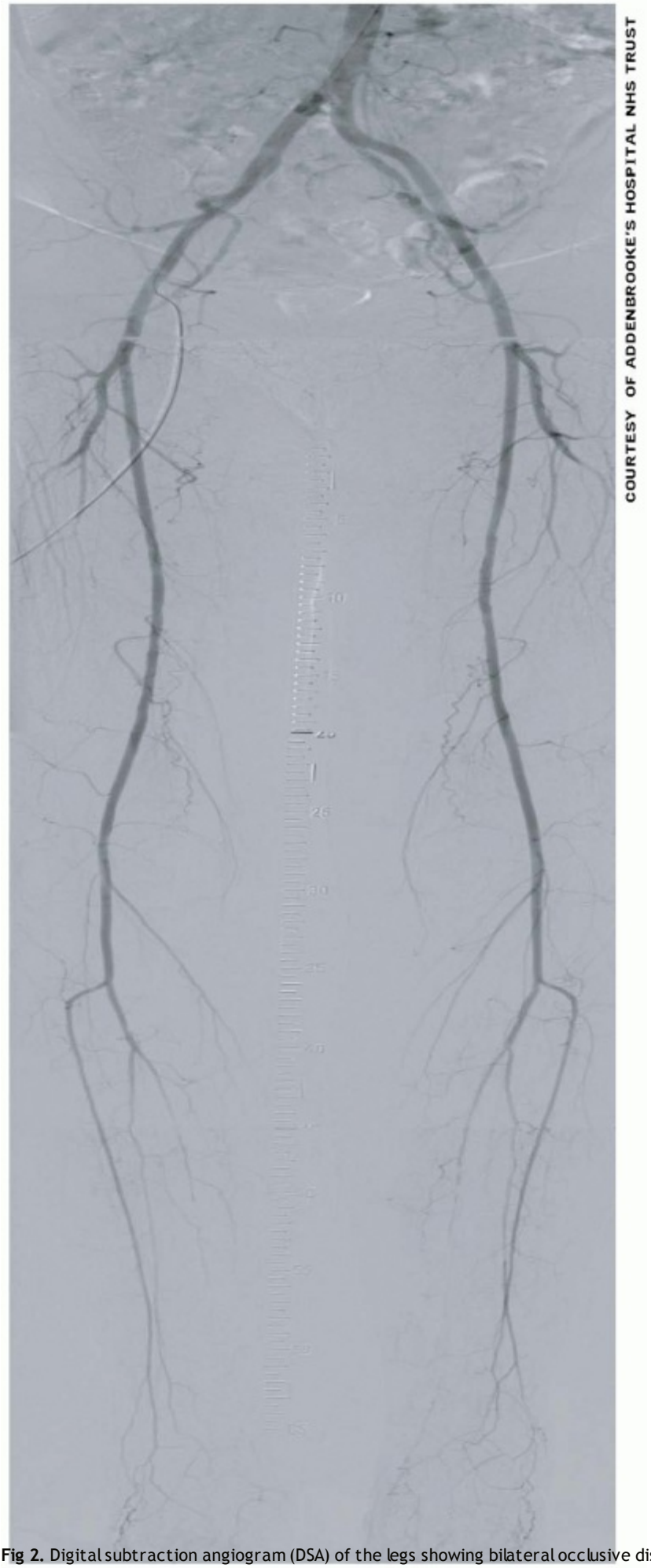


Fig 2. Digital subtraction angiogram (DSA) of the legs showing bilateral occlusive disease in the posterior tibial arteries. This patient had gangrene in his toes.

Acute limb ischaemia
Acute ischaemia

This may be due to thrombosis *in situ* (~40%), emboli (38%), graft/angioplasty occlusion (15%), or trauma. There is little difference in presenting signs. Mortality: 22%. Amputation rate: 16%.

Symptoms & signs:

6 **P**S—the part is **p**ale, **p**ulseless, **p**ainful, **p**aralysed, **p**araesthetic, and '**p**erishing with cold'. Onset of fixed mottling implies irreversibility. Emboli commonly arise from the heart (infarcts, AF) or an aneurysm (aorta, femoral, or popliteal). ▸The limb may be red, but only when dependent, leading to disastrous misdiagnosis of gout or cellulitis.

Management:

▸This is an emergency and may require urgent open surgery or angioplasty. If diagnosis is in doubt, do urgent arteriography. If the occlusion is embolic, the options are surgical embolectomy (Fogarty catheter) or local thrombolysis, eg ***tissue plasminogen activator*** (t-PA, p331), balancing the risks of surgery with the haemorrhagic complications of thrombolysis.**MET**$_{139}$

Anticoagulate with ***heparin*** after either procedure. Later, look for the emboli's source: echocardiogram; ultrasound of aorta, popliteal and femoral arteries. Ischaemia following trauma and acute thrombosis may require urgent reconstruction. ▸Always be aware of the possibility of post-operative **reperfusion injury** and subsequent **compartment syndrome** (OHCS, p736).

Obstruction of the bowel

Features of obstruction

Vomiting with relief, nausea and anorexia. Fermentation of the intestinal contents in established obstruction causes 'faeculent' vomiting ('faecal' vomiting is found when there is a colonic fistula with the proximal gut). **Colicky** abdominal pain is seen in early obstruction and may be absent in long-standing complete obstruction. **Constipation** need not be absolute (ie no faeces or flatus passed) if obstruction is high, though in distal obstruction nothing will be passed. Abdominal **distension** becomes more marked as the obstruction progresses. There are active, 'tinkling' bowel sounds.

Cardinal features of intestinal obstruction

- Vomiting
- Colic
- Constipation
- Distension

The key decisions:

1. ***Is the obstruction of the small or large bowel?*** In small bowel obstruction, vomiting occurs earlier, distension is less, and pain is higher in the abdomen. **The AXR plays a key role in diagnosis**—see p716. In small bowel obstruction, AXR shows central gas shadows and no gas in the large bowel. Small bowel is identified by *valvulae conniventes* that completely cross the lumen (large bowel haustral folds do **not** cross all the lumen's width).

   In large bowel obstruction, pain is more constant; AXR shows gas proximal to the blockage (eg in caecum) but not in the rectum, unless you have done a PR examination ▸which is always essential! If the ileocaecal valve is competent (ie doesn't allow reflux) pain may be felt over a distended caecum (see below).

2. ***Is there an ileus or mechanical obstruction?*** In ileus (functional obstruction due to reduced bowel motility) there is no pain and bowel sounds are absent.

3. ***Is the bowel strangulated?*** The patient is more ill than you would expect. There is a sharper and more constant pain than the central colicky pain of the obstruction and it tends to be localized. Peritonism is the cardinal sign. There may be fever + WCC↑ along with other signs of mesenteric ischaemia (p594).

Management

- ***General principles:*** The site, speed of onset, and completeness of obstruction determine definitive therapy: strangulation and large bowel obstruction require surgery soon, while ileus and incomplete small bowel obstruction can be managed conservatively, at least initially.
- ***Immediate action:*** ▸'Drip and suck'—NGT and give IV fluids to rehydrate and correct electrolyte imbalance, see p656. Simply being nil by mouth does not give adequate rest for the bowel because the intestine can produce up to 9L of fluid/d.
- ***Further imaging:*** There is a case for investigating the cause by colonoscopy in some instances of suspected mechanical obstruction, though there is a danger of inducing perforation. A water-soluble contrast (eg Gastrografin®) follow-through study may be helpful in determining the level of obstruction —it also has some therapeutic action against mild mechanical obstruction. CT may show dilated, fluid-filled bowel and a transition zone at the site of obstruction (**figs 1** & **2**).
- ***Surgery:*** ▸Strangulation requires emergency surgery, as does 'closed loop obstruction'—large bowel obstruction with tenderness over a grossly dilated caecum (>12cm requires urgent decompression), which occurs when the ileocaecal valve remains competent despite bowel distension. For less urgent large bowel obstruction, there is time for a water-soluble enema to try to clear the obstruction and to correct fluid imbalance. Small bowel obstruction secondary to adhesions should rarely lead to surgery—see BOX, p567.

Typical causes

- Constipation (p240)
- Hernias (p630)
- Adhesions (p567)
- Tumours (p612)

Rarer causes

- Crohn's disease
- Gallstone ileus (p590)
- Intussusception (p600)
- Diverticular stricture
- TB (developing world)
- Volvulus
  - Gastric (p595)
  - Caecal
  - Sigmoid (see BOX)
- Foreign body

Paralytic ileus or pseudo-obstruction?

Paralytic ileus

The cause of obstruction is known to be adynamic bowel due to the absence of normal peristaltic contractions. Contributing factors include abdominal surgery, pancreatitis (or any localized peritonitis), spinal injury, hypokalaemia, hyponatraemia, uraemia, peritoneal sepsis and drugs (eg tricyclic antidepressants).

Pseudo-obstruction

is like mechanical GI obstruction but with no cause for obstruction found. **Acute** colonic pseudo-obstruction is called Ogilvie's syndrome (p700), and clinical features are similar to that of mechanical obstruction.[140] Predisposing factors: puerperium; pelvic surgery; trauma; cardiorespiratory disorders.

Treatment:

Manage conservatively. ***Neostigmine*** or colonoscopic decompression are sometimes useful. In **chronic** pseudo-obstruction weight loss from malabsorption is a problem.[141]

Sigmoid volvulus

Sigmoid volvulus occurs when the bowel twists on its mesentery, which can produce severe, rapid, strangulated obstruction. There is a characteristic AXR with an 'inverted U' loop of bowel that looks a bit like a coffee bean. It tends to occur in the elderly, constipated and co-morbid patient, and is often managed by sigmoidoscopy and insertion of a flatus tube. Sigmoid colectomy is sometimes required. ▸If not treated successfully, it can progress to perforation and fatal peritonitis. For ***gastric volvulus*** see p595.

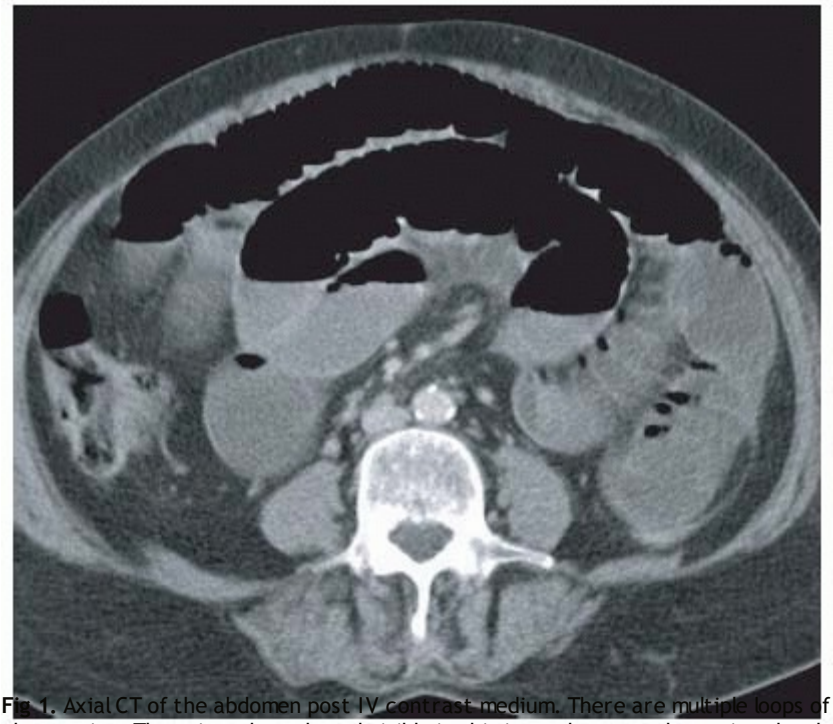


Fig 1. Axial CT of the abdomen post IV contrast medium. There are multiple loops of dilated and fluid filled small bowel in a patient with small bowel obstruction. There is no large bowel visible in this image because the patient has had a colectomy and formation of an ileoanal pouch (a prodecure done in ulcerative colitis).

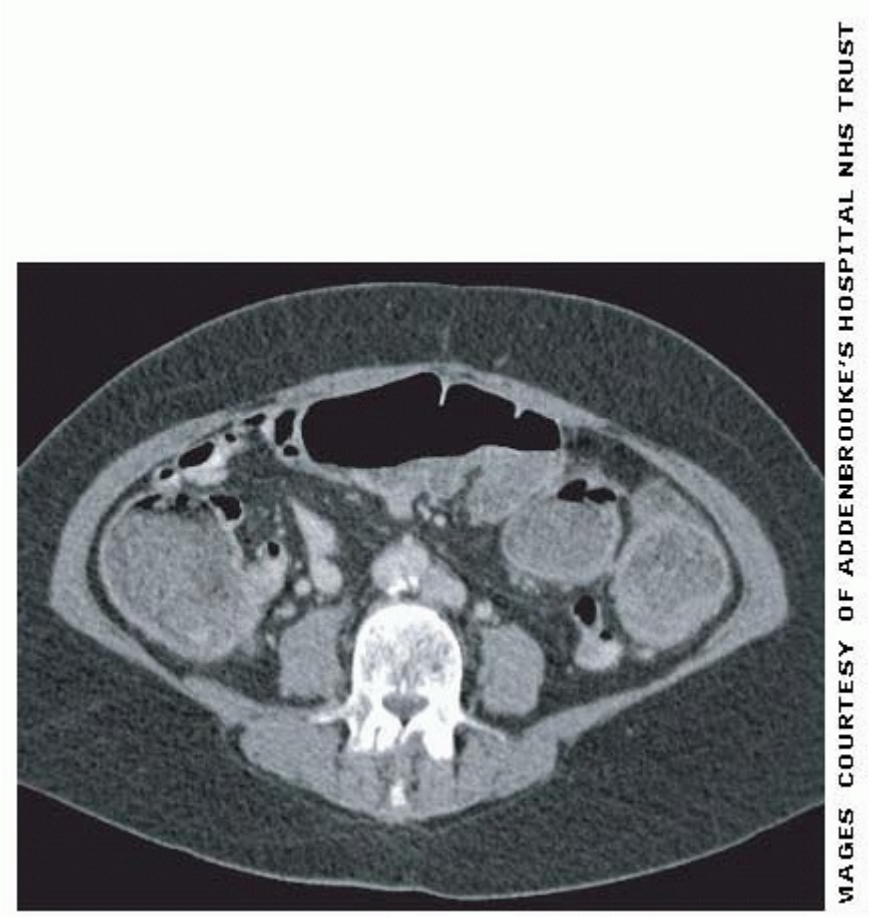


Fig 2. Axial CT of the abdomen post IV contrast medium showing dilated loops of fluid and air filled large bowel. The cause or level of obstruction is not discernable from this image. A 'transition zone' from dilated to non-dilated bowel may be present at the point of obstruction.

Some paediatric surgical emergencies

Congenital hypertrophic pyloric stenosis

▸See OHCS p172. This usually presents not at birth but in the first 3-8wks as projectile vomiting (4 in1000 live births). ♂:♀ ≈ 4:1. The baby is malnourished and always hungry and the diagnosis is made by palpating a pyloric mass in the RUQ during a feed. There may also be visible gastric peristalsis passing from the LUQ. The baby can be severely alkalotic and depleted of water and electrolytes because of the vomiting. This needs correcting **before** surgery. Experienced operator US may be useful in assessment. Pass a NGT (p747).

Treatment:

Ramstedt's pyloromyotomy, which involves incision of the muscle down to the mucosa.

Intussusception

The small bowel telescopes, as if it were swallowing itself by invagination (see BOX).

Presentation:

Patients may be any age (usually 5-12 months) presenting with **episodic** intermittent inconsolable crying, with drawing the legs up (colic) ± bilious vomiting. He may (but need not) pass blood PR (like redcurrant jam or cranberry sauce: 🖫$_{142}$ do a PR). A sausage-shaped abdominal mass may be felt. He may become shocked and moribund.

Tests/Management:

The least invasive approach is US with reduction by air enema (preferred to barium). Pneumatic reduction, by passing a balloon catheter PR under radiographic control, is another option that is effective in up to 80%. If reduction by enema fails, surgical reduction is needed. Prompt treatment is required to avoid the main complication of necrosis of the intussuscepting bowel, which if present, will need to be excised at surgery.

Pre-op care:

▸▸Resuscitate, crossmatch blood, pass NGT.

NB: Children >4yrs present differently: rectal bleeding is less common, and they are more likely to have a long history (>3wks) and some sort of contributing pathology, eg Henoch-Schönlein purpura, cystic fibrosis, Peutz-Jeghers' syndrome or tumours, eg lymphomas—in the latter, obstructive symptoms caused by intussusception are the chief mode of presentation. Recurrence rate: ~5%.

Midgut malrotation

During embryonic development, the mid-gut undergoes 270° of anticlockwise rotation. If this is faulty (malrotation) then the gut is prone to undergo volvulus upon its abnormally-pedicled mesentery. This usually presents in the neonatal period with dark green bilious vomiting, distension, and rectal bleeding, though it can be asymptomatic for years before an acute presentation.

Treatment:

▸▸Resuscitation, then surgical correction of the malrotation involves broadening of the mesentery and replacing the bowel in a non-rotated position.

Torsion of the testis

The aim is to recognize this condition before the cardinal signs and symptoms are fully manifest, as prompt surgery saves testes. ▸If in any doubt, surgery is required.

Symptoms:

Sudden onset of pain in one testis, which makes walking uncomfortable. Pain in the abdomen, nausea, and vomiting are common.

Signs:

Inflammation of one testis—it is tender, hot, and swollen. The testis may lie high and transversely. Torsion may occur at any age but is most common at 11-30yrs.

Tests:

Doppler USS (may demonstrate lack of blood flow to testis) and isotope scanning may be useful, but must not delay surgical exploration.

Treatment:

▸Ask consent for possible orchidectomy + **bilateral** fixation (orchidopexy)—see p554. At surgery expose and untwist the testis. If its colour looks good, return it to the scrotum and fix **both** testes to the scrotum

ΔΔ:

The main one is epididymo-orchitis (p618) but with this the patient tends to be older, there may be symptoms of urinary infection, and more gradual onset of pain. Also consider tumour, trauma, and an acute hydrocele. **NB: Torsion of the hydatid of Morgagni**—a remnant of the Müllerian duct—occurs a little earlier, and causes less pain (**fig 1**). Its tiny blue nodule may be discernible under the scrotum. It is thought to be due to the surge in gonadotrophins which signal the onset of puberty. **Idiopathic scrotal oedema** is a benign condition usually between ages 2-10yrs, and is differentiated from torsion by the

absence of pain and tenderness.

Tips on examining the abdomen in children

Examining the abdomen of a child or infant can prove extremely difficult and requires patience, practice and opportunism. So:

- An age-directed approach will help develop your relationship with the child.
- Remember that the parents will be closely involved in what you do.
- Play specialists may be able to provide distraction.
- Examining the abdomen may require an unorthodox approach, eg whilst sitting in mum's lap.
- There is no hope of eliciting any signs whilst the child is crying and tensing their tummy—everyone will be better off if you return when the child has settled down!
- Examining for rebound tenderness in young children is probably of little use for us and definitely uncomfortable for them.
- You should always examine the scrotum and inguinal regions in young boys to exclude the possibility of testicular torsion or a strangulated hernia.
- Performing a PR examination, if required, is best left to a specialist.
- Unless you have a magical way with children, don't be surprised to get the cold shoulder once in a while!

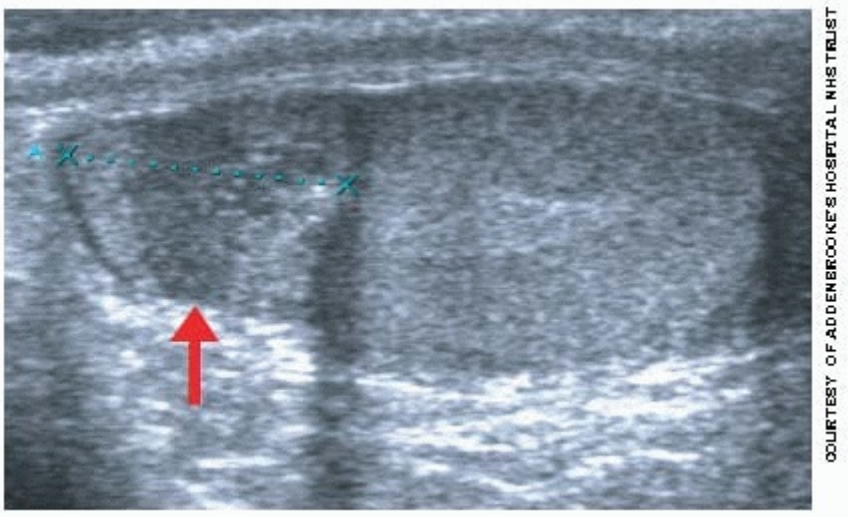
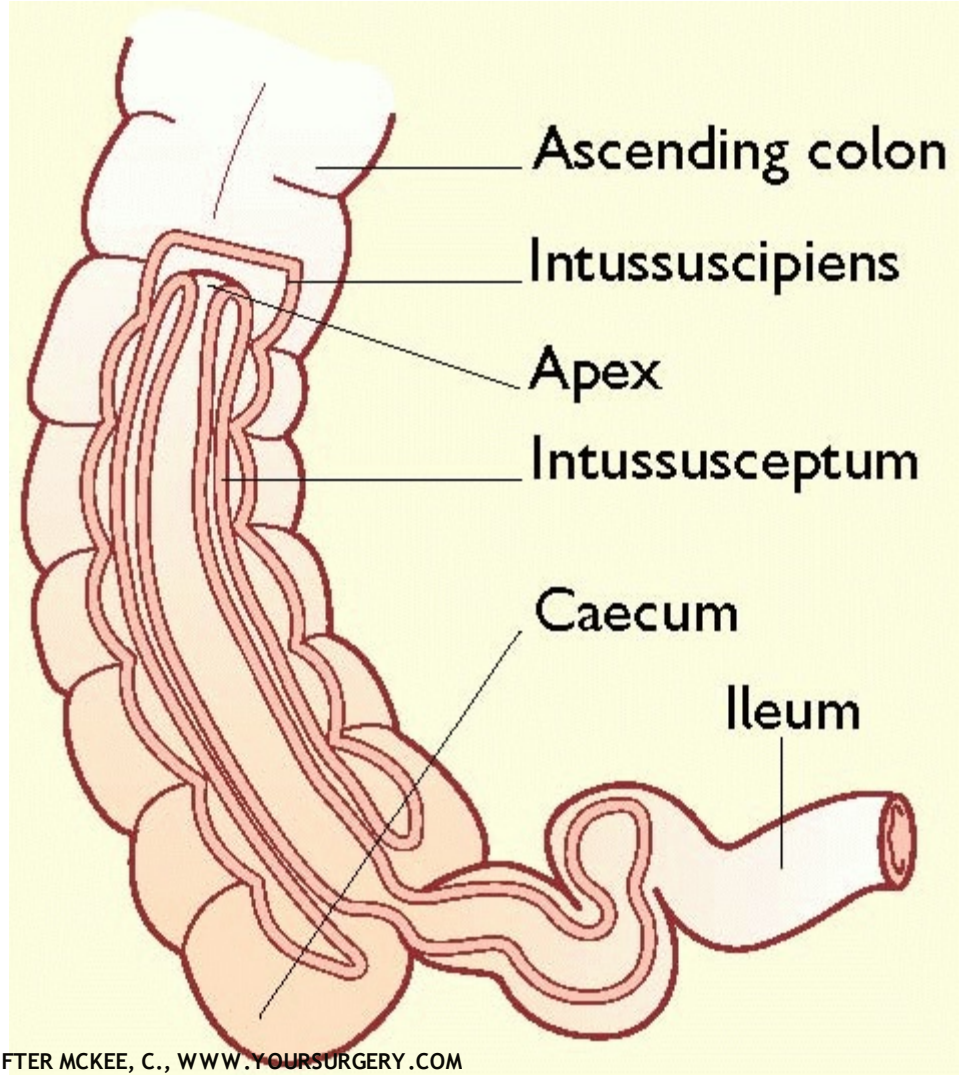


Fig 1. Ultrasound of the testis showing a torsion of a hydatid Morgagni (appendix of the testis). This is a hypoechoic area at the superior pole separate from the normal head of the epididymis (arrow).

Intussusception



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Urinary retention & benign prostatic hypertrophy

Retention means not emptying the bladder (∵ **obstruction** or ↓**detrusor power**).

Acute retention

The bladder is usually tender, containing ~600mL of urine. The cause in men is usually prostatic obstruction, eg precipitated by anticholinergics, 'holding on', constipation, pain, anaesthetics, alcohol, infection (p282). Questions to detect obstruction: see p40.

Examine:

Abdomen, PR, perineal sensation (cauda equina compression).

Tests:

MSU, U&E, FBC, and prostate-specific antigen (PSA, p681).[1] Renal ultrasound if renal impairment.

Tricks to aid voiding:

Analgesia, privacy on hospital wards, ambulation, standing to void, voiding to the sound of running taps—or in a hot bath.

If the tricks fail:

Catheterize (p750) and try a prostate procedure (below). After eg 7 days, trial without catheter may work (esp. if <75yrs old and <1L drained or retention was triggered by a passing event, eg general anaesthesia), p751.

Prevention:

Finasteride reduces prostate size and retention risk. ***Tamsulosin*** reduces risk of needing recatheterization after acute retention.[143]

Chronic retention

is more insidious. Bladder capacity may be >1.5L. Presentation: overflow incontinence, acute on chronic retention, a lower abdominal mass, UTI, or renal failure eg in the form of bilateral obstructive uropathy—see EMERGENCY BOX. Prostatic enlargement is the common cause. Others: pelvic malignancy;

rectal surgery; DM; CNS disease eg transverse myelitis/MS; zoster (S2-S4). ▸Only catheterize the patient if there is pain, urinary infection, or renal impairment (eg urea >12mmol/L). Institute definitive treatment promptly. Intermittent selfcatheterization is sometimes required (p751).

Catheters and catheterization

See p750.

Prostate cancer

p606.

Benign prostatic hypertrophy (BPH)

is common (24% if aged 40-64; if older, 40%). ↓Urine flow (eg <15mL/s) is associated with frequency, urgency (▸p40) and voiding difficulty.

Managing BPH:

Assess severity of symptoms and impact on life. PR exam. Tests: MSU; U&E; ultrasound (residual volume↑, hydronephrosis—see **fig 1**). Rule out cancer: PSA,[1] transrectal ultrasound ± biopsy. Then consider:

1. ***Transurethral resection of the prostate*** (TURP, a common operation; ≤14% become impotent—see BOX). Crossmatch 2U. Consider perioperative antibiotics, eg ***cefuroxime*** 1.5g/8h IV, three doses. Beware excessive bleeding post-op and clot retention. ~20% of TURPs need redoing within 10yrs.
2. ***Transurethral incision of the prostate*** (TUIP) involves less destruction than TURP, and less risk to sexual function, but gives similar benefit.**RCT**$_{144}$ It achieves this by relieving pressure on the urethra. It is perhaps the best surgical option for those with small glands <30g—ie ~50% of those operated on in some areas.
3. ***Retropubic prostatectomy*** is an open operation.
4. ***Transurethral laser-induced prostatectomy*** (TULIP) may be as good as TURP.**RCT**$_{145}$
5. ***Drugs*** may be useful in mild disease, and while awaiting TURP, eg:
   - α-blockers: eg ***tamsulosin*** 400µg/d PO; alternatives: ***alfuzosin***, ***doxazosin***, ***terazosin***. These ↓smooth muscle tone (prostate *and* bladder). SE: drowsiness, depression; dizziness; BP↓; dry mouth; ejaculatory failure; extra-pyramidal signs; nasal congestion; weight↑. They are the drugs of choice.
   - 5α-reductase inhibitors: ***finasteride*** 5mg/d PO (↓testosterone's conversion to dihydrotestosterone).[2] It is excreted in semen, so warn to use condoms; females should avoid handling crushed pills. SE: impotence; ↓libido. Effects on prostate size are limited and slow, so, if α-blockers fail, many try surgery next.
6. ***Phytotherapy*** (pharmacological use of plants) **Saw palmetto** (*Sereona repens*) is said to help symptoms of BPH (no more than drugs$_{146}$); trials are disappointing.**RCT**$_{147}$
7. ***Wait and see*** is an option, but risks incontinence, retention, and renal failure.

Advice for patients concerning transurethral prostatectomy

Pre-op consent issues may centre on risks of the procedure, eg:

- Haematuria/haemorrhage
- Haematospermia
- Hypothermia
- Urethral trauma/stricture
- Post TURP syndrome (T°↓; Na+↓)$_{148}$
- Infection; prostatitis
- Impotence ~10%
- Incontinence ≤10%
- Clot retention near strictures
- Retrograde ejaculation (common)

Post-operative advice:

- Avoid driving for 2wks after the operation.
- Avoid sex for 2wks after surgery. Then get back to normal. The amount ejaculated may be reduced (as it flows backwards into the bladder—harmless, but may cloud the urine). It means you may be infertile. Impotence may be a problem after TURP, but do not expect this: in some men, erections improve. Rarely, orgasmic sensations are reduced.
- Expect to pass blood in the urine for the first 2 weeks. A small amount of blood colours the urine bright red. Do not be alarmed.
- At first you may need to urinate **more** frequently than before. Do not be despondent. In 6 weeks things should be much better—but the operation cannot be guaranteed to work (8% fail, and lasting incontinence is a problem in 6%; 12% may need repeat TURPs within 8yrs, compared with 1.8% of men undergoing open prostatectomy).
- If feverish, or if urination hurts, take a sample of urine to your doctor.

Obstructive uropathy

In someone with chronic urinary retention, an episode of **acute** retention may go unnoticed for several days and, because of their background symptoms, may only present when overflow incontinence becomes a nuisance—pain is not necessarily a feature.

After making the diagnosis of acute on chronic retention and inserting a catheter, the bladder residual can be as much as 1.5L of urine. Don't be surprised to be called by the biochemistry lab to be told that the serum creatinine is 1500 µmol/L! The good news here is that renal function usually returns to the baseline after a few days, (remembering that there may be some mild background impairment). Request an urgent US of the renal tract (**fig 1**) and consider the following in the acute setting to ensure a safe course:

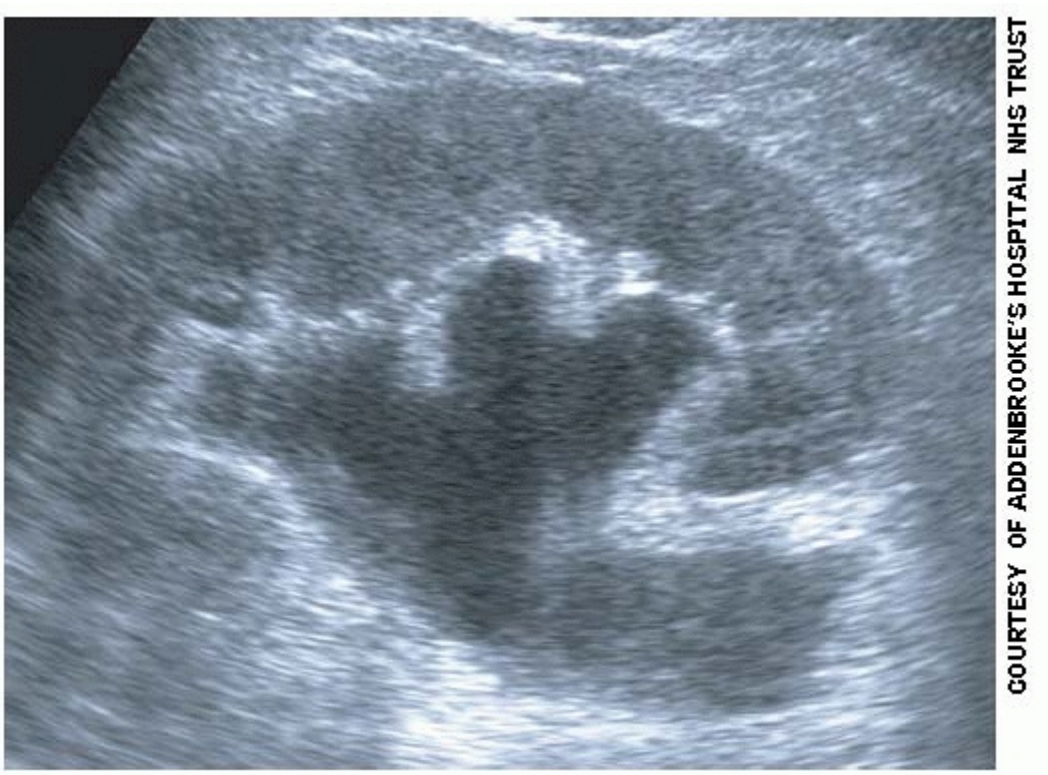


Fig 1. Ultrasound of an obstructed kidney showing hydronephrosis. The renal pelvis and ureter are dilated and the calyces are clubbed.

- **Hyperkalaemia:** Treat accordingly (p821).
- **Metabolic acidosis:** On ABG there is likely to be a respiratory compensated metabolic acidosis. Concerns should prompt discussion with a renal specialist (a good idea anyway), in case haemodialysis is required (p296).
- **Post-obstructive diuresis:** In the acute phase after relief of the obstruction, the kidneys produce **a lot** of urine—as much as a litre in the first hour. It is vital to provide resuscitation fluids and then match input with output. ▸Fluid depletion rather than overload is the danger here.
- **Sodium and bicarbonate-losing nephropathy:** As the kidney undergoes diuresis, Na+ and bicarbonate are lost in the urine in large quantities. Replace 'in for out' (as above) with isotonic 1.26% sodium bicarbonate solution—this should be available from ITU. Some advocate using 0.9% saline, though the chloride load may exacerbate acidosis. Withhold any nephrotoxic drugs.
- **Infection:** Treat infection, bearing in mind that the WCC↑ and CRP↑ may be part of the stress response. Send a sample of urine for MC+S.

[1] Do venepuncture for PSA **before** PR, as PR can ↑total PSA by ~1ng/mL (free PSA ↑by 10%). It is difficult to evaluate whether acute retention raises PSA, but we know that relieving obstruction causes it to drop!

[2] ***Finasteride*** can prevent retention but has odd effects on risk of prostate cancer. The PCPT trial showed a ↓risk of indolent cancers, but ↑risk of Gleason >7 (p607).

Urinary incontinence

▸Think twice before inserting a urinary catheter.

▸Carry out rectal examination to exclude faecal impaction.

▸Is the bladder palpable after voiding (retention with overflow)?

▸Is there neurological co-morbidity: eg MS; Parkinson's disease; stroke; spinal trauma?

Anyone might 'wet themselves' on a long coach ride (we all would if the journey was long enough). Do not think of people as either dry or incontinent but as incontinent in certain circumstances. Attending to these circumstances is as important as focusing on the physiology.

Incontinence in men

Enlargement of the prostate is the major cause of incontinence: urge incontinence (see below) or dribbling may result from the partial retention of urine. TURP & other pelvic surgery may weaken the bladder sphincter and cause incontinence. Troublesome incontinence needs specialist assessment.

Incontinence in women

(See also **Voiding difficulty**, OHCS p307.)

1. ***Functional incontinence*,** ie when physiological factors are relatively unimportant. The patient is 'caught short' and too slow in finding the toilet because of immobility or unfamiliar surroundings, for example.
2. ***Stress incontinence:*** Leakage of urine due to incompetent sphincter, typically occuring when intra-abdominal pressure rises (eg coughing, laughing). There may be slippage of the proximal 1/3 of the urethra and the bladder neck out of the abdominal cavity. Increasing age and obesity are risk factors. The key to diagnosis is the loss of small (but often frequent) amounts of urine when coughing, etc. Examine for pelvic floor weakness/prolapse.$_{149}$ Look for cough leak with the patient standing and with full bladder. Stress incontinence is common in pregnancy and following birth. It occurs to some degree in about 50% of post-menopausal women. In elderly women, pelvic floor weakness, eg with uterine prolapse or urethrocele (OHCS p290) is the commonest cause.
3. ***Urge incontinence*** (also known as 'overactive bladder syndrome') is the chief type seen in hospital practice. The urge to urinate is quickly followed by uncontrollable and sometimes complete emptying of the bladder as detrusor contracts. Large amounts of urine flow down the patient's legs. In the elderly it is usually related to **detrusor instability** (a urodynamic diagnosis—see BOX) or organic brain damage. Look for evidence of: stroke; Parkinson's; dementia. Other causes: urinary infection; diabetes; diuretics; 'senile' vaginitis; urethritis.

In both sexes incontinence may result from diminished awareness due to confusion or sedation. Occasionally incontinence may be purposeful (eg preventing admission to an old people's home) or due to anger.

Management

Check for:

UTI; DM; diuretic use; faecal impaction. Do U&E.

Stress incontinence:

Pelvic floor exercises may help. Intravaginal electrical stimulation may also be effective, but is not acceptable to many women. A ring pessary may help uterine prolapse, eg while awaiting surgical repair. ***Duloxetine*** 40mg/12h PO is a new treatment; the main SE is nausea.**RCT**$_{150}$ Surgical options include **Burch colposuspension** and **sling procedures**.**MET**$_{151}$ A variety of minimal access techniques (eg tension-free vaginal tape) are also available.

Urge incontinence:

Examine for spinal cord and CNS signs (including cognitive test, p47); and for vaginitis—treat with ***estriol*** 0.1% cream (eg Ovestin®, one applicator dose twice weekly for a few months)—consider cyclical ***progesterone*** if for prolonged use and no hysterectomy, to avoid risk of uterine cancer. The patient (or carer) should complete an 'incontinence' chart for 3 days to define the pattern of incontinence. Maximize access to toilet; advise on toileting regimen (eg every 4h). The aim is to keep bladder volume below that which triggers emptying. Drugs may help reduce night-time incontinence (see BOX) but are generally disappointing. Consider aids (absorbent pad; Paul's tubing if ♂).

▸Do urodynamic assessment (cystometry & urine flow rate measurement) before any surgical intervention to exclude detrusor instability or sphincter dyssynergia.

Managing detrusor instability

Agents for detrusor instability:	Symptoms that they may improve:
Tolterodine 1-2mg/12h PO; SE: dry mouth, eyes, and skin; drowsiness, abdominal pain, urinary retention.**RCT**$_{152}$	Frequency, urgency (alternative: ***oxybutynin***, but more SE).**MET**$_{153}$ Avoid in myasthenia, and if glaucoma or UC are uncontrolled.

Solifenacin 5mg/24h (max 10mg)	Urinary frequency, urgency, and urge incontinence. SE: gastro-oesophageal reflux; altered taste; fatigue; oedema.
Imipramine 50mg PO at night	Nocturia, enuresis, coital incontinence
Oestrogens	Post-menopausal urgency, frequency + nocturia may be improved by raising the bladder's sensory threshold.
Surgery, eg clam ileocystoplasty	Usually reserved for troublesome or intractable symptoms. The bladder is bisected, opened like a clam, and 25cm of ileum is sewn in.
Neuromodulation via transcutaneous electrical stimulation[154]	(Stimulates afferent nerve fibres to modulate bladder reflexes, suppressing involuntary detrusor contractions.)
Hypnosis, psychotherapy, bladder training	(These all require good motivation.)
NB: ***desmopressin*** nasal spray 20µg as a night-time dose may have a role in ↓urine production, but not suitable in the elderly (SEs: fluid retention, heart failure, hyponatraemia).	

A reminder about urinary symptoms

See also p40

Filling/storage symptoms

- Nocturia
- Urgency
- Urge incontinence
- Frequency

Voiding symptoms

- Poor stream
- Terminal dribbling
- Strangury
- Hesitancy
- *Pis en deux*=going twice.

Urinary tract malignancies[155]

Renal cell carcinoma

(hypernephroma, Grawitz tumour) arises from the proximal renal tubular epithelium.

Epidemiology:

90% of renal cancers; mean age; 55yrs. ♂:♀=2:1. 15% of those on haemodialysis develop renal cell carcinoma.

Clinical features:

50% are incidental findings during abdominal imaging for other symptoms. Haematuria, loin pain, abdominal mass, anorexia, malaise, weight loss, and PUO may all occur—often in isolation. Rarely, invasion of left renal vein compresses the left testicular vein causing a left varicocele. Spread may be direct (renal vein), via lymph nodes, or haematogenous (bone, liver, lung).

Tests:

Blood: FBC (polycythaemia from erythropoietin secretion); ESR; U&E, alk phos (bony mets?). **Urine:** RBCs; cytology. **Imaging:** US (p730); CT/MRI (including 3D, **fig 1**);[156] renal angiography (if partial nephrectomy or palliative embolization are being considered; angiography can also be done by CT/MR); IVU (filling defect in kidney ± calcification); CXR ('cannon ball' metastases).[157]

Treatment:

Radical nephrectomy has been the gold-standard, though there may be a role for nephron-sparing surgery in small tumours ($\lesssim$4cm).**MET**[158] Metastatic disease is reason to consider immunotherapy with interferon-× and interleukin-2.[159]

Prognosis:

5yr survival: 45%.

Transitional cell carcinoma (TCC)

may arise in the bladder (50%), ureter, or renal pelvis.

Epidemiology:

Age >40yrs; ♂:♀ = 4:1.

Risk factors:

p608.

Presentation:

Painless haematuria; frequency; urgency; dysuria; urinary tract obstruction.

Diagnosis:

Urine cytology; IVU; cystoscopy + biopsy; CT/MRI scan.

Treatment:

See **Bladder tumours**, p608.

Prognosis:

Varies with clinical stage/histological grade: 10-80% 5yr survival.

Wilms' tumour

(nephroblastoma, OHCS p133) is a childhood tumour of primitive renal tubules and mesenchymal cells.

Prevalence:

1:100 000; the chief abdominal malignancy in children. It presents with an abdominal mass and haematuria. Check for associated syndromes (eg Beckwith-Wiedemann, OHCS p638).

Tests:

Urine cytology; US; IVU; renal angiography; CT/MRI scan. Avoid biopsy.

Treatment:

Nephrectomy; radiotherapy; chemotherapy.

Prognosis:

90% 5yr survival.

Prostate cancer

is the 2nd commonest malignancy of men.

Incidence:

Rises with age: 80% in men >80yrs (in autopsy studies).

Associations:

↑testosterone, +ve family history (p512). Most are adenocarcinomas arising in the peripheral prostate. Spread may be local (seminal vesicles, bladder, rectum) via nodes, or haematogenously (sclerotic bony lesions).

Symptoms:

May be asymptomatic or nocturia, hesitancy, poor stream, terminal dribbling, or urinary obstruction. Weight↓ ± bone pain suggests metastases.

PR exam:

May show a hard, irregular prostate.

Diagnosis:

↑PSA (p681; normal in 30% of small cancers); transrectal ultrasound and biopsy; bone x-rays; bone scan; CT/MRI.

Staging:

MRI. If contrast-enhancing magnetic nanoparticles are used, sensitivity for detecting affected nodes rises from 35% to 90%.[160]

Treatment:

Local disease: Which is better: radical prostatectomy (+ immediate ***goserelin*** if node +ve; a widely used regimen), radiotherapy or watchful waiting with serial PSA monitoring? The follow up to one trial found that at 10 years, radical prostatectomy significantly improved disease-specific mortality and local progression when compared with watchful waiting.**RCT**[161] (But radical surgery does double rates of erectile dysfunction and incontinence.) Radiotherapy combined with hormone therapy improves survival in advanced local disease.**RCT**[162] Do transurethral resection for obstruction. Brachytherapy is being assessed for local disease. **Metastatic disease:** Hormonal drugs may give benefit for 1-2yrs. Gonadotrophin-releasing analogues, eg 12-weekly ***goserelin*** (10.8mg SC as Zoladex LA®) first stimulate, and then inhibit pituitary gonadotrophin output. Alternatives: ***cyproterone acetate***; ***flutamide***; ***diethylstilboestrol***.

Symptomatic treatment:

Analgesia; treat hypercalcaemia; radiotherapy for bone metastases or spinal cord compression.

Prognosis:

10% die in 6 months, but 10% live >10yrs.

Screening:

Rectal exam; PSA; transrectal ultrasound. There are problems with all (p681).

Advice to asymptomatic men asking for a PSA test

The prostate lies below the bladder, and surrounds the tube taking urine out. Prostate cancer is common in older men. Many men over 50 (to whom this advice applies) consider a PSA blood test to detect prostatic cancer. *Is this wise?*

- The test is not very accurate, and we cannot say that those having the test will live longer—even if they do turn out to have prostate cancer. This is because the cancer is often very lazy, so that, in most men with prostate cancer, death is from an unrelated cause.
- The test itself has no side-effects, provided you don't mind giving blood and time. But if the test is falsely positive, you may needlessly have more tests, such as sampling the prostate by the back passage (which may cause bleeding and infection in 1-5% of men).
- Only one in three of those with a high PSA level will have cancer.
- You may also be worried needlessly if later tests put you in the clear.

- Even if a cancer is found, there is no way to tell *for sure* if it will impinge on your health. Treatment may be recommended—and then you might end up having a bad effect from treatment which was not even needed.
- There is much uncertainty on treating those who **do** turn out to have prostate cancer: options are radical surgery to remove the prostate (this treatment may be fatal in 0.2-0.5% of patients), radiotherapy, or hormones.
- There is indirect evidence of benefit of screening from the USA where fewer radical prostatectomies reveal cancer-affected lymph nodes than those done before widespread PSA-based screening. Intensive screening and treatment for prostate cancer does not, however, appear to be associated with lower prostate-specific mortality in retrospective studies.[163]

▸ Ultimately, you must decide for yourself what you want.

Prognostic factors in prostate cancer

A number of prognostic factors help determine if 'watchful waiting' or aggressive therapy should be advised: • Age • Pre-treatment PSA level • Tumour stage (as measured by the TNM system),[164] and tumour grade—as measured by its Gleason score. Gleason grading is from 1 to 5, with 5 being the highest grade, and carrying the poorest prognosis. A pathologist determines Gleason grades by analysing histology from two separate areas of tumour specimen, and adding them to get the total Gleason score for the tumour, from 2 to 10. 8-10 suggest an aggressive tumour; 5-7 suggest intermediate grade; 2-4 is indolent. In one recent (provisional) study, 15yr prostate cancer mortality for conservative management of PSA-detected cancers was 0-2% for Gleason <7, 9-31% for Gleason score 7, and 28-72% for Gleason scores >7.[165]

Patients with high Gleason scores are more likely to be treated aggressively, (eg if younger and/or have higher stage disease). If 55-59yrs old at diagnosis, the predicted absolute 15yr survival benefit from radical (curative) treatment is about 0, 12, and 26% for Gleason scores <7, 7, and >7, respectively.[166]

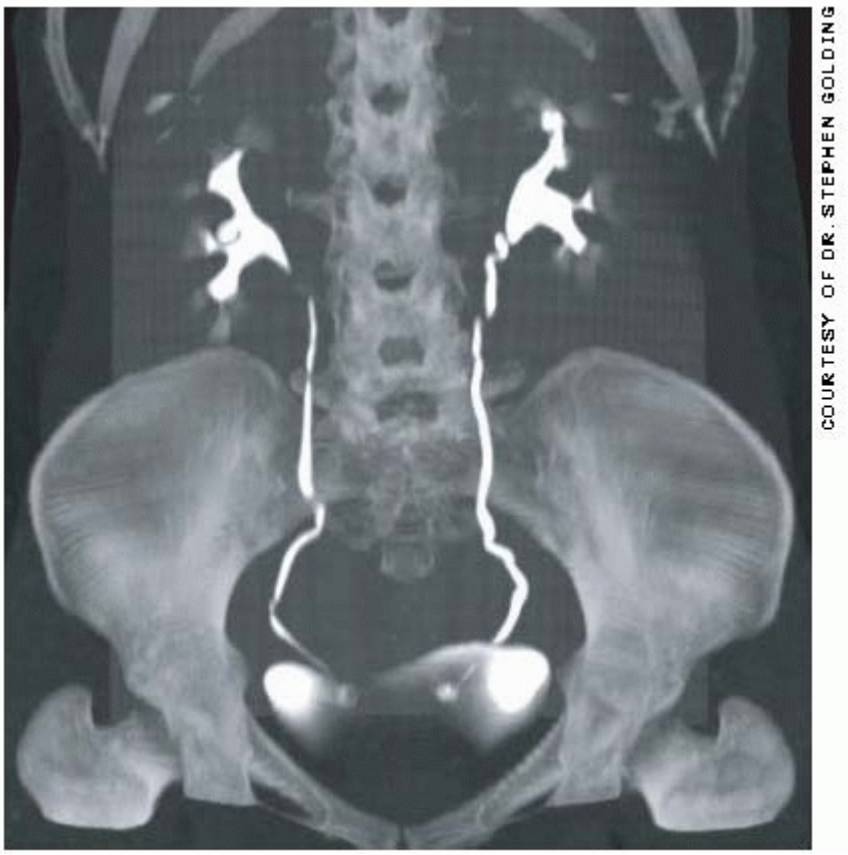


Fig 1. 3D CT urography of the urinary tract.

Bladder tumours

What appear as benign papillomata rarely behave in a purely benign way. They are almost certainly indolent transitional cell (urothelial) malignancies. Adenocarcinomas and squamous cell carcinomas are rare in the West (the latter may follow schistosomiasis). UK incidence ≈ 1 : 5000/yr. ♂:♀ ≈ 4:1. Histology is important for prognosis: **Grade 1**—differentiated; **Grade 2**—intermediate; **Grade 3**—poorly differentiated. 80% are confined to bladder mucosa, and only ~20% penetrate muscle (increasing mortality to 50% at 5yrs).

Presentation

Painless haematuria; recurrent UTIs; voiding irritability.

Associations

Smoking; aromatic amines (rubber industry); chronic cystitis; schistosomiasis (↑risk of squamous cell carcinoma); pelvic irradiation.

Tests

- Urine: microscopy/cytology (cancers may cause sterile pyuria).
- IVU may show filling defects ± ureteric involvement.
- Cystoscopy with biopsy is diagnostic.
- Bimanual EUA helps assess spread.
- CT/MRI or lymphangiography may show involved pelvic nodes.

Staging:

See TABLE.

Treatment of transitional cell carcinoma (TCC) of the bladder

- ***Tis/Ta/T1:*** (80% of all patients.) Diathermy via transurethral cystoscopy. Consider intravesical chemotherapeutic agents (eg ***mitomycin C***) for multiple small tumours or high-grade tumours. Immunotherapy with intravesical ***BCG*** (which stimulates a non-specific immune response) is useful in high-grade tumours and carcinoma-*in-situ*, and may be better at preventing tumour progression than **mitomycin C** in superficial disease.MET$_{167}$ 5yr survival ≈ 95%.
- ***T2-3:*** Radical cystectomy is the 'gold standard'. Radiotherapy gives worse 5yr survival rates than surgery, but preserves the bladder. 'Salvage' cystectomy can be performed if radiotherapy fails, but yields worse results than primary surgery. Post-op chemotherapy (eg M-VAC: ***methotrexate***, ***vinblastine***, ***adriamycin***, and ***cisplatin***) is toxic but effective, and there may also be a role for neoadjuvant chemotherapy.**MET**$_{168}$ Methods to preserve the bladder with transurethral resection/ partial cystectomy + systemic chemotherapy have been tried, but long-term results are disappointing. If the bladder neck is not involved, orthotopic reconstruction rather than forming a urostoma is an option (both using ~40cm of the patient's ileum), but adequate tumour clearance must not be compromised. ▸The patient should have all these options explained by a urologist and an oncologist.
- **T4***:* Usually palliative chemo/radiotherapy. Chronic catheterization and urinary diversions may help to relieve pain.

Follow up

History, examination, and regular cystoscopy: • ***High-risk tumours:*** Every 3 months for 2yrs, then every 6 months; • ***Low-risk tumours:*** First follow-up cystoscopy after 9 months, then yearly.

Tumour spread

Local → to pelvic structures; lymphatic → to iliac and para-aortic nodes; haematogenous → to liver and lungs.

Survival

This depends on age at surgery. For example, the 3yr survival after cystectomy for T2 and T3 tumours is 60% if 65-75yrs old, falling to 40% if 75-82yrs old (in whom the operative mortality is 4%). With unilateral pelvic node involvement, only 6% of patients survive 5yrs. The 3yr survival with bilateral or para-aortic node involvement is nil.

Complications:

Cystectomy can result in sexual and urinary malfunction. Massive bladder haemorrhage may complicate treatment; consider ***alum*** solution bladder irrigation (safer than formalin): it is an in-patient procedure.[169]

TNM staging of bladder cancer

Tis	Carcinoma-*in-situ*	Not felt at EUA
Ta	Tumour confined to epithelium	Not felt at EUA

T1	Tumour in lamina propria	Not felt at EUA
T2	Superficial muscle involved	Rubbery thickening at EUA
T3	Deep muscle involved	EUA: mobile mass
T4	Invasion beyond bladder	EUA: fixed mass

EUA = examination under anaesthetic

Is asymptomatic microscopic haematuria significant?

Dipstick tests are often done routinely for new admissions. If microscopic haematuria is found, but the patient has no related symptoms, what does this mean? Before rushing into a barrage on investigations, consider:

One study found incidence of urogenital disease (eg bladder cancer) was no higher in those with asymptomatic microhaematuria than those without.[170]

- Asymptomatic microscopic haematuria is the sole presenting feature in only 4% of bladder cancers, and there is no evidence that these are less advanced than malignancies presenting with macroscopic haematuria.
- When monitoring those with treated bladder cancer for recurrence, microscopic haematuria tests have a sensitivity of only 31% in those with superficial bladder malignancy, in whom detection would be most useful.
- Although 80% of those with flank pain due to a renal stone have microscopic haematuria, so do 50% of those with flank pain but no stone.[171]

The conclusion is not that urine dipstick testing is useless, but that results should not be interpreted in isolation. Take a holistic view. Smokers and those with +ve family history for urothelial cancer may be investigated differently from those with no risk factors (eg ultrasound, cystoscopy ± referral to a renal physician in some patients), but in a young fit athlete, the diagnosis is more likely to be exercise-induced haematuria.[172] Wise doctors liaise with their patients. 'Shall we let sleeping dogs lie?' is a reasonable question for **some** patients. Give the facts and let him decide, reserving to yourself the right to present the facts in certain ways, depending on your instincts, and those of a trusted colleague. Remember that medicine is for gamblers (p646), and wise gamblers assess the odds against a shifting set of circumstances.

Breast lumps & breast carcinoma see NICE.org.uk

▸All solid lumps need histo-/cytological assessment.

History

Previous lumps, family history, pain (rarely in cancer), nipple discharge or inversion, change in size related to menstrual cycle, number of pregnancies, first/last/latest period, drugs (eg HRT). Don't forget that 1% of all breast cancers are found in men.

Examination

Inspect (arms up and down). Note position, size, consistency, mobility, fixity, and local lymphadenopathy. Any nipple discharge/inversion? Is the skin involved: dimpling; ulceration; *peau d'orange*?

Investigation

All lumps should undergo *'quadruple' assessment:* Clinical examination (above) + histology/cytology + mammography + ultrasound; see flow chart.

Common lumps

- Fibroadenoma

- Cyst
- Cancer
- Fibroadenosis (focal or diffuse nodularity)

Rare lumps

- Periductal mastitis
- Fat necrosis
- Galactocoele
- Abscess
- 'Non-breast' eg lipoma or sebaceous cyst

Breast cancer

Risk factors:

Risk is related to family history, age and uninterrupted oestrogen exposure, hence: nulliparity; 1st pregnancy >30yrs old, early menarche; late menopause; HRT; obesity; BRCA genes (p512); not breast-feeding; the Pill (possibly); past breast cancer (metachronous rate ≈2%, synchronous rate ≈1%).

TNM staging:

T1 <2cm. **T2** 2-5cm. **T3** >5cm. **T4** Fixity to chest wall or *peau d'orange*. **N1** Mobile ipsilateral nodes. **N2** Fixed nodes. **M1** Distant metastases.

Treating early cancer

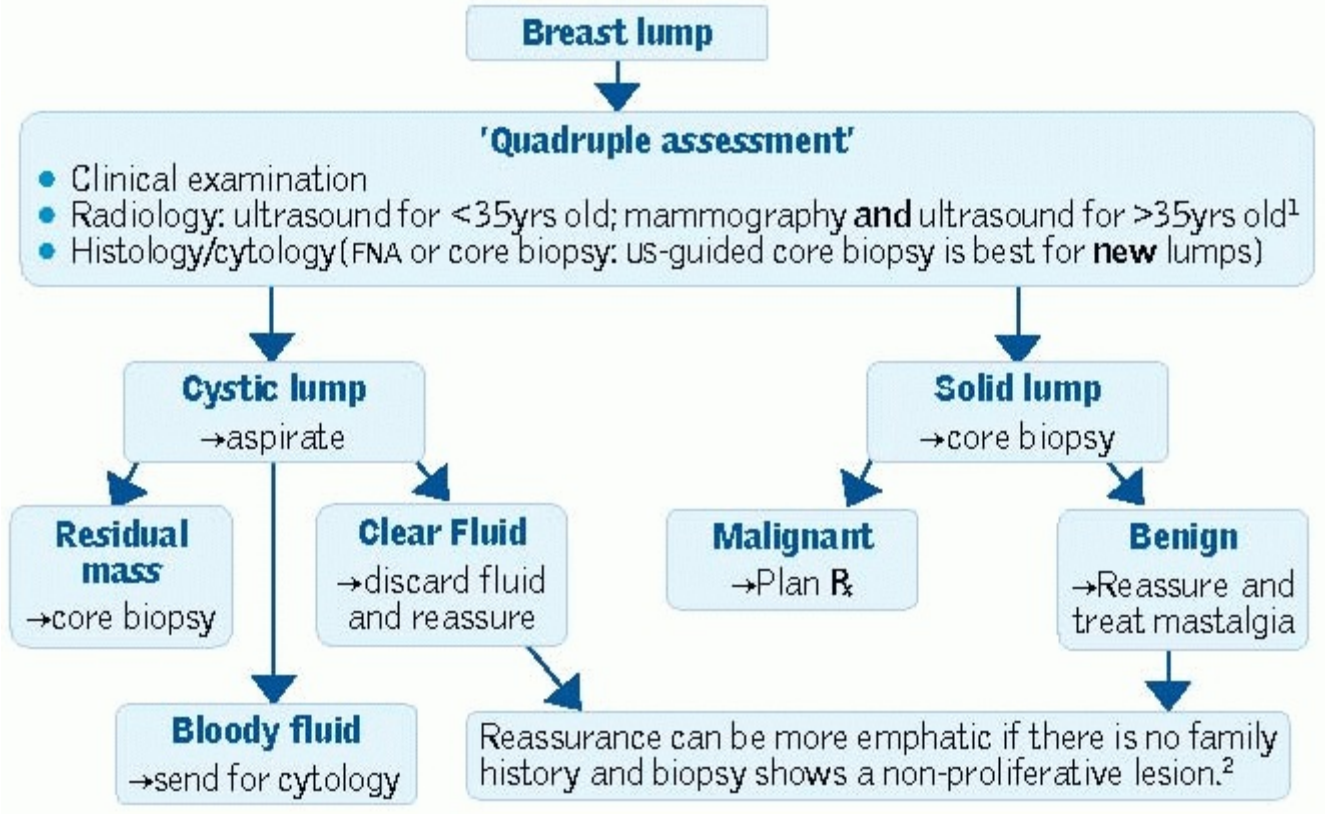
• *Surgery:* Wide local excision (WLE) or mastectomy ± breast reconstruction + axillary node sampling or surgical clearance. Local excision followed by radiotherapy gives equal survival, but higher local recurrence rates, than mastectomy. • *Radiotherapy:* For tumours at high risk of local recurrence, post-mastectomy radiotherapy to the chest wall ↓local recurrence and may ↑overall survival.[173] Radiotherapy to the breast following WLE ↓local recurrence.[174] Radiotherapy to the axilla is used if lymph node +ve on sampling and complete surgical clearance was not performed. SE: pneumonitis, pericarditis, rib fractures, lymphoedema, brachial plexopathy. • *Chemotherapy* improves survival (esp. if younger and node +ve), eg an anthracycline (***epirubicin*** is less cardiotoxic than ***doxorubicin***) + ***5FU*** + ***cyclophosphamide*** ± ***methotrexate***. ***Trastuzumab*** (Herceptin®, below) also has a role. If these fail, ***vinorelbine*** or ***capecitabine*** + ***docetaxel*** (a taxane) may be used. • *Endocrine therapy* aims to ↓oestrogen activity, and is used in all (o)estrogen receptor (ER) or progesterone receptor (PR) +ve disease. The ER blocker ***tamoxifen*** is widely used, eg 20mg/d PO for 5yrs post-op (may rarely cause uterine cancer so warn to report vaginal bleeding).[175] Aromatase inhibitors (eg ***anastrozole***) targeting oestrogen synthesis can also be used, and may be better tolerated than ***tamoxifen***. They are commonly used in post-menopausal women. In pre-menopausal women with ER+ve tumours, ovarian ablation either via surgery, radiotherapy, or GnRH analogues (p606, eg ***goserelin***) improves recurrence and survival.[176] • *Support:* Involve specialist breastcare nurses at from the start— they will have the closest contact with patients all the way through treatment.

Treating distant disease

Assess LFT, Ca^{2+}, CXR, skeletal survey, bone scan, liver US, or CT. DXT (p518) to painful bony lesions. ***Tamoxifen*** is commonly used in ER+ve disease; if relapse after initial success, consider chemotherapy. Tumours +ve for HER2 protein may respond to the monoclonal antibody ***trastuzumab*** (Herceptin®).[177]

Preventing breast cancer deaths

• Promote ***breast awareness*** • ***Mammography*** every ~3yrs, eg if 50-70yrs old; screening ↓ breast cancer deaths by 25% in this group. 2-view mammograms are used. Radiation risk is 'negligible'. Detection rates are 6.4 cancers/1000 'healthy'women. Annual mammograms don't lower mortality, much further. **NB:** The fall in death rates from 51 to 35 per 100,000 during 1990- 2000 is largely attributed to wide use of ***tamoxifen***.[178] ***Raloxifene*** (used in post-menopausal osteoporosis and similar to tamoxifen and has less risk of uterine cancer & DVT) may have a role in preventing ER+ve cancers in women at ↑risk.[179] N=19,747



Nipple discharge

Causes of discharge

Duct ectasia (green/brown/red, often multiple ducts and bilateral), intraductal papilloma/adenoma/carcinoma (bloody discharge, often single duct), lactation.

Management:

Diagnose the cause (mammogram, ultrasound, ductogram); then treat appropriately. Cessation of smoking reduces discharge from duct ectasia. Microdochectomy/total duct excision can be considered if other measures fail, though may give no improvement in symptoms.

Sentinel node biopsy

▸Sentinel node biopsy may reduce the number of needless axillary clearances in lymph node -ve patients, thus decreasing post-op morbidity.[180] In keeping with the history of conservative breast surgery, it remains controversial.

A typical procedure is as follows:

- Patent blue dye (SE: anaphylaxis) and/or radiocolloid is injected perioperatively into the periareolar area or the area of the primary tumour.
- A small incision is made in the axilla, and a gamma probe/visual inspection is used to identify the sentinel node.
- The sentinel node is biopsied and sent for histology ± immunohistochemistry.

Multi-centre trials suggest that the sentinel node can be identified in 90% of patients. False negative rates of 9-14% are reported, though these drop to <5% as surgeons become more experienced with the technique.

Prognostic factors in breast cancer

Many factors help assess prognosis in breast cancer, including tumour size, grade, lymph node status, ER/PR status, and presence of lympho-vascular invasion. The Nottingham Prognostic Index (NPI) is widely used to predict survival and risk of relapse, and thus help select appropriate adjuvant systemic therapy:[3]

$$NPI = 0.2 \times \text{tumour size (cm)} + \text{histological grade} + \text{nodal status}$$

If treated with surgery alone, the 10yr survival rates are: NPI <2.4: 95%; NPI 2.4-3.4: 85%; NPI 3.4-4.4: 70%; NPI 4.4-5.4: 50%; NPI >5.4: 20%.

Colorectal adenocarcinoma

This is the 2nd most common cause of cancer deaths in the UK (19,000 deaths/yr). 56% of presentations are in those >70yrs old. Synchronous tumours are found in ~2.5% and metachronous tumours in ~1%. See BOX for tumour sites.

Predisposing factors

Neoplastic polyps (see below), UC, Crohn's, familial adenomatous polyposis, HNPCC (p512), previous cancer, and low-fibre diet.[181] NSAIDs and ***aspirin*** may be protective.[182]

Genetics:

No close relative affected: colorectal cancer risk is 1 : 50. One 1st degree relative affected: risk=1:17; if 2 affected, 1:10 (refer when 10yrs younger than the youngest affected relative).

Presentation

depends on site:

Left-sided:

Bleeding/mucus PR; altered bowel habit; tenesmus; mass PR (60%).

Right:

Weight↓; Hb↓; abdominal pain.

Either:

Abdominal mass; obstruction; perforation; haemorrhage; fistula.

Tests

FBC (microcytic anaemia); faecal occult blood (FOB); proctoscopy, sigmoidoscopy, barium enema or colonoscopy (see **figs 1** & **2**, p248), which can be done 'virtually' by CT—**fig 6**, p729); LFT, CT/MRI (**fig 1**); liver ultrasound. CEA (p680) may be used to monitor disease and effectiveness of treatment (p680). If polyposis in family, refer for DNA testing once a patient is >15yrs old. Genetic testing may also help determine who will benefit from chemotherapy—see p512.

Staging:

see TABLE.

Spread

Local, lymphatic, by blood (liver, lung, bone) or transcoelomic.

Treatment[183]

Surgery

aims to cure. Exact technique may ↑survival times by up to 50% (eg in TME[1]): so expert training is vital. •**Right hemicolectomy** is for caecal, ascending or proximal transverse colon tumours. •**Left hemicolectomy** is for tumours in the distal transverse or descending colon. •**Sigmoid colectomy** is for tumours of sigmoid colon. •**Anterior resection** is for low sigmoid or high rectal tumours. Anastomosis is achieved at the first operation—stapling devices are safe and effective.[184] •**Abdomino-perineal (A-P) resection** is for tumours low in the rectum (≲8cm from anal canal): permanent colostomy and removal of rectum and anus (but see p568 for total anorectal reconstruction).

[1] TME = total mesorectal excision. It entails sharp dissection to yield an intact mesorectal envelope.

Radiotherapy

may be used pre-op in rectal cancer to ↓local recurrence and ↑5yr survival.[185] It may be associated with a higher rate of post-operative complication eg DVT, pathological fractures, fistulization.[186] Pre-op radiotherapy ± ***5-FU*** is also used to downstage initially unresectable rectal tumours. Post-op radiotherapy is only used in patients with rectal tumours at high risk of local recurrence.

Chemotherapy:

There is good evidence that ***5-FU*** ± other agents (eg ***folinic acid***, ***levamisole***) reduce Dukes' C mortality by ~25%.[187] The role of chemotherapy in Dukes' B tumours is under investigation. Chemotherapy is also used in palliation of metastatic disease; newer agents (eg ***irinotecan***, ***oxaliplatin***) may provide more options. Patients with single-lobe hepatic metastases and no extrahepatic spread may be suitable for curative surgery with liver resection.[188]

Prognosis

60% are amenable to radical surgery, and 75% of these will be alive at 7yrs (or will have died from other causes). Post-op anastomotic leakage has been shown to ↓survival rates in otherwise potentially curative operations.[189] Investigation for a suspected leak (↑T°, abdominal pain, peritonism) is with water-soluble contrast enema or CT with rectal contrast.

Polyps

are lumps that appear above the mucosa. There are 3 types:

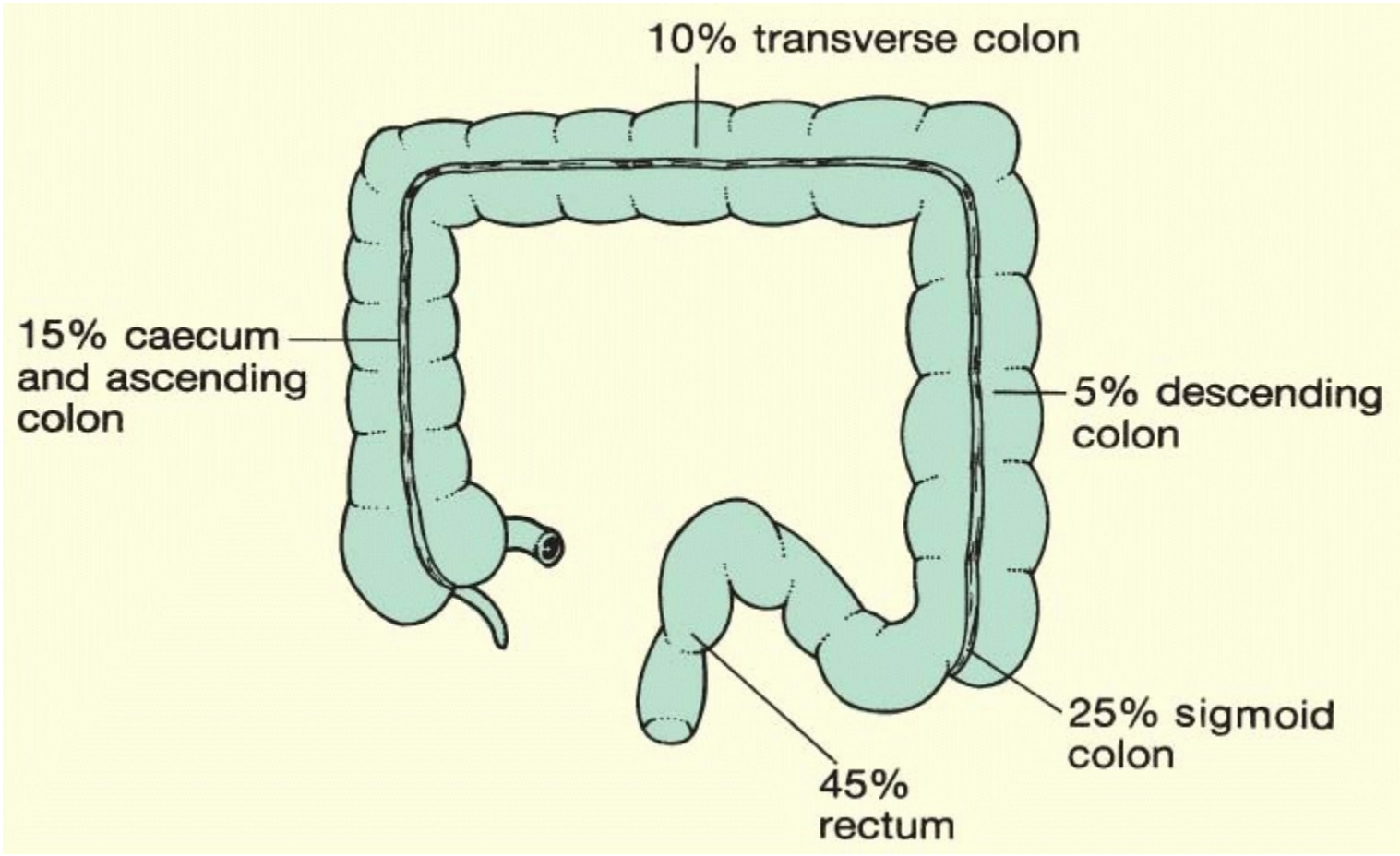
1. *Inflammatory:* Ulcerative colitis, Crohn's, lymphoid hyperplasia.
2. *Hamartomatous:* Juvenile polyps, Peutz-Jeghers' syndrome (p700).
3. *Neoplastic:* Tubular or villous adenomas: malignant potential, esp. if >2cm.

Symptoms of polyps:

Passage of blood/mucus PR. They should be biopsied and removed if they show malignant change. Most can be reached by the flexible colonoscope and diathermy can avoid the morbidity of partial colectomy. Check resection margins are clear of tumour.

Location of cancers of the large bowel

NB: These are averages: black females tend to have more proximal neoplasms. White men tend to have more distal neoplasms.



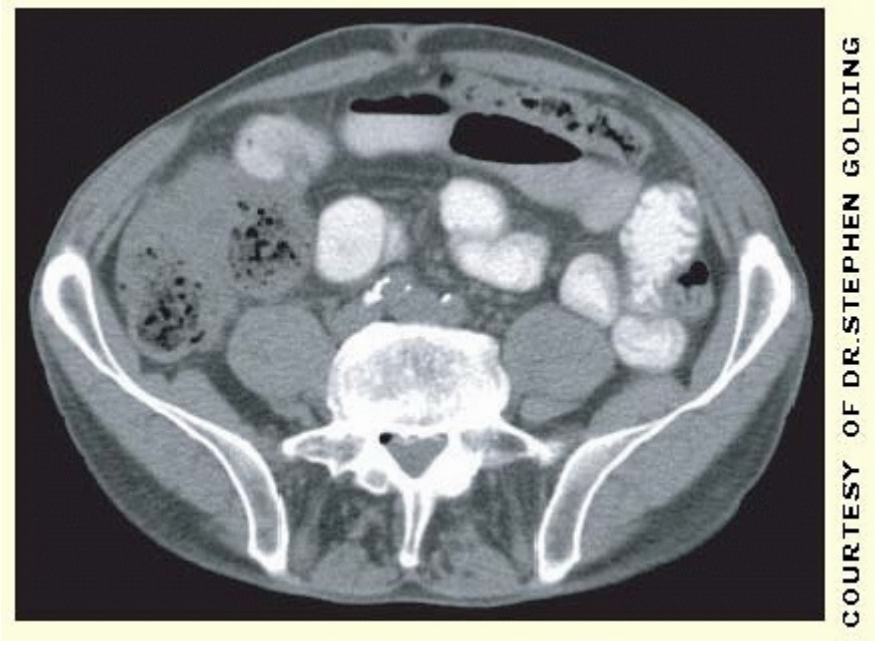


Fig 1. Axial CT of the abdomen with PO contrast medium showing thickening of the wall of the caecum (lying in the right iliac fossa) from

adenocarcinoma.

Dukes' classification for the staging of colorectal cancer

Stage	Description	Treated 5yr survival rate (%)
A	Confined to beneath muscularis mucosae	~90
B	Extension through muscularis mucosae	~65
C	Involvement of regional lymph nodes	~30
D	Distant metastases	<10

Examples of scenarios prompting urgent referral for surgeon's assessment within 2 weeks

- Rectal bleeding and a persistent change in bowel habit for >6wks.
- Persistent rectal bleeding without anal symptoms in those over 45yrs, with no obvious external evidence of benign anal disease.
- Iron-deficiency anaemia without an obvious cause and Hb <10g/dL.
- A palpable abdominal or rectal mass.
- Recent onset of looser stools and/or ↑frequency of defecation, persisting for >6wks. See p525 for review of the logic behind '2-week rules'.

Universal adult screening for colorectal cancer

▸A number of screening methods have been proposed.[190]

- *FOB* screening every 2yrs with home tests reduces mortality by 15-33%, but false +ve rates are high (up to 10% of those screened) and there are problems with acceptability. The patient has to be on a special diet while 2 out of 3 consecutive stool samples are tested. Sample rehydration improves sensitivity but increases false +ves.
- *Sigmoidoscopy* can be used to screen for left-sided lesions with 90% sensitivity and 99% specificity within the region of the scope. One recent RCT reported good tolerability and a pick-up rate of any cancer or adenoma of up to 8% in women and up to 12% in men.[191] Limitations include acceptability, cost, and not picking up right-sided lesions.
- *Colonoscopy* examines the **entire** colon and is the most accurate test. It is already used in those at ↑risk of colorectal cancer due to personal or family history, adenoma, or IBD. Perforation rate is higher than sigmoidoscopy (0.2% *vs* 0.01%) and limitations include cost, need for sedation, acceptability to patients, and the availability of trained endoscopists.

Carcinoma of the stomach

Incidence of adenocarcinoma at the gastro-oesophageal junction is increasing in the West, though incidence of distal & body gastric carcinoma has fallen sharply. It remains a tumour notable for its gloomy prognosis and non-specific presentation.

Incidence

23/100,000/yr in the UK, but there are unexplained wide geographical variations, being especially common in Japan. Associations:

- Blood group A
- *H. pylori* (p234)
- Atrophic gastritis; pernicious anaemia
- Adenomatous polyps
- Social class↓
- Smoking

Pathology

The adenocarcinoma may be polypoid, ulcerating, or leather bottle type (*linitis plastica*). Some are confined to mucosa and submucosa—so-called 'early' gastric carcinoma.

Presentation

Symptoms:

Often non-specific. Dyspepsia (p234) lasting >1 month in patients aged ≥55yrs demands GI investigation. Others: weight ↓, vomiting, dysphagia; anaemia.

Signs

suggesting incurable disease: epigastric mass, hepatomegaly; jaundice, ascites (p624); large left supraclavicular (Virchow's) node (=Troisier's sign); acanthosis nigricans (p546).

Spread

is local, lymphatic, blood-borne, and transcoelomic eg to ovaries (Krukenberg tumour).

Tests

Gastroscopy + multiple ulcer edge biopsies. ▸**Aim to biopsy all gastric ulcers as even malignant ulcers may appear to heal on drug treatment.** Endoscopic ultrasound (EUS) and CT/MRI are useful for staging. Staging laparoscopy is recommended for locally advanced tumours if metastases are not detected on other investigations.[192]

Treatment

See p636 for a description of surgical resections. For tumours in the distal? a partial gastrectomy may suffice, but, if more proximal, total gastrectomy may be needed. Combination chemotherapy (eg ***epirubicin***, ***cisplatin*** and ***5-fluorouracil***) appears to increase survival in advanced disease.[193] Endoscopic mucosal resection is used for early tumours confined to the mucosa.[194]

Palliation is often needed for obstruction, pain, or haemorrhage. In metastatic disease, chemotherapy increases quality of life and survival. Judicious use of surgery and radiotherapy may also be useful.

5yr survival

<10% overall, but nearly 20% for patients undergoing radical surgery. The prognosis is much better for 'early' gastric carcinoma.

Carcinoma of the oesophagus

Incidence

Australia <5/100,000/yr; UK <9; Brittany >50; Iran >100.

Risk factors:

Diet, alcohol excess, smoking, achalasia, Plummer-Vinson syndrome (p232), obesity, reflux oesophagitis ± Barrett's oesophagus (p686; there is a 44- fold ↑risk of adenocarcinoma if severe reflux for >10 years).

Site

20% occur in the upper part, 50% in the middle, and 30% in the lower part. They may be squamous cell or adenocarcinomas (incidence rising).

The patient

Dysphagia; weight↓; retrosternal chest pain; lymphadenopathy (rare).

Signs from upper from the upper third of the oesophagus:

Hoarseness; cough (may be paroxysmal if aspiration pneumonia). △△: See **Dysphagia**, p232.

Tests

Barium swallow, CXR, oesophagoscopy with biopsy/brushings/EUS, CT/MRI. Staging laparoscopy if significant infra-diaphragmatic component.

Staging:

TABLE.

Treatment

Survival rates are poor with or without treatment. If localized T1/T2 disease, radical curative oesophagectomy may be tried. Transhiatal oesophagectomy causes less morbidity than extended transthoracic resection, though the latter may be associated with ↑long-term survival. Pre-op chemotherapy (***cisplatin*** + ***5-FU***) improves survival but causes some morbidity.[195] Surgery alone may be preferable.[196] If surgery is **not** indicated, then chemo-radiotherapy may be better than radiotherapy alone.[197] Palliation in advanced disease aims to restore swallowing with chemo/radiotherapy, stenting, and laser use.

The multi-disciplinary cancer meeting

Over recent years there has been development of the multi-disciplinary meeting as an essential part of the care for patients with cancer. They are a result of the reform of cancer services across the UK, which aimed to improve quality of life for cancer sufferers by standardising and optimising screening, early detection and treatment of cancer.[198] At any meeting you should be able to spot:

- Paired surgeons and physicians (eg upper GI surgeon and gastroenterologist).
- Radiologists
- Pathologists
- Oncologists
- Specialist care nurses
- Meeting administrators

This expert forum aims to provide the most up-to-date and relevant options for treatment for each individual patient. However, despite everyone's best efforts, there can still remain an inherent uncertainty as to what is **exactly** the best treatment for the patient—something which in the end may only be known to the patient themselves when given the options.

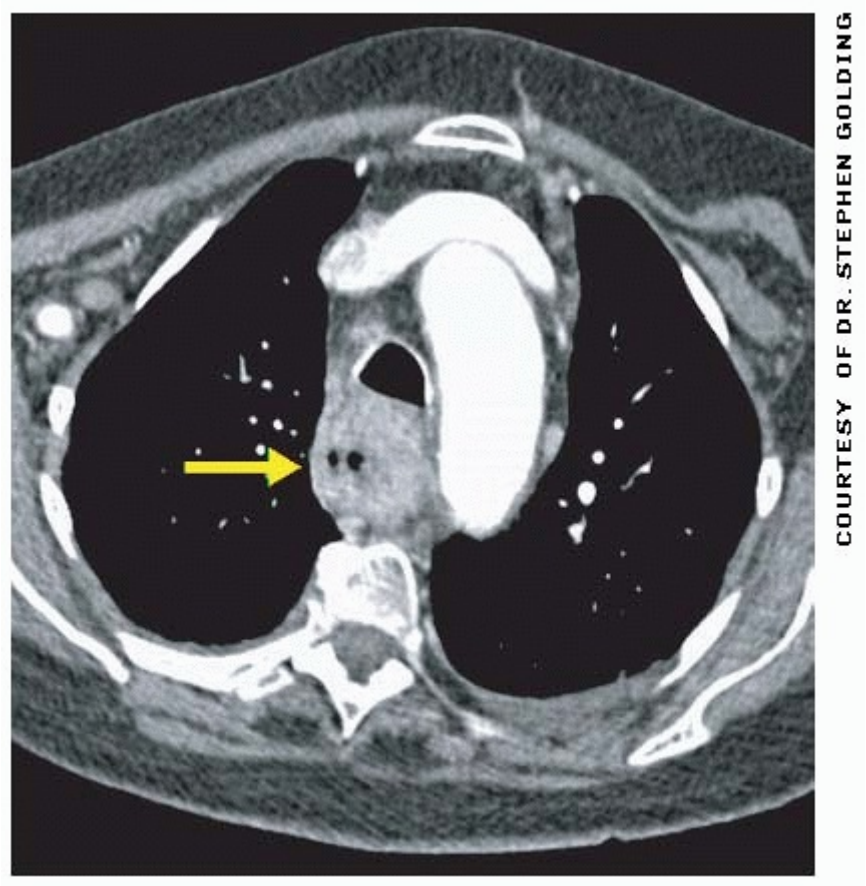


Fig 1. Axial CT of the chest after IV contrast medium showing concentric thickening of the oesophageus (arrow); the diagnosis here is oesophageal carcinoma. Loss of the fatty plane around the oesophagus suggests local invasion. Anterior to the oesophagus is the trachea and next to it is the arch of the aorta.

TNM staging in oesophageal cancer

Spread of oesophageal cancer is direct, by submucosal infiltration and local spread—or to nodes, or, later, via the blood.

T_{is}	carcinoma-*in-situ*	**Nx**	nodes cannot be assessed
T1	invading lamina propria/submucosa	**N0**	no node spread
T2	invading muscularis propria	**N1**	regional node metastases
T3	invading adventitia	**M0**	no distant spread
T4	invasion of adjacent structures	**M1**	distant metastasis

Lumps

▸Examine the regional lymph nodes as well as the lump. If the lump is a node, examine its area of drainage.

History

How long has it been there? Does it hurt? Any other lumps? Is it getting bigger? Ever been abroad? Otherwise well?

Physical exam

Remember the '**6 S'S:** site, size, shape, smoothness, surface, and surroundings.

Other questions:

Does it transilluminate (see below)? Is it fixed to skin or underlying structures (see BOX)? Is it fluctuant? Lumps in certain sites call to mind particular pathologies (see lumps in groin and scrotum, p618). Remember to feel if a lump is pulsatile; this may seem to be a minor detail until faced with a surprise on a minor operations list—assessment with US duplex may help.

Transilluminable lumps

After eliminating as much external light as possible, place a bright, thin 'pencil' torch on the lump, from behind, so the light is shining through the lump towards your eye. If the lump glows red it is said to transilluminate—a fluid-filled lump such as a hydrocele is a good example.

Lipomas

These benign fatty lumps, occurring wherever fat can expand (ie **not** scalp or palms), have smooth, imprecise margins, and a hint of fluctuance. They only cause symptoms via pressure. Malignant change is very rare (suspect if rapid growth, hardening, or vascularization). Multiple scattered lipomas, which may be painful, occur in Dercum's disease, typically in postmenopausal women.[199]

Sebaceous cysts

These are intradermal, so you cannot draw the skin over them. Look for the characteristic punctum marking blocked sebaceous outflow. Infection is quite common, and foul pus exits through the punctum.

Treatment:

Shelling them out whole can be tricky: learn from an expert.

Causes of lymph node enlargement

Infection:

Glandular fever; brucellosis; TB; HIV; toxoplasmosis; actinomycosis; syphilis.

Infiltration:

Malignancy (carcinoma, lymphoma); sarcoidosis.

Cutaneous abscesses

Staphylococci are the most common organisms. Haemolytic *Streptococci* are only common in hand infections. *Proteus* is a common cause of non-staphylococcal axillary abscesses. Below the waist faecal organisms are common (aerobes and anaerobes).

Treatment:

Incision and drainage alone usually cures.

Boils (furuncles)

are abscesses which involve a hair follicle and its associated glands.

A carbuncle

is an area of subcutaneous necrosis which discharges itself on to the surface through multiple sinuses. Think of *hidradenitis suppuritiva* if there are recurrent inguinal or axillary abscesses.

Rheumatoid nodules

are collagenous granulomas which appear in established rheumatoid arthritis on the extensor aspects of joints—especially the elbows.

Ganglia

These are degenerative cysts from an adjacent joint or synovial sheath commonly seen on the dorsum of the wrist or hand and dorsum of the foot. They may transilluminate. 50% will disappear spontaneously. Aspiration may be effective, especially when combined with instillation of steroid and **hyaluronidase**.$_{200}$ For the rest, the treatment of choice is excision rather than the traditional blow from your bible (the *Oxford Textbook of Surgery*!).

Fibromas

These may occur anywhere in the body, but most commonly under the skin. These whitish, benign tumours contain collagen, fibroblasts, and fibrocytes.

Dermoid cysts

contain dermal structures; found at the junction of embryonic cutaneous boundaries eg in the midline or lateral to the eye.

Malignant tumours of connective tissue

include the fibrosarcoma, liposarcoma, leiomyosarcoma (smooth muscle), and rhabdomyosarcoma (striated muscle). Sarcomas are staged using a modified TNM system which includes tumour grade. Needle-core (Trucut®) biopsies of large tumours precede excision. Any lesion suspected of being a sarcoma should not be simply enucleated in what might wrongly be considered a 'conservative' procedure. ▸Refer to a specialist.

In or under the skin?
Intradermal

- Sebaceous cyst
- Abscess
- Dermoid cyst
- Granuloma

Subcutaneous

- Lipoma

- Ganglion
- Neuroma
- Lymph node

If a lump is intradermal, you cannot draw the skin over it, while if the lump is subcutaneous you should be able to manipulate it independently from the skin.

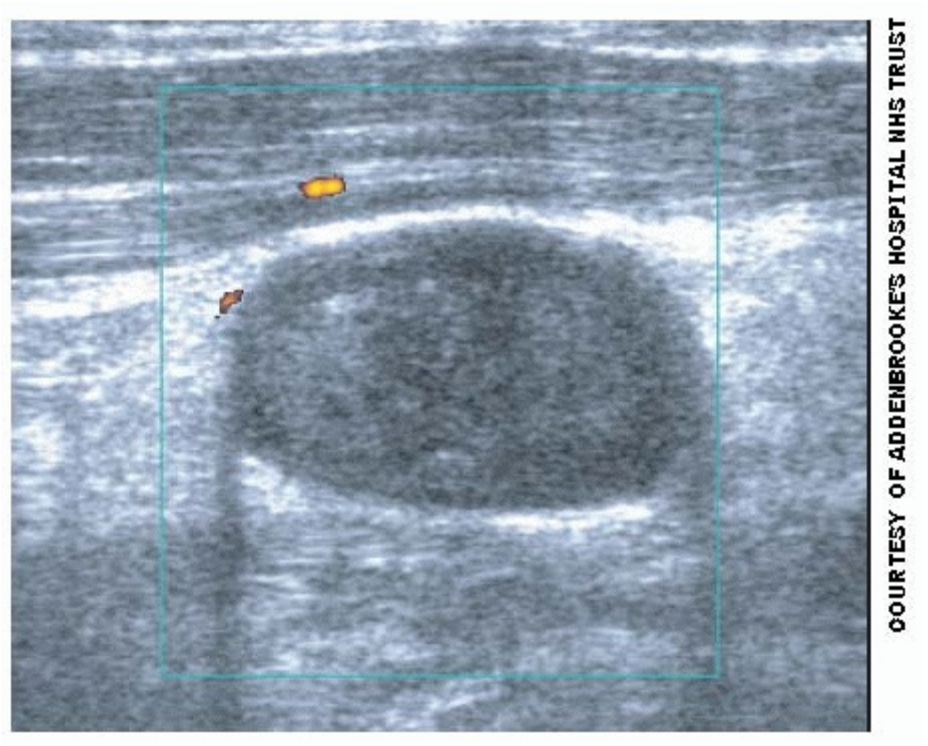


Fig 1. Ultrasound of a malignant lymph node. A sign of malignant infiltration is loss of the fatty hilum. Duplex mode (within the green box) shows loss of the normal hilar vascularity.

Salivary gland pathology

There are 3 pairs of major salivary glands: parotid, submandibular, and sublingual (there are also numerous minor glands).

History:

Lumps; swelling related to food; pain; taste; dry eyes.

Examination:

Note external swelling; look for secretions; bimanual palpation for stones. Examine VIIth nerve and regional lymph nodes.

Cytology:

This may be ascertained by FNA.

Recurrent unilateral pain and swelling

is likely to be due to a stone. 80% are submandibular. The classical story is of pain and swelling on eating— with a red, tender, swollen, but uninfected gland. The stone may be seen on plain x-ray or by sialography. Distal stones are removed via the mouth but deeper stones may require excision of the gland.

Chronic bilateral symptoms

may coexist with dry eyes and mouth and autoimmune disease, eg Mikulicz's or Sjögren's syndrome (p698 & p702).

Fixed swellings

may be from tumour, sarcoid, or are idiopathic.

Salivary gland tumours:

'80% are in the parotid, 80% of these are pleomorphic adenomas, 80% of these are in the superficial lobe.' ▸Any salivary gland swelling must be removed for assessment if present for >1 month. VIIth nerve palsy signifies malignancy.

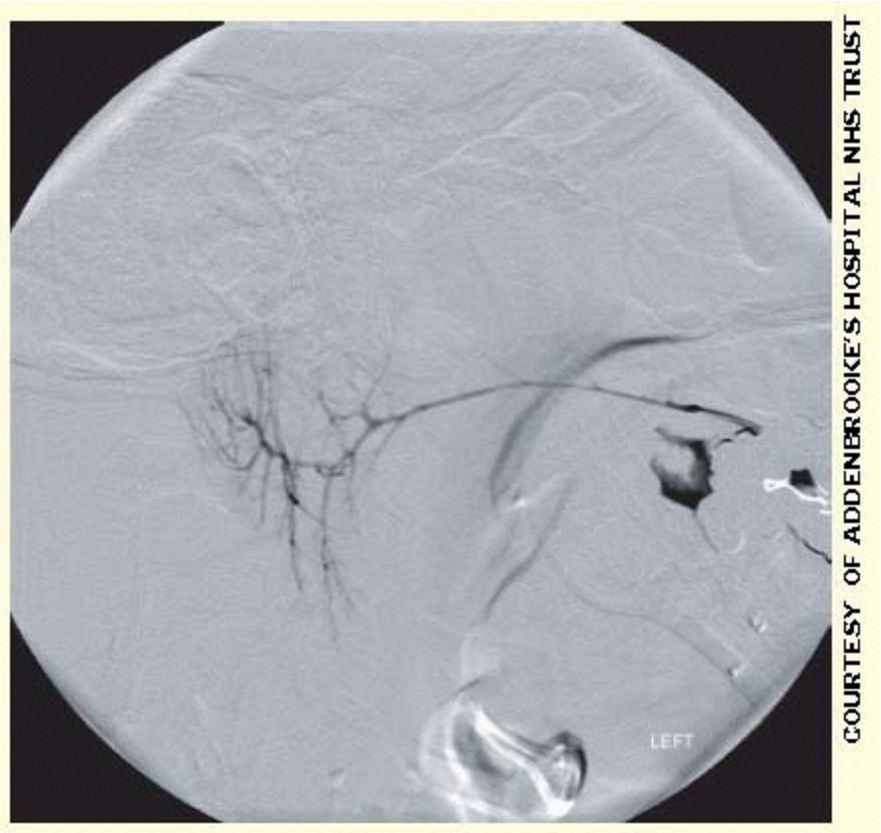


Fig 1. Normal sialogram of the parotid gland. The parotid duct (Stensen's duct) opens into the mouth opposite the 2nd upper molar.

Benign or malignant	Malignant	Malignant
Cystadenolymphoma	Mucoepidermoid	Squamous or adeno Ca
Pleomorphic adenoma	Acinic cell	Adenoid cystic Ca

Pleomorphic adenomas often present in middle age and grow slowly. Remove by superficial parotidectomy. Adenolymphomas: usually older men; soft; treat by enucleation. Carcinomas: rapid growth; hard fixed mass; pain; facial palsy. Treatment: surgery + radiotherapy. Surgery complications:

1. Facial palsy. Have a facial nerve stimulator in theatre to aid identification.
2. Salivary fistula (often close spontaneously).
3. Frey's syndrome (gustatory sweating);[1] interposition of a soft-tissue flap at surgery may be preventative. *201* Tympanic neurectomy may also help.

Lumps in the groin and scrotum

▸Any lump within the tunica vaginalis is cancer until proved otherwise.

▸Acute, tender enlargement of the testis is torsion (p600) until proved otherwise.

Diagnosing groin lumps:

See BOX.

Diagnosis of lumps in the scrotum:

1. *Can you get above it?* If not, it is an inguinoscrotal hernia (inguinal hernia extending into scrotum, p632), or a hydrocoele extending proximally (see below).
2. *Is it separate from the testis?*
3. *Is it cystic or solid?* (Does it transilluminate? See p616.)
   - Separate and cystic—epididymal cyst.
   - Separate and solid—epididymitis (may also be orchitis).
   - Testicular and cystic—hydrocele.

▸ Testicular and solid—**tumour**, orchitis, granuloma (p178), gumma (p419). Ultrasound may help in sorting out testis tumours from other lumps (fig 1). Do not assume that an injured testis was normal before the injury: this is not a rare mode of tumour presentation; ultrasound may help here.

Epididymal cysts

usually develop in adulthood and contain clear or milky (spermatcele) fluid. They lie above and behind the testis. Remove if symptomatic.

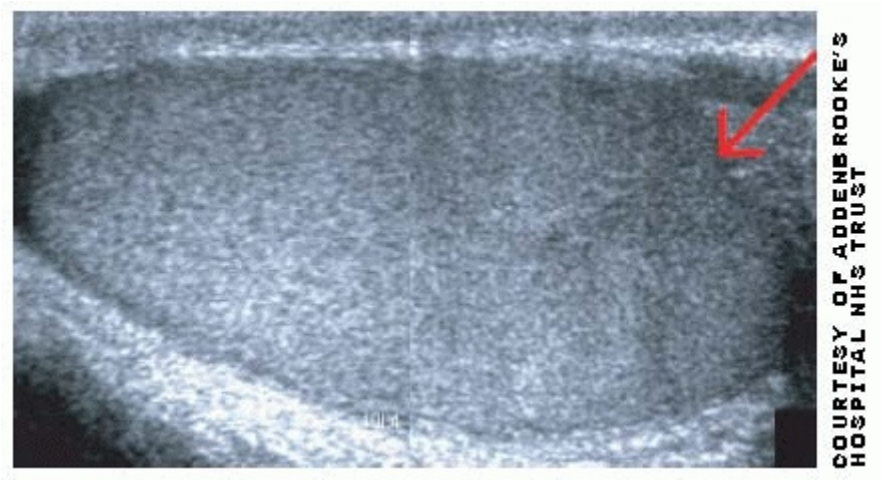


Fig 1. US of the testis; there is heterogeneity (arrow) at the lower pole suggesting a tumour.

Hydroceles

(fluid within the tunica vaginalis) may be *primary* (associated with a patent processus vaginalis, which typically resolves during the 1st year of life) or *secondary* to testis tumour, trauma, or infection. Primary hydroceles are more common, larger, and usually develop in younger men. Treat by surgery or aspiration (may need repeating) ▸Is the testis normal after aspiration? If *any* doubt, do ultrasound.

Epididymo-orchitis

Causes: *Chlamydia* (eg if >35yrs); *E. coli*; mumps; *N. gonorrhoea*; TB. The area is usually tender. Take a urine sample; look for urethral discharge. A '1st catch' may be more helpful than an MSU. Consider a GUM screen. Warn about possible infertility 202 and that symptoms worsen before they improve.

[prescription take]:

If <35yrs; ***doxycycline*** 100mg/12h PO for 10d (covers chlamydia; treat sexual partners). 203 If >35yrs old, associated UTI is common so try ***ofloxacin*** 300mg/12h PO for 10d. 204

Testis tumours

are the commonest malignancies in males aged 15-44.

Varieties:

Seminoma (30-65yrs); 205 teratoma (20-30yrs); tumours of Sertoli or Leydig cells; lymphoma. ~10% of malignancies occur in undescended testes, even after orchidopexy. A contralateral tumour is found in 5%.

Typical presentation:

Painless testicular lump, noticed after trauma or infection.

Risk factors:

Undescended testis; infant hernia; infertility.

Staging

is essential: **1** No evidence of metastasis. **2** Infradiaphragmatic node involvement (spread is via the para-aortic nodes and **not** inguinal nodes). **3** Supradiaphragmatic node involvement. **4** Lung involvement (haematogenous).

Tests:

(To allow staging) CXR, CT, excision biopsy. α-fetoprotein (eg >3iu/mL)[1] and β-human chorionic gonadotrophin (β-HCG) are useful tumour markers and help monitor treatment; check **before** and **during** treatment.

Treatment:

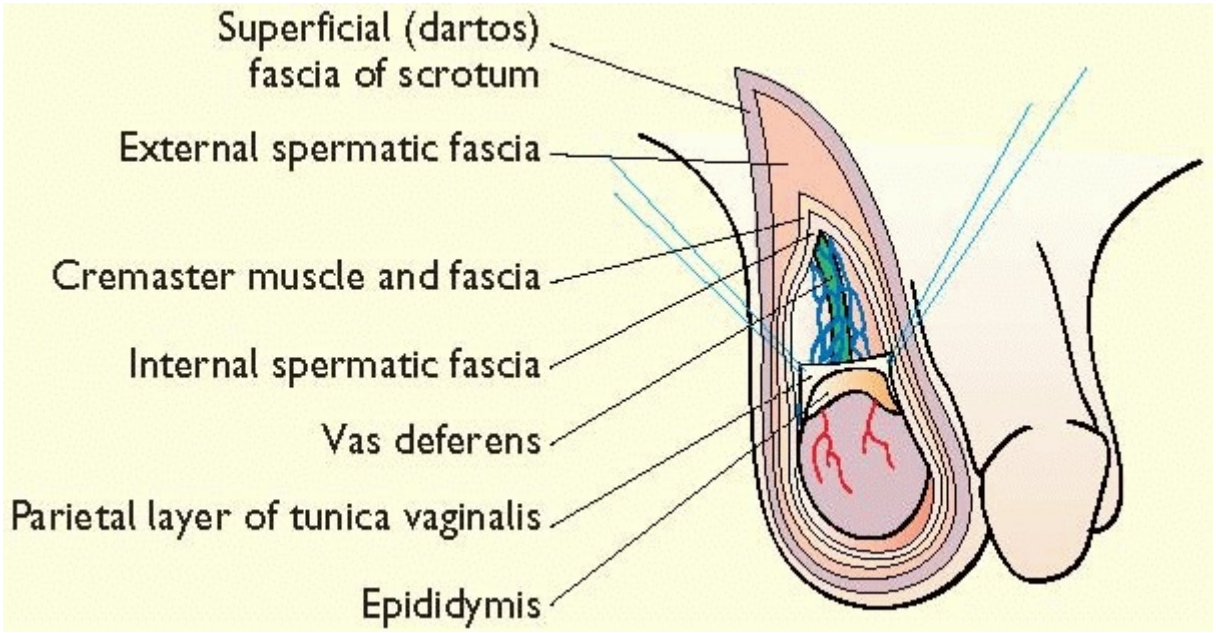
Orchidectomy (inguinal incision; occlude the spermatic cord before mobilization to ↓risk of intra-operative spread). Options are constantly updated (surgery, radiotherapy, chemotherapy). Seminomas are exquisitely radiosensitive. Stage 1 seminomas: orchidectomy + radiotherapy gives a cure rate of ~95%. Do close follow-up to detect relapse. Cure of teratomas, even if metastases are present, is achieved by 3-4 cycles of ***bleomycin*** + ***etoposide*** + ***cisplatin***. Prevention of late presentation: self-examination. 5yr survival >90% in all groups.

Diagnosing groins lumps: lateral to medial thinking

- Psoas abscess—may present with back pain, limp and swinging pyrexia
- Neuroma of the femoral nerve
- Femoral artery aneurysm
- Saphena varix—like a hernia, it has a cough impulse
- Lymph node
- Femoral hernia
- Inguinal hernia
- Hydrocele or varicocele1

Also consider an undescended testis (cryptorchidism).

The layers of fascia in the scrotum



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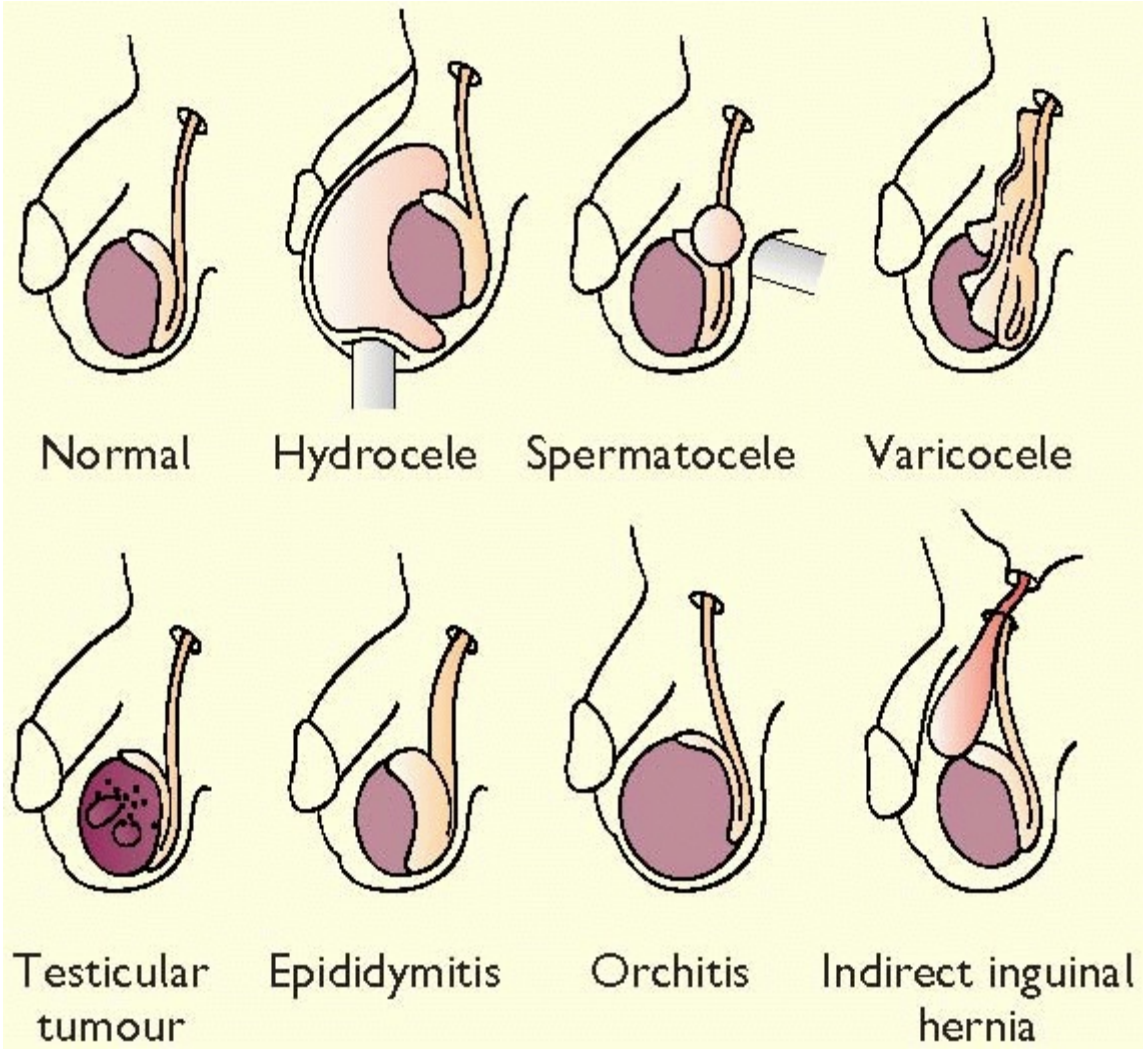
Diagnosis of scrotal masses[1]



After RD Judge, GD Zuidema, FT Fitzgerald Clinical Diagnosis 5th edn, Little, Brown, Boston

[1] A varicocele is formed by dilated veins in the pampiniform plexus of the spermatic cord, often visible as distended scrotal blood vessels that feel like 'a bag of worms'. They are associated with subfertility, but repair (via surgery or embolization) seems to have little effect on subsequent pregnancy rates.

Lumps in the neck

▸Don't biopsy lumps until tumours within the head and neck have been excluded by an ENT surgeon. Culture all biopsied lymph nodes for TB.

Diagnosis

First of all, ask how long the lump has been present. If <3wks, self-limiting infection is the likely cause and extensive investigation is unwise. Next ask yourself where the lump is. Is it intradermal—eg sebaceous cyst with a central punctum (p616)? Is it a lipoma (p616)? If the lump is not intradermal, and is not of recent onset, you are about to start a diagnostic hunt over complicated terrain:

Midline lumps:

• If patient is <20yrs old, the likely diagnosis is a *dermoid cyst* (p616). • If it moves **up** on protruding the tongue and is below the hyoid, it is likely to be a *thyroglossal cyst* (fluctuant lump developing in cell rests in thyroid's migration path; treatment: surgery; they are the commonest congenital cervical cystic lump). • In patients >20yrs old, it is probably a *thyroid isthmus* mass. • If it is bony hard, the diagnosis may be a *chondroma*.

Submandibular triangle:

(Below jaw; above anterior belly of digastric.) • If <20yrs, self-limiting lymphadenopathy is likely. If >20yrs, exclude *malignant lymphadenopathy* (eg firm, and non-tender). ▸Is TB likely? • If it is not a node, think of submandibular *salivary stone*, *sialadenitis*, or *tumour*.

Anterior triangle:

(Below digastric and in front of sternocleidomastoid.) Nodes are common (see above): examine the areas which they serve (skin, mouth, throat, thyroid; is the spleen enlarged?—this may indicate lymphoma). • *Branchial cysts* emerge under the anterior border of sternocleidomastoid where the upper third meets the middle third (age <20yrs). They are due to non-disappearance of the cervical sinus (where the 2nd branchial arch grows down over the 3rd and 4th). Lined by squamous epithelium, their fluid contains cholesterol crystals. Treat by excision. There may be communication with the pharynx in the form of a fistula. • *Cystic hygromas* arise from the jugular lymph sac and transilluminate brightly. Treat by surgery or hypertonic saline sclerosant injection. Recurrence can be troublesome. • If the lump is in the supero-posterior area of the anterior triangle, is it a *parotid tumour* (more likely if >40yrs)? • *Laryngoceles* are an uncommon cause of anterior triangle lumps. They are painless and may be made worse by blowing. These cysts are classified as

external, internal, or mixed, and may be associated with laryngeal cancer. • *Carotid body tumours* (chemodectoma) are very rare, move from side to side but not up and down, and splay out the carotid bifurcation. It is usually firm and occasionally soft and pulsatile. It does not usually cause bruits. It may be bilateral, familial, and malignant (5%). This tumour should be suspected in masses just anterior to the upper third of sternomastoid. Diagnose either by duplex ultrasonography (looking for splaying at the carotid bifurcation) or digital computer angiography. Treatment is extirpation by a vascular surgeon.

Posterior triangle:

(Behind sternocleidomastoid, in front of trapezius, above clavicle.) • If there are many small lumps, think of *nodes*—TB, viruses such as HIV or EBV (infectious mononucleosis), any chronic infection or, if >20yrs, consider lymphoma or metastases eg from GI or bronchial or head and neck neoplasia.[1] • *Cervical ribs* may intrude into this area. • *Pharyngeal pouches* can protrude into the posterior triangle on swallowing—see **fig 1**.

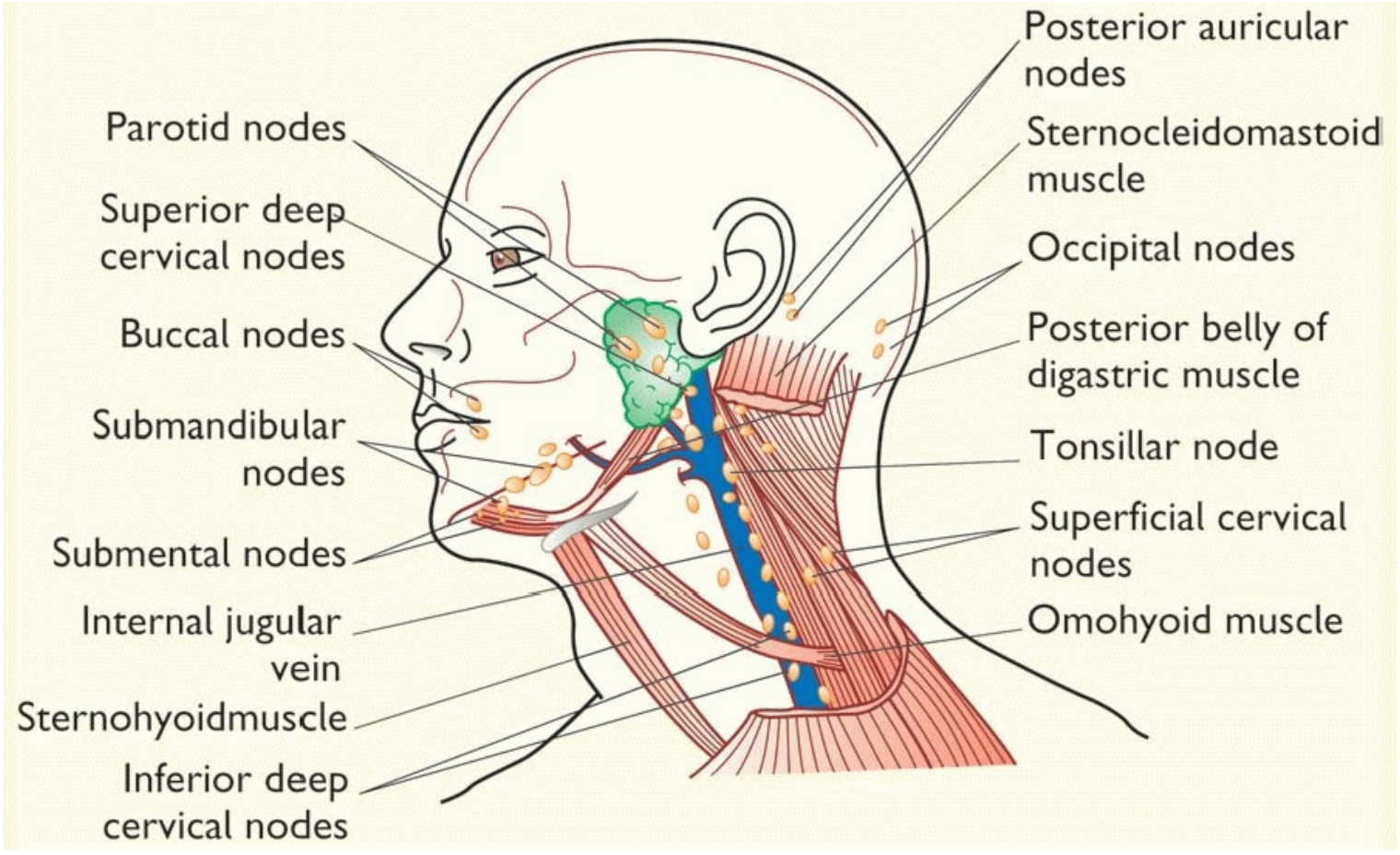
[1] In young Asian women **Kikuchi's disease** (necrotising lymphadenitis) is a rare and benign cause of cervical lymphadenopathy. Diagnosis is made on excision biopsy.

Tests

Ultrasound shows lump consistency: cystic, solid, complex, vascular. CT defines masses in relation to their anatomical neighbours. Do virology and Mantoux test. CXR may show malignancy or reveal bilateral hilar lymphadenopathy; here you should consider sarcoid. Consider fine-needle aspiration (FNA)—►but remember the opening caveat.

See BOX on p617 for *Salivary gland pathology*.

The distribution of lymph nodes in the head and neck



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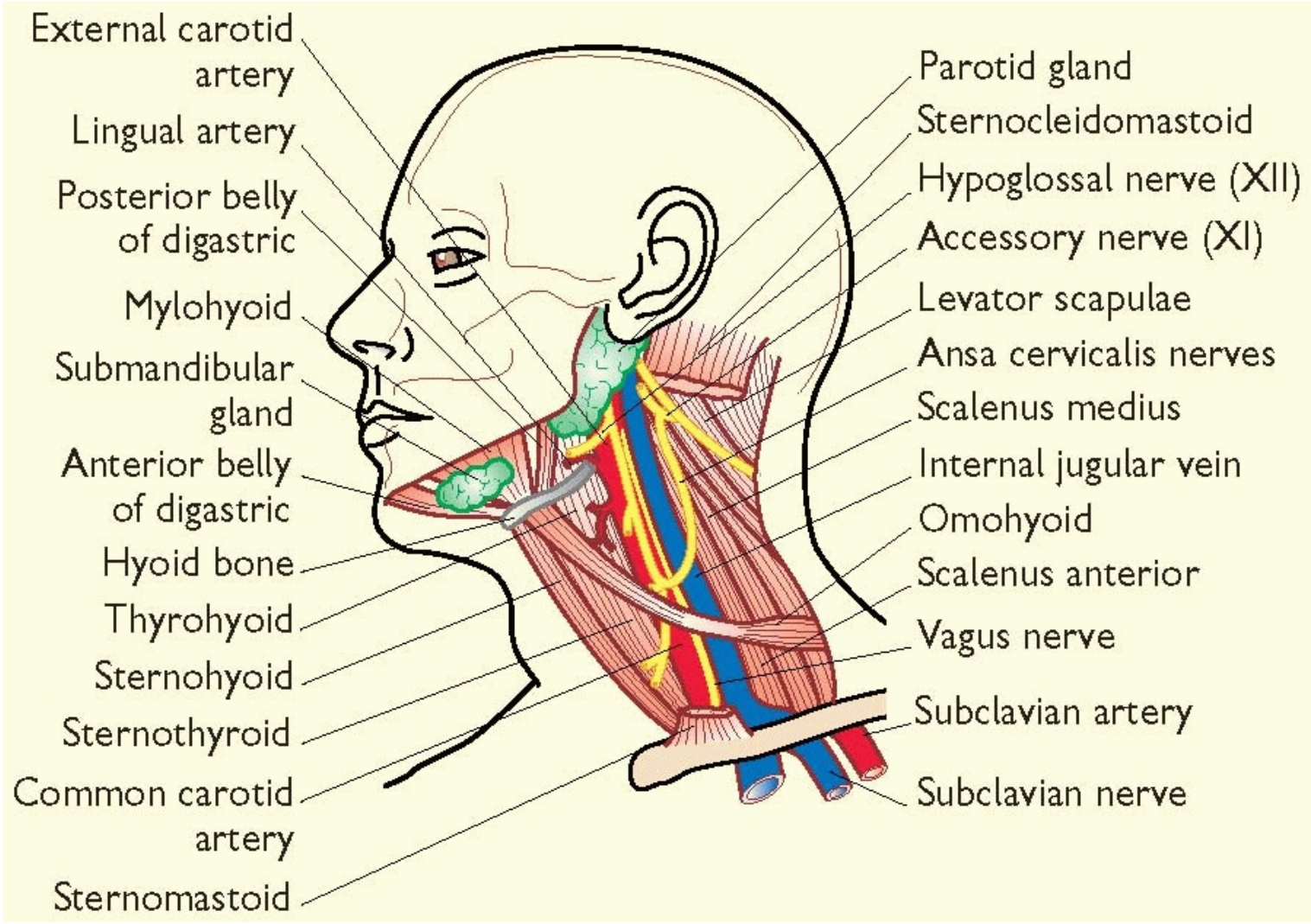
Important relations to the carotid artery and internal jugular vein in the neck



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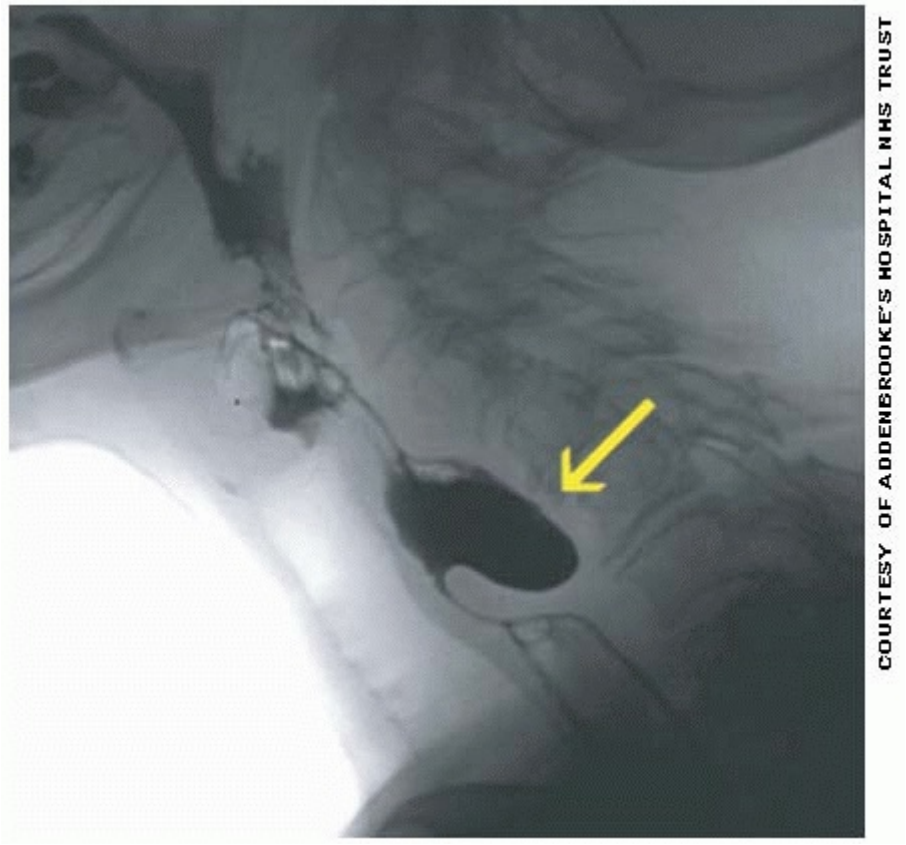


Fig 1. Contrast swallow study showing a pharyngeal pouch (arrow). It is a pulsion diverticulum that protrudes between the fibres of the inferior pharyngeal constrictor muscle. The patient may have a history of halitosis, sore throats and regurgitation of undigested food. As the pouch enlarges, there may be dysphagia as it presses against the oesophagus. These symptoms usually precede a palpable swelling in the neck which, if felt, would emanate from behind the trachea and sternocleidomastoid.

Lumps in the thyroid

Examination

Watch the neck whilst the patient swallows water. Stand behind and feel thyroid for size, shape (smooth?, one or many nodules?), tenderness, and mobility. Ask the patient to swallow again. Percuss for retrosternal extension. Any lymph nodes or bruits? If the thyroid is enlarged (goitre), ask yourself 3 questions:

1. Is the thyroid smooth or nodular?
2. Is the patient euthyroid, thyrotoxic (p202), or hypothyroid (p204)?

   Smooth, non-toxic goitre: Endemic (iodine deficiency); congenital; goitrogens; thyroiditis; physiological; Hashimoto's thyroiditis (an autoimmune disease thought to be due to apoptosis induced by lymphocytes bearing Fas ligands combining with thyrocytes bearing Fas).

   Smooth, toxic goitre: Graves' disease—see **fig 1**.
3. Any nodules? Many or one? If >4cm across, malignancy is more likely. *Multinodular goitre:* Usually euthyroid but hyperthyroidism may develop. Hypothyroidism and malignancy are rare.

Single thyroid lump

is a common problem; ~10% will be malignant. First ask: Is he/she thyrotoxic? • Do T3 & T4. • Ultrasound (**fig 2**), to see if the lump is solid, cystic, complex or part of a group of lumps. • Radionuclide scans may show malignant lesions as hypofunctioning or 'cold', whereas a hyper-functioning 'hot' lesion suggests adenoma. • FNA (fine needle aspiration) and do cytology on the fluid. ▸No clinical/lab test is good enough to tell for sure if follicular neoplasms found on FNA are benign, so such patients are normally referred for surgery.[206]

Single thyroid lump

- Cyst
- Adenoma
- Malignancy
- Discrete nodule in multi-nodular goitre

What should you do if high-resolution ultrasound shows impalpable nodules?

Such thyroid nodules can usually just be observed provided they are:

- <1cm across (which is most; ultrasound can detect lumps <2mm; such 'incidentalomas' occur in 46% of routine autopsies) and asymptomatic.
- There is no past history of thyroid cancer or radiation.
- No family history of medullary cancer. (If any present, do ultrasound-guided FNA; excise if cytology is malignant.)

Thyroid neoplasia 207

There are 5 types:

1. *Papillary:* 60%. Often in young. Spread: nodes & lung. [prescription take]: total thyroidectomy to remove non-obvious tumour ± node excision ± radioiodine (^{131}I) to ablate residual cells may all be needed. Give T4 to suppress TSH. Prognosis: better if young & ♀.
2. *Follicular:* ≤25%. Middle-aged, spreads early via blood (bone, lungs). Welldifferentiated. [prescription take]: total thyroidectomy + T4 suppression + radioiodine ablation.
3. *Medullary:* 5%. Sporadic (80%) or part of MEN syndrome (p207). May produce calcitonin. They do not concentrate iodine. ▸Perform a phaeochromocytoma screen pre-op. Do thyroidectomy + node clearance. External beam radiotherapy should be considered to prevent regional recurrence.
4. *Lymphoma:* 5%. ♀:♂≈3:1. May present with stridor or dysphagia. Do full staging pre-treatment (chemoradiotherapy). Assess histology for mucosaassociated lymphoid tissue (MALT) origin (associated with a good prognosis).
5. *Anaplastic:* Rare. ♀:♂≈3:1. Elderly, poor response to any treatment. In the absence of unresectable disease, excision + radiotherapy may be tried.

Thyroid surgery

Indications:

Pressure symptoms, hyperthyroidism, carcinoma, cosmetic reasons. Render euthyroid pre-op with antithyroid drugs and/or ***propranolol***. Check vocal cords by indirect laryngoscopy pre- and post-op.

Complications:

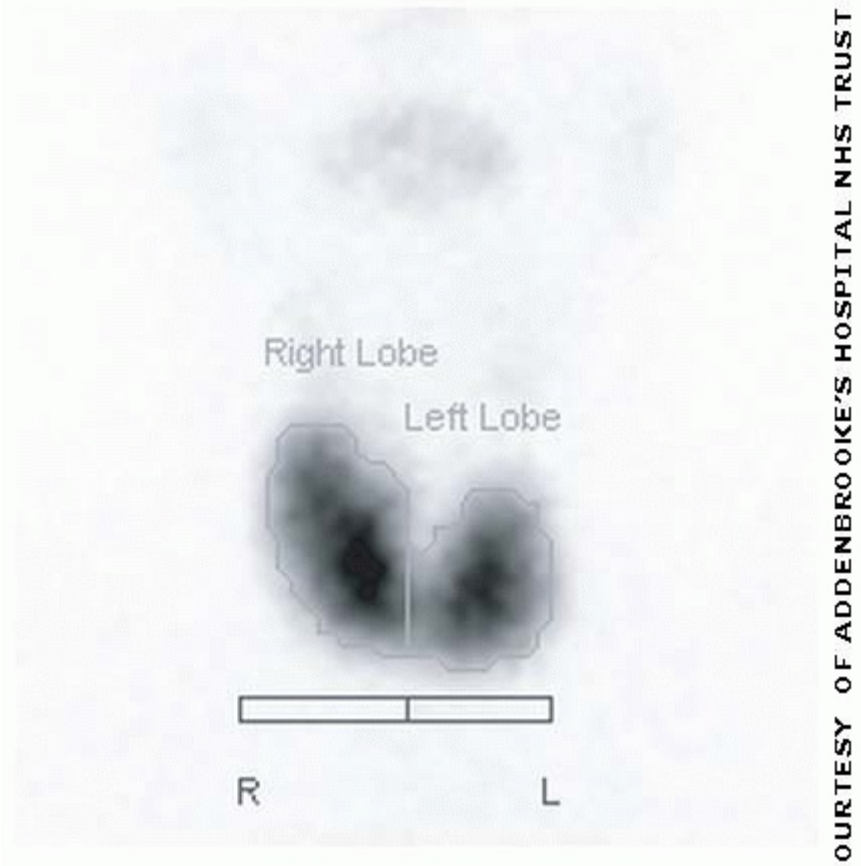
Also see p566.

Early:

Recurrent laryngeal nerve palsy, haemorrhage (▸▸if compresses airway, instantly remove sutures for evacuation of clot); hypoparathyroidism (check plasma Ca^{2+} daily; there is commonly a transient drop in serum concentration); thyroid storm (symptoms of severe hyperthyroidism—treat by ***propranolol*** PO or IV, antithyroid drugs, and iodine, p816).

Late:

Hypothyroidism; recurrent hyperthyroidism.



BOTH IMAGES COURTESY OF ADDENBROOKE'S HOSPITAL NHS TRUST

Fig 1. Radionuclide study of the thyroid showing changes consistent with Graves' disease (see also **Nuclear Medicine**, p724). There is increased uptake of the radionuclide trace throughout both lobes of the gland (right>left in this image).

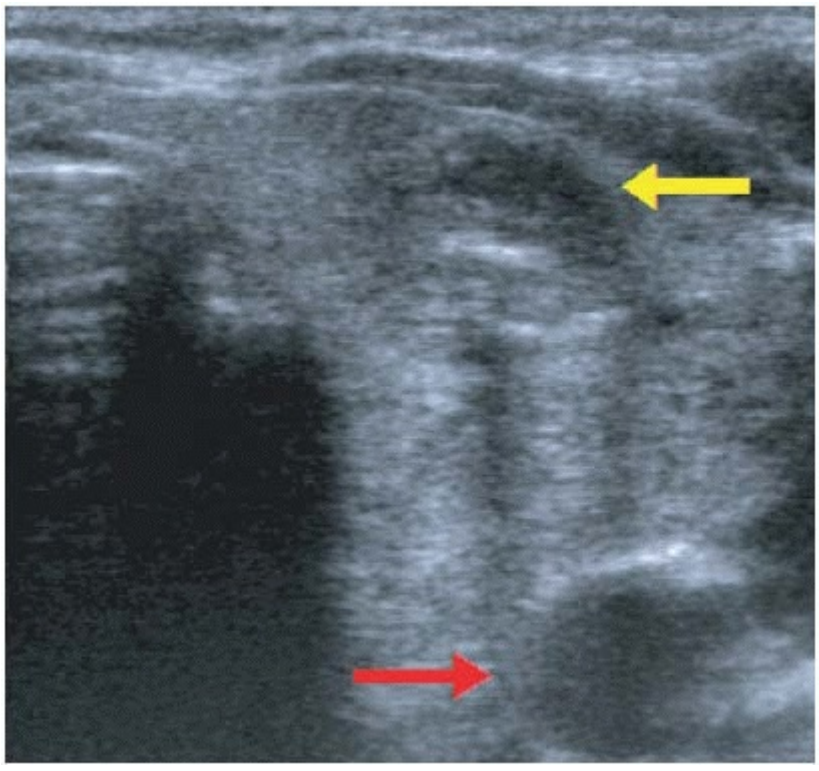
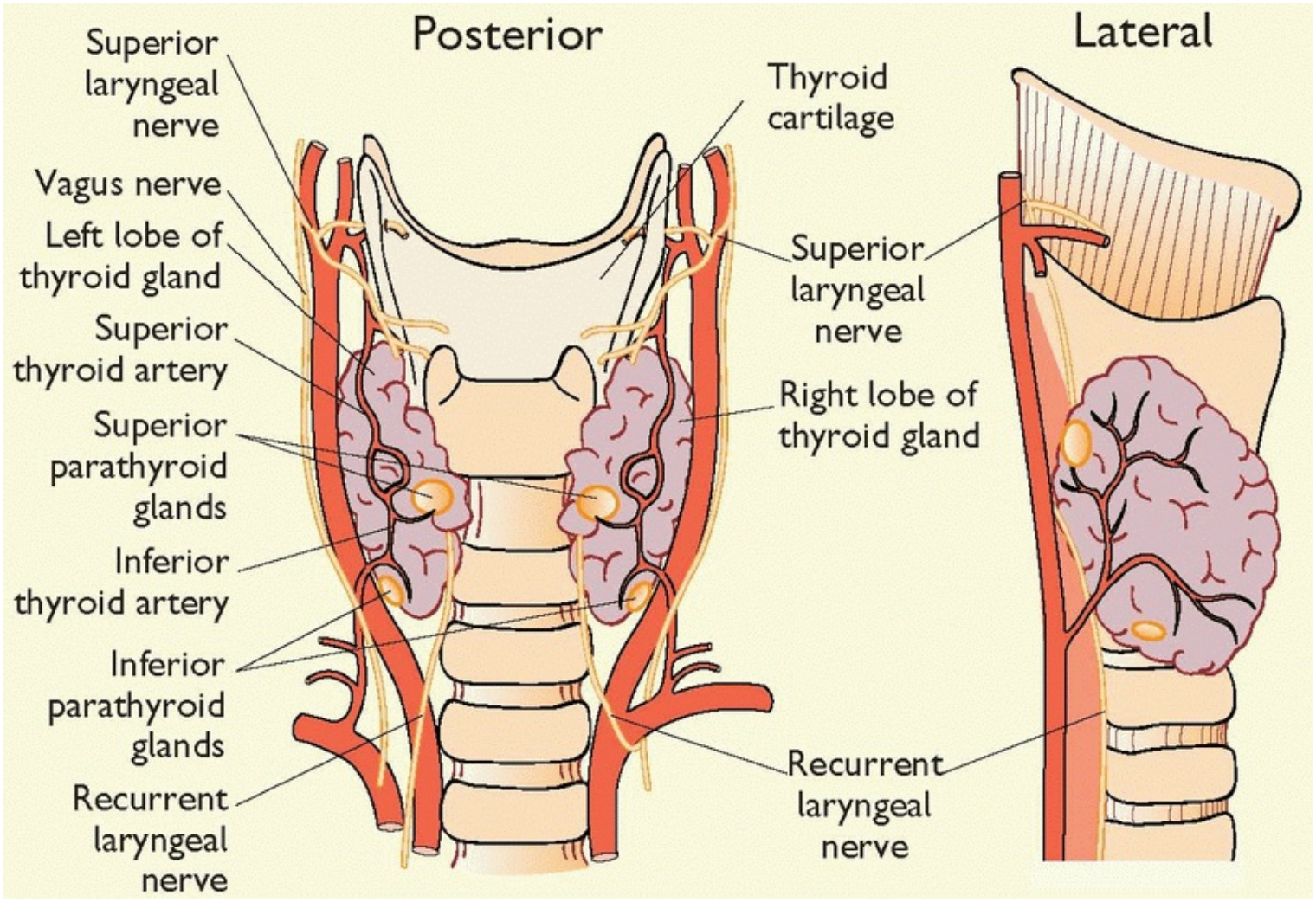


Fig 2. Transverse ultrasound of the left lobe of the thyroid showing a heterogeneous but mainly cystic lesion (yellow arrow). Note the proximity of the internal jugular vein to the gland (red arrow). Careful dissection is required during surgery to avoid the vital structures that surround the thyroid.

The anatomy of the region of the thyroid gland



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The important structures that must be considered when operating on the thyroid gland include:

- Recurrent laryngeal nerve
- Superior laryngeal nerve
- Parathyroid glands
- Trachea
- Common carotid artery
- Internal jugular vein (not depicted-see fig 2).

After RCSI website

Abdominal masses

As with any mass, determine size, site, shape, and surface. Find out if it is pulsatile and if it is mobile. Examine supraclavicular and inguinal nodes. Is the lump ballottable (like bobbing an apple up and down in water)?

Right iliac fossa masses:		
• Appendix mass/abscess	• Intussusception	• Transplanted kidney (**fig 1**)

• Caecal carcinoma	• TB mass	• Kidney malformation
• Crohn's disease	• Amoebic abscess	• Tumour in an undescended testis
• Pelvic mass (see below)	• Actinomycosis (p409)	

Abdominal distension

Flatus, fat, fluid, faeces, or fetus (p52)? Fluid may be outside the gut (ascites) or sequestered in bowel (obstruction; ileus). To demonstrate ascites elicit signs of a fluid thrill and/or shifting dullness (p41).

Causes of ascites:		*Ascites with portal hypertension:*	
• Malignancy★	• CCF; pericarditis	• Cirrhosis	• Portal nodes
• Infections★—esp TB	• Pancreatitis★	• Budd-Chiari syndrome★ (p688)	
• ↓Albumin (eg nephrosis)	• Myxoedema	• IVC or portal vein thrombosis	

Tests:

Aspirate ascitic fluid (paracentesis, p753) for cytology, culture, & protein level ($\gtrsim$30g/L in diseases marked★) with a 21G needle in RIF (p752); ultrasound. Protein level rarely helps diagnostically; it tends to rise with diuretic therapy.

Left upper quadrant mass

Is it spleen, stomach, kidney, colon, pancreas, or a rare cause (eg neurofibroma)? Pancreatic cysts may be true (congenital; cystadenomas; retention cysts of chronic pancreatitis; cystic fibrosis) or pseudocysts (fluid in lesser sac from acute pancreatitis).

Splenomegaly

Causes are often said to be **infective**, **haematological**, **neoplastic**, etc., but grouping by **associated feature** is more useful clinically:

Splenomegaly with fever	*With lymphadenopathy*	*With purpura*

- Infection[HS] (malaria, SBE/IE hepatitis,[HS] EBV,[HS] TB, CMV, HIV)
- Glandular fever[HS]
- Leukaemias; lymphoma
- Septicaemia; typhus
- DIC; amyloi
- Sarcoid; malignancy[HS]
- Sjögren's syndrome
- Meningococcaemia

With arthritis

- Sjögren's syndrome
- Rheumatoid arthritis; SLE
- Infection, eg Lyme (p418)
- Vasculitis/Behçet's (p542)

With ascites

- Carcinoma
- Portal hypertension[HS]

With a murmur

- SBE/IE
- Rheumatic fever
- Hypereosinophilia
- Amyloid[HS] (p354)

With anaemia

- Sickle-cell;[HS] thalassaemia[HS]
- Leishmaniasis;[HS] leukaemia[HS]
- Pernicious

With weight↓ + CNS signs

- Cancer; lymphoma
- TB; arsenic poisoning
- Paraproteinaemia[HS]

Massive splenomegaly

- Malaria; leishmaniasis
- Myelofibrosis; CML[HS]
- Gaucher's

anaemia (p320)

syndrome[HS]

- POEM (p204)

See webmentorlibrary.com for a full list of causes by **any** association; [HS]=causes of hepatosplenomegaly.

Smooth hepatomegaly

Hepatitis, CCF, sarcoid, early alcoholic cirrhosis (a small liver is typical later); tricuspid incompetence (→ pulsatile liver).

Craggy hepatomegaly

Secondaries or 1° hepatoma. (Nodular cirrhosis typically causes a small, shrunken liver, not an enlarged craggy one.)

Pelvic masses

- Fibroids
- Fetus
- Bladder
- Ovarian cysts or malignancies

Pelvic masses

Is it truly pelvic?—Yes, if by palpation you cannot get 'below it'.

Investigating lumps

There is much to be said for performing an early CT to save time and money compared with leaving the test to be the last in a long chain. If unavailable, *ultrasound* is the first test (transvaginal approach may be useful—**fig 2**).

Others:

IVU; liver and spleen radioisotope scans; Mantoux test (p386). Routine tests: FBC (with film); ESR; U&E; LFT; proteins; Ca^{2+}; CXR; AXR; biopsy tests—a tissue diagnosis may be made using a fine needle guided by ultrasound or CT control. MRI also has a role.

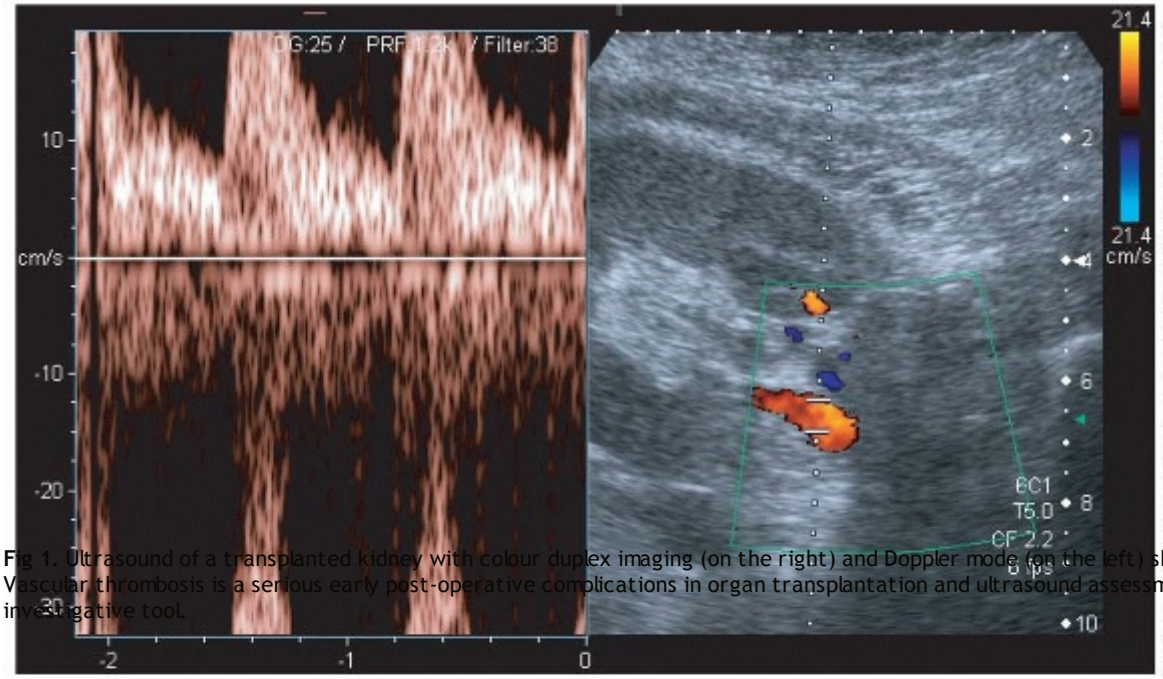


Fig 1. Ultrasound of a transplanted kidney with colour duplex imaging (on the right) and Doppler mode (on the left) showing flow in the graft vessels. Vascular thrombosis is a serious early post-operative complications in organ transplantation and ultrasound assessment is an invaluable investigative tool.

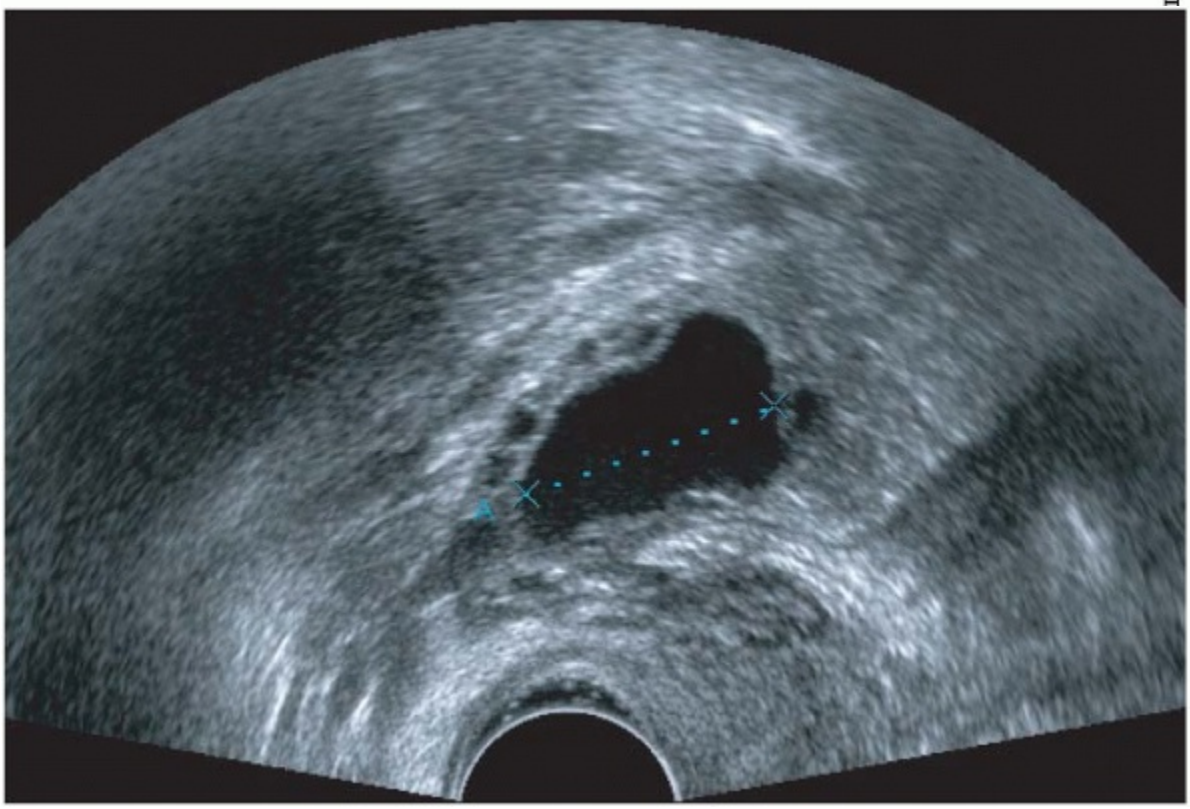


Fig 2. Transvaginal ultrasound showing a cystic lesion in the right ovary. Ovarian masses can grow to fill the abdomen and therefore may be seen in general surgical clinics. The fan shaped view of this ultrasound image is produced by the curved footplate of the probe.

Footnotes in History

In 1809 an American surgeon by the name of Ephraim McDowell performed an astonishing operation: the first successful elective laparotomy for an abdominal tumour. It was an ovariotomy for an ovarian mass in a 44-year old who, prior to physical examination by McDowell, was believed to be gravid. Not only was this feat performed in the age before anaesthesia and antisepsis, but it was also performed on a table in the front room of McDowell's Kentucky home, at that time on the frontier of the West in the United States. His account of the operation makes fascinating reading.[1] Whilst the strength of his diagnostic convictions combined with his speed and skill at operating is to be admired (the operation took 25 minutes), there is an even more laudable part played in this story. The patient, Mrs Jane Todd-Crawford, was fully willing to be involved with what can only be described as experimental surgery in the face of uncertainty. She defied pain simply by reciting psalms and hymns, and was back at home within 4 weeks with no complications. We would be well served in remembering commitment of Mrs Todd-Crawford as most exceptional. In the rush and hurry of our daily tasks perhaps it is all to easy to forget that the undertaking of surgery today may be no less fear-provoking for patients than it was 200 years ago.

Around the anus

Pruritus ani

Itch occurs if the anus is moist or soiled, eg fissures, incontinence, poor hygiene, tight pants, threadworm, fistula, dermatoses, lichen sclerosis, anxiety, contact dermatitis (eg perfumed goods).

Treatment:

- Careful hygiene
- No spicy food
- Moist wipe post-defecation
- No steroid/antibiotic creams
- Try anaesthetic cream
- Capsaicin may help[208]

Fissure-in-ano

This is a midline longitudinal split in the squamous lining of the lower anal canal—often, if chronic, with a sentinel mucosal tag at the external aspect. 90% are posterior (anterior ones follow parturition). ♂:♀ is 1>1.

- Most are due to hard faeces, which makes defecation very painful—'like passing glass'. Spasm may constrict the inferior rectal artery, causing ischaemia, making healing difficult and perpetuating the problem.[209]
- Rare causes (multiple ± lateral): Syphilis; herpes; trauma; Crohn's; anal Ca; psoriasis.
- Examine with a bright light. Do a PR ± sigmoidoscopy, if tolerated. Groin nodes suggest a complicating factor (eg immunosuppression from HIV).
- Try 5% ***lidocaine*** ointment, extra dietary roughage and fluids + good anal toilet. ***Glyceryl trinitrate*** (GTN) ointment (0.2-0.3%) relieves pain and ischaemia caused by chronic fissures and spasm, and can prevent need for surgery, but may cause headache. Trials suggest that ***botulinum toxin*** injection (eg 20U) is more effective than GTN.[210] If conservative measures fail, try day-case *lateral partial internal sphincterotomy*; *manual anal dilatation* (under GA) is also used, but has fallen out of favour due to the greater risk of post-op anal incontinence.[211] Pre-operative assessment with anorectal ultrasound and manometry is recommended, especially for postpartum fissures.

Fistula-in-ano

The fistula track communicates between the skin and the anal canal or rectum. Blockage of deep intramuscular gland ducts is thought to predispose to abscess formation, which then discharge to form the fistula.

Goodsall's rule

determines the path of the fistula track between openings: if anterior, the track is in a straight line; if posterior, the internal opening is **always** at the 6 'o' clock position.

Causes:

Abscesses (see below); Crohn's disease, TB, diverticular disease.

Tests:

MRI;[212] endoanal US scan.[213]

Treatment:

Fistulotomy + excision if ≤low transsphincteric; tight or loose seton insertion. Staged sphincter repair may be required.

Anorectal abscesses

are usually caused by gut organisms (rarely staphs or TB). ♂:♀≈1.8.

Location:

Perianal (~45%), ischiorectal (≤30%), intersphincteric (>20%), supralevator (~5%). Redness and swelling may spread well into the buttock. PR may be too painful. Do incision & drainage, eg under GA (+ fistulotomy if, eg in Crohn's disease).

Associations:

DM, Crohn's, malignancy. Don't rely on antibiotics.

The perianal haematoma

(also called a thrombosed external pile—see BOX, p629). Strictly, both names are wrong because it is actually a clotted venous saccule. It appears as a 2-4mm 'dark blue berry' under the skin. It may be evacuated via a small incision under local anaesthesia or left alone if present for >1d.

Pilonidal sinus

Obstruction of natal cleft hair follicles ~6cm above the anus, with ingrowing of hair, excites a foreign body reaction, and may cause devious secondary tracks which open laterally ± abscesses, with foul-smelling discharge. (Barbers get these sinuses between their fingers.) ♂:♀≈10:1.

Treatment

is excision of the sinus tract ± primary closure, but is unsatisfactory in 10%. Consider pre-op ***cefuroxime*** 1.5g + ***metronidazole*** 500mg IV. Complex tracks can be laid open and packed individually, or skin flaps can be used to cover the defect.[214]

Rectal prolapse

The mucosa, or rectum in all its layers, may descend through the anus. This leads to incontinence in 75%. It is due to a lax sphincter and prolonged straining.

Treatment

is by fixing the rectum to the sacrum (rectopexy) ± mesh insertion ± rectosigmoidectomy, or encircling the anus with a Thiersch wire.[215]

Anal ulcers

are rare. Consider Crohn's disease, anal cancer, TB, and syphilis.

Skin tags

seldom cause trouble but are easily excised.

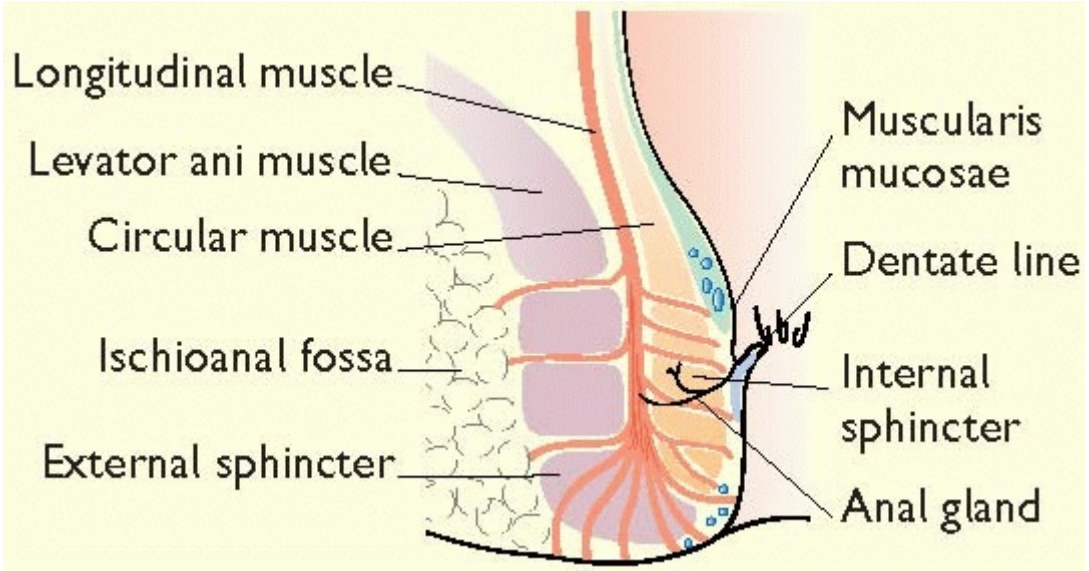
Piles

See p628.

Examination of the rectum and anus

▸It is necessary to have a chaperone present for the examination. Explain what you are about to do. Make sure curtains are pulled and doors are closed. The patient (and passers-by!) will appreciate it. Have the patient on his left side, his knees brought up towards the chest. Use gloves and lubricant. Part the buttocks and inspect the anus. Press your index finger against the side of the anus. Ask the patient to breathe deeply and insert your finger slowly; press with the pad of the finger first then twist and push in the tip. Feel for masses (haemorrhoids are not palpable) or impacted stool. Twist your arm so that the pad of your finger is feeling anteriorly. Feel for the cervix or prostate. Note consistency and size of prostate. Obliteration of its midline sulcus is a sign (unreliable) of prostate cancer. If there is a concern about the spinal cord, ask the patient to squeeze your finger and note the tone; also check perineal sensation. Note stool or blood on the glove and test for occult blood. Wipe the anus. Consider proctoscopy (for the anus) or sigmoidoscopy (which mainly inspects the rectum).

Anatomy of the anal canal



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Anal cancer

UK incidence:

300/yr.

Risk↑:

Syphilis, anal warts (HPV 16, 6, 11, & 18 implicated), anoreceptive homosexuals (often young).

Histology:

Squamous cell (80%); rarely basaloid, melanoma, or adenocarcinoma.

The patient

may present with bleeding, pain, bowel habit change, pruritus ani, masses, stricture. △△: Condyloma acuminata (warts[1]) or lata (syphilis, p419); leucoplakia; lichen sclerosis; Bowen's disease; Crohn's disease.

[1] Pink or grey soft, moist, cauliflower-like papules on moist surfaces with many discrete projections on a broad base—or just simple small bumps. Confluent nodules (giant *condylomata acuminata* of Buschke & Loewenstein) may evolve into verrucous cancers (a low grade non-metastasizing squamous type).

Treatment:

Radiotherapy + ***5-fluorouracil*** + ***mitomycin/cisplatin*** is usually preferred to anorectal excision & colostomy; 75% retain normal anal function.$_{216}$

Haemorrhoids (piles)

The anus is lined mainly by discontinuous masses of spongy vascular tissue—the anal cushions, which contribute to anal closure. Viewed from the lithotomy position, their positions are at 3, 7, & 11 o'clock. They are attached by smooth muscle and elastic tissue, but are prone to displacement and disruption, either singly or together. The effects of gravity (our erect posture), increased anal tone (?stress), and the effects of straining at stool may make them become both bulky and loose, and so to protrude to form piles (Latin *pila*, meaning a ball). They are vulnerable to trauma and bleed readily from the capillaries of the underlying lamina propria, hence their other name, haemorrhoids, (≈*running blood* in Greek). Because loss is from capillaries, it is bright red. **NB:** Piles are **not** varicose veins.

As there are no sensory fibres above the dentate line (squamomucosal junction), piles are not painful unless they thrombose when they protrude and are gripped by the anal sphincter, blocking venous return.

Differential diagnosis:

Perianal haematoma; anal fissure; abscess; tumour; *proctalgia fugax* (idiopathic, intense, stabbing rectal pain). ▸Never ascribe rectal bleeding to piles without adequate examination or investigation.

Causes

Constipation with prolonged straining is a key factor. In many the bowel habit may be normal. Congestion from a pelvic tumour, pregnancy, CCF, or portal hypertension are important in only a minority of cases.

Pathogenesis

There is a vicious circle: vascular cushions protrude through a tight anus, become more congested, so hypertrophying to protrude again more readily. These protrusions may then strangulate. See TABLE for classification.

The patient

notices bright red rectal bleeding, often coating stools or dripping into the pan after defecation. There may be mucous discharge and *pruritus ani*. Severe anaemia may occur. Symptoms such as weight loss, tenesmus and change in bowel habit should prompt thoughts of other pathology. In all rectal bleeding do:

- An abdominal examination to rule out other diseases.
- PR exam: prolapsing piles are obvious. Internal haemorrhoids are not palpable.
- Proctoscopy to see the internal haemorrhoids.
- Sigmoidoscopy to identify rectal pathology higher up (you can get no higher up than the rectosigmoid junction).

The best treatment

Unknown, as meta-analyses differ.

Infra-red coagulation

applied for 1.5-2s, 3-8 times to localized areas of piles works by coagulating vessels, and tethering mucosa to subcutaneous tissue. Doing all the piles may take a few sessions.

Sclerosants:

2mL of 5% ***phenol*** in oil is injected into the pile above the dentate line; SE: impotence; prostatitis).

Rubber band ligation:

SE: bleeding; infection. Do <3 band-treatments per session; a cheap treatment, but needs skill. Banding produces an ulcer to anchor the mucosa (SE: bleeding, infection; pain— infra-red coagulation is as successful and may be less painful).[217]

Cryotherapy

(freezing) is also used but can produce a lot of watery discharge after the procedure. A high-fibre diet may also help.

In all but 4th degree piles, these measures may obviate need for *haemorrhoidectomy* (excision of piles ± ligation of vascular pedicles, as day-case surgery, needing ~2wks off work). SE: haemorrhage or stenosis. Stapled haemorrhoidectomy may result in less pain, a shorter hospital stay and quicker return to normal activity than conventional surgery, provided the surgeon has the technical experience.[218] 1 week's ***lactulose*** + ***metronidazole*** (p371) starting pre-op reduces pain and time off work.[219]

Complications:

Constipation; infection; stricture; bleeding.

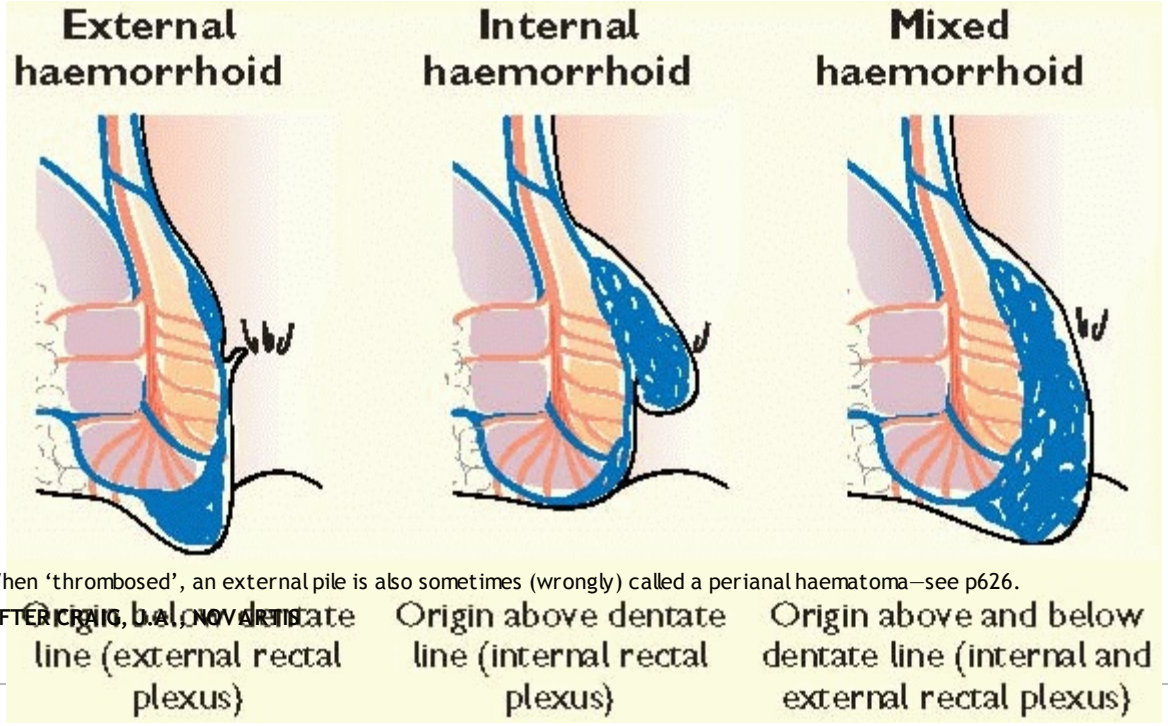
Prolapsed, thrombosed piles

are treated with analgesia, ice packs and bed rest. Pain usually resolves in 2-3 weeks and surgery is seldom necessary.

Classification of haemorrhoids

1st-degree	Remain in the rectum
2nd-degree	Prolapse through the anus on defecation but spontaneously reduce
3rd-degree	As for second-degree but require digital reduction
4th-degree	Remain persistently prolapsed

Internal and external haemorrhoids



When 'thrombosed', an external pile is also sometimes (wrongly) called a perianal haematoma—see p626.

AFTER CRAIG, D.A., NOVARTIS

Hernias

Definition

Any structure passing through another so ending up in the wrong place is a **hernia**. Hernias involving bowel are said to be **irreducible** if they cannot be pushed back into the right place. This does not mean that they are either necessarily obstructed or strangulated. **Incarceration** implies that the contents of the hernial sac are stuck inside by adhesions. Gastrointestinal hernias are **obstructed** if bowel contents cannot pass through them—the classical features of intestinal obstruction soon appear (p598). They are **strangulated** if ischaemia occurs—the patient becomes toxic and requires urgent surgery. Care must be taken when attempting reduction (see p632 for the technique) as it is possible to perform **reduction *en masse***, pushing the strangulated bowel and hernial sac back into the abdominal cavity, but giving the initial appearance of successful reduction.

Inguinal hernia

The commonest kind, described on p632.

Femoral hernia

Bowel enters the femoral canal, presenting as a mass in the upper medial thigh or above the inguinal ligament where it points down the leg, unlike an inguinal hernia which points to the groin. They occur as often in women than men (inguinal hernias are far more common in men) and are likely to be irreducible and to strangulate.

Anatomy:

The neck of the hernia is felt inferior and lateral to the pubic tubercle (inguinal hernias are superior and medial to this point). The boundaries of the femoral canal are **anteriorly** and **medially** the inguinal ligament; **laterally** the femoral vein and **posteriorly** the pectineal ligament and pectineus. The canal contains fat and Cloquet's node.

Treatment:

Repair is recommended.

Paraumbilical hernias

These occur just above or below the umbilicus. Risk factors are obesity and ascites. Omentum or bowel herniates through the defect. Surgery involves repair of the rectus sheath. Also see BOX.

Epigastric hernias

These pass through *linea alba* above the umbilicus.

Incisional hernias

These follow breakdown of muscle closure after previous surgery (seen in 11-20%). If obese, repair is not easy. A randomized trial of repairs favoured mesh over suture techniques.[220]

Spigelian hernias

These occur at the lateral edge of the rectus sheath, below and lateral to the umbilicus.

Lumbar hernias

These occur through 1 of the 2 lumbar triangles.

Richter's hernia

This involves bowel wall only—not the whole lumen.

Maydl's hernia

This involves a herniating 'double loop' of bowel. The strangulated portion may reside as a single loop **inside** the abdominal cavity.

Littre's hernia

This is a hernial sac containing a strangulated Meckel's diverticulum.

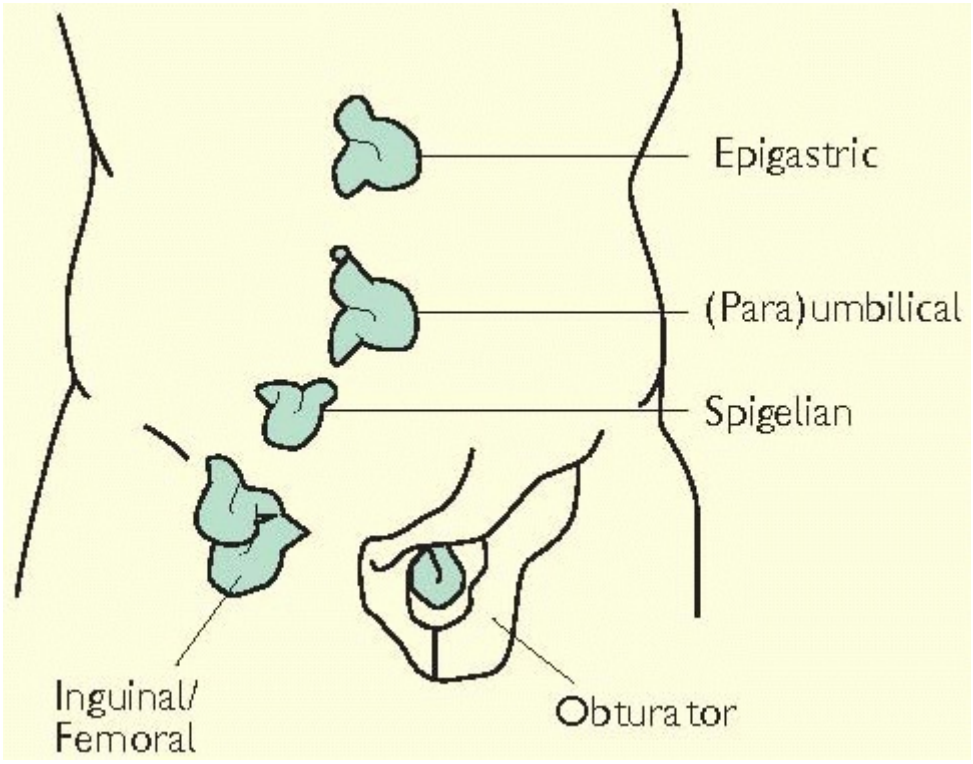
Obturator hernias

These occur through the obturator canal. Typically there is pain along the medial side of the thigh in a thin woman.

Other examples of hernias:

- Of the nucleus pulposus into the spinal canal (slipped disc).
- Of the uncus and hippocampal gyrus through the tentorium (tentorial hernia) in space-occupying lesions.
- Of the brainstem and cerebellum through the foramen magnum (Arnold-Chiari malformation, p686).
- Of the stomach through the diaphragm (hiatus hernia, p236).
- Of the terminal (intravesical) portion of the ureter into the bladder, with cystic ballooning between the mucosa and muscle layers. This is a *ureterocele* (*kēlē* is Greek for hernia), and results from stenosis of the ureteral meatus. Causes may be congenital (eg persistence of Chawalla's membrane), or rarely schistosomiasis or phaeochromocytoma. This intra-bladder hernia may cause obstruction ± UTI— or even herniate into the urethra and present as an interlabial mass. Management may involve endoscopic meatotomy or ureterocelectomy ± reimplantation.

Some examples of hernias



Abdominal wall defects in children (see OHCS, p130)

During embryonic development, the testis is led down from its original position on the posterior abdominal wall into the scrotum by the gubernaculum. If the connection between the peritoneal cavity and the tunica vaginalis fails to close behind the testis, then there is a *patent processus vaginalis*. It is through this that an indirect inguinal hernia occurs. About 4% of all male infants have an indirect inguinal hernia (prematurity is a risk factor), whereas it is very uncommon in female infants and, if found, should prompt thoughts of testicular feminisation. If the patent *processus vaginalis* contains peritoneal fluid only, then it is a *communicating hydrocele*. Repair is the same for both, involving high ligation and division of the protruding

peritoneal sac. Reinforcement of the posterior wall (eg with a mesh) is not required because the internal ring has not been chronically dilated.

True umbilical hernias

(**3**% of live births) are a result of a persistent defect in the transversalis fascia—the umbilical ring, through which the umbilical vessels passed to reach the foetus—whereas *paraumbilical hernias* are found in adults in a canal bordered by the umbilical fascia posteriorly, the linea alba anteriorly and the rectus sheath laterally. True umbilical hernias can recur in adulthood eg in pregnancy (**3**rd trimester) or gross ascites (**fig 2**, p253). Surgical repair is rarely needed in children (**3** in 1000) as most resolve by the age of **3**.

Protrusion of the abdominal contents through a defect in the anterior abdominal wall to the right of the umbilicus is seen in *gastroschisis*, with the protruding bowel covered by a thin 'peel'. Prompt surgical repair is performed after fluid resuscitation.[221] Concomitant congenital abnormalities are rare.

Exomphalos

(also called *omphalocele*),[1] however, is associated with other congenital abnormalities, such as anencephaly, cardiac defects, hydrocephalus and spina bifida. In this condition the abdominal contents are found outside the abdomen, covered in a three layer membrane consisting of peritoneum, Wharton's jelly and amnion. Surgical repair is less urgent than in gastroschisis because the bowel is protected by these membranes. The challenge of surgery is to fit the contents back into the relatively small abdominal cavity without compromising venous return and lung ventilation. *Meckel's diverticulum:* p698.

Inguinal hernias

Indirect hernias pass through the internal inguinal ring and, if large, out through the external ring—see BOX, p631 for the embryological story. Direct hernias push their way directly forward through the posterior wall of the inguinal canal, into a defect in the abdominal wall. Predisposing conditions: chronic cough, constipation, urinary obstruction, heavy lifting, ascites, previous abdominal surgery (eg damage to the iliohypogastric nerve during appendicectomy). There are 2 landmarks to identify: *The internal ring* may be defined as being the **mid-point of the inguinal ligament**, ~1 1/2 cm above the femoral pulse (which crosses the **mid-inguinal point**). *The external ring* is a split in the external oblique aponeurosis just superior and medial to the pubic tubercle (the bony prominence forming the medial attachment of the inguinal ligament). Relations of the inguinal canal are:

- *Floor:* Inguinal ligament and lacunar ligament medially.
- *Roof:* Fibres of transversalis, internal oblique and conjoint tendon medially.
- *Front:* External oblique aponeurosis + internal oblique for the lateral 1/3.
- *Back:* Laterally, transversalis fascia; medially, conjoint tendon.
- *Contents:* see BOX.

Examination

Look for previous scars; feel the other side; examine the external genitalia. Then ask: • Is the lump visible? If so, ask the patient to reduce it—if he cannot, make sure that it is not a scrotal lump. Ask him to cough. Inguinal hernias appear inferomedial to the external ring. • If no lump is visible, feel for a cough impulse. • Repeat the examination with the patient standing.

Distinguishing direct from indirect hernias:

This is loved by examiners but is of little clinical use—not least because repair is the same for both (see below). The best way is to reduce the hernia and occlude the internal ring with two fingers. Ask the patient to cough or stand—if the hernia is restrained, it is indirect, if it pops out, it is direct.

Indirect hernias:	*Direct hernias:*	*Femoral hernias:*
• Common (80%)	• Less common (20%)	• More frequent in females
• Can strangulate	• Reduce easily	• Frequently irreducible
	• Rarely strangulate	• Frequently strangulate

Irreducible hernias

You may be called because a long-standing hernia is now irreducible and painful. It is always worth trying to reduce these yourself—to prevent strangulation and bowel necrosis (a grave event, demanding prompt laparotomy). Learn how to do this from an expert—ie one of your patients who has been reducing his hernia for years—then you will be well-equipped to act correctly when the incipient emergency presents. Notice that such patients use the flat of the hand, directing the hernia from below, up towards the contralateral shoulder. Sometimes, as the hernia obstructs, reduction requires perseverance, which may be rewarded by a gurgle from the retreating bowel and a kiss from the attending spouse who had thought that surgery was inevitable.

Repairs

Advise to diet (if over-weight) and stop smoking pre-op. Mesh techniques (eg Lichtenstein repair) have replaced older methods such as the 'Shouldice' repair, with its multilayered suture involving both anterior and posterior walls of the inguinal canal. In mesh repairs, a polypropylene mesh reinforces the posterior wall. Recurrence rate is less than with other methods (eg <2% *vs* 10%). Local anaesthetic techniques and day-case 'ambulatory' surgery may halve the price of surgery. This is important because this is one of the most common operations (>100,000 per year in the UK).

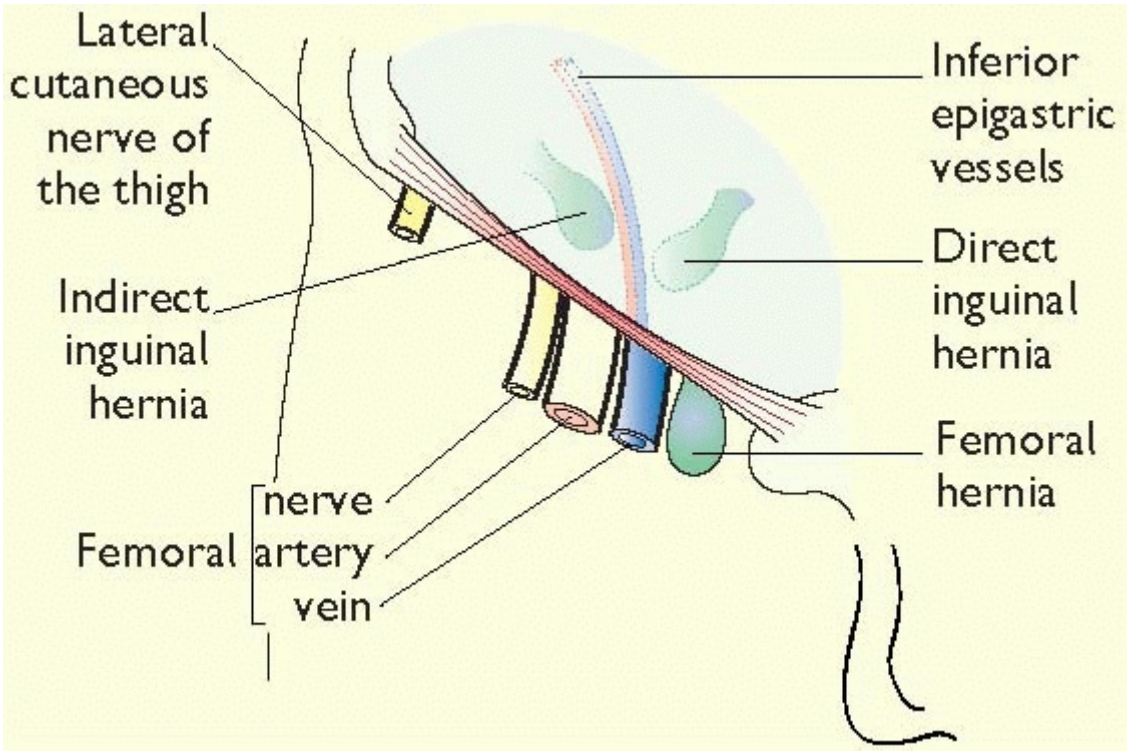
Laparoscopic repair

is also possible, and gives similar recurrence rates, but is not currently recommended as standard practice.[222] Benefits include less post-operative pain, an earlier return to work and indentification of undiagnosed contralateral hernias, though the set-up may cost more than conventional surgery (p640).

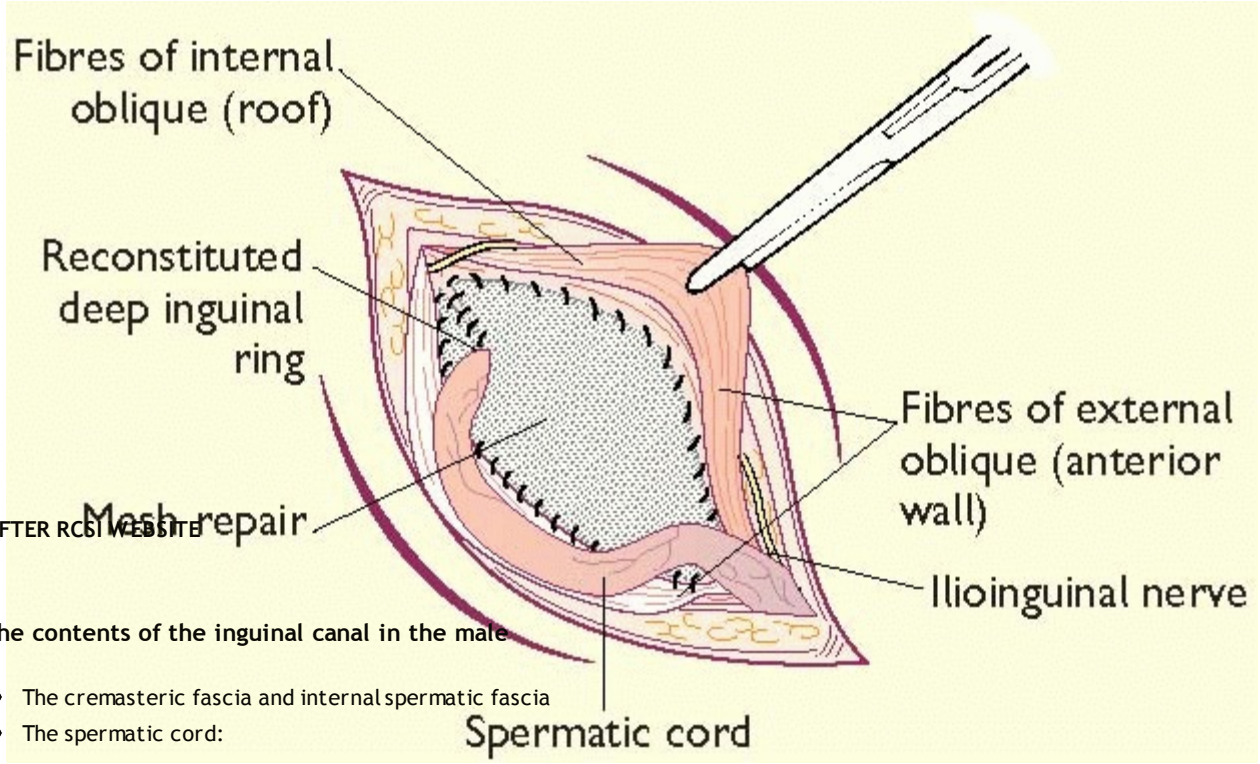
Return to work:

We used to advise 4wks' rest and convalescence over 10wks, but with new mesh (or laparoscopic) repairs, if comfortable, return to manual work (& driving) after ≤2wks is OK; explain this pre-operatively.

The anatomy of the inguinal canal



Inguinal hernia mesh repair



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The contents of the inguinal canal in the male

- The cremasteric fascia and internal spermatic fascia
- The spermatic cord:
  - Vas deferens, obliterated processus vaginalis, and lymphatics
  - Arteries to the vas, cremaster, and the testis
  - The pampiniform plexus and the venous equivalent of the above
  - The genital branch of the genitofemoral nerve and sympathetic nerves
- The ilioinguinal nerve, which enters the inguinal canal via the anterior wall and runs anteriorally to the cord.

NB: In the female the round ligament of the uterus is in place of the male structures. A hydrocele of the Canal of Nuck is the female equivalent of a hydrocele of the cord.

Varicose veins (VVs)

Blood from superficial veins of the leg passes into the deep veins by means of perforator veins (perforating deep fascia) and at the sapheno femoral and saphenopopliteal junctions. Valves prevent blood from passing from deep to superficial veins. If they become incompetent there is venous hypertension and dilatation (**varicosities**) of the superficial veins occurs. Risk factors include prolonged standing, obesity, pregnancy, family history, and the 'pill'.[223]

Symptoms

'My legs are ugly'. Note that pain, cramps, tingling, heaviness, and restless legs are often attributed to VVs, but careful studies show these common symptoms are only slightly commoner in those with VVs.

Primary causes (95%)

- Unknown
- Congenital valve absence (very rare)

Secondary causes *(5%)*

- Obstruction: DVT, fetus, ovarian tumour
- Valve destruction: DVT
- Arteriovenous malformation (↑pressure)

Signs

Oedema; eczema; ulcers; haemosiderin skin staining; haemorrhage; phlebitis; *atrophie blanche* (white scarring around a healing ulcer); lipodermatosclerosis (skin hardness from subcutaneous fibrosis caused by chronic inflammation and fat necrosis). On their own VVs don't cause DVTs (*proximally spreading phlebitis* of the long saphenous vein in the thigh may be an exception).

Method of examination

(Start with the patient standing.)

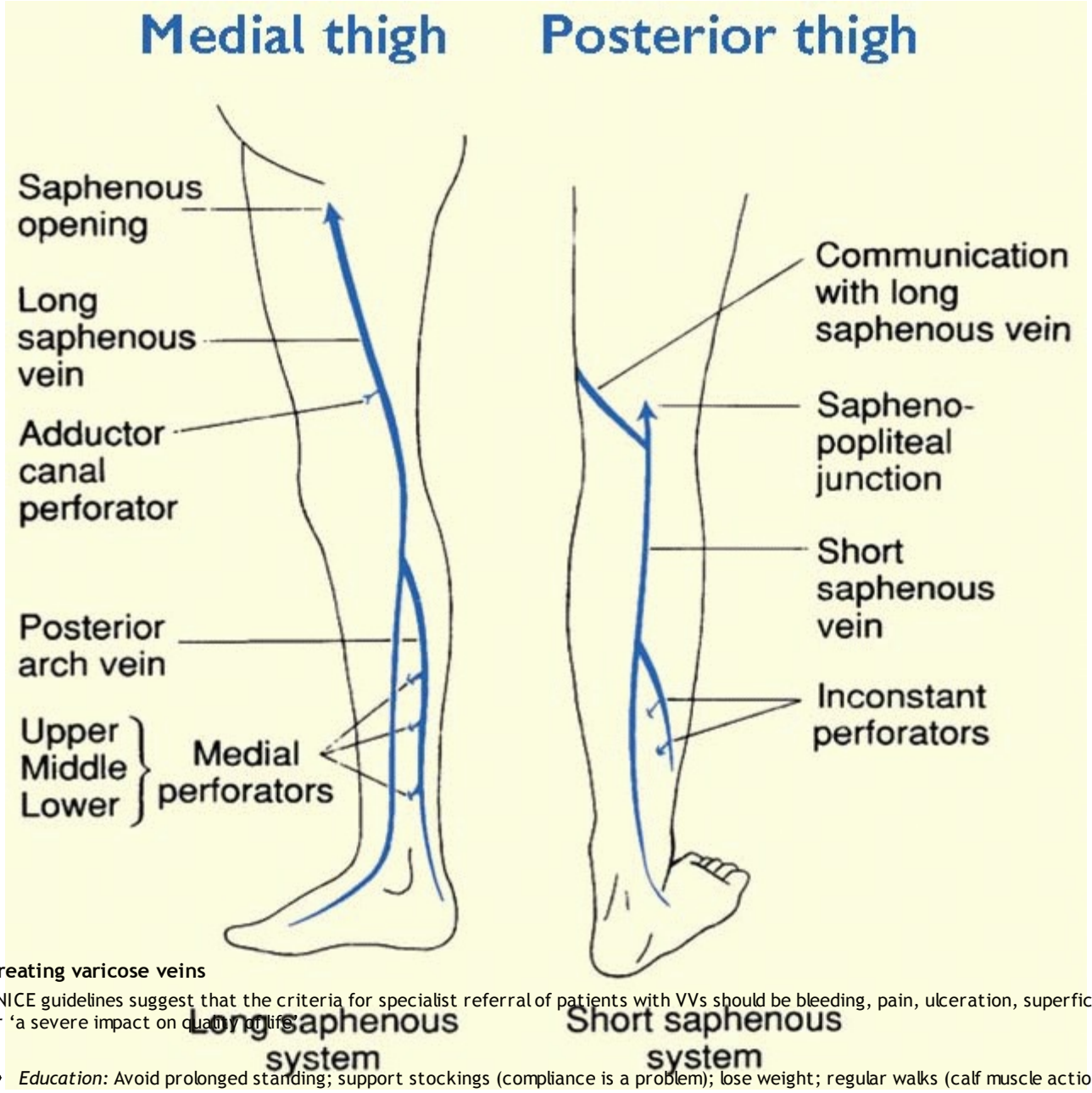
1. Note signs of poor skin nutrition: ulcers usually above the medial malleolus (varicose ulcers, OHCS p604) with deposition of haemosiderin causing brown edges, eczema, and thin skin. Inspect the legs from anterior thigh to medial calf (long saphenous vein) and the back of the calf (short saphenous vein). Palpate veins for tenderness (due to phlebitis) and hardness (due to thrombosis).
2. Feel for a *cough impulse* at the sapheno femoral junction (" incompetence). *The percussion test:* Tap the top of a vein and feel how far down its length you can feel repercussions (interrupted by competent valves).
3. *Trendelenburg's test* assesses if the saphenofemoral junction (SFJ) valve is competent: lie the patient down and raise the leg to empty the vein. Place 2 fingers on the SFJ (5cm below and medial to femoral pulse). Ask him to stand keeping the fingers in place. If the varicosities are controlled, they will not rapidly fill. Release the fingers to confirm that they then fill. This shows that there is SF incompetence and the operation of SF disconnection (Trendelenburg's operation) should help. If the varicosities are not controlled, then there must be incompetence at a lower level.
4. *The tourniquet test* is similar to Trendelenburg's test, but instead of controlling varicosities with the fingers, use a tourniquet tied around the thigh at the level of the SFJ. If the varicosities are not controlled, repeat the test with the tourniquet just above and then just below the knee, until the level at which there is incompetence is identified.
5. *Perthes' test* determines if the deep femoral veins are competent. With the patient standing and veins filled, a tourniquet is placed around the mid-thigh and the patient walks for 5min. If the saphenous veins collapse below the tourniquet, the deep veins are patent and the communicating veins are competent; if unchanged, both saphenous and communicating veins are incompetent; if the veins increase in prominence and pain occurs, the deep veins are occluded.
6. *Doppler ultrasound probes* have overtaken the above tests. They listen for flow in incompetent valves, eg the SFJ, or the short saphenous vein behind the knee (the calf is squeezed: flow on release lasting over 1/2-1 second indicates significant reflux). If incompetence is not identified and treated, varicosities will return.

▸Before surgery and after venous mapping, ensure that all varicosities are indelibly marked **to either side** (to avoid tattooing if the incision is made through inked skin).

Saphena varix

This is a dilatation (varicosity) in the saphenous vein at its confluence with the femoral vein (the SFJ). It is one of the many causes of a lump in the groin (p619). Because it transmits a cough impulse, it may be mistaken for an inguinal or femoral hernia, but on closer inspection it may have a bluish tinge.

The superficial veins of the leg



Treating varicose veins

▸NICE guidelines suggest that the criteria for specialist referral of patients with VVs should be bleeding, pain, ulceration, superficial thrombophlebitis, or 'a severe impact on quality of life'.

- *Education:* Avoid prolonged standing; support stockings (compliance is a problem); lose weight; regular walks (calf muscle action aids venous return).
- *Injection sclerotherapy:* Especially for varicosities below the knee if there is no gross sapheno-femoral incompetence. Sclerosant (eg ***ethanolamine***) is injected at multiple sites and the vein compressed for a few weeks to avoid thrombosis (intravascular granulation tissue obliterates the lumen). It is unsuitable for perforation sites. A novel development of this technique involves mixing the sclerosant with air to form a foam that is injected at a single site, and spreads rapidly throughout the veins. Ultrasound monitoring prevents inadvertent spread of foam into the femoral vein.[224]
- *Surgery:* There are several choices, depending on vein anatomy and surgical preference, eg saphenofemoral ligation; multiple avulsions; stripping from groin to upper calf (stripping to the ankle is not needed, and may damage the saphenous nerve). *Post-op:* Bandage legs tightly, and elevate for 24h. Then encourage regular walking eg 3miles/d, taken as many short walks. Surgery is more effective than sclerotherapy in the long-term.[225]

When do varicose veins become an illness?

The obvious answer is that they do so when they hurt, but for some patients, this is too simple. Thanks to Albert Camus, we know that 'certain illnesses are desirable: they provide a compensation for a functional disorder which, in their absence, would express itself in a more serious disturbance'; this is common with VVs.[226] Perhaps many opt for surgery as a displacement activity to confronting deeper problems. ▸We adopt the sickness role when we want sympathy. Somatization is hard to manage: here is one general approach to consider: Give time; don't dismiss these patients as 'just the "worried well"'.

- Explore the factors perpetuating illness behaviour (disordered physiology, misinformation, unhelpful 'coping' behaviour, social stressors).
- Agree a plan that makes sense to the patient's holistic view of himself.

Treat any underlying depression (drugs & cognitive therapy, OHCS p372).

Gastric surgery and its aftermath

▸Indications for gastric surgery include gastric cancer (p614) and peptic ulcers, though medical therapy (p234) has made elective surgery for the latter rare.

Operations for benign gastric ulceration

Those near the pylorus may be considered similarly to duodenal ulceration (p638). Away from the pylorus, elective operation is rarely needed as ulcers respond well to medical treatment, stopping smoking, and avoidance of NSAIDs. In patients who are unable to tolerate medical treatment, a laparoscopic highly selective vagotomy (HSV) can be done (p638).

▸▸*Emergency surgery*

may be needed for haemorrhage or perforation. Haemorrhage is usually treated by underrunning the bleeding ulcer base or excision of the ulcer. If the former is done, then a biopsy should be taken to exclude malignancy. Perforation is usually managed by excision of the hole for histology, then closure.

Operations for duodenal ulceration

See p638.

Gastric carcinoma

Localized disease may be treated by curative gastrectomy, either D_1 resection (excision of tumour and perigastric nodes) or D_2 resection (basically a D_1 resection extended to include nodes around the coeliac axis—see BOX for the lymphatic drainage of the stomach). There is considerable controversy as to which should be performed, as some studies have shown worse morbidity and mortality for D_2 resections performed in Western countries. It is likely that the results reflect the lack of dedicated specialists such as those in Japan, where gastric carcinoma is particularly common. D_2 resections should therefore only be performed in specialist centres.[227]

*Partial gastrectomy (the Billroth operations—***see BOX)

- *Billroth I:* Partial gastrectomy with simple re-anastomosis (rejoining).
- *Billroth II (Polya gastrectomy):* Partial gastrectomy. The duodenal stump is oversewn (leaving a blind loop), and anastomosis is achieved by a longitudinal incision further down (into the proximal jejunum).

Physical complications of gastrectomy and peptic ulcer surgery

▸As peptic ulcer surgery is largely obsolete, these complications are mainly of historical interest only.

- *Recurrent ulceration:* Symptoms are similar to those experienced pre-operatively but complications are more common and response to medical treatment is poor. Further surgery is difficult.
- *Abdominal fullness:* Feeling of early satiety (± discomfort and distension) improving with time. Advise to take small, frequent meals.
- *Bilious vomiting:* This is difficult to treat—but often improves with time.
- *Diarrhoea:* May be disabling after vagotomy. ***Codeine phosphate*** may help.
- *Gastric tumour:* A rare complication of any surgery which ↓acid production.
- *Amylase↑:* If with abdominal pain, this may indicate afferent loop obstruction after Billroth II surgery and requires emergency surgery.[228]

Metabolic complications

- *Dumping syndrome*:[229] Fainting and sweating after eating due to food of high osmotic potential being dumped in the jejunum, causing oligaemia from rapid fluid shifts. 'Late dumping' is due to rebound hypoglycaemia and occurs 1-3h after meals. Both tend to improve with time but may be helped by eating less sugar, and more guar and pectin (slows glucose absorption). ***Acarbose*** may also help to reduce the early hyperglycemic stimulus to insulin secretion.[230]
- *Weight loss:* Often due to poor calorie intake.
- *Bacterial overgrowth ± malabsorption* (blind loop syndrome) may occur.
- *Anaemia:* Usually from lack of iron hypochlorhydria and stomach resection. B_{12} levels are frequently low but megaloblastic anaemia is rare.
- *Osteomalacia:* There may be pseudofractures which look like metastases.

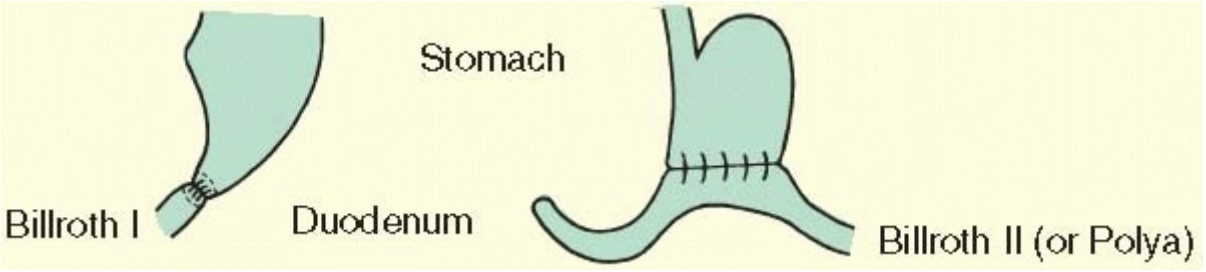
Complications of peptic ulcer surgery

	Partial gastrectomy	Vagotomy & pyloroplasty	Highly selective vagotomy

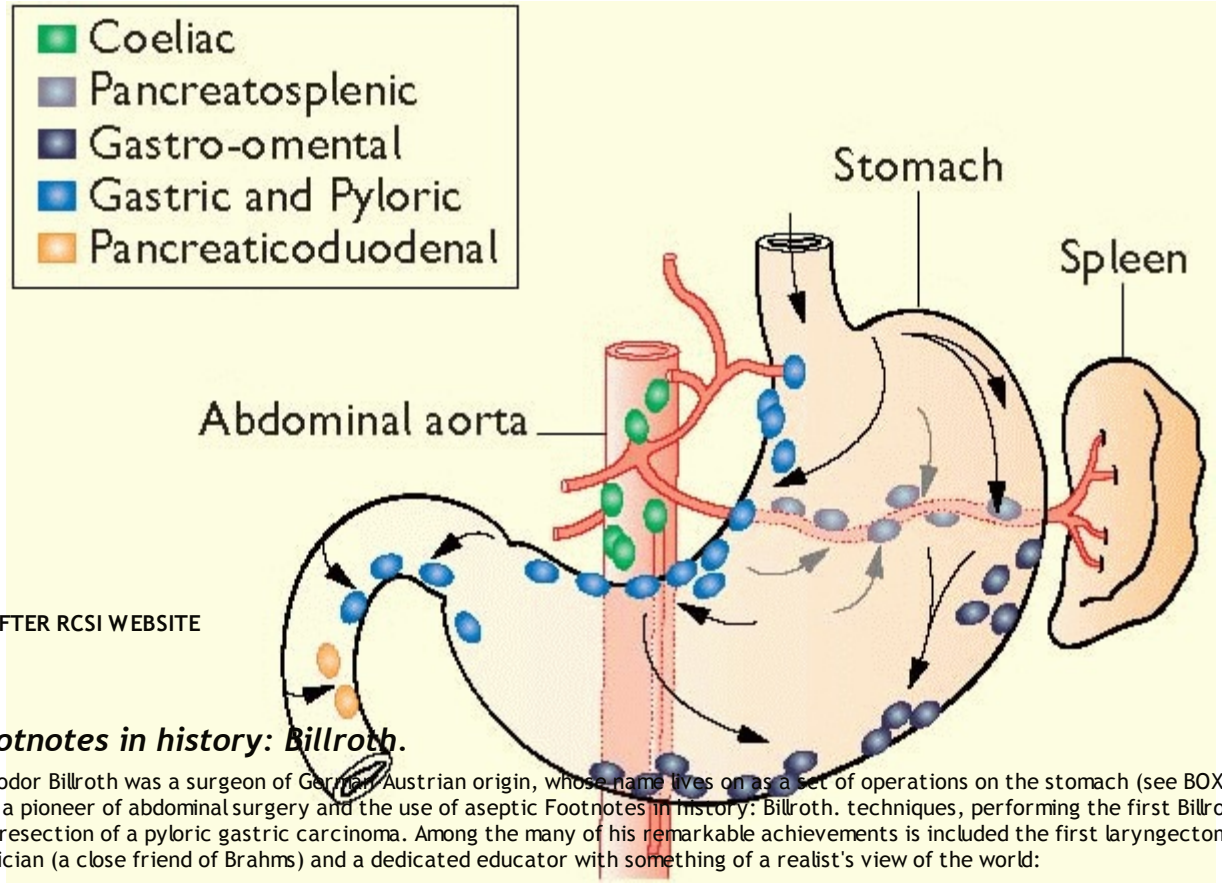
Recurrence	2%	7%	>7%
Dumping	20%	14%	6%
Diarrhoea	1%	4%	<1%
Metabolic	++++	++	0

(These values are approximate and depend on the skill of the surgeon.)

The Billroth operations



Lymphatic drainage of the stomach



AFTER RCSI WEBSITE

Footnotes in history: Billroth.

Theodor Billroth was a surgeon of German/Austrian origin, whose name lives on as a set of operations on the stomach (see BOX, The Billroth operations). He was a pioneer of abdominal surgery and the use of aseptic Footnotes in history: Billroth. techniques, performing the first Billroth I procedure in 1881 for the resection of a pyloric gastric carcinoma. Among the many of his remarkable achievements is included the first laryngectomy. He was also a talented musician (a close friend of Brahms) and a dedicated educator with something of a realist's view of the world:

The pleasure of a physician is little, the gratitude of patients is rare, and even rarer is material reward, but these things will never deter the student who feels the call within him.

Theodor Billroth (1829-94)[231] [232]

Operations for peptic ulcers

Peptic ulcers usually present as epigastric pain and dyspepsia (p234). There is no reliable method of distinguishing clinically between gastric and duodenal ulcers. Although management of both is usually medical in the 1st instance (eg with *H. pylori* eradication, p235), surgery still has a role.

Surgery is usually only required for complications such as *haemorrhage*, *perforation*, and *pyloric stenosis*, though may be considered for the few patients who are not responsive to or tolerant of medical therapy.

Several types of operation have been tried but, as whenever considering an operation, one must consider efficacy, side-effects, and mortality.

1. Elective surgery:
   - *Highly selective vagotomy:* May be useful in patients unable to tolerate medical treatment. The vagus supply is denervated only where it supplies the lower oesophagus and stomach. The nerve of Latarget to the pylorus is left intact; thus, gastric emptying is unaffected (see BOX). The results of surgery are greatly dependent on the skill of the surgeon.[233]
   - *Vagotomy and pyloroplasty:* A vagotomy reduces acid production from the stomach body and fundus, and reduces gastrin production from the antrum. However, it interferes with emptying of the pyloric sphincter and so a drainage procedure (eg pyloroplasty) must be added. This operation is now almost obsolete, and is only performed in exceptional circumstances.
   - *Gastrectomy* (p636) is rarely required (eg Zollinger-Ellison syndrome, p708).
2. Emergency surgery may be required for the following complications:
   - *Haemorrhage* may be controlled endoscopically by ***adrenaline*** injection, diathermy, laser coagulation, or heat probe. Operation should be considered for severe haemorrhage or rebleeding, especially in the elderly—see p246 for indications. At surgery, the bleeding ulcer base is underrun or oversewn.
   - *Perforation* (**Fig 1**) Most patients undergo surgery, though some advocate an initial conservative approach in patients without generalized peritonitis (NBM, NG tube, IV antibiotics—this can prevent surgery in up to 50% of such cases). If emergency surgery is required, laparoscopic repair of the hole will usually suffice (though has a worse recurrence rate than open repair).[234] *H. pylori* eradication should be commenced post-op (p234).
   - *Pyloric stenosis* This is a late complication, presenting with vomiting of large amounts of food some hours after meals. (Adult pyloric stenosis is a complication of duodenal ulcers, and has nothing to do with congenital hypertrophic pyloric stenosis, p600.) *Treatment:* Endoscopic balloon dilatation, followed by maximal acid suppression (p234), may be tried in the 1st instance (**NB:** 5% risk of perforation). If this is unsuccessful, a drainage procedure (eg gastro-enterostomy or pyloroplasty) ± highly selective vagotomy may be performed, often laparoscopically. The operation should be done on the next available list, after correction of the metabolic defect—a hypochloraemic, hypokalaemic metabolic alkalosis.

Fundoplication for gastro-oesophageal reflux

The goal

This is to re-establish lower oesophageal sphincter tone.

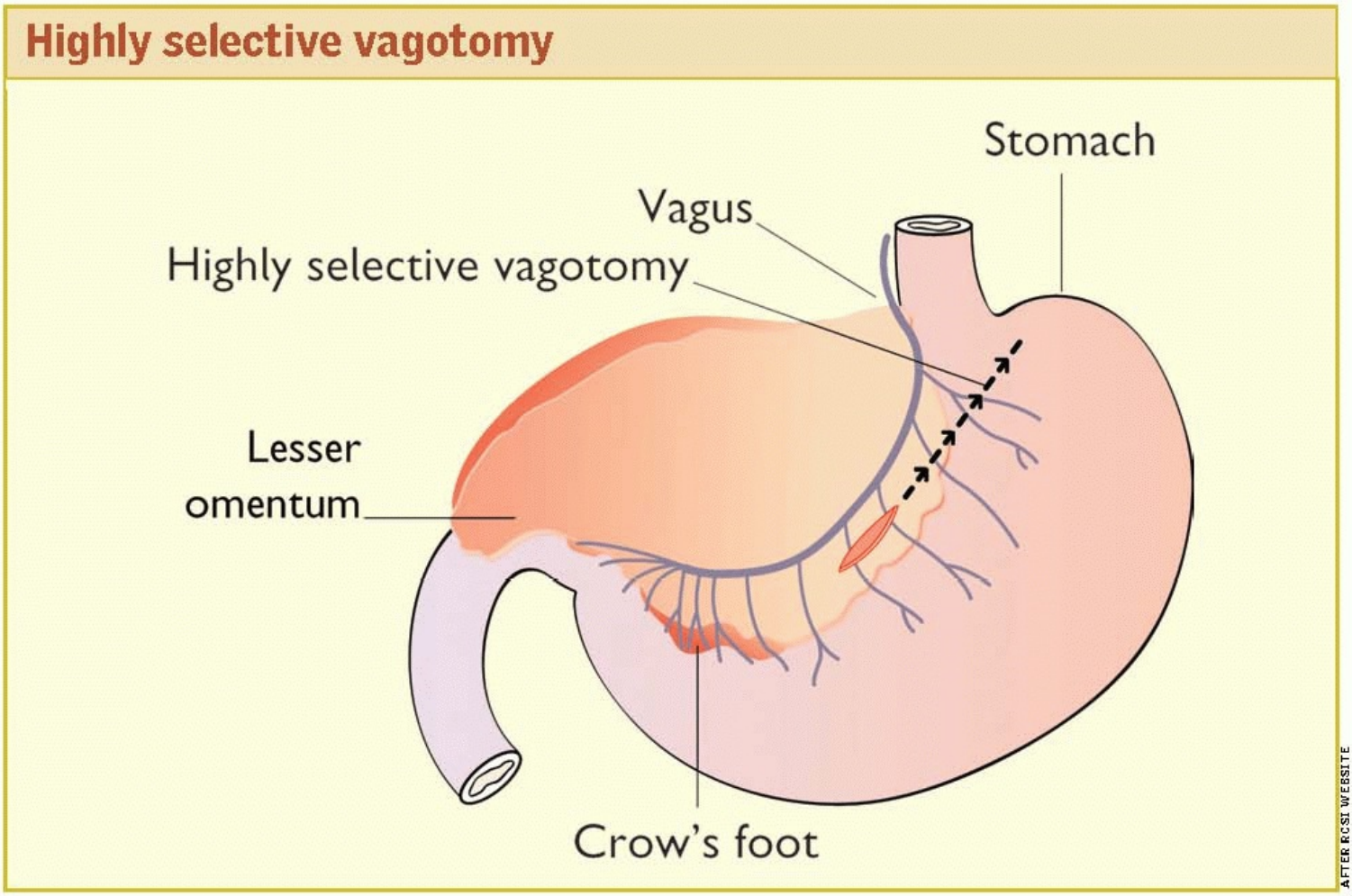
The procedure

Involves wrapping the gastric fundus around the lower oesophagus, closing the hiatus, and securing the wrap in the abdomen—see BOX. There are various types of procedure eg Nissen (360° wrap), Toupet (270° posterior wrap), Watson (anterior hemifundoplication).

Access

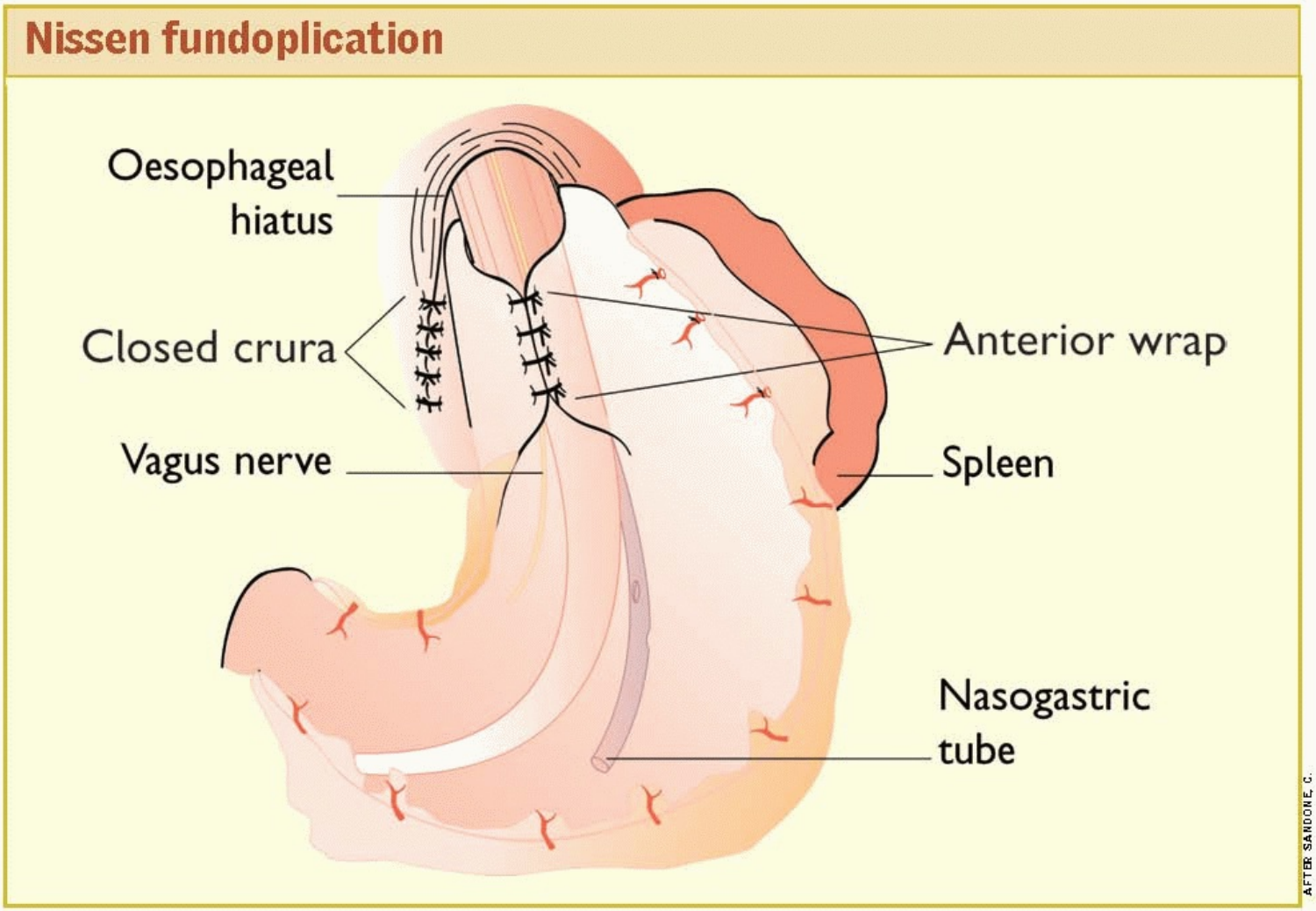
Usually laparoscopic, which in specialist centres is at least as effective at controlling reflux as open surgery but with a lower mortality. Wound infections and respiratory complications are also more common in open surgery, though the incidence of dysphagia is similar for the two procedures—but see p640.

Highly selective vagotomy



AFTER RCSI WEBSITE

Nissen fundoplication



AFTER SANDONE, C.

Minimally invasive surgery

The terms 'keyhole surgery' or minimal access surgery may be preferred, because these procedures can be as invasive as any laparotomy, having just the same set of side-effects—plus some new ones. It is the size of the incision and the use of laparoscopes which marks out this branch of surgery. Laparoscopy has been well established in gynaecology for many years where initially a purely optical telescope, held by the surgeon, was used for visualization. The development of miniaturized video cameras was the impetus to the widespread use of laparoscopy, as it allowed an assistant to have the same view as the surgeon. The surgeon could therefore operate with both hands, while his assistant held the laparoscope and retracted the viscera. Laparoscopic cholecystectomy was shown to be possible, and became the method of choice. Laparoscopy is now in widespread use for diagnostic purposes and for other conditions, such as appendicectomy,[235] fundoplication, splenectomy, and adrenalectomy. It is currently under evaluation for hernia repair,[236] colectomy,[237] nephrectomy (in renal transplants), parathyroidectomy, sentinel node biopsy, and perforated peptic ulcer repair.[238]

As a rule of thumb, whatever can be done by laparotomy can also be done with the laparoscope. This does not mean that it **should** be done, but if the patient feels better sooner, has less post-operative pain, and can return to work earlier, and have fewer complications, then these specific techniques will gain ascendency— provided hospitals can afford the equipment. Laparoscopic surgery may also have the benefit of a less suppressive effect on the immune system.[239]

It is worth noting that advantages do not include time. In upper GI surgery, laparoscopic surgery takes longer than open procedures. Also, the patient needs to spend a night in hospital, usually. This has economic implications when comparing laparoscopic inguinal hernia repair with open surgery done under local anaesthesia (after which the patient can go home the same day). On the other side of the economic equation for hernia repair is that pain >24h post-op is less after laparoscopic procedures, and the patient can return to full employment after a week. In addition, laparoscopic repair allows detection of a previously undiagnosed contralateral hernia. Which method makes economic sense depends on who is doing the calculation; NICE concluded that open hernia repair was cheaper, but their calculations did not include out of hospital costs.[240]

Problems with minimal access surgery: for the surgeon

Inspection:

Anatomy looks different due to the different surgical approach.

Palpation

is impossible during laparoscopic procedures. This may make it hard to locate colon lesions prior to cutting them out. This means that pre-operative tests may need to be more extensive (eg colonoscopy **and** barium enema).

Skill:

Here the problem is not just that a new skill has to be learned and taught. Old skills may become attenuated if operations are performed laparoscopically, and new surgeons may not achieve quite the level of skill in either sphere if they try to do both.

Problems for patients and GPs

Post-operative complications:

What may be easily managed on a well-run surgical ward (eg haemorrhage) may be a challenge for a GP and terrify the patient, who may be all alone after early discharge.

Loss of tell-tale scars:

Afterwards there may only be a few abdominal wounds, so future carers have to guess at what has been done. The answer here is to communicate carefully with the patient, so that he knows what has been done—see BOX.

Problems for hospitals

Just because minimal access surgery is often cost-effective, it does not follow that hospitals can afford the procedures. Instruments are continuously being refined, and quickly become obsolete—so that many are now produced in disposable single-use form. Because of budgeting boundaries, hospitals cannot use the cash saved, by early return to work or by freeing-up bed use, to pay for capital equipment and extra theatre time that may be required.

Exposing patients to our learning curves. The jury is still out…

All surgeons, indeed all doctors, get better over time (for a while), as they perform new techniques with increasing ease and confidence. Mortality rates inevitably vary. When Wertheim did his first radical hysterectomies, his first dozen patients died—but then someone survived, and he assumed it was a good operation, and pressed ahead. He was a brave man, and thousands of women owe their lives to him. But if he had tried to do this today, he would have been stopped. The UK's General Medical Council (GMC), and other august bodies constantly tell us that we must protect the public by reporting doctors whose patients have low survival rates. The reason for this is partly ethical, and partly an attempt to preserve self-regulation.

The defining feature of any profession lies, the GMC assumes, in self-regulation. To preserve this, we have the toughest professional codes of practice and disciplinary procedures of any group of workers. It is assumed that doctors are loyal to each other out of self-interest, and that this loyalty is bad. This has never been tested formally, and is not evidence-based. We can imagine two clinical worlds: one of constant 'reportings' and recriminatory audits, and another of trust and team-work. Both are imperfect, but we should not assume that the first world would be better for our patients.

It is easy to say that our patients demand honesty, and so long as we are doing our best, and referring where needed, all will be well. But honesty is opaque at the bedside. We never know the **whole** truth about our past performance. (All our patients with such-and-such a colostomy left hospital alive—but perhaps they all committed suicide later?) Should we tell our patient that this is the first time we have done this sort of operation unsupervised? When patients are sick with fear, they do not, perhaps, want to know everything. We may tell to protect ourselves. We may **not** tell to protect ourselves. Perhaps what we should do is, in the privacy of our own hearts, to appeal to those 12 dead women-of-Wertheim—a jury as infallible as sacrificial—and try to hear their reply. And to those who complain that in doing so we are playing God, it is possible to reply with some humility that, whatever it is, it does not seem like play.

'It is amazing what little harm doctors do when one considers all the opportunities they have'—Mark Twain

Acknowledgements

▸▸These are the three conditions where the promptest surgery is essential; ▸notify the duty surgical registrar or consultant, and theatre, **at once** (urology, for torsion).

We thank Mr Ashok Handa who is our Specialist Reader for this chapter.

Editors: Longmore, Murray; Wilkinson, Ian B; Turmezei, Tom; Cheung, Chee Kay
Title: *Oxford Handbook of Clinical Medicine, 7th Edition*

15

Epidemiology

An example of epidemiology at work

Some decades ago, epidemiologists tested the hypothesis that smoking and hypertension were associated with cardiovascular disease. Painstaking cohort studies confirmed that these were indeed ***risk markers*** (a term that does not imply causality). Over the years, as evidence accumulates, the term 'risk marker' may give way to ***risk factor***, which implies causation, and the separate idea that risk-factor modification will cause a reduction in disease. Demonstrating a dose-response relationship (with the correct time sequence) is good evidence of a causal relationship—eg showing that the greater the number of cigarettes smoked, the greater the risk, or the higher the blood pressure, the greater the cardiovascular mortality. It is still possible that BP is a risk marker of some other phenomenon, but this is less likely if the relationship between BP and cardiovascular mortality is found to correlate *while keeping other known risk factors constant*. The work of the epidemiologist does not stop here. He or she can use actuarial statistics to weigh the relative merits and interactions of a number of risk factors, to give an overall estimate of risk for an individual. It is then possible to say things like: 'If the 5-yr risk of a serious cardiac event in people with no overt cardiac disease is >15%, then drug treatment of hyperlipidaemia may begin to be cost-effective—and a 10% 5-yr risk may be a sufficient point to trigger antihypertensive treatment in someone with, say, a BP of 150/90'. These figures are a guide only: only ~60% of those in the top 10% of the risk distribution will have an adverse coronary event in the 5-yr period. Nevertheless, this is more accurate than taking into account risk factors singly—and so we are led to our first important conclusion: ***epidemiology improves and informs our dialogue with our patients***. We can give patients good evidence on which to base their choices.

Risk equations (ideally as part of computerized medical records) may be given as follows (a, m, μ, and σ are variables relating risk factors):

If $\alpha = 11.1122\text{-}[0.9119 \times \ln(\mathbf{BP})]\text{-}(0.2767 \times \mathbf{SMO})\text{-}[0.7181 \times \ln(\mathbf{FAT})]\text{-}(0.5865 \times \mathbf{LVH})$ and for males $m = \alpha\text{-}[1.4762 \times \ln(\mathbf{AGE})]\text{-}0.1759 \times \mathbf{DIAB}$ and for females $m = a\text{-}5.8549 + [1.8515 \times \ln(\mathbf{AGE}/74)^2]\text{-}(0.3758 \times \mathbf{DIAB})$ and $\mu = 4.4181 + m$ and $\sigma = e^{-(0.3155\text{-}0.278m)}$ and $v = [\ln(5) - \mu/\sigma]$

then **5-yr risk ≈ 1-(e-(ev))** if **AGE** is 30-74yrs, **BP** is the mean systolic, eg 3 readings—and **SMO**, **DIAB**, and **LVH** are each 1 if a patient is a smoker, has diabetes or left ventricular hypertrophy on ECG; if not present, each is 0. **FAT** is the ratio of total cholesterol to HDL. This is the EMIS formulation of the 'Dundee equations'; see J Robson 1997 BMJ ii 277 & corrected Sheffield tables for primary prevention of heart disease.[1]

▸Note that results from these equations are approximations only: beware spurious accuracy. Also, populations differ: figures taken from American cohorts in the past underestimated risk by as much as 48% in UK manual workers and 31% for non-manual workers. Very many more underprivileged people are eligible for preventive treatment if UK data are used.[2]

The essence of epidemiology

Epidemiology is the study of the distribution of clinical phenomena in populations. Its chief measures are prevalence and incidence.

Definitions

The *period prevalence* is the number of cases, at any time during the study period, divided by the population at risk. If the population at risk is unclear, then the population must be specified—eg the prevalence of uterine cancer varies widely, depending on whether you specify the general population (men, women, boys, and girls) or only women, or women who have not already had a hysterectomy.

The *incidence* is the number of new cases within the study period which must be specified, eg annual incidence. *Point prevalence* is the prevalence at a point in time. The *lifetime* prevalence of hiccups is ~100%; the (UK) incidence is millions/year—but the point prevalence may be 0 at 3AM today if no one is actually having hiccups.

Association

Epidemiological research is concerned with comparing rates of disease in different populations, eg rates of lung cancer in a population of men who smoke, compared with men who do not. A difference in rates points to an association (or dissociation) between the disease and factors which distinguish the populations (in this case, smoking or not). If the rates are equal, association is still possible, with a confounding variable (eg both groups share the same smoky environment).

Ways of accounting for associations:

A may cause *B*; *B* cause *A*; a 3rd unknown agent, *P*, causes *A* and *B*; or it may be a chance finding.

There are 2 types of studies which explore causal connections:

Case-control (retrospective) studies:

The study group consists of those with the disease (eg lung cancer); the control group consists of those without the disease. The previous occurrence of the putative cause (eg smoking) is compared between each group. Case-control studies are retrospective in that they start after the onset of the disease (although cases may be collected prospectively).

Cohort (prospective) studies:

The study group consists of subjects exposed to the putative causal factor (eg smoking); and the control group consists of subjects not exposed. The incidence of the disease is compared between the groups over time. ▸A cohort study generates incidence data, whereas a case-control study does not.

Matching

An association between *A* and *B* may be due to another factor *P*. To eliminate this possibility, matching for *P* is often used in case-control studies. One powerful, but unreliable (if numbers are small), way to do this in clinical trials is for the subjects to be allocated to groups randomly; check important *P*s have been distributed evenly between groups.

Overmatching

If unemployment causes low income, and low income causes depression, then matching study and control groups for income would mask the genuine causal link between unemployment and depression. ▸Avoid matching factors which may intervene in the causal chain linking *A* and *B*.

Blinding

If the subject does not know which of two trial treatments she is having, the trial is single blind. To further reduce risk of bias, the experimenter should also not know (double blind).

▸In a good treatment trial, the blind lead the blind.

Evidence-based medicine (EBM)[3]

This is the conscientious and judicious use of current best evidence from clinical research in the management of individual patients.

The problem

More than 2,000,000 papers are published each year. Patients benefit directly from a tiny fraction of these papers. How do we find them?

A partial solution

50 or so leading journals are scanned not by experts in a specialized field, but by searchers trained to identify papers which have a direct message for clinical practice, and meet predefined criteria of rigour (below). Summaries are then published, eg in *Evidence-based Medicine*.[4]

Questions used to evaluate papers:

- Are the results valid? Randomized? Blinded? Were all patients accounted for who entered the trial? Was follow-up complete? Were the groups similar at the start? Was everyone treated equally, apart from the experimental intervention? NB: randomized trials are now recognised as blunt instruments: adaptive (Bayesian) designs may sometimes be a more efficient way to get to the truth.[5]
- What are the results? How large (and precise) was the treatment effect?
- Will the results help my patients (cost/benefit sum).[6]

Problems with the solution

▸*The concept of scientific rigour is opaque*. What do we want? The science, the rigour, the truth, or what will be most useful to patients? These may overlap, but they are not the same.

- Will the best be the enemy of the good? Are useful papers rejected due to some blemish? Answer: appraise *all* evidence (often impossible).
- By reformulating in terms of answerable questions, EBM risks missing patient's reason for consulting. He may only want to express his fears, rather than be used as a substrate for an intellectual exercise.
- Is the standard the same for the evidence for *all* changes to our practice? We might avoid prescribing drug X for constipation if there is any chance that it might cause colon cancer, as the choice of drugs is wise. More robust evidence is needed to persuade us to do something rather counterintuitive, eg giving heparin in DIC (p336). There is no science to tell us how robust the data need to be: we decide off the top of our head (albeit a wise head, we hope).
- What about the correspondence columns of the journals from which the winning papers are extracted? It takes years for unforeseen but fatal flaws to surface, and be reported in correspondence columns.
- There is a danger that by always asking 'What is the evidence …' we will divert resources from hard-to-prove areas (eg physiotherapy, which may be very valuable) to easy-to-prove services. The unique personal attributes of the therapist may be as important as the objective regimen.
- EBM is never 100% up-to-date, and reworking meta-analyses takes time and money, so specialists may ostensibly reject a new trial due to a tiny flaw, when the real reason is that they dread it might flip their once-perfect formulation.
- 'My increased knowledge gradually permeated or repressed the world of intuitive premonitions …' (*Carl Jung*). These premonitions may be vital!
- If EBM is prescriptive, patient choice declines: not all patients are amenable to rational dialogue. Does our zeal for EBM make us arrogant and inflexible?
- The patient before us may not quite fit the type of patient who provided the research basis—and we may be tempted to ignore these small differences which may then have major unforeseen adverse effects.

Advantages of EBM

This is mainly that patients get better faster—also:

- Our reading habits improve, and we can offer more rational choices to patients.
- EBM leads us to ask questions, and then to be sceptical of the answers.
- As taxpayers, we should like it (wasteful practices can be abandoned).

EBM may not have as much impact as we hope, as gaining evidence is time-consuming and expensive, and sometimes impossible. Despite these caveats, EBM is here to stay, so we may as well subscribe to its ideals—and to its journals.

Six to five against

Your surgical consultant asks whether Gobble's disease is more common in men or women. You have no idea, and make a guess. What is the chance of getting it right? Common sense decrees that it is even chances; 'Sod's Law' predicts that whatever you guess, your answer will always be wrong. A less pessimistic view is that the balance is slightly tipped against you: according to Damon Runyon, 'all life is six to five against'.[7]

Do new symptoms suggest a new disease or are they from an existing disease?

The answer is often counter-intuitive. Suppose **s** is quite a rare symptom of Gobble's disease (seen in 5% of patients), but that it is a very common symptom of disease **A** (seen in 90%). If we have a man whom we already know has Gobble's disease and who goes on to develop symptom **s**, is not **s** more likely to be due to disease **A**, rather than Gobble's disease? The answer is usually no: *it is generally the case that* **s** *is due to a disease which is already known, and does not imply a new disease*.

The 'odds ratio' makes this clearer, ie the ratio of [the probability of the symptom, given the known disease] to [the probability of the symptom given the new disease × *the probability of developing the new disease*]. This ratio is, usually, vastly in favour of the symptom being due to the old disease because of the prior odds of the two diseases.

Doctors as gamblers

To the average mind it is distasteful to learn that doctors gamble with patients' lives. One of us (JML) has just finished consulting with 26 patients. Not too many, perhaps: it might be argued that each of symptom, especially if *serious*, should be investigated until the cause is found.

Let us look at this critically. What counts as a serious symptom? One that, might mean death, disfigurement, or disability. Some of these patients offered 5 symptom groups before being dissuaded from going on. During elucidation of these symptoms others emerged, yielding a potentially endless cycle of investingation. Certainly some of their symptoms might not seem serious ('this pain in my toe…'). But toe pain might be mortal if caused by emboli or osteomyelitis. Fingernail problems with a slight rash might mean arsenic poisoning; lethargy may mean cancer, and so on. So medicine is not for pessimists—almost anything can be made to seem fatal, so that a pessimistic doctor would never get any sleep at night for worrying about the meanings of his patients' symptoms.

Medicine is not for blind optimists either, who too easily embrace a fool's paradise of false reassurance. Rather, ***medicine is for gamblers***: Gamblers who are happy to use subtle clues to change their outlook from pessimism to optimism and vice versa. Sometimes the gambling is scientific, rational, and methodical (odds-ratio analysis): sometimes it is not, as when the gambling is based on prior knowledge (vital but ill-defined) of one's patient, or the faint apprehension of terror in this new patient's eyes which shows you that there is something wrong, and that you don't yet know what it is.

Being lucky in both types of gambling is a requisite for being a successful doctor: after all we would all rather have a lucky doctor than a wise one. In this game, especially when it gets deadly serious, the chips are not just financial (the most cost-effective next step). They betoken time (for you are spending yourself as surely as you are spending money, as you walk the wards), your reputation, and the health or otherwise of your patient. So do not worry about the fact of gambling: ***gambling is your job***. If you cannot gamble you cannot cure. But make sure you assemble sufficient evidence to maximize your chances of being lucky.

An example of the odds ratio at work

A 50-yr-old man with known carcinoma of the lung has some transient neurological symptoms and a normal CT scan. Are these symptoms due to secondaries in the brain or to transient ischaemic attacks (TIAs)?

- The chance of secondaries in the brain which cause transient neurological symptoms is 0.045 given carcinoma of the lung.
- The chance of such secondaries not showing up on a CT scan is 0.1. Therefore the chance of this cluster of symptoms is 0.0045 (ie 0.045 × 0.1).
- The chance of a normal CT + transient CNS symptoms given a TIA is 0.9.
- The chance of a 50-yr-old man developing TIA is 0.0001. Therefore the odds ratio is 0.0045/(0.9 × 0.0001). This equals 50.

That is, the odds ratio is ~50 to 1 in favour of secondaries in the brain.

NB: It is only very rarely that the prior odds of a new disease are so high that the new disease is more likely, eg someone presenting with anaemia already known to have breast cancer, who lives in an African community where 50% of people have hookworm-induced anaemia, is likely to have anaemia due to hookworm *as well as* breast carcinoma.

Investigations change the odds

Only rarely does a single test provide a definitive diagnosis. More often tests alter the odds of a diagnosis. When taking a history and examining patients, we make various wagers with ourselves (often barely consciously) as to how likely various diagnoses are. Further test results simply affect these odds. A test is worthwhile if it alters diagnostic odds in a clinically useful way.

The effect of an investigation on the diagnostic odds

To work this out you need to know the *sensitivity* and *specificity* of the test. All tests have false positive and false negative rates, as summarized below:

Test result	Patients with the condition	Patients without the condition
Subjects appear to have the		

condition	True +ve (*a*)	False +ve (*b*)
Subjects appear *not* to have condition	False -ve (*c*)	True -ve (*d*)

Specificity:

How reliably is the test -ve in health? *d*/d+*b*.

Sensitivity:

How reliably is the test +ve in the disease? *a*/*a*+*c*. Screening tests need to have a high sensitivity: we know that 3-6% of chest pain patients sent home from casualty departments on the basis of a single ECG actually have myocardial infarction (MI). A single ECG is specific (77-100%), but not very sensitive for MI (56%). Troponin tests (p104) are more sensitive. So a doctor might use sensitivity/specificity data to act as follows.[8] If history and ECG suggest MI, admit (thrombolysis, p782). If story and ECG are not typical of MI, do a troponin test 6h after onset of chest pain—only send home if 'normal'.[1] This strategy reduces inappropriate discharge to ~1%.[2] Note that studies showing these effects are *very* dependent on the local prevalence of MI. A few more MIs in the 'troponin normal' group would radically alter these results.

Suppose we have a test of sensitivity 0.8 and specificity 0.9. The *likelihood ratio* of the disease given a positive result (LR+) is the ratio of the chance of having a positive test if the disease is present to the chance of having a positive test if the disease is absent [0.8/(1-0.9)]; ie 8:1 in the above example. In general: LR+ = sensitivity/(1-specificity)

LR-(likelihood ratio of the disease given a negative result) = (1-sensitivity)/specificity. (1-0.8/0.9, ie 2:9 in the above example.)

[1] Troponin T (TnT) ≲0.1μg/L (or troponin I ≲0.2μg/L; labs vary); what is normal is itself a statistical issue, p652—as is what counts as an MI.

Is there any point to this test?

Work out the 'posterior odds' assuming a first a +ve and then a -ve test result—via the equation: *posterior odds* = (*prior odds*) × (*likelihood ratio*). If your clinical assessment of a man with exercise-induced chest pain is that the odds of this being due to coronary artery disease (CAD) are 4 : 1 (80%), is it worth his doing an exercise tolerance test (sensitivity 0.72; specificity 0.8)?[9] If the test were positive, the odds in favour of CAD would be 4 × (0.72)/(1-0.8) = 14:1 (93%). If negative, they would be 4 × (1 - 0.72)/0.8 = 1.4 : 1 (58%), so the test has not in any way 'ruled out' CAD.

Experienced doctors are likely to have higher prior odds for the most likely diagnosis. The above shows that with high prior odds, a test must have high sensitivity and specificity for a negative result to bring the odds below 50%.

Another example is John, who is a 40-yr-old (not on NSAIDs, with no prior peptic ulcer) referred for '?endoscopy' because of dyspepsia. Before the result of a bedside test for *Helicobacter pylori* is known, he has a 50% chance of harbouring this organism, which, if present, is the probable cause of an ulcer.[10] The likelihood ratio for a -ve test result is 0.13[11] (sensitivity 0.88, specificity 0.91). ***If the test is negative***, the chance of John having *H. pylori* is <11% —and it may be OK to send him home with symptomatic treatment (eg ranitidine) without endoscopy—if there are no 'cancer (alarm) symptoms' (weight loss, dysphagia, etc, p235).[12] ***If the test is +ve***, the probability of *H. pylori* is >90%, strongly suggesting the need for specific anti-ulcer (anti-helicobacter) therapy, p235 and endoscopy if this does not cure his symptoms.

Number needed to treat (NNT)

If the risk of dying from an MI after 'standard treatment' is 10%, and a new treatment reduces this to 8%, then the **absolute risk reduction** is 2% (10 - 8%). The effect of the new drug is often made to look more impressive by quoting the **relative risk reduction**, ie 20% [(10 - 8/10) × 100%]. However, if 100 people with MI receive the drug, only ~2 would be expected to derive any benefit. In terms of **numbers needed to treat**, we might say that 50 patients would need treating to save one additional life ([1/absolute risk reduction] × 100). NNTs provide a useful way of quantifying benefit, but do not take into account treatment costs or the degree of potential benefit. The converse of NNT is number needed to harm. This is the number of people who must receive a treatment in order to produce one adverse event.

In some preventive studies of mild hypertension in the young, ~800 people may need treating according to a certain regimen to prevent one stroke. When expressed like this, the treatment seems less wonderful.

One of the strengths of NNT is that it is context-dependent. If a new antihypertension regimen is being compared with an old regimen where the NNT was 800 and the new regimen is only marginally better, the NNT to prevent one death or stroke *by adopting the new regimen in place of the old* may run into many thousands, as will your drugs bill if the new drug is more expensive.

One problem with NNTs occurs if there is a large placebo effect, eg in pain relief. Say the placebo response rate is 40% and that of a new analgesic is 60%. NNT is 5. Perhaps it is better to say to patients starting the new drug that 60% respond. Also, one needs to be clear whether the mean or median is given as the length of follow-up.[13] For further examples, see www.nntonline.net.

Screening

Modified Wilson criteria for screening

(1-10 spells ***iatrogenic***[1] —to remind us that in treating healthy populations we have an especial duty to do no harm.)

1. The condition screened for should be an **i**mportant one.
2. There should be an **a**cceptable treatment for the disease.
3. Diagnostic and **t**reatment facilities should be available.
4. A **r**ecognizable latent or early symptomatic stage is required.
5. **O**pinions on who to treat as patients must be agreed.
6. The test must be of *high discriminatory power* (see below), *valid* (measuring what it purports to measure, not surrogate markers which might not correlate with reality), and be *reproducible*—with safety **g**uaranteed.
7. The **e**xamination must be acceptable to the patient.
8. The untreated **n**atural history of the disease must be known.
9. A simple **i**nexpensive test should be all that is required.
10. Screening must be **c**ontinuous (ie not a 'one-off' affair).

Summary: screening tests must be cost-effective.

Problems

All screening programs do harm; some do good as well. J Muir Gray 2004 *Brit J Gen Pr* 54 292

1. Those most at risk do not present for screening, thus increasing the gap between the healthy and the unhealthy—the *inverse care law* (p12).
2. The 'worried well' overload services by seeking repeat screening.
3. Services for investigating those testing positive are inadequate.
4. Those who are false positives suffer stress while awaiting investigation, and remain anxious about their health despite reassurance.

▸Before screening, the chances of harming a patient (by anxiety or subsequent invasive tests), as well as any benefits must be quantified: this is ***Rees' rule***.[14]

Examples of NNTs

Study	*Outcome*	*NNT*
Statins (p101) for primary prevention[1]	Death (MI)	931 (78) for 5yrs
Statins for secondary prevention (4S)	Death (MI)	30 (15) for 5.4yrs
Mild hypertension (MRC trial)	Stroke	850 for 1yr
Systolic hypertension in elderly (SHEP)	Stroke	43 for 4.5yrs
Aspirin in acute MI (ISIS-1)	Death	40

Streptokinase in acute MI (ISIS2)	Death	40
ACE-i for CCF (NYHA class IV (p121))	Death	6 for 1yr

[1] Meta-analysis *Bandolier* 17(7), 41(3), 50(8)

Keep your eye on the question

NNTs can vary markedly if the question is slightly rephrased—eg from being about primary prevention to being about secondary prevention (as in the statin example above).[15]

NNT confidence intervals

Get these by taking reciprocals of the values defining the confidence interval for the absolute risk reduction (ARR). If ARR ≈ 10% with a 95% confidence interval of 5-15%, NNT ≈ 10 (ie 100/10) and the 95% NNT-confidence interval ≈ 6.7-20 (ie 100/15 to 100/5). Non-significant treatment effects are problematic as NNTs can only be positive; here, give NNT *without* confidence intervals (Altman's rule).[16]

Examples of effective screening

Cervical smears for cancer

Mammography for breast cancer

Finding smokers (+quitting advice)

Looking for malignant hypertension

Unproven/ineffective screening

Mental test score (dementia)

Urine tests (diabetes; kidney disease)

Antenatal procedures (OHCS p8)

PSA screening (prostate cancer, p607)

NB: Screening for cervical cancer (OHCS p272) and mammography (p610) are far from perfect: both are liable to false negatives, and a negative result is interpreted as 'I'm fine' *(*and may be seen as a licence to take risks). So signs of interval cancers (arising between screenings) may be wished away by patients who assume they are in the clear.

Acknowledgements

See also *QALYS*, p12

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Clinical Chemistry

On being normal in the society of numbers

Laboratory medicine reduces our patients to a few easy-to-handle numbers: this is the discipline's great attraction—and its greatest danger. The normal range (reference interval) is usually that which includes 95% of patients. If variation is randomly distributed, 2.5% of our results will be 'too high', and 2.5% 'too low' on an average day, when dealing with apparently normal people. This statistical definition of normality is the simplest. Other definitions may be *normative*—ie stating what an upper or lower limit *should* be. Eg the upper end of the reference interval for plasma cholesterol may be given as 6mmol/L because this is what biochemists state to be the *desired* maximum, while the risk of CHD increases above 5.2mmol/L. 40% of people in some populations will have a plasma cholesterol greater than 6mmol/L and thus may be at increased risk. The WHO definition of anaemia in pregnancy is an Hb of <11g/dL, which makes 20% of mothers anaemic. This 'lax' criterion has the presumed benefit of triggering actions which result in fewer deaths by haemorrhage. So do not just ask 'What is the normal range?'—also enquire about who set the range, for what population, and for what reason.

▸Normal values can have hidden historical, social, and political desiderata—just like the normal values novelists ascribe to their characters: '*…Conventions and traditions, I suppose, work blindly but surely for the preservation of the normal type; for the extinction of proud, resolute and unusual individuals… Society must go on, I suppose, and society can only exist if the normal, if the virtuous, and the slightly deceitful flourish, and if the passionate, the headstrong, and the too-truthful are condemned to suicide and to madness. Yes, society must go on; it must breed, like rabbits. That is what we are here for … But, at any rate, there is always Leonora to cheer you up; I don't want to sadden you. Her husband is quite an economical person of so normal a figure that he can get quite a large proportion of his clothes ready-made. That is the great desideratum of life…*'

Ford Maddox Ford 1915 *The Good Soldier*, Penguin, p214 & p228

The essence of laboratory medicine

Only do a test if the result will influence management. Make sure you look at the result! Explain to the patient where this test fits in to his or her overall plan of management. ▸Do not interpret laboratory results except in the light of clinical assessment (unless forced to by examiners).

▸If there is disparity: trust clinical judgement and repeat the test. Reference intervals (normal ranges) are usually defined as the interval, symmetrical about the mean, containing 95% of results on the population studied. The more tests you run, the greater the probability of an 'abnormal' result of no clinical significance: see p737.

Artefacts

Delayed analysis for plasma potassium (p654).

Anion gap (AG)

Reflects unmeasured anions (p658).

Biochemistry results major disease patterns

(↑ = raised, ↓ = lowered)

Dehydration:

Urea↑, albumin↑ (useful to plot change in a patient's condition). Haematocrit (PCV)↑, creatinine↑; also urine volume↓; skin turgor↓.

Renal failure:

Creatinine↑, urea↑, AG↑, K^+↑, PO_4^{3-} ↑, HCO_3^-↓.

Thiazide and loop diuretics:

Sodium↓, potassium↓, HCO_3^-↑, urea↑.

Bone disease	*Ca^{2+}*	*PO_4^{3-}*	*Alk phos*
Osteoporosis	Normal	Normal	Normal
Osteomalacia	↓	↓	↑
Paget's	Normal	Normal	↑↑

Myeloma	↑	↑, normal	Normal
Bone metastases	↑	↑, normal	↑
1° Hyperparathyroidism	↑	↓, normal	Normal, ↑
Hypoparathyroidism	↓	↑	Normal
Renal failure (low GFR)	↓	↑	Normal, ↑

Hepatocellular disease:
Bilirubin↑, AST↑ (alk phos slightly↑, albumin↓). For details of the differences between AST and ALT, see p275.

Cholestasis:
Bilirubin↑, γGT↑↑, alk phos↑↑, AST↑.

Myocardial infarction:
troponin T/I ↑, CK↑, AST↑, LDH↑ (p105).

Diabetes mellitus:
Glucose↑, (HCO_3^-↓ if acidotic).

Addison's disease:
Potassium↑, sodium↓.

Cushing's syndrome:
May show potassium↓, HCO_3^-↑, sodium↑.

Conn's syndrome:
May present with potassium↓, HCO_3^-↑ (and high blood pressure). Sodium normal or ↑.

Diabetes insipidus:
Sodium↑, plasma osmolality↑, urine osmolality ñ (both hypercalcaemia and hypokalaemia may cause nephrogenic diabetes insipidus).

Inappropriate ADH secretion:
Na^+↓ with normal or low urea and creatinine, plasma osmolality ñ. Urine osmolality ↑ (and > than plasma osmolality), urine Na ↑ (>20mmol/L).

Excess alcohol intake:
Evidence of hepatocellular disease. Early evidence in ÿGT ↑, MCV↑, ethanol in blood before lunch.

Some immunodeficiency states:
Normal serum albumin but *low* total protein (low as immunoglobulins are missing—also making cross-matching difficult because expected haemagglutinins are absent; OHCS p198).

Life-threatening biochemical derangements
See p655.

The laboratory and ward tests

▸Laboratory staff like to have contact with you.

A laboratory decalogue

1. Interest someone from the laboratory in your patient's problem.
2. Fill in the request form fully.
3. Give clinical details, not your preferred diagnosis.

4. Ensure that the lab knows who to contact.
5. Label specimens as well as the request form.
6. Follow the hospital labelling routine for cross-matching.
7. Find out when analysers run, especially batched assays.
8. Talk with the lab before requesting an unusual test.
9. Be thoughtful: at 1630h the routine results are being sorted.
10. Plot results graphically: abnormalities show sooner.

Artefacts and pitfalls in laboratory tests

- Do not take blood sample from an arm which has IV fluid running into it.
- Repeat any unexpected result before acting on it.
- For clotting time do not sample from a heparinized IV catheter.
- Serum K^+ is overestimated if sample is old or haemolysed (this occurs if venepuncture is difficult).
- If using Vacutainers, fill *plain* tubes first—otherwise, anticoagulant contamination from previous tubes can cause errors.
- Total calcium results are affected by albumin concentration (p670).
- INR may be overestimated if citrate bottles are under-filled.
- Drugs may cause *analytic* errors (eg prednisolone cross-reacts with cortisol). Be suspicious if results are unexpected.
- Food may affect result, eg bananas raise urinary HIAA (p270).

Using dipsticks

Store dipsticks in a closed container in a cool, dry place, not refrigerated. If improperly stored, or past expiry date, do not use. For urine tests, dip the dipstick briefly in urine, run edge of strip along container and hold strip horizontally. **Read at the specified time**—check instructions for the type of stick. For haematuria, proteinuria, etc., see p278.

Urine specific gravity

(SG) can be measured by dipstick. It is not a good measure of osmolality. Causes of low SG (<1.003) are: diabetes insipidus, renal failure. Causes of high SG (>1.025) are: diabetes mellitus, adrenal insufficiency, liver disease, heart failure, acute water loss. Hydrometers underestimate SG by 0.001 per 3°C above 16°C.

Sources of error in interpreting dipstick results

Bilirubin:

False +ve: phenothiazines. False -ve: urine not fresh, rifampicin.

Urobilinogen:

False -ve: urine not fresh. Normally present in urine due to metabolism of bilirubin in the gut by bacteria and subsequent absorption. Excess may give a false +ve test for prophobilinogen.

Ketones:

L-dopa affects colour (can give false +ve). 3-hydroxybutyrate gives a false -ve.

Blood:

False +ve: myoglobin, profuse bacterial growth. False -ve: ascorbic acid.

Urine glucose:

Depends on test. Pads with glucose oxidase are not affected by other reducing sugars (unlike Clinitest®) but can give false +ve to peroxide, chlorine; and false -ve with ascorbic acid, salicylate, L-dopa.

Protein:

Highly alkaline urine can give false +ve.

Blood glucose:

Sticks use enzymatic method and are glucose specific. A major source of error is applying too little blood (a large drop to cover the pad is necessary), and poor timing. Reflectance meters increase precision but introduce new sources of error.

Laboratory results: when to take action NOW

- On receiving a dangerous result, first check the name and date.
- Go to the bedside. If the patient is conscious, turn off any IVI (until fluid is checked: a mistake may have been made) and ask the patient how he or she is. *Any fits, faints, collapses, or unexpected symptoms?*
- Be sceptical of an unexpectedly wildly abnormal result with a well patient. Compare with previous values. Could the specimens have got muddled up? Is there an artefact? Was the sample taken from the 'drip' arm? Is a low calcium be due to a low albumin (p670)? Perhaps the lab is using a new analyser with a faulty wash cycle? ▸*When in doubt, repeat the test.*

The values chosen below are somewhat arbitrary and must be taken as a guide only. Many results less extreme than those below will be just as dangerous if the patient is old, immunosuppressed, or has some other pathology such as pneumonia.

Plasma biochemistry

(beware electrocardiological ± CNS events, eg fits)

Calcium (corrected for albumin) >3.5mmol/L. *If shortening* Q-T *interval on* ECG (p82), *then dangerous hypercalcaemia.* See p672.

Calcium (corrected for albumin) <2.0mmol/L + symptoms such as tetany or long Q-T = *Dangerous hypocalcaemia.* See p670.

Glucose <2mmol/L = *Hypoglycaemia. Glucose 50*mL *50% IV if coma.*

Glucose >20mmol/L = *Severe hyperglycaemia. Is parenteral insulin needed?* See p814.

Potassium <2.5mmol/L = *Dangerous hypokalaemia, esp. if on digoxin.*

Potassium >6.5mmol/L = *Dangerous hyperkalaemia.* See p668.

Sodium <120mmol/L = *Dangerous hyponatraemia.* See p666.

Sodium >155mmol/L = *Dangerous hypernatraemia.* See p666.

Blood gases

P_aO_2 <8.0kPa = *Severe hypoxia. Give* O_2. Go to p172.

pH <7.1 = *Dangerous acidosis. Go to* p658 *to determine the cause.*

Haematology results

Hb <7g/dL with low mean cell volume (<75fL) or history of bleeding.

This patient may need urgent transfusion (no spare capacity). See p570.

Platelets <40×10^9/L *May need a platelet transfusion; call a haematologist.*

Plasmodium falciparum seen *Start antimalarials now.* See p384.

ESR >30mm/h + headache *Could there be giant cell arteritis?* See p542.

CSF results

>1 neutrophil/mm^3 *Is there meningitis: usually >1000 neutrophils?* See p806.

Gram stain *Talk to a microbiologist; urgent blind therapy.* See p806.

Conflicting, equivocal, or inexplicable results

▸Get prompt help.

Intravenous fluid therapy (See also p664 & p666)

If fluids cannot be given orally, they are normally given intravenously. Alternatives are via a central venous line or subcutaneously. However, remember that all cannulae carry a risk of MRSA infection: femoral > jugular > subclavian > peripheral.

Three principles of fluid therapy

1. **Maintain normal daily requirements** About 2500mL fluid containing roughly 100mmol sodium and 70mmol potassium per 24h are required. A good regimen is 2L of 5% dextrose and 1L of 0.9% saline every 30h with 20-30mmol of potassium per litre of fluid. Post-operative patients may need more fluid and more saline depending on operative losses. If the serum sodium is rising, then more dextrose and less saline is required.
2. **Replace additional losses** The amount and type of fluid lost is a guide (check fluid charts, drainage bottles, etc.). Remember that febrile patients have increased insensible losses. In practice, the problem is usually whether to give saline or dextrose. Most body fluids (eg vomit) contain salt, but less than plasma, and thus replacement will require a mixture of saline and dextrose. Shocked patients require resuscitation with saline, or a colloidal plasma expander, eg Dextran® or Haemaccel®, but not dextrose (caution in liver failure, see below). Note that Dextran® interferes with platelet function and may prolong bleeding. Patients with acute blood loss require transfusion with packed cells or whole blood. As a holding measure, colloid or saline may be used while blood is being cross-matched. If more than 1L is required then group O-negative or group-specific blood should be used (see p778).
3. **Special cases** Patients with ***heart failure*** and the ***elderly*** are at greater risk of pulmonary oedema if given too much fluid. They also tolerate saline less well since Na+ retention accompanies heart failure. If IV fluids must be given, use with care. Patients with ***liver failure***, despite being oedematous and often hyponatraemic, have increased total body sodium, and saline should **not** be used in resuscitation; salt-poor albumin solution or blood should be given. Fluid maintenance for ***children*** is calculated as: 100mL/kg for the first 10kg; 50mL/kg for the next 10kg; and 20mL/kg thereafter—all per 24hrs. Usually given as dextrose-saline (4% dextrose 0.18% saline).

Types of fluid

0.9% saline ('normal saline')

has about the same sodium content as plasma (150mmol/L) and is isotonic with plasma.

5% dextrose

is isotonic, but only contains 278mmol/L glucose, ie 50g/L (dextrose is glucose), and is a way of giving water, since the liver rapidly metabolizes all the glucose leaving only water. It provides little energy. More concentrated glucose solutions exist, and may be used in the treatment of hypoglycaemia. They are hypertonic and irritant to veins. Therefore, care in their use is needed, and infusion sites should be inspected regularly, and flushed with saline after use.

Dextrose-saline (one-fifth normal saline)

is also isotonic, containing 0.18% saline (30mmol/L of sodium) and 4% glucose (222mmol/L). It has roughly the concentration of saline required for normal fluid maintenance, when given 10 hourly. Hypertonic and hypotonic saline solutions are available, but are for specialist use only.

Hartmann's solution

contains: Na^+ 131mmol/L, Cl^- 111mmol/L, lactate 29mmol/L, K^+ 5mmol/L, HCO_3^- 29 mmol/L, and Ca^{2+} 2mmol/L. Some consider it more 'physiological'.[1]

▸The maximum concentration of K^+ that is safe to infuse via a peripheral line is 80mmol/L, at a maximum rate of 40mmol/h. Higher concentrates risk phlebitis, and faster rates dysrhythmias. Give more concentrated solutions via a central line.

▸Examine patients regularly to assess fluid balance: look for signs of heart failure (p120)—excess fluid given? Excess dextrose iv may lead to water overload (p666).

▸Daily weighing helps to monitor overall fluid balance, as will fluid balance charts.

IV fluids on the surgical ward

Pre-op fluids

Avoid rushing dehydrated patients to theatre before adequate resuscitation. Anaesthesia compounds shock by causing vasodilatation and depressing cardiac contractility. Exceptions are exsanguination from a ruptured ectopic pregnancy, major trauma, a ruptured aortic aneurysm, or severe upper GI haemorrhage, where blood is lost faster than it can be replaced.

Post-operative fluids

A normal requirement is 2-3L/24h which allows for urinary, faecal, and insensible loss.

A standard regimen:

(One of many) 2L 5% dextrose with 1L 0.9% saline/24h. Add K^+ post-op (20mmol/L). See p656 for other examples. More K^+ is needed if losses are from the gut (eg diarrhoea, vomiting, intestinal fistula, high output stoma). More saline is appropriate for those at risk of hyponatraemia: ▸See BOX.

When to increase the above regimen:

- Dehydration: this may be ≥5L if severe. Replace this slowly.
- Shock (all causes, except for cardiogenic shock).
- Operative losses: check operation notes for extent of bleeding in theatre.
- Losses from gut: replace NGT aspirate volume with 0.9% saline.
- Transpiration losses: feverish patients and burns.
- Pancreatitis: large pools of sequestered fluid which must be considered.
- Losses from surgical drains: check fluid charts and replace significant losses.
- Low urine output (the night after surgery) is almost always due to inadequate infusion of fluid. Check JVP, and review for signs of cardiac failure. Treat by increasing IVI rate unless patient is in heart or renal failure, or profusely bleeding (when blood should be transfused). If in doubt, a fluid challenge may be indicated: 200mL of colloid (eg Gelofusine®) over 30-60 min, with monitoring of urine output. Then you may increase IVI rate to 1L/h of 0.9% saline for 2-3h. Only if output does not increase should a diuretic be considered; a CVP line may be needed if estimation of fluid balance is difficult. A normal value is 0-5cm of water relative to the sternal angle. Measuring urinary Na^+ may also help.

If not catheterized exclude retention, but otherwise do not catheterize until absolutely necessary.

When to decrease the above regimen:

Renal failure—give 500mL plus the previous day's output (▸with no K^+). *Heart failure*—halve the volume (1-1.5L/24h).

Guidelines for success (see also p664)

- Be simple. Chart losses and replace them. Know the urine output. Aim for 60mL/h; 30mL/h is the minimum in adults (½mL/kg/h).
- Measure plasma U&E if the patient is ill. Regular U&Es are not needed on young, fit people with good kidneys.
- Start oral fluids as soon as possible.

What fluids to use

▸*Haemorrhagic/hypovolaemic shock* (see p778):

Insert 2 large IV cannulae, for fast fluid infusion. Start with crystalloid (eg 0.9% saline) or colloid (eg Gelofusine®) until blood is available. The advantage of crystalloids is that they are cheap—but they do not stay as long in the intravascular compartment as colloids, as they equilibrate with the total extracellular volume (dextrose is useless for resuscitation as it rapidly equilibrates with the enormous intracellular volume). In practice, the best results are achieved by combining crystalloids and colloids. Aim to keep the haematocrit at ~0.3, and urine flowing at >30mL/h. Monitor pulse and BP often.

Septicaemic shock:

Use a plasma-like substance (eg Gelofusine®).

Heart or liver failure:

Avoid sodium loads: use 5% dextrose.

Excessive vomiting:

Use 0.9% saline: replace losses, including K^+.

Acid-base balance

Arterial blood pH is closely regulated in health to 7.40 ± 0.05 by various mechanisms including bicarbonate, other plasma buffers, and the kidney. Acid-base disorders needlessly confuse many people, but if a few simple rules are applied, then interpretation and diagnosis are easy.

- pH <7.35 is an acidosis; pH >7.45 is an alkalosis.
- CO_2 is an acidic gas (normal concentration 4.7-6.0kPa).
- HCO_3^- alkaline (normal concentration 22-28mmol/L).
- 1° changes in HCO_3^- are termed ***metabolic***, and of CO_2 ***respiratory***.

1. Look at the pH: is there an acidosis or alkalosis?
2. Is the CO_2 abnormal? If so, is the change in keeping with the pH (ie if there is an acidosis, is CO_2 raised)? If so it is a ***respiratory*** problem. If there is no change, or an OPPOSITE one, then the change is compensatory.
3. Is the HCO_3^- abnormal, and if so, is the change in keeping with the pH? If so the problem is a ***metabolic*** one.

An example

pH 7.05, CO_2 2.0kPa, HCO_3^- 8.0mmol/L.

There is an *acidosis*, and the CO_2 is low, and so is a compensatory change. The HCO_3^- is low, and is thus the cause; ie a *metabolic acidosis*.

Metabolic acidosis

pH ↓, HCO_3^- ↓

To help diagnosis, work out the anion gap (AG)—this estimates unmeasured anions (they are hard to measure directly). It is calculated as the difference between plasma cations (Na^+ & K^+) and anions (Cl^- & HCO_3^-). Normal range: 10-18mmol/L. It is a measure of 'fixed' or organic acids—eg phosphate, ketones, and lactate.

Causes of metabolic acidosis and increased anion gap:

Due to increased production of fixed/organic acids. HCO_3^- falls and unmeasured anions associated with the acids accumulate.

- Lactic acid (shock, infection, hypoxia).
- Urate (renal failure).
- Ketones (diabetes mellitus, alcohol).

- Drugs/toxins (salicylates, biguanides, ethylene glycol, methanol).

Causes of metabolic acidosis and normal anion gap:

Due to loss of bicarbonate or ingestion of H^+ ions (Cl^- is retained).

- Renal tubular acidosis.
- Diarrhoea.
- Drugs (acetazolamide).
- Addison's disease.
- Pancreatic fistulae.
- Ammonium chloride ingestion.

Metabolic alkalosis

pH↑, HCO_3^-↑

- Vomiting.
- K^+ depletion (diuretics).
- Burns.
- Ingestion of base.

Respiratory acidosis

pH↓ CO_2↑

• Any lung, neuromuscular, or physical cause of respiratory failure (p172).

▸Look at the P_aO_2. It will probably be low. Is oxygen therapy required?

▸Use O_2 with care if chronic obstructive pulmonary disease (COPD) is the underlying cause, as too much oxygen may make matters worse (p168).

Respiratory alkalosis

pH↑, CO_2↓

A result of hyperventilation.

CNS causes:

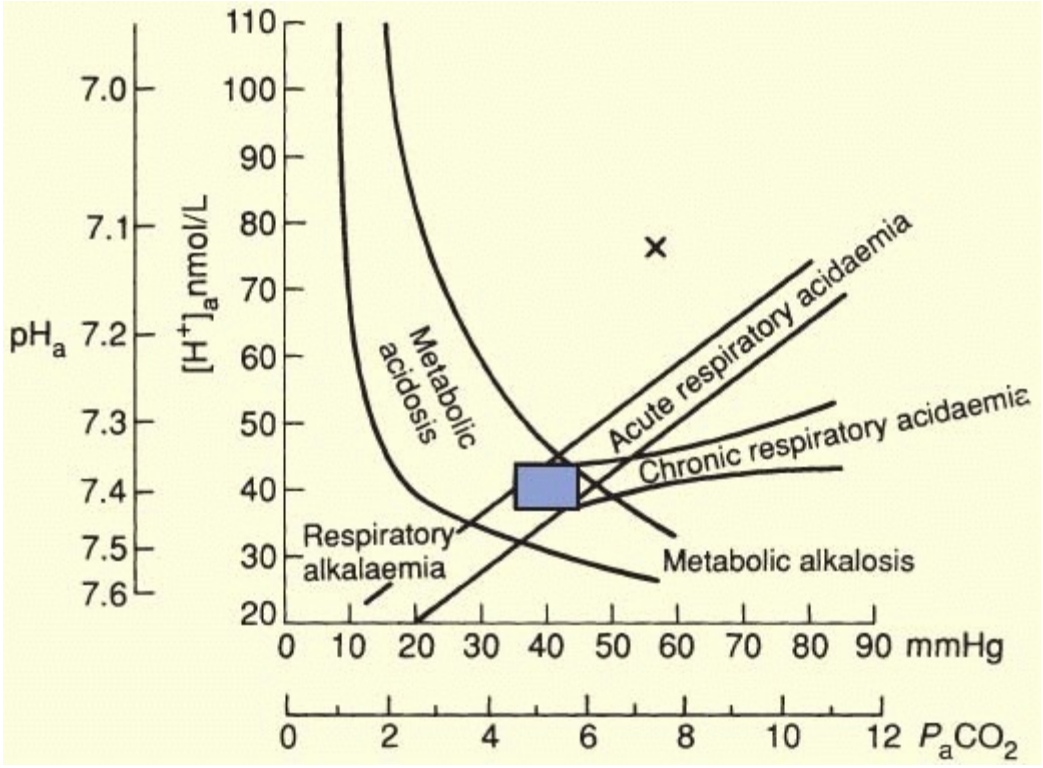
Stroke; subarachnoid bleed; meningitis.

Others:

Anxiety; altitude; T°↑; pregnancy; pulmonary emboli (reflex hyperventilation); drugs, eg salicylates.

Terminology

To aid understanding, we have used the terms acidosis and alkalosis, where a purist would sometimes have used acid-, alkal-aemia.



The shaded area represents normality. This method is very powerful. The result represented by point ×, eg indicates that the acidaemia is in part respiratory and in part metabolic. Seek a cause for each.

Kidney function [2]

The kidney controls the elimination of many substances. It also makes erythropoietin, renin, and 1,25-dihydroxycholecalciferol. Filtered sodium is exchanged with potassium and hydrogen ions by exchanges and channels in the distal tubule. Glucose spills over into urine when plasma concentration is above renal threshold for reabsorption (≈10mmol/L, but varies from person to person, and is lower in pregnancy).

Creatinine clearance

is a measure of glomerular filtration rate (GFR)—the volume of fluid filtered by glomeruli per minute. About 99% of this fluid is reabsorbed. Creatinine once filtered is only slightly reabsorbed. Thus:

$[\text{Creatinine}]^{\text{plasma}} \times \text{creatinine clearance} = [\text{creatinine}]^{\text{urine}} \times \text{urine flow rate}$

GFR can also be measured by injection of a radioisotope followed by repeated blood sampling (eg Cr^{51}EDTA) or an isotope scan (eg DTPA Tc^{99}). These methods allow a more accurate estimate of GFR and may also provide split renal function.

To measure creatinine clearance

Collect urine over 24h. At the start, void and discard urine; from then on, and at end of 24h, void into the bottle. Take sample for plasma creatinine once during 24h. Use formula above. Take care with units. Major sources of error are calculation (eg units) and failure to collect all urine. Normal value is ≈125mL/min. The conversion factor from µmol/L to mg/dL for creatinine is 88.4; i.e. mg/dL = µmol ÷ 88.4.

Estimating kidney function

24hr urine collection is often unreliable, and an alternative approach is to estimate creatinine clearance or GFR using either the Cockcoft-Gault or MDRD equations (see BOX). The protein : creatinine ratio in a spot morning urine is an alternative way to monitor chronic renal decline: see p278.

Abnormal kidney function

There are three major biochemical pictures.

- **Low GFR** (classic acute renal failure)

  Plasma biochemistry: The following are raised: urea, creatinine, potassium, hydrogen ions, urate, phosphate, anion gap.

  The following are lowered: calcium, bicarbonate.

  Other findings: Oliguria.

  Diagnosis: Low GFR (creatinine clearance).

  Causes: Early acute oliguric renal failure (p292), long-standing chronic renal failure (p294).

- **Tubular dysfunction** (damage to tubules)

  Plasma biochemistry: The following are lowered: potassium, phosphate, urate, bicarbonate. There is acidosis. Urea and creatinine are normal.

  Other findings *(highly variable):* Polyuria with glucose, amino acids, proteins (lysozyme, β_2-microglobulin), and phosphate in urine.

Diagnosis: Test renal concentrating ability (p224).

Cause: Recovery from acute renal failure. Also: hypercalcaemia, hyperuricaemia, myeloma, pyelonephritis, hypokalaemia, Wilson's disease, galactosaemia, heavy metal poisoning.

- **Chronic renal failure:** As GFR reduces, creatinine, urea, phosphate and urate all increase. Bicarbonate (and Hb) decrease(s). Eventually potassium increases and pH decreases. There may also be osteomalacia.

Assessment of renal failure may need to be combined with other investigations to reach diagnosis, eg urine microscopy (p278), radiology (p280), or renal biopsy (in glomerulonephritis), or ultrasound.

Creatinine clearance: a worked example

Suppose: urine creatinine concentration = **u** mmol/L; plasma creatinine concentration = **p** µmol/L; 24h urine volume = **v** /mL.

There are 1440min/24h (used below to convert urine flow rate from volume/24h into volume per min). **p**/1000 is used to convert micromoles to millimoles.

Creatinine clearance = **u** × **v**/1440 ÷ **p**/1000mL/min **u** × **v**/**p** × 0.7.

Thus, if: **u**=5mmol/L; **p** =120µmol/L; **v** = 2500mL;

creatinine clearance = 5 × (2500/120) × 0.7 = 73mL/min.

Estimating GFR

Calculating GFR is useful because it is easy to underestimate the degree of renal impairment if just serum creatinine is measured—especially in the elderly and women. Subjects with low muscle mass can have a 'normal' serum creatinine, despite a significant reduction in GFR eg 70mL/min. This can be particularly important when potentially toxic drugs that are largely excreted by the kidney, or renotoxic drugs are prescribed.

A number of formulae can be used. The **MDRD** (*Modification of Diet in Renal Disease Study Group*) equation provides an estimate of GFR from 4 simple parameters: ***serum creatinine, age, gender and race (black/non-black)***, and is one of the best validated.[3] Many labs are now routinely reporting estimated GFR (eGFR) on all U&E reports. However, the confidence intervals can be wide (90% of values are within 30% of the true value, and 98% within 50%), and care should be taken in unusual situations eg rapidly changing renal function, very low muscle mass. It is also better in subjects with a low GFR.

Cockcroft-Gault equation provides an estimate of creatinine clearance:[4]

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age in years}) \times (\text{wt in kg})}{72 \times \text{serum creatinine in mg/dL}}$$

For women, multiply above by 0.85. Unreliable if: unstable renal function; very obese; oedematous. For an example adjusting for ideal body weight, see p434.

Classifying renal impairment in chronic kidney disease (CKD)

Chronic kidney disease can be classified based on the presence of kidney damage and the GFR, irrespective of the diagnosis.[1]

Stage	GFR (mL/min)	Notes
1	>90	Normal or ↑GFR with other evidence of renal damage

2	60-89	Slight ↓GFR with other evidence of renal damage
3	30-59	Moderate ↓GFR with(out) evidence of renal damage
4	15-29	Severe ↓GFR with(out) evidence of renal damage
5	<15	Established renal failure

Other evidence of renal damage = proteinuria, haematuria, or evidence of renal disease. One reason to classify renal impairment is to motivate secondary prevention, eg to 'mandate' ACE-i or ARA if BP >140/85 especially if proteinuria is present or stage ≥3. *Problems using MDRD formula to grade renal disease:*

- The MDRD formula was validated for patients with *established* renal failure: its use for screening *general* populations is questionable.
- The formula is less accurate the milder the CKD. In one unpeer-reviewed study using ^{51}Cr-EDTA measured GFR (n=178), only 79% were correctly placed in stage 3, and 59% in stage 2.[5] ▸Remember that the eGFR is only a screening test and, especially in mild renal impairment, may err on the side of pessimism.

Urate and the kidney

Causes of hyperuricaemia

High levels of urate in the blood (hyperuricaemia) may result from increased turnover or reduced excretion of urate. Either may be drug-induced.

- ***Drugs:*** Cytotoxics; thiazides; pyrazinamide.
- ***Increased cell turnover:*** Lymphoma; leukaemia; psoriasis; haemolysis; muscle death (rhabdomyolysis, p299 *Tumour lysis syndrome:* See p514.
- ***Reduced excretion:*** Primary gout (p534); chronic renal failure; lead nephropathy; hyperparathyroidism; pre-eclampsia (OHCS p48).
- ***In addition:*** Hyperuricaemia may be associated with hypertension and hyperlipidaemia. Urate may be raised in disorders of purine synthesis such as the Lesch-Nyhan syndrome (OHCS p648).

Hyperuricaemia and renal failure

Severe renal failure from any cause may be associated with hyperuricaemia, and very rarely this may give rise to gout. Sometimes the relationship of cause and effect is reversed so that it is the hyperuricaemia that causes the renal failure. This can occur following cytotoxic treatment (***tumour lysis syndrome***), eg in leukaemia; and in muscle necrosis.

How urate causes renal failure

In some instances, ureteric obstruction from urate crystals occurs. This responds to retrograde ureteric catheterization and lavage. More commonly, urate precipitates in the renal tubules. This may occur at plasma levels ≥1.19mmol/L.

Prevention of renal failure

Before starting chemotherapy, ensure good hydration; consider alkalinization of the urine; and initiate allopurinol (a xanthine oxidase inhibitor), which prevents a sharp rise in urate following chemotherapy. For a specific dosage regimen, see p514. There is a remote risk of inducing xanthine nephropathy.

Treatment of hyperuricaemic acute renal failure

Prompt rehydration and alkalinization of the urine after excluding bilateral ureteric obstruction. Once oliguria is established, haemodialysis is required and should be used in preference to peritoneal dialysis.

Gout

See p534.

Electrolyte physiology

Most sodium is extracellular and is pumped out of the cell by the sodium pump, in exchange for K^+ (ratio of 3:2) which requires energy from ATP.

Osmolarity is the number of osmoles per *litre* of solution.

Osmolality is the number of osmoles per kilogram of solvent (*normal:* 280-300).

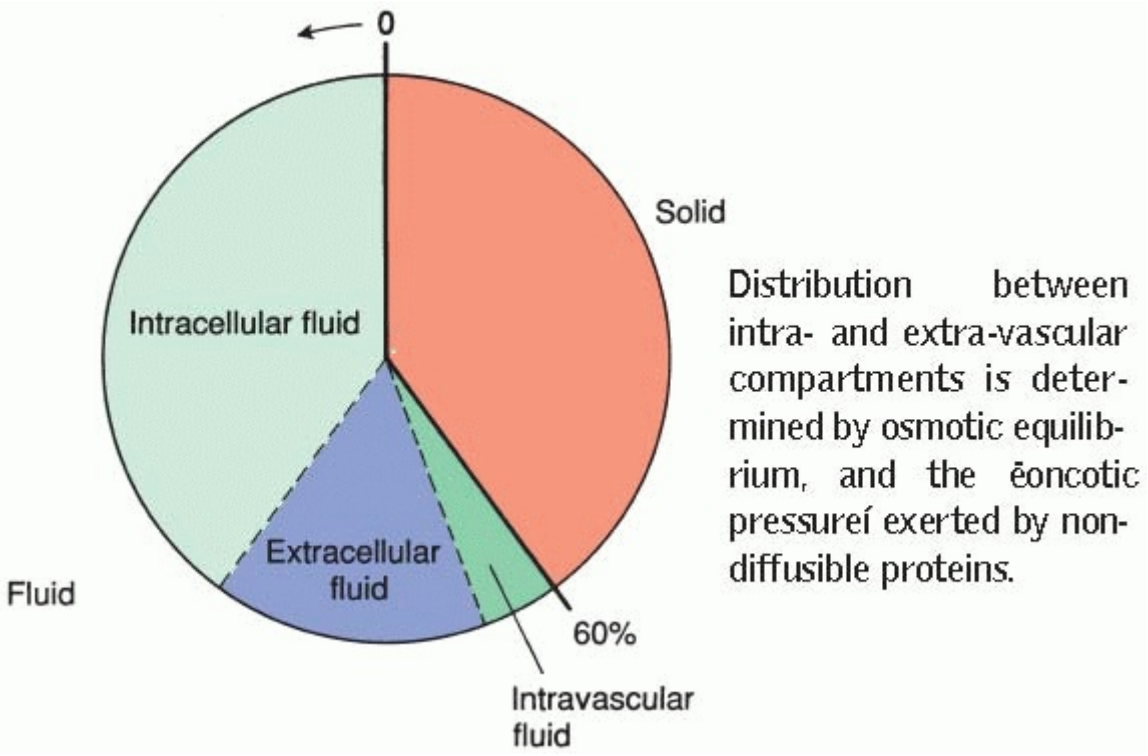
A mole is the molecular weight expressed in grams.

To estimate plasma osmolality:

$2(Na^+ + K^+)$ + Urea + Glucose. If the measured osmolality is greater than this (ie an osmolar gap of >10mmol/L), consider: diabetes mellitus, high blood ethanol, methanol, mannitol, or ethylene glycol.

Fluid compartments

For 70kg man: *total fluid* = 42L (60% body weight). *Intracellular fluid* = 28L (67% body fluid), *extracellular fluid* = 14L (33% body fluid). *Intravascular component* = 5L of blood (3L plasma).



Fluid balance

over 24h is roughly:

Input (mL water)	*Output (mL water)*
Drink: 1500	Urine: 1500
In food: 800	Insensible loss: 800
Metabolism of food: 200	Stool: 200

Total: **2500**	Total: **2500**

Control of sodium

Renin is produced by the juxtaglomerular apparatus in response to decreased renal blood flow, and catalyses the conversion of *angiotensinogen* (a peptide made by the liver) to *angiotensin I*. This is then converted by angiotensin-converting enzyme (ACE), which is located in the lung and blood vessels to *angiotensin II*. The latter has several important actions including efferent renal arteriolar constriction (so increasing perfusion pressure); peripheral vasoconstriction; and stimulation of the adrenal cortex to produce *aldosterone*, which activates the sodium pump in the distal renal tubule leading to reabsorption of sodium and water from the urine, in exchange for potassium and hydrogen ions.

High GFR

*(*p660*) results in high sodium loss*.

High renal tubular blood flow

and haemodilution decrease sodium reabsorption in the proximal tubule.

Control of water

Controlled mainly by sodium concentration. ↑Plasma osmolality causes thirst, and the release of antidiuretic hormone (ADH) from the posterior pituitary which increases the passive water reabsorption from the renal collecting duct, by opening water channels to allow water to flow from the hypotonic luminal fluid into the hypertonic renal interstitium.

Natriuretic peptides

Secretory granules have long been known to exist in the atria, and if homogenized atrial tissue is injected into rats, their urine volume (and Na+ excretion) rises. This is evidence of endocrine action via the effects of atrial natriuretic peptide (ANP). BNP is a similar hormone originally identified from pig brain (hence the B), but most BNP is secreted from ventricular myocardium. Plasma BNP is closely related to left ventricular pressure.

In myocardial infarction and left ventricular dysfunction, these hormones can be released in large quantities. Secretion is also increased by tachycardia, glucocorticoids, and thyroid hormones. Vasoactive peptides (endothelin-1, angiotensin II) also influence secretion. ANP and BNP both increase GFR and decrease renal Na^+ resorption; they also decrease preload by relaxing smooth muscle. ANP partly blocks secretion of renin and aldosterone.

BNP as a biomarker of heart failure[1]

As plasma BNP reflects myocyte stretch, BNP is used to diagnose heart failure. ↑BNP distinguishes heart failure from other causes of dyspnoea more accurately than left ventricular ejection fraction, ANP, and N-terminal ANP (sensitivity: >90%; specificity: 80-90%). BNP is highest in decompensated heart failure, intermediate in left ventricular dysfunction but no acute heart failure exacerbation, and lowest if no heart failure or LV dysfunction.

What BNP threshold for diagnosing heart failure?

If BNP >100ng/L, this 'diagnoses' heart failure better than other clinical variables or clinical judgement in on-call settings (history, examination, and CXR). BNP can be used to 'rule out' heart failure if <50ng/L—negative predictive value (PV) 96%, ie the chance of BNP being <50ng/L given that heart failure is absent in 96%, see p646. In those with heart failure, BNP is higher in systolic dysfunction than in isolated diastolic dysfunction (eg hypertrophic or dilated cardiomyopathy), and is highest in those with systolic *and* diastolic dysfunction.

Threshold (ng/L)	Sensitivity (%)	Specificity (%)	Positive PV	Negative PV	Accuracy (%)
≥50	97	62	71	96	79
≥80	93	74	77	92	83
≥100	90	76	79	89	83
≥125	87	79	80	87	83

≥150	85	83	83	85	84[2]

[2] Abnormal remodelling (cell slippage producing a more spherical LV + systolic dysfunction) is seen on echo or CT/MRI; it is measured as the *wall motion index* or the *left ventricular end-diastolic volume index* (EDVI, mL/m2). If EDVI is ≥5mL/m^2 ~6 months post-MI (compared with an initial post-MI value), remodelling has occurred. *Sustained* ↑BNP reflects progressive ventricular remodelling long after acute MI. Abnormal remodelling is preventable in CCF by ACE-i and exercise training.

BNP increases in proportion to right ventricular dysfunction, eg in primary pulmonary hypertension, cor pulmonale, PE, and congenital heart disease, but rises are less than in left ventricular disorders.

Prognosis in heart failure:

The higher the BNP, the higher the cardiovascular and all-cause mortality (independent of age, NYHA class p121, previous MI and LV ejection fraction). ↑BNP in heart failure is also associated with sudden death. Serial testing may be important: persistently high BNP levels despite vigorous anti-failure treatment predict adverse outcomes. In one study, those with heart failure randomized to get N-terminal BNP-guided (rather than symptom-guided) therapy had fewer adverse events.

Prognosis in angina and MI:

BNP has some prognostic value here (adverse left ventricular remodelling;[3] LV dysfunction; death post-MI).[6]

Prognosis in cor pulmonale/primary pulmonary hypertension:

BNP is useful.

Cautions with BNP:

A BNP >50ng/L does not exclude other co-existing diseases such as pneumonia. Also, assays vary, so liaise with your lab.

Sodium: hyponatraemia

Signs & symptoms

depend on severity and rate of change in serum sodium, and include: confusion, seizures, hypertension, cardiac failure, oedema, anorexia, nausea, muscle weakness.

Diagnosis

See tree in diagram OPPOSITE. The key question is: Is the patient dehydrated? History and urine analysis are your guides.

Causes of hyponatraemia

(For a full list, see the diagram OPPOSITE.)

- *Diuretics*, especially thiazides.
- *Water excess*, either orally, or as excess 5% dextrose IV.
- *Pseudohyponatraemia:* (1) If serum volume ↑ from high lipids or protein, Na^+ falls, but plasma osmolality is ↔. (2) If plasma glucose ≳20mmol/L, make a correction.[1] (3) Na^+ will be ↓ if blood is from an arm with a dextrose IVI.

[1] Add ~4.3mmol/L to plasma Na^+ for every 10mmol/L rise in glucose above normal.

Management

▸Don't base treatment on plasma Na^+ concentration alone. The presence of symptoms, duration, and state of hydration influence treatment. If possible, correct the underlying cause. If chronic: fluid restriction, or cautious rehydration with saline if dehydrated, is often sufficient if asymptomatic, although demeclocycline may be required. If symptomatic, saline may be given, but do not correct chronic changes rapidly (max 15mmol/d rise in serum sodium). Acute hyponatraemia may be treated with saline infusion and furosemide.

Hypervolaemic hyponatraemia

(cirrhosis, CCF) treat the underlying disorder.

In emergency

(seizures, coma), consider IVI of 0.9% saline or hypertonic saline (eg 1.8% saline) at 70mmol Na^+/h. Aim for a gradual increase in plasma sodium to ≈125mmol/L. Can combine with furosemide. Watch for heart failure, and central pontine myelinolysis. ▸Seek expert help.

Syndrome of inappropriate ADH secretion (SIADH)

An important, but overdiagnosed, cause of hyponatraemia. The diagnosis requires concentrated urine (sodium >20mmol/L and osmolality >500mosmol/kg) in the presence of hyponatraemia (<125mmol/L) or low plasma osmolality (<260mosmol/kg), and the absence of hypovolaemia, oedema, or diuretics.

Causes:

Malignancy, eg lung small-cell; pancreas; prostate; lymphoma. CNS *disorders:* Meningoencephalitis; abscess; stroke; subarachnoid, subdural haemorrhage; head injury; Guillain-Barré; vasculitis, p542, eg SLE.

Chest disease: TB; pneumonia; abscess; aspergillosis.

Metabolic disease: Porphyria; trauma.

Drugs: Opiates; psychotropics; SSRIs; cytotoxics.

Treatment:

Treat the cause, fluid restrict, occasionally demeclocycline.

Hypernatraemia

Signs & symptoms

Look for thirst, confusion, coma, and fits—with signs of dehydration: dry skin, ↓skin turgor, postural hypotension, and oliguria if water deficient. Laboratory features: ↑PCV, ↑albumin, ↑urea.

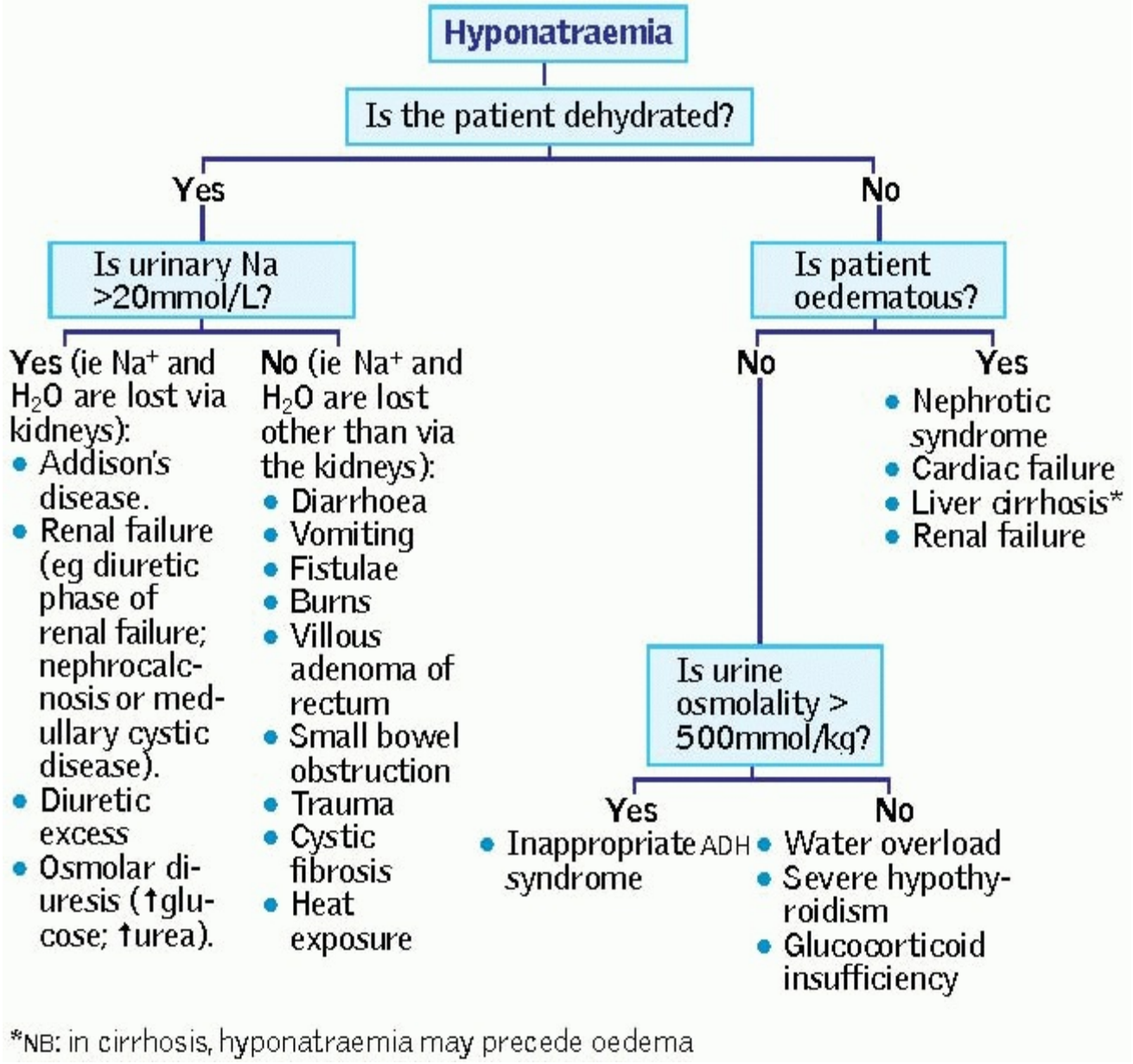
Causes

Usually due to water loss in excess of sodium loss:

- Fluid loss without water replacement (eg diarrhoea, vomit, burns).
- Incorrect IV fluid replacement (excessive saline).
- Diabetes insipidus (p224). Suspect if large urine volume. This may follow head injury, or CNS surgery, especially pituitary.
- Osmotic diuresis (for diabetic coma, see p814).
- Primary aldosteronism: suspect if BP↑, K^+↓, alkalosis (HCO_3^- ↑).

Management

Give water orally if possible; if not, dextrose 5% IV slowly (~4L/24h) guided by urine output and plasma Na^+. Some authorities recommend 0.9% saline (esp. if hypovolaemic) as this causes less marked fluid shifts and is hypotonic in a hypernatraemic patient. Avoid hypotonic solutions.



Hyponatraemia: it matters—and it is preventable[7]

If 5% dextrose is infused post-operatively, the dextrose is quickly used, rendering the fluid hypotonic. This causes hyponatraemia (nausea, headaches, weakness, cognition↓, coma, death)—especially in those at risk: on excessive doses of thiazide diuretics, females (especially pre-menopausal) and those undergoing physiological stress, which causes inappropriate ADH secretion, hence the low Na+. In some individuals, only marginally low plasma Na+ levels cause serious effects (eg ~128mmol/L). Risk of harm is minimized by following these rules:

- Know the pre-op U&E.
- Don't infuse dextrose without saline.
- Do a post-op U&E. Look at the result (Obvious, and so forgettable).
- Don't attribute odd CNS signs to non-existent strokes/TIAs if Na+↓.
- Don't ignore low sodiums. Get help if you don't know what to do.

Treatment:

(▸p666) 0.9% saline IVI; do U&E every 2h; aim to bring Na^+ up to 130mmol/L by 1-2mmol/L per hour. Diuretics eg furosemide may be useful in acute hyponatraemia, or if the patient is symptomatic. Hypertonic saline (eg 1.8% saline) should only be used in emergencies when the patient has profound neurological symptoms (seizures, coma).

Potassium

General points

Most potassium is intracellular, and thus serum potassium levels are a poor reflection of total body potassium. The concentrations of K^+ and H^+ ions in extracellular fluid tend to vary together. This is because these ions compete with each other in the exchange with sodium which occurs across most cell membranes (sodium is pumped out of the cell) and in the distal tubule of the kidney (sodium is reabsorbed from the urine). Thus, if H^+ ion concentration is high, fewer K^+ ions will be excreted into the urine. Similarly K^+ will compete with H^+ for exchange across cell membranes and extracellular K^+ will accumulate. Insulin and catecholamines both stimulate K^+ uptake into cells by stimulating the Na^+/K^+ pump.

Hyperkalaemia

▸A plasma potassium >6.5mmol/L needs urgent treatment (p821) but first ensure that this is not an artefact (eg due to haemolysis inside the bottle).

Signs & symptoms

Cardiac arrhythmias. Sudden death. ECG: Tall tented T waves; small P wave; wide QRS complex becoming sinusoidal, VF. (see OPPOSITE)

Causes

- Oliguric renal failure
- K^+-sparing diuretics
- Rhabdomyolysis (p299), burns
- Metabolic acidosis (DM)
- Excess K^+ therapy
- Addison's disease (see p210)
- Massive blood transfusion
- Drugs, eg ACE-i, suxamethonium
- Artefact. Haemolysis of sample; delay in analysis—K^+ leaks out of RBCs; thrombocythaemia—platelets leak K^+ as sample clots in tube.

Treatment

Treat underlying cause. ▸In emergency, see p821.

Hypokalaemia

If K^+ <2.5mmol/L, urgent treatment is required. Note that hypokalaemia exacerbates digoxin toxicity.

Signs & symptoms

Muscle weakness, hypotonia, cardiac arrhythmias, cramps, and tetany. ECG: Small or inverted T waves; prominent U wave (after T wave); prolonged P-R interval; depressed ST segment.

Causes

- Diuretics
- Vomiting and diarrhoea
- Pyloric stenosis
- Villous adenoma rectum
- Intestinal fistulae
- Cushing's syndrome/steroids/ACTH
- Conn's syndrome
- Alkalosis
- Purgative and liquorice abuse
- Renal tubular failure (p660).

If on diuretics, then ↑bicarbonate is the best indication that hypokalaemia is likely to have been long-standing. Magnesium may be low, and hypokalaemia is often difficult to correct until magnesium levels are normalized. In hypokalaemic periodic paralysis, intermittent weakness lasting up to 72h appears to be caused by K^+ shifting from extra- to intracellular fluid. See OHCS p652. Suspect Conn's syndrome if hypertensive, hypokalaemic alkalosis in someone not taking diuretics (p212).

Treatment

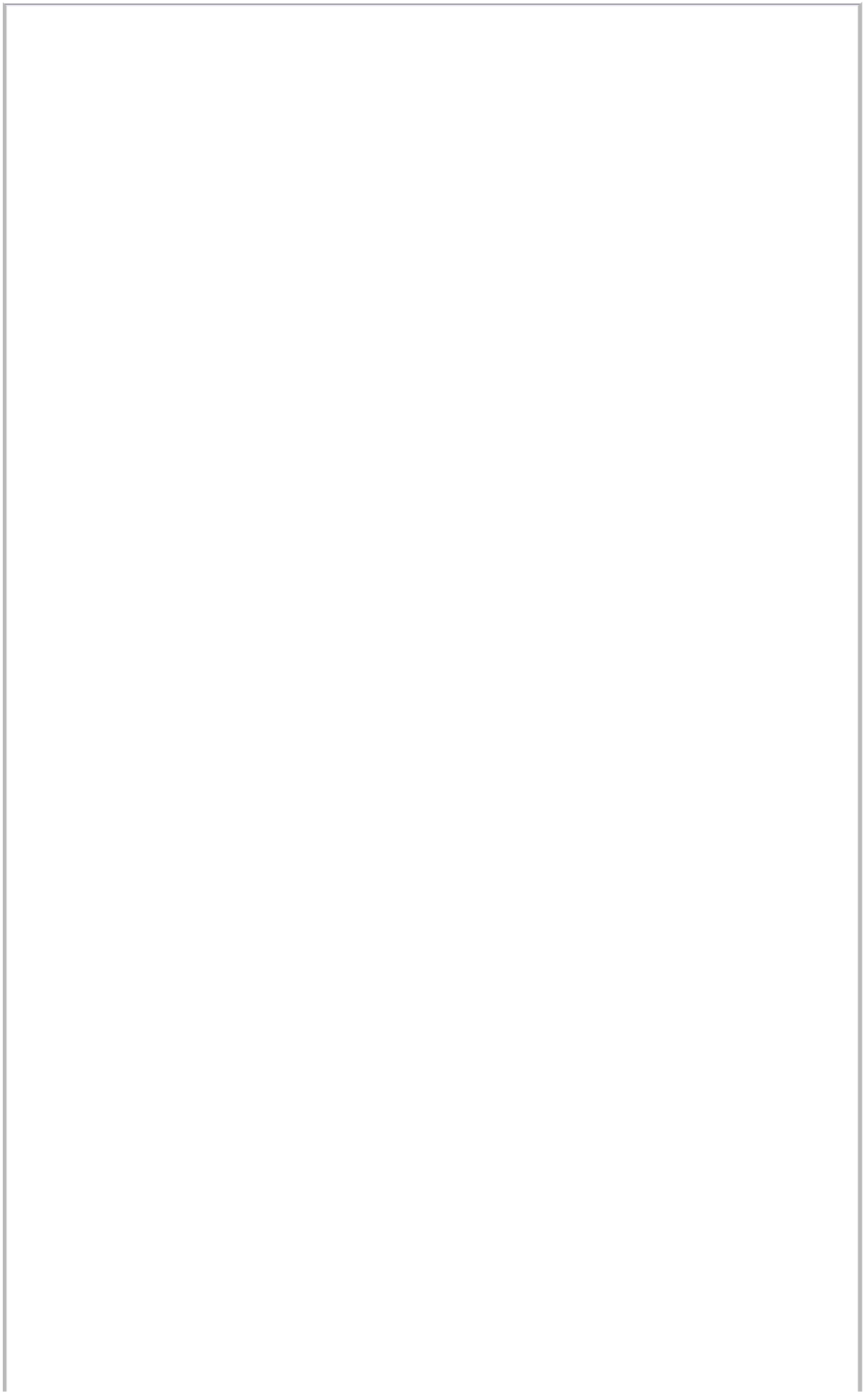
If mild:

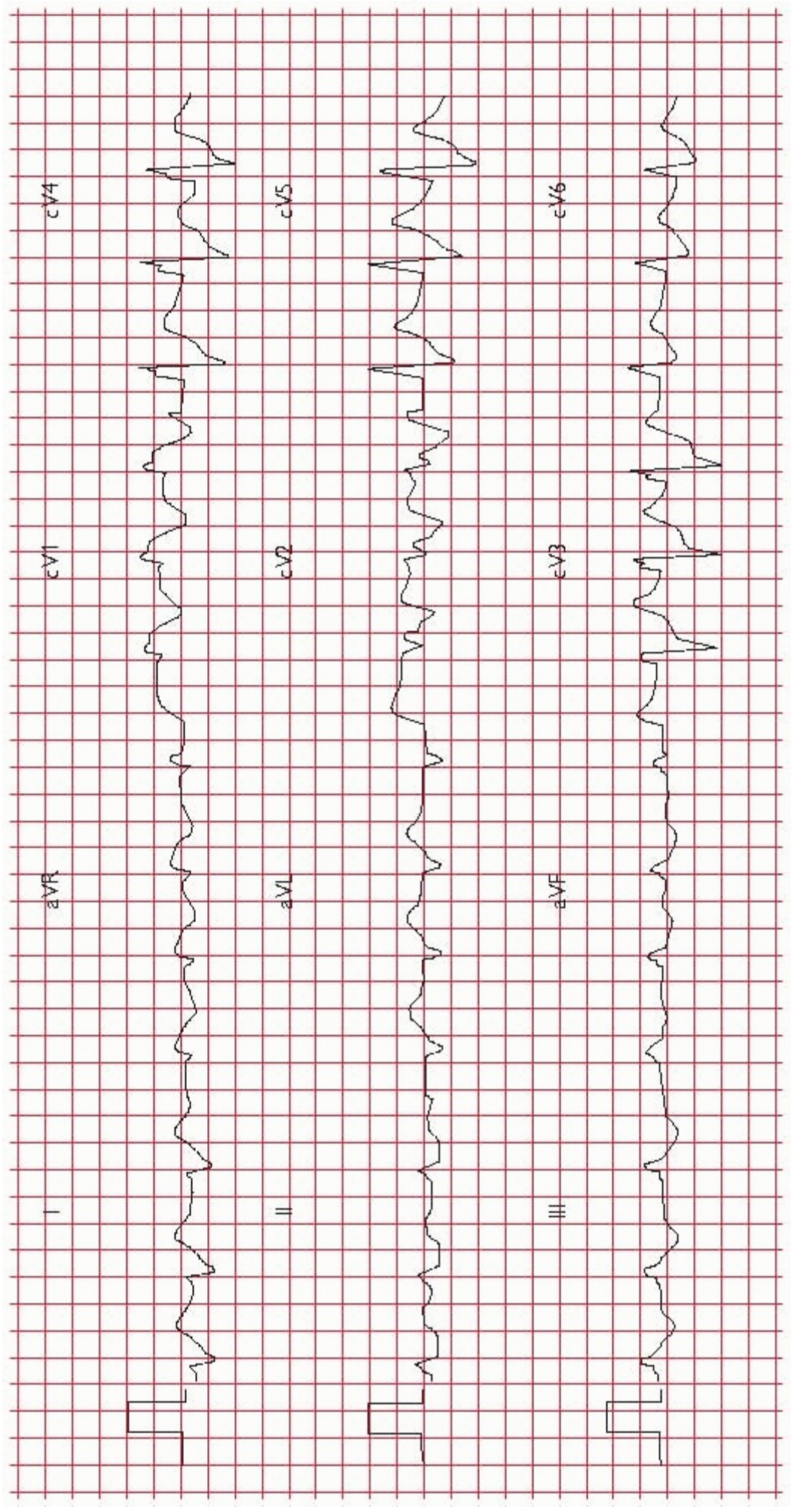
(>2.5mmol/L, no symptoms) give oral K^+ supplement (≥80mmol/24h, eg Sando-K® 2 tabs/6-8h). If taking a thiazide diuretic, hypokalaemia >3.0mmol/L rarely needs treating.

If severe:

(<2.5mmol/L, and/or dangerous symptoms) give IV potassium cautiously, not more than 20mmol/h, and not more concentrated than 40mmol/L. Do not give potassium if oliguric.

▸**Never** give potassium as a fast 'stat' bolus dose.





ECG 13—hyperkalaemia—note the flattening of the P-waves, prominent T-waves, and widening of the QRS complex.

Calcium: physiology

General points

About 40% of plasma calcium is bound to albumin. Usually it is total plasma calcium which is measured, although it is the unbound, ionized portion which is important. Therefore, *adjust total calcium level for albumin as follows:* Add 0.1mmol/L to calcium concentration for every 4g/L that albumin is below 40g/L, and a similar subtraction for raised albumin. However, many factors affect binding (eg other proteins in myeloma, cirrhosis, individual variation) so be cautious in your interpretation. If in doubt over a high calcium, take blood specimens uncuffed (remove tourniquet after needle in vein, but before taking blood sample), and with the patient fasted.

The control of calcium metabolism

- ***Parathyroid hormone (PTH):*** A rise in PTH causes a rise in plasma Ca^{2+} and a decrease in plasma PO_4^{3-}. This is due to ↑Ca^{2+} and ↑ PO_4^{3-} reabsorption from bone; and ↑Ca^{2+} but ↓ PO_4^{3-} reabsorption from the kidney. PTH secretion enhances active vitamin D formation. PTH secretion is itself controlled by ionized plasma calcium levels.
- ***Vitamin D:*** Calciferol (Vit D_3), and ergocalciferol (Vit D_2) are biologically identical in their actions. Serum Vit D is converted in the liver to 25-hydroxy Vit D (25(OH) Vit D). In the kidney, a second hydroxyl group is added to form the biologically active 1,25-dihydroxy Vit D ($1,25(OH)_2$ vit D), also called calcitriol, or the much less active $24,25(OH)_2$ Vit D. Calcitriol production is stimulated by ↓Ca^{2+}, ↓ PO_4^{3-}, and PTH. Its actions include ↑Ca^{2+} and ↑ PO_4^{3-} absorption from the gut; ↑Ca^{2+} and ↑ PO_4^{3-} reabsorption in the kidney; enhanced bone turnover; and inhibition of PTH release. Disordered regulation of $1,25(OH)_2$ Vit D underlies familial normocalcaemic hypercalciuria which is a major cause of calcium oxalate renal stone formation (p284).
- ***Calcitonin:*** Made in C-cells of the thyroid, this causes a decrease in plasma calcium and phosphate, but its physiological role is unclear. It is a marker to detect recurrence or metastasis in medullary carcinoma of the thyroid.
- ***Thyroxine:*** May ↑plasma calcium although this is rare.
- ***Magnesium:*** ↓Mg^{2+} prevents PTH release, and may cause hypocalcaemia.

Hypocalcaemia

▸Apparent hypocalcaemia may be an artefact of hypoalbuminaemia (above).

Signs & symptoms

Tetany, depression, perioral paraesthesiae, carpo-pedal spasm (wrist flexion and fingers drawn together) especially if brachial artery occluded with blood pressure cuff (*Trousseau's sign*), neuromuscular excitability, eg tapping over parotid (facial nerve) causes facial muscles to twitch (*Chvostek's sign*). Cataract if chronic Ca^{2+}↓. **ECG:** Q-T interval↑.

Causes

It may be a consequence of thyroid or parathyroid surgery. *If phosphate raised,* then either chronic renal failure (p294), hypoparathyroidism, pseudohypoparathyroidism (p206), or acute rhabdomyolysis. If phosphate ↔ or ↓ then either osteomalacia (high alkaline phosphatase), over-hydration or pancreatitis. In respiratory alkalosis, the total Ca^{2+} may be normal, but ionized Ca^{2+}↓ and the patient may have symptoms because of this.

Treatment

If *symptoms are mild,* give calcium 5mmol/6h PO. Do daily plasma calcium levels. ▸For chronic renal failure, see p294. If necessary add alfacalcidol; start at 0.5-1µg/24h PO. If *symptoms are severe*, give 10mL of 10% calcium gluconate (2.25mmol) IVI over 30min (bolus injections are only needed very rarely). Repeat as necessary. If due to respiratory alkalosis, correct the alkalosis.

Hypercalcaemia

Signs & symptoms

'Bones, stones, groans, and psychic moans'. Abdominal pain; vomiting; constipation; polyuria; polydipsia; depression; anorexia; weight loss; tiredness; weakness; hypertension, confusion; pyrexia; renal stones; renal failure; corneal calcification; cardiac arrest. **ECG:** Q-T interval↓.

Causes and diagnosis

Most commonly malignancy (myeloma, bone metastases, PTHrP↑, p353) and 1° hyperparathyroidism. Others include sarcoidosis, vit D intoxication, and familial benign hypocalciuric hypercalcaemia (rare; defect in calcium-sensing receptor). Pointers to malignancy are: ↓albumin, ↓Cl^-, ↓K^+, alkalosis, ↓PO_4^{3-} ↑alk phos. Other investigations (eg isotope bone scan, CXR, FBC) may also be of diagnostic value.

Treat

the underlying cause. If Ca^{2+} >3.5mmol/L, and severe abdominal pain, vomiting, pyrexia, or confusion, aim to reduce calcium as follows:

- ***Blood tests:*** Measure U&E, Mg^{2+}, creatinine, Ca^{2+}, PO_4^{3-}, alk phos.
- ***Fluids:*** Rehydrate with IVI 0.9% saline, eg 4-6L in 24h as needed. Correct hypokalaemia/hypomagnesaemia (mild metabolic acidosis needs no treatment). This will reduce symptoms, and ↑renal Ca^{2+} loss. Monitor U&E.
- ***Diuretics:*** Furosemide 40mg/12h PO/IV, once rehydrated. Avoid thiazides.
- ***Bisphosphonates:*** A single dose of pamidronate (see table, p515 will lower Ca^{2+} over 2-3d. Maximum effect is at 1wk. It inhibits osteoclast activity, and so bone resorption.
- ***Steroids:*** Occasionally used, eg prednisolone 40-60mg/d for sarcoidosis.
- ***Salmon calcitonin:*** Now rarely used (8U/kg/8h IM). More side effects than bisphosphonates, but quicker onset. Again inhibits osteoclasts.
- ***Other:*** Chemotherapy may ↓Ca^{2+} in malignant disease, eg myeloma.

Magnesium

Magnesium is distributed 65% in bone and 35% in cells; plasma concentration tends to follow that of Ca^{2+} and K^+. Magnesium excess is usually caused by renal failure, but rarely requires treatment in its own right.

Magnesium deficiency

causes paraesthesiae, fits, tetany, arrhythmias. Digitalis toxicity may be exacerbated.

Causes:

Severe diarrhoea; ketoacidosis; alcohol; total parenteral nutrition (monitor weekly); accompanying hypocalcaemia; accompanying hypokalaemia (especially with diuretics) and hypophosphataemia.

Treatment:

If needed, give magnesium salts, PO or IV (dose example: 8mmol $MgSO_4$ IVI over 3min to 2h, depending on severity; monitor Mg^{2+} often).

Hypermagnesaemia

is usually iatrogenic, or excessive antacids.

Features:

Neuromuscular depression, ↓BP, CNS depression, coma.

Zinc

Zinc deficiency

This may occur in parenteral nutrition or, rarely, from a poor diet (too few cereals and dairy products; anorexia nervosa; alcoholism). Rarely it is due to a genetic defect.

Signs & symptoms:

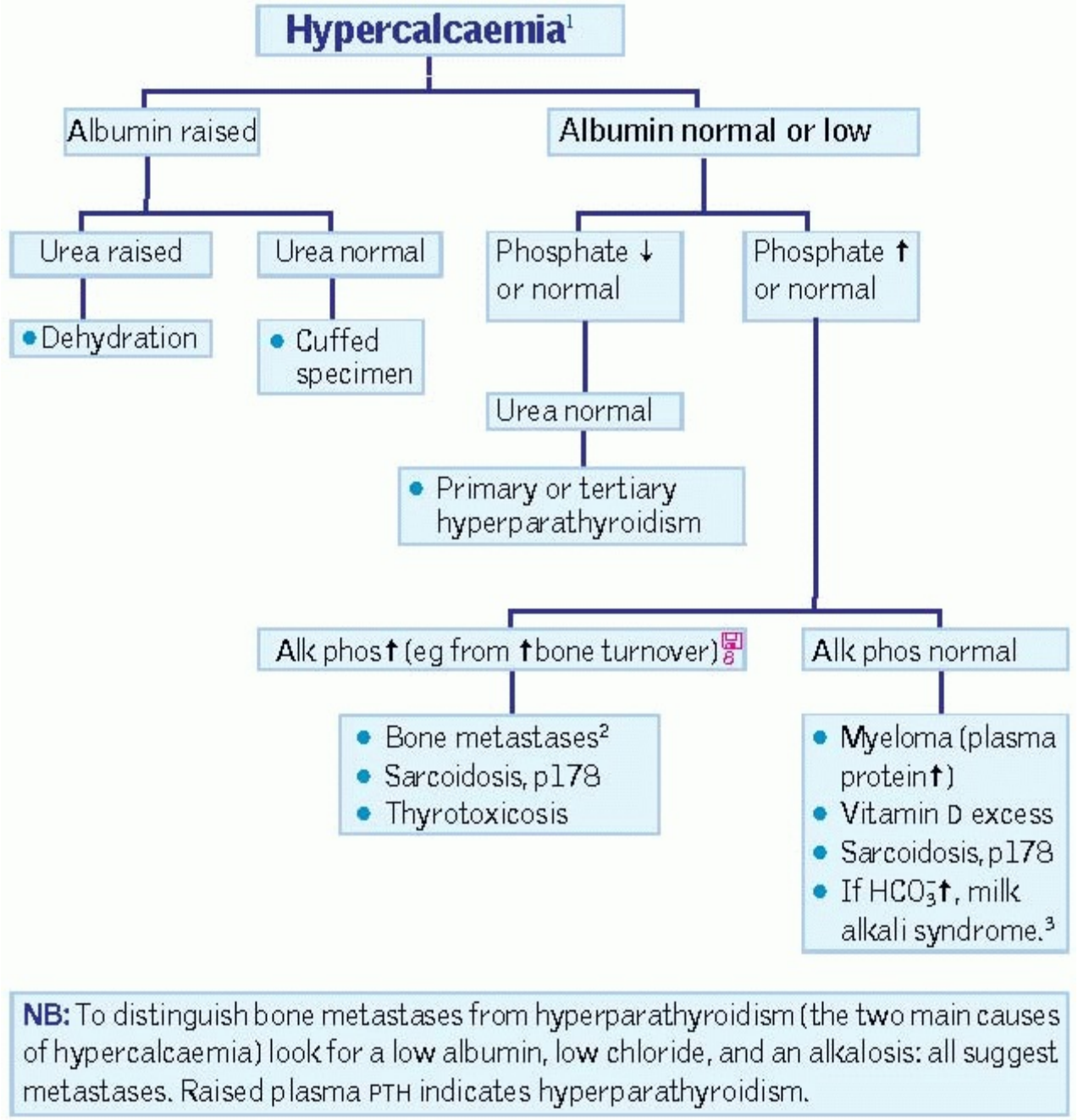
Look for red, crusted skin lesions especially around nostrils and corners of mouth.

Diagnosis:

Therapeutic trial of zinc (plasma levels are unreliable as they may be low, eg in infection or trauma, without deficiency).

Selenium

An essential element present in cereals, nuts, and meat. Low soil levels in some parts of Europe and China cause deficiency states. Required for the antioxidant glutathione peroxidase, which ↓harmful free radicals. It is also antithrombogenic, and is required for sperm motility proteins. Deficiency may increase the frequency of neoplasia and atheroma, and may lead to a cardiomyopathy or arthritis. Serum levels are a poor guide. Toxic symptoms may also be found with over-energetic replacement.



Metabolic bone diseases 1. Osteoporosis

Osteoporosis implies reduced bone density. If trabecular bone is mostly affected, crush fractures of vertebrae are common (accounting for the 'littleness' of little old ladies—and their dowager's hump); if cortical bone is mostly affected, fracture of a long bone is more likely, eg femoral neck: *the* big cause of death and orthopaedic expense, especially in older women.

Prevalence:

35% of over 50s ♀:♂ ≈4:1.

Risk of future osteoporotic fracture

is increased if:

- Slender or anorectic
- Smoker or alcoholic
- Prolonged rest; old age
- Hyperparathyroidism
- >5mg/d prednisolone
- Vertebral deformity
- Early menopause
- Cushing's syndrome

- Malabsorption
- Thyrotoxicosis
- Myeloma
- Amenorrhoea
- Osteoporosis in family
- Primary biliary cirrhosis
- Rheumatoid arthritis
- Hypogonadism
- Past low-trauma fracture
- Mastocytosis (OHCS p610).

Diagnosis:

X-ray (easier with hindsight afforded by bone fracture), but low sensitivity and specificity. Bone densitometry (OPPOSITE). Serum Ca^{2+}, PO_4^{3-}, and alk phos normal. Biopsy specimens may be unrepresentative.

Prevention:

Exercise; good, Ca^{2+}-rich diet; avoid smoking and excess alcohol. For those at ↑risk, eg on corticosteroids (eg >7.5mg/d of prednisolone), bisphosphonates ↓risk. **NB:** hormone replacement therapy (HRT) can prevent osteoporosis, but the UK Committee on Safety of Medicines (CSM) says that owing to HRT's propensity to cause breast cancer (and other problems) it should no longer be a first-line option for preventing osteoporosis.

Treatment:

- Ca^{2+}-rich diet.
- *Bisphosphonates* are used for the prevention and treatment of osteoporosis. eg Alendronic acid 10mg/d (SE: abdo pain; nausea; photosensitivity, oesophageal ulcers). ▸Explain the need to swallow the pill while remaining upright (for >30min) with plenty of water 20min before breakfast (and any other drugs); stop if dysphagia or pain. A single weekly dose is available (70mg). Or didronel PMO® (14d of etidronate 400mg/d and 76d of calcium carbonate 1.25g in 90-day cycles). It is important to maintain a good calcium and vit. D intake, so consider adding a daily supplement.
- *Others:* ***Vitamin D*** is effective[9] (watch serum Ca^{2+}). ***Raloxifene*** (a selective oestrogen receptor modulator 'SERM') may also ↓ breast cancer risk. Its role is unclear. ***Calcitonin*** may be considered; reduces pain post vertebral fracture (now available intra-nasally). ***Recombinant* PTH** (teriparatide) stimulates new bone and is effective in preventing fractures;[10] NICE recommends it to prevent recurrent fractures in those intolerant of bisphosphonates.[11] ***Strontium ranelate*** contains 2 atoms of strontium (same periodic group as calcium) and seems to increase bone formation and reduce reabsorption. Effective in reducing fractures.

2. Paget's disease of bone

There is increased bone turnover associated with increased numbers of osteoblasts and osteoclasts with resultant remodelling, bone enlargement, deformity, and weakness. Rare in the under-40s. Incidence rises with age (3% over 55yrs old). Commoner in temperate climes, and Anglo-Saxons. It may be asymptomatic or cause pain and enlargement of skull, femur, clavicle—and bowed (*sabre*) tibia—also pathological fractures, nerve deafness (bone overgrowth), and high-output CCF.

X-rays:

Localized enlargement of bone. Patchy cortical thickening with sclerosis, osteolysis, and deformity (*osteoporosis circumscripta* of the skull). Affinity for axial skeleton, long bones, and skull.

Blood biochemistry:

Ca^{2+} and PO_4^{3-} normal; alk phos markedly raised.

Complications:

Bone sarcoma (1% of those affected for >10yrs). Symptoms of nerve compression, eg deafness.

Treatment:

If analgesia fails, alendronic acid (see above) may be tried, to reduce pain and/or deformity. It is more effective than etidronate or calcitonin, and as effective as IV pamidronate. Follow expert advice.

Understanding Dexa bone scan results: WHO osteoporosis criteria

Typical sites examined are the lumbar spine (preferably 3 vertebrae) and hip. Bone mineral density (BMD, in g/cm^2) is compared with that of a young healthy adult. The 'T-score' relates to the number of standard deviations the BMD is from the average. If the T-score is:

>0	BMD is better than the reference.
0 to -1	BMD is in the top 84%: no evidence of osteoporosis.
-1 to -2.5	Osteopenia, with risk of later osteoporotic complication, so consider preventive measures (see OPPOSITE).
-2.5 or worse	BMD is ≥2.5 standard deviations below the mean value for young adults: osteoporosis is present—severe if there is 1 or more fragility fracture.

An example of a suitable indication for densitometry is before embarking on prednisolone treatment (>6 months, at >7.5mg/d; steroids contribute to osteoporosis by promoting osteoclast bone resorption, and decreasing muscle mass and ↓GI calcium absorption).

Benefits of universal screening for osteoporosis are unproven.

Further reading:

See Masud 2000 BMJ **ii** 397 www.bmj.com/cgi/content/full/321/7258/396

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3. Osteomalacia

In osteomalacia there is a normal amount of bone but its mineral content is low (there is excess uncalcified osteoid and cartilage). Rickets is the result if this process occurs during the period of bone growth; osteomalacia is the result if it occurs after fusion of the epiphyses.

Forms

- ***Vitamin D deficiency:*** Due to malabsorption (p272), poor diet, or lack of sunlight.
- ***Renal osteomalacia:*** Renal failure leads to 1,25-dihydroxycholecalciferol— [1,25$(OH)_2$vitamin D] deficiency (p294).
- ***Drug-induced:*** Anticonvulsants may induce liver enzymes, leading to an increased breakdown of 25-hydroxycholecalciferol.
- ***Vitamin D resistance:*** A number of mainly inherited conditions in which the osteomalacia responds to high doses of vitamin D (see below).
- ***Liver disease:*** Reduced production of 25-hydroxy vitamin D (25(OH)-vitamin D), and malabsorption of vitamin D, eg cirrhosis (p252).

Investigations

Plasma:

Mildly ↓Ca^{2+}; ↓ PO_4^{3-}; alk phos↑; PTH high; 25(OH)vitamin D↓, except in resistant cases; in renal failure 1,25$(OH)_2$vitamin D↓ (p294).

Biopsy:

Shows incomplete mineralization.

X-ray:

Cupped, ragged metaphyseal surfaces (in rickets). In osteomalacia there is a loss of cortical bone; also, apparent partial fractures without displacement may be seen especially on the lateral border of the scapula, inferior femoral neck and medial femoral shaft (Looser's zones).

Signs & symptoms

Rickets:

Knock-kneed; bow-legged. Features of hypocalcaemia—usually mild (p694). Children with rickets are ill.

Osteomalacia:

Bone pain; fractures (neck of femur); proximal myopathy (waddling gait), due to ↓ PO_4^{3-} and vitamin D deficiency *per se*.

Treatment

Calcium-with-vitamin D (400U) tablets: 1-2 tablets/d.

- If due to malabsorption, give calciferol tablets, up to 1mg (=40,000U) daily or parenteral calciferol, eg 7.5mg monthly.
- If vitamin-D-resistant, give calciferol 10,000 units/24h PO.
- If due to renal disease, give alfacalcidol (1α-hydroxy vitamin D) 1μg/24h PO and adjust dose according to plasma calcium.
- Monitor plasma calcium, initially weekly, and if nausea/vomiting.

▸Vitamin D therapy (esp. alfacalcidol) can cause dangerous hypercalcaemia.

Vitamin D-resistant rickets

exists in 2 forms. Type I with low renal 1×-hydroxylase activity, and type II with end organ resistance to 1,25(OH)2vitamin d, due to a point mutation in the receptor. Both are treated with large doses of 1,25(OH)2vitamin d (calcitriol).

X-linked hypophosphataemic rickets

Dominantly inherited—due to a defect in renal phosphate handling (due to mutations in the PEX or PHEX genes which encode an endopeptidase). Rickets develops in early childhood and is associated with poor growth. Plasma phosphate is low, alkaline phosphatase high, and there is phosphaturia. Treatment is with high doses of oral phosphate, and 1,25(OH)2vitamin D. Hypophosphataemic osteomalacia may develop in patients consuming phosphate binders, eg aluminium hydroxide, or some rare tumour, and is accompanied by severe muscle weakness.

See also ***Renal bone disease***, p294.

Plasma proteins

Electrophoresis distinguishes a number of bands (see figure OPPOSITE).

Albumin

is synthesized in the liver; $t_{½}$≈20d. It binds *bilirubin*, *free fatty acids*, Ca^{2+}, and some *drugs*.

Low albumin

results in oedema. *Causes:* Liver disease, nephrotic syndrome, burns, protein-losing enteropathy, malabsorption, malnutrition, late pregnancy, artefact (eg from arm with IVI), posture (5g/L higher if upright), genetic variations, malignancy.

High albumin—Causes:

Dehydration; artefact (eg stasis).

α1 zone:

$α_1$-antitrypsin, thyroxine-binding globulin, and high-density lipoprotein (HDL). α1-antitrypsin deficiency (autosomal recessive) leads to cirrhosis and emphysema: unopposed phagocyte proteases. Accelerated age-related decline in FEV_1 from a normal of ~35mL/yr to 80mL/yr, exacerbated by smoking. Signs: dyspnoea; weight↓; cor pulmonale; PCV↑; LFT↑ (hepatocytes cannot secrete the protein).

α2 zone:

$α_2$-macroglobulin, caeruloplasmin, very low density lipoprotein (VLDL, p682), and haptoglobin (p322).

β zone:

Transferrin, low-density lipoprotein (LDL), fibrinogen, C3 and C4 complement. Reduced in active nephritis, glomerulonephritis, and SLE.

γ zone:

Immunoglobulins, factor VIII, C-reactive protein (CRP), and α-fetoprotein. *Diffusely raised* in: chronic infections, liver cirrhosis, sarcoidosis, SLE, RA, Crohn's disease, TB, bronchiectasis, PBC, hepatitis, and parasitaemia. It is *low* in: nephrotic syndrome, malabsorption, malnutrition, immune deficiency (severe illness, diabetes mellitus, renal failure, malignancy, or congenital).

Paraproteinaemia

See p354.

Acute phase response

The body responds to a variety of insults with, amongst other things, the synthesis, by the liver, of a number of proteins (normally present in serum in small quantities)—eg α_1-antitrypsin, fibrinogen, complement, haptoglobin, and CRP. An increased density of the α_1- and α_2-fractions, often with a reduced albumin level, is characteristic of conditions such as infection, malignancy (especially α_2-fraction), trauma, surgery, and inflammatory disease.

CRP

Levels help monitor inflammation/infection. Normal <8mg/L. Like the ESR, it is raised in many inflammatory conditions, but changes more rapidly; increases in hours and falling within 2-3d of recovery. Therefore, it can be used to follow the response to therapy (eg antibiotics) or disease activity (eg Crohn's disease). CRP values in mild inflammation 10-50mg/L; active bacterial infection 50-200mg/L; severe infection or trauma >200mg/L; see OPPOSITE. CRP levels also predict outcome in patients with cardiovascular disease if measured using a highly sensitive assay. Low risk <1mg/L; moderate risk 1-3; and high risk >3mg/L.[12]

Urinary proteins

If urinary protein loss >0.15g/24h, then pathological. See p278.

Albuminuria

Usually caused by renal disease. Microalbuminuria (protein excretion between 3 and 300mg/d may be seen with diabetes or hypertension).

Bence Jones protein

consists of light chains excreted in excess by some patients with myeloma (p352). They are not detected by dipsticks and may occur with normal serum electrophoresis.

Haemoglobinuria

p324.

Myoglobinuria

(rhabdomyolysis) p299.

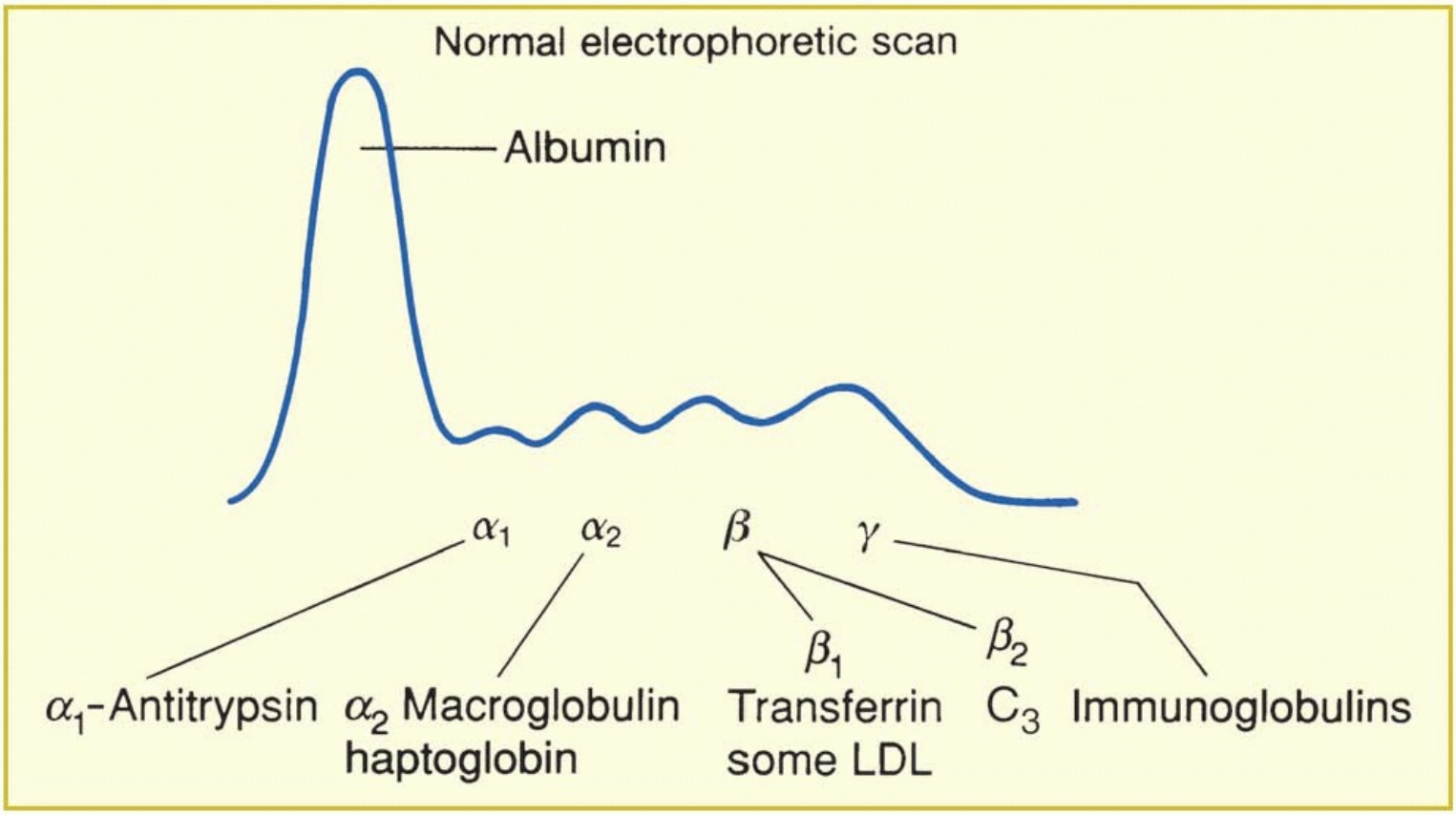
Microalbuminuria

(seen in DM; ↑BP; SLE; glomerulonephritis)—see p301 for role in diabetes.

C-reactive protein (CRP)

Marked elevation	*Normal-to-slight elevation*
Bacterial infection	Viral infection
Abscess	Steroids/oestrogens
Crohn's disease	Ulcerative colitis

	SLE
Connective tissue diseases (except SLE)	
	Atherosclerosis
Neoplasia	
Trauma	
Necrosis (eg MI)	



Plasma enzymes

▸Reference intervals vary between laboratories.

Raised levels of specific enzymes can be a useful indicator of a disease. However, remember that most can be raised for other reasons too. The major causes of ***raised enzymes*** are given below. Normal values: see p742.

Alkaline phosphatase

- Liver disease (suggests cholestasis).

- Bone disease (isoenzyme distinguishable, reflects osteoblast activity) especially Paget's, growing children, healing fractures, osteomalacia, metastases, hyperparathyroidism, and renal failure.
- Pregnancy (placenta makes its own isoenzyme).

Alanine-amino transferase (ALT; SGPT)

- Liver disease (suggests hepatocyte damage). Also raised in shock.

a-Amylase

- Acute pancreatitis (not chronic pancreatitis as little tissue remaining).
- Severe uraemia, diabetic ketoacidosis.

Aspartate-amino transferase (AST; SGOT)

- Liver disease (suggesting hepatocyte damage).
- Myocardial infarction (p104).
- Skeletal muscle damage and haemolysis.

Creatine kinase (CK)

- Myocardial infarction (p104; isoenzyme 'CK-MB'. MI diagnosed if CK-MB>6% total CK, or CK-MB mass >99 percentile of normal).
- Muscle damage (rhabdomyolysis, p299; prolonged running; haematoma; seizures; IM injection; defibrillation; bowel ischaemia; myxoedema; dermatomyositis, p538)—and *drugs* (eg statins). ▸A raised CK does not necessarily mean an MI.

Gamma-glutamyl transferase (GGT, ÿGT)

- Liver disease (particularly alcohol-induced damage, cholestasis, drugs).

Lactate dehydrogenase (LDH)

- Myocardial infarction (p104).
- Liver disease (suggests hepatocyte damage).
- Haemolysis, pulmonary embolism, and tumour necrosis.

Troponin

- Myocardial infarction (p104).
- Pericarditis, myocarditis, PE, sepsis, renal failure (elevation less marked).

Tumour markers[13]

Tumour markers are rarely sufficiently specific to be of diagnostic value. Their main value is in monitoring the course of an illness and the effectiveness of treatment. Reference ranges vary between laboratories.

Alpha-fetoprotein

↑In hepatocellular Ca (p262), germ cell tumours (not pure seminoma) hepatitis; cirrhosis; pregnancy; open neural tube defects.

CA 125

Raised in carcinoma of the ovary, uterus, breast, and hepatocellular carcinoma. Also raised in pregnancy, cirrhosis, and peritonitis.

CA 15-3

Raised in carcinoma of the breast and benign breast disease.

CA 19-9

Raised in colorectal and pancreatic carcinoma, and cholestasis.

Carcino-embryonic antigen (CEA)

↑In gastrointestinal neoplasms, especially colorectal CA. Also cirrhosis, pancreatitis, and smoking.

Human chorionic gonadotrophin

Raised in pregnancy and germ cell tumours. For hydatidiform moles and choriocarcinoma, see OHCS p264.

Neurone specific enolase (NSE)

↑in small-cell lung cancer and neuroblastoma.

Placental alkaline phosphatase (PLAP)

↑ in: pregnancy, ca, seminoma, smoking.

Prostate specific antigen (PSA)

As well as being a marker of prostate cancer, PSA is (unfortunately) raised in benign prostatic hypertrophy. See prostate cancer (p606) and p607 for advising men who ask for a PSA test. 25% of large benign prostates give PSA up to 10 µg/L; levels may be higher if recent ejaculation; therefore, avoid ejaculation for 24h prior to measurement. Other factors causing raised PSA: recent rectal examination, prostatitis, and UTI (PSA levels may not return to base-line for some months after the latter).[1] Plasma reference interval is age specific, an example of the top end of the reference interval for total PSA is:

Healthy males of age (yrs)	*PSA µg/L*
40-50	2.5
50-59	3.5
60-69	5.0
70-79	6.5
80-89	7.5

The above is a rough guide only; different labs have different reference ranges, and populations vary. More specific assays, such as free PSA/total PSA index, and PSA density, are also becoming available, which may partly solve these problems. It is shown to illustrate the common problem of interpreting a PSA of ~8—and as a warning against casual requests for PSAs in the (vain) hope of simple answers. The following indicates the proportion of patients with a raised PSA and benign hypertrophy or carcinoma.

	PSA µg/L		
Benign prostatic hypertrophy	<4 in 91%		
	4-10 in 8%		
	>10 in 1%	}	PSA will be ~50% lower after 6 months on 5× reductase inhibitors (to ↓prostate size, see p602)
Prostate carcinoma	<4 in 15%		
	4-10 in 20%		
	>10 in 65%		

Enzyme Inducers and Inhibitors

Liver enzymes, including those involved in the metabolism of drugs (eg the cytochrome P450 enzyme family), may be either induced or inhibited by a range of commonly used drugs and food substances:

Enzyme inducers	Enzyme Inhibitors
Phenytoin	SSRIs
Rifampicin	Ciprofloxacin

Carbamazepine	Cimetidine
Omeprazole	Erythromycin
Alcohol	Ketoconazole
St John's wort	Grapefruit juice

This can lead to important interactions or side-effects. For example phenytoin reduces the effectiveness of the Pill due to more rapid oestrogen metabolism, and ciprofloxacin retards the metabolism of methylxanthines (aminophylline) which leads to higher plasma levels and potentially more side-effects. The BNF contains a list of the major interactions between drugs.

Hyperlipidaemia

Cholesterol is a major risk factor for coronary heart disease (CHD). Half the UK population have a serum cholesterol putting them at significant risk of CHD. Do not treat in isolation, assess other risk factors: smoking, BP↑, DM, family history—see ***risk equation***, p642. Benefits of treatment must be set against cost, and imposition of diets and tablet-taking (with expensive follow-up plans).

Trial evidence that treating hypercholesterolaemia is worthwhile

- *'4S' study.*[14] Secondary prevention trial (patients with ischaemic heart disease) using simvastatin ≥20mg/d PO nocte in 4444 men aged 35-70 (cholesterol 5.5-8.0mmol/L). Number needed to treat (NNT, p650) to prevent 1 fatal MI was 25 (over 6yrs), and 14 for non-fatal events.
- *WOSCOPS.*[15] Primary prevention trial in Scotland with over 6500 men (cholesterol >6.5mmol/L), pravastatin 40mg/24h PO nocte. NNT to prevent 1 fatal MI was 142 (over 5yrs), and for all cardiac events was 55.
- *CARE study.*[16] Secondary prevention trial with 40mg of pravastatin/24h PO in >4000 people, post-MI, with 'normal' cholesterol (<6.2mmol/L). NNT for fatalities was 91 (over 5yrs), and for non-fatal MI was 38.
- *HEART PROTECTION STUDY.*[17] Secondary prevention trial with 40mg simvastatin to patients irrespective of cholesterol. NNT for death = 55. No evidence of 'threshold of cholesterol' for benefit.

Who to screen

- CHD or risk↑, eg DM, BP↑.
- Family history of hyperlipidaemia, or CHD before 65yrs old.
- Xanthomata or xanthelasmata.
- Corneal arcus before 50yrs old.

Management[18]

- Exclude familial or 2° hyperlipidaemias. Treat as appropriate.
- Lifestyle advice. Aim for BMI of 20-25. Diet with <10% of calories from saturated fats; ↑fibre, fresh fruit & vegetables, omega-3 fatty acids . ↑Exercise.
- Treat those with known CHD.
- If *no* CHD, risk tables (p642). P_x when MI risk is >3%/yr, eg cholesterol >5.5 for 50-yr-old û smoker with DM, LVH & BP↑, but cholesterol >6.9 if no LVH or DM.
- 'Statins' (p101) are first choice; they ↓cholesterol synthesis in the liver (eg ***simvastatin*** 40mg PO at night). CI: porphyria, LFT↑. SE: myositis (stop if CK↑ by ≥10-fold. If any muscle aches, check CK; risk is 1/100,000 treatment yrs[19]); abdominal pain; LFT↑ (stop if AST ≳100U/L).
- 2nd-line therapy: fibrates, eg bezafibrate (useful in familial mixed hyperlipidaemias); cholesterol absorption inhibitors eg ezetimibe (useful in combination with a statin to enhance cholesterol reduction); anion exchange resins, eg cholestyramine; also consider nicotinic acid (HDL↑; LDL↓; SE: severe flushes—aspirin 300mg ½h pre-dose helps this).

- Hypertriglyceridaemia responds best to fibrates, nicotinic acid, or fish oil.

Familial or primary hyperlipidaemias

Risk of CHD↑↑ . Lipids travel in blood packaged with proteins as lipoproteins. There are four classes: chylomicrons (mainly triglyceride); LDL (mainly cholesterol, the lipid correlating most strongly with CHD); VLDL (mainly triglyceride); HDL (mainly phospholipid, correlating *inversely* with CHD). See table OPPOSITE.

Secondary hyperlipidaemias

A result of diabetes mellitus; alcohol abuse; T4↓; renal failure, nephrosis, and cholestasis.

Xanthomata

These yellowish lipid deposits may be: eruptive (itchy nodules in crops in hypertriglyceridaemia); tuberous (yellow plaques on elbows and knees); planar—also called palmar (orange-coloured streaks in palmar creases), virtually diagnostic of remnant hyperlipidaemia; or deposits in tendons p76, eyelids (xanthelasmata p101), or cornea (arcus p76).

Primary hyperlipidaemias

Chol = plasma cholesterol mmol/L Trig = plasma triglyceride (mmol/L); **coloured numerals** = **WHO** phenotype

Familial hyperchylomicronaemia (lipoprotein lipase deficiency or apoCII deficiency)[I]	Chol <6.5 Trig 10-30 Chylomicrons	↑	Eruptive xanthomata; lipaemia retinalis; hepatosplenomegaly (HSM)
Familial hypercholesterolaemia[II] (LDL receptor defects)	Chol 7.5-16 Trig <2.3	LDL↑	Tendon xanthoma; corneal arcus; xanthelasma
Familial defective apoprotein B-100[IIa]	Chol 7.5-16 Trig <2.3	LDL↑	Tendon xanthoma; arcus; xanthelasma
Polygenic hypercholesterolaemia[IIa]	Chol 6.5-9 Trig <2.3	LDL↑	*The commonest 1° lipidaemia* xanthelasma; corneal arcus
Familial combined hyperlipidaemia[IIb, IV or V]	Chol 6.5-10 Trig 2.3-12	LDL↑VLDL↑ HDL↓	*Next commonest 1° lipidaemia;* xanthelasma; arcus
Dysbetalipoproteinae- mia (remnant particle disease)[III]	Chol 9-14 Trig 9-14	IDL↑ HDL↓ LDL↓	Palmar striae; tuberoeruptive xanthoma

Familial hypertriglyceridaemia[IV]	Chol 6.5-12 Trig 3.0-6.0	VLDL↑	
Type V hyperlipoproteinaemia	Trig 10-30; chylomicrons		Eruptive xanthoma; lipaemia retinalis; HSM

Primary HDL abnormalities Hyperalphalipoproteinaemia ↑HDL chol >2

Hypoalphalipoproteinaemia (Tangier disease) ↓HDL chol <0.92

Primary LDL abnormalities Abetalipoproteinaemia Trig<0.3, Chol<1.3, missing LDL, VLDL and chylomicrons, and fat malabsorption, retinopathy, and acanthocytosis

Hypobetalipoproteinaemia chol<1.5 LDL↓, HDL ↓. Increased longevity

▸What are the priorities in treating diet-resistant hyperlipidaemia?1

Top priority: *Treat those with known cardiovascular disease.*

2nd priority: *Treat those with* DM *if risk of CV disease* >2% per year.

3rd priority: Those with a risk of CV disease >2% per year.

Abbreviations

IDL = intermediate-density lipoprotein (HDL and LDL denote high and low density, respectively); chol = cholesterol; trig = triglyceride.

The porphyrias

The acute porphyrias

are rare genetic diseases caused by errors in the pathway of haem biosynthesis resulting in the toxic accumulation of porphobilinogen and σ-aminolaevulinic acid (porphyrin precursors). Characterized by acute neurovisceral crises, due to the increased production of porphyrin precursors, and their appearance in the urine. Some forms have cutaneous manifestations. Prevalence: 1-2/100,000.

Acute intermittent porphyria

A low-penetrant autosomal dominant condition (porphobilinogen deaminase gene); 28% have no family history (*de novo mutations*). ~10% of those with the defective gene have neurovisceral symptoms. Attacks are intermittent, more common in women, and may be precipitated by many drugs (see below). Urine porphobilinogens are raised during attacks and often (50%) between them (the urine may go deep red on standing). Faecal porphyrin levels are normal. There are no skin manifestations.

Variegate porphyria and hereditary coproporphyria

Autosomal dominant, characterized by photosensitive blistering skin lesions and/or acute attacks. The former is prevalent in Afrikaners in South Africa. Porphobilinogen is high only in an attack, and other metabolites may be detected in faeces.

Features of an acute attack

Colic ± vomiting ± fever ± WCC↑—so mimicking an acute abdomen (anaesthesia can be disastrous here)—also:

- Hypertension
- Hyponatraemia
- Hypokalaemia
- Hypotonia
- Proteinuria
- Psychosis/odd behaviour[1]
- Peripheral neuritis
- Paralysis
- Seizures
- Sensory impairment

- Sight may be affected
- Shock (± collapse).

Drugs to avoid in acute intermittent porphyria

are legion (they may precipitate above symptoms ± quadriplegia, see BNF/OTM), they include: *alcohol*; *several anaesthetic agents* (barbiturates, halothane); *antibiotics* (chloramphenicol, sulfonamides, tetracyclines); *painkillers* (pentazocine); *oral hypoglycaemics*; *contraceptive pill*.[20]

Treatment of an acute attack

- Remove precipitants, then:
- IV fluids to correct electrolyte imbalance.
- High carbohydrate intake (eg Hycal®) by NG tube if necessary.
- IV haematin is probably the treatment of choice in most centres now.
- Nausea controlled with prochlorperazine 12.5mg IM.
- Sedation if necessary with chlorpromazine 50-100mg PO/IM.
- Pain control with: aspirin, dihydrocodeine, or morphine.
- Seizures can be controlled with diazepam.
- Treat tachycardia and hypertension with propranolol.

Non-acute porphyrias

Porphyria cutanea tarda*, *erythropoietic protoporphyria, and ***congenital erythropoietic porphyria*** are characterized by cutaneous photosensitivity alone, as there is no overproduction of porphyrin precursors, only porphyrins.

▸Alcohol, lead, and iron deficiency cause abnormal porphyrin metabolism.

▸Offer genetic counselling (OHCS p154) to all patients and their families.

Acknowledgements

Relevant pages in other sections: Reference intervals (p736); acute renal failure (p292, p293).

1 We thank Dr Paul Flynn who is our Specialist Reader for this chapter.

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17

Eponymous Syndromes

See also OHCS p638-55

Alice in Wonderland syndrome (Todd's syndrome)

Disturbance of one's view of oneself ± fast-forwarding of intrapsychic time. Can occur in epilepsy, migraine, or infectious mononucleosis.

Arnold-Chiari malformation

The cerebellar tonsils and medulla are malformed congenitally and herniate through the foramen magnum. This may cause infantile hydrocephalus with mental retardation, optic atrophy, ocular palsies and spastic paresis of the limbs. Spina bifida, syringomyelia (p508), or focal cerebellar and brainstem signs may occur eg ataxia, dysphagia, oscillopsia, nystagmus (p44). There may be bony abnormalities of the base of the skull (basilar impression). MRI is better than CT in aiding diagnosis.

Baker's cyst

This is when fluid from a knee effusion escapes to form a popliteal cyst, often swollen and painful.

Differential:

A ruptured Baker's cyst may mimic a DVT. Ultrasound can differentiate the two.

Treatment:

Aspiration is possible, but recurrence is common.

Barrett's oesophagus

In chronic reflux oesophagitis (p236), columnar gastric epithelium extends upwards replacing normal oesophageal squamous epithelium (the squamocolumnar junction migrates upwards). Intestinal metaplasia occurs in these cells. The length affected may be a few cm only or all the oesophagus, and can be continuous or patchy. The changes are visible on endoscopy. There is a 40-fold ↑risk of oesophageal adenocarcinoma. Once diagnosed, endoscopic surveillance programmes vary depending on age and general health; there is little evidence that these programmes have reduced deaths from oesophageal cancer.

Management

depends on what histology is found on biopsy. If pre-malignant changes (high-grade dysplasia) are found, oesophageal resection is generally advocated, especially in younger, fit patients; endoscopic mucosal ablation by epithelial laser or photodynamic ablation is used in others. Photodynamic therapy (PDT) involves lightinduced activation of an orally administered photosensitizer such as 5-aminolaevulinic acid which causes the accumulation of protoporphyrin IX in GI mucosal cells. Local laser light then causes necrosis, which is confirmed by finding squamous re-epithelialization. PDT remains experimental. If no pre-malignant changes are found, regular endoscopy + biopsy, and intensive antireflux measures including long-term proton pump inhibitors are used. Exactly who to screen and how often is not clear.

Bazin's disease

Localized areas of fat necrosis with ulceration and an indurated rash, characteristically on adolescent girls' calves. Originally thought to be a form of skin TB, but cases unrelated to tuberculosis have been seen.

Behçet's disease

A systemic vasculitis of unknown cause, associated with HLA-B51. It is most commonly found in Turkey, the Mediterranean and Japan.

Features:

recurrent oral and genital ulceration, ocular inflammation (eg anterior or posterior uveitis), skin lesions (eg erythema nodosum, papulopustular lesions), neurological (eg aseptic meningitis, encephalitis, CN palsies, confusion), vasculitis, joints (non-erosive large joint oligoarthropathy), GI: diarrhoea, colitis.

Diagnosis

is mainly clinical. Pathergy test: needle prick leads to papule formation within 48 hours.

[prescription take]:

Steroids, ciclosporin, azathioprine or cyclophosphamide are used in severe disease eg with ocular involvement. [1] Colchicine may be effective in treating ulceration.

Berger's disease (IgA nephropathy)

p288. The commonest glomerulonephritis, causing episodic haematuria, often coinciding with viral infections. Secondary causes include alcoholic liver disease, ankylosing spondylitis, coeliac disease, HIV.

Bickerstaff's brainstem encephalitis

This disease is related to Miller-Fisher syndrome (p695): in addition to ophthalmoplegia, ataxia and areflexia, there are extensor plantars and reduced consciousness—a reversible brain death picture may occur (no structural damage has been demonstrated). Plasmapheresis may help.

Eponyms are so-called because they take their names from their chief protagonists (either doctors or patients). They are the sole route to medical fame: 'if one was a drunkard and one's name was Johnny Walker one could form a society called *Alcoholics Eponymous*'.

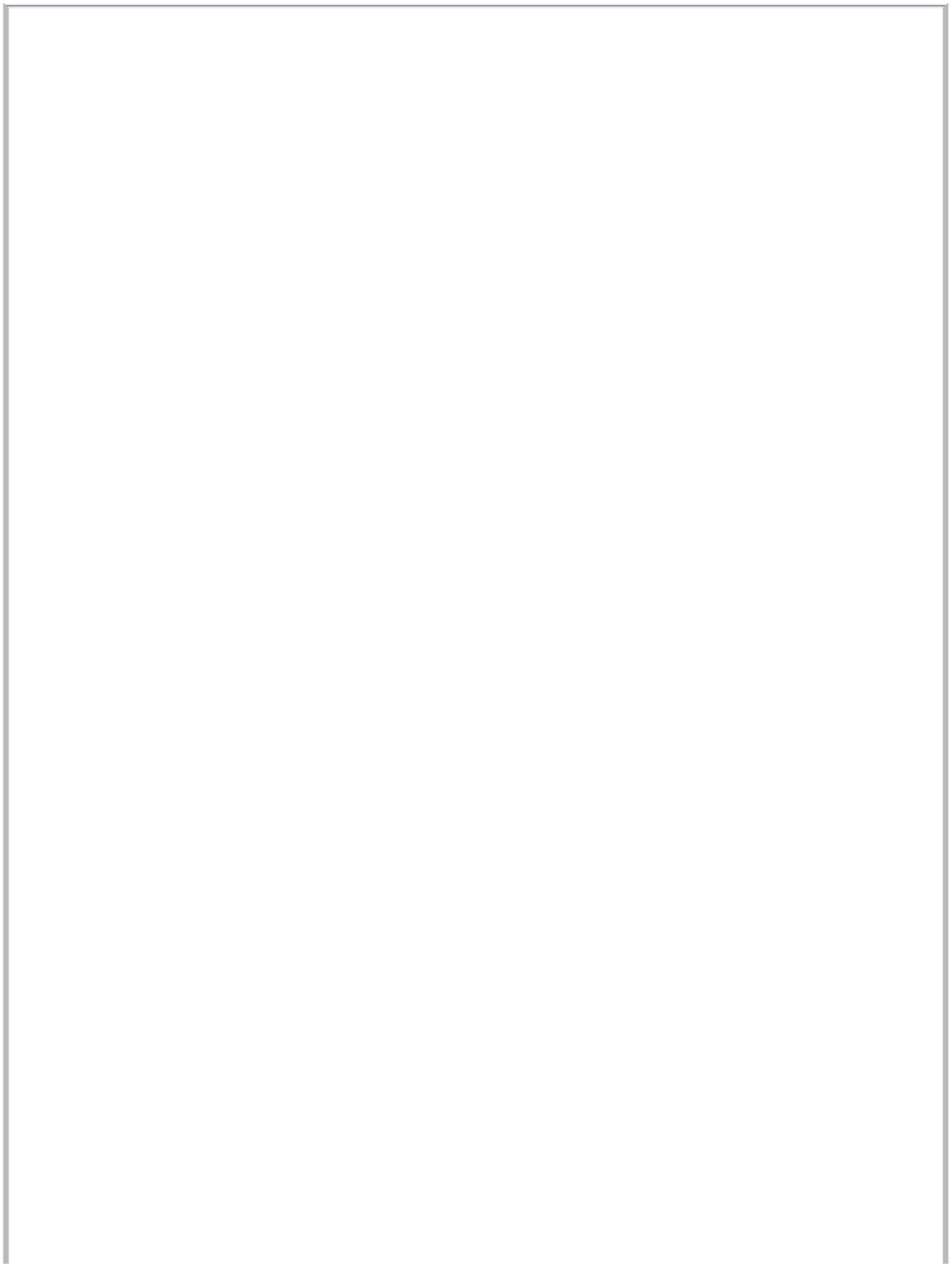
Alan Bennett

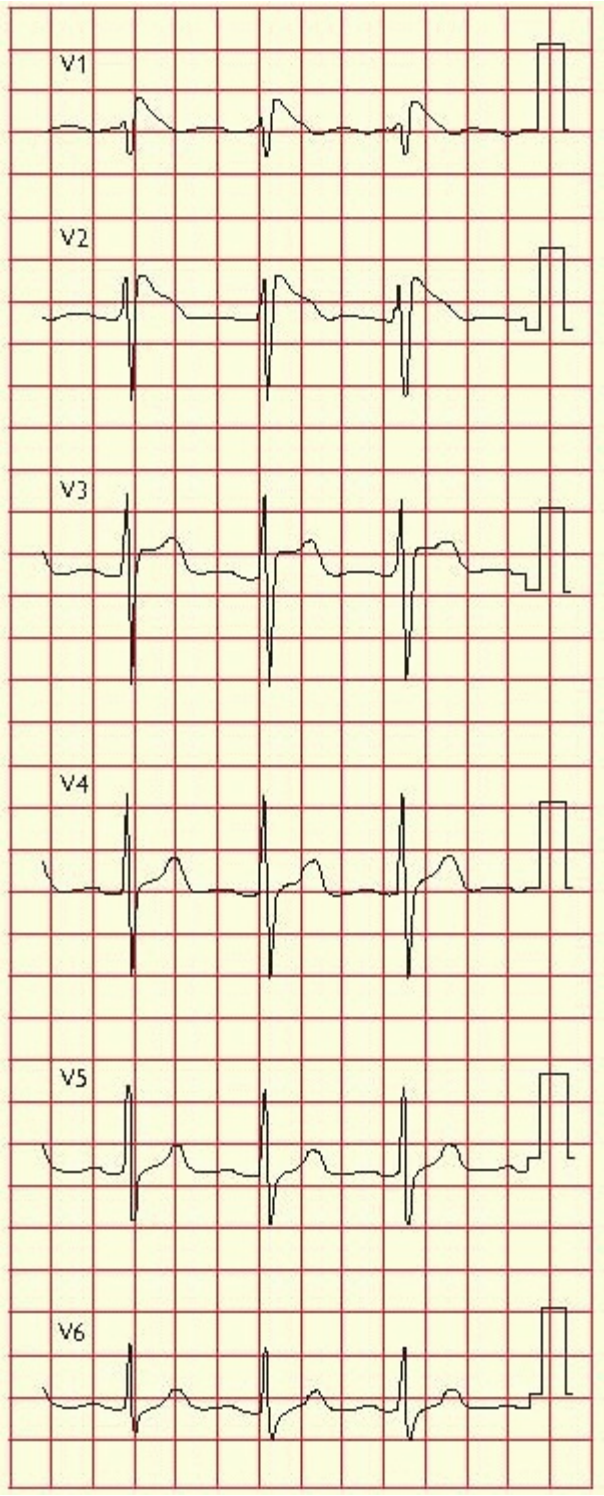
Consult the index for eponymous covered in other chapters.

For biographical details, see www.whonamedit.com

ECG of Brugada syndrome

Note right bundle branch block and the unusual morphology of the raised ST segments in V1-3. This inherited condition causing a faulty sodium channel predisposes to fatal arrhythmias, eg ventricular fibrillation, typically in young males, which is preventable by using an implantable defibrillator. ▸*Consider primary electrical cardiac disease in all those with unexplained syncope*. Relatives of those with sudden unexplained death may undergo unmasking of arrhythmias by IV ajmaline tests—but some results are false +ve. [2] Use judgment in subjecting those with ST abnormalities but no symptoms to electrophysiological tests, right ventricular myocardial biopsy, and MRI. Sequencing SCN5A loci may identify the R367H missense mutation in affected families.[1]





ECG 14—Brugada syndrome. Note right bundle branch block and ST morphology in leads V1-3.

Brown-Séquard syndrome

A lesion in one half of the cord (due to hemisection or unilateral cord lesion) causes

- Ipsilateral UMN weakness below the lesion (severed corticospinal tract, causing spastic paraparesis, brisk reflexes, extensor plantar reflex)
- Ipsilateral loss of proprioception and vibration (severed dorsal column) and
- Contralateral loss of pain and temperature sensation (severed spinothalamic tract which has crossed over; see **fig 1**, p508).

Causes:

Trauma, tumour, degenerative disease (eg disk herniation, cervical spondylosis), MS.

Budd-Chiari syndrome

Hepatic vein obstruction by thrombosis or tumour causes ischaemia and hepatocyte damage, presenting with liver failure, or insidious cirrhosis. Abdominal pain, hepatomegaly, ascites and ↑ALT occur. Portal hypertension occurs in chronic forms.

Causes:

include hypercoagulable states (the Pill, pregnancy, malignancy, paroxysmal nocturnal haemoglobinuria, polycythaemia rubra vera, thrombophilia) or liver, renal or adrenal tumour.

Tests:

Ultrasound + hepatic vein Dopplers, CT or MRI. Angioplasty, transjugular intrahepatic portosystemic shunt (TIPS) or a surgical shunt may be needed. Anticoagulate (lifelong) unless there are varices. Consider liver transplant in fulminant hepatic necrosis or cirrhosis.[3]

Buerger's disease (thromboangiitis obliterans)

This is inflammation of arteries, veins, and nerves with thrombosis in the middle sized arteries, often in male cigarette smokers. It may lead to gangrene. The underlying cause is unknown.

Caplan's syndrome

This is multiple lung nodules in coal workers with rheumatoid arthritis, caused by an inflammatory reaction to the external allergen. CXR: bilateral peripheral nodules (0.5-5cm).

[prescription take]:

None are specific—treat symptoms (p184).

Charcot-Marie-Tooth syndrome (peroneal muscular atrophy)

This inherited neuropathy starts in puberty with weak legs and foot drop, with variable loss of sensation and reflexes. The peroneal muscles atrophy, leading to an inverted champagne bottle appearance. Atrophy of hand and arm muscles also occurs. The most common form, CMT1A (caused by mutations in the PMP22 myelin gene on chromosome 17), is inherited in an autosomal dominant manner. It is seldom *totally* incapacitating. Hand pain/paraesthesiae may respond to nerve release.

Churg-Strauss syndrome

is a triad of asthma (often late-onset), eosinophilia and vasculitis, affecting the lungs, peripheral nerves and skin. Glomerulonephritis may occur, but renal failure is rare. ANCA is +ve. Most respond to steroids.

Creutzfeldt-Jakob disease (CJD)

The cause is a prion (PrPSc): an altered form of a normal protein (PrPc), that can transform other normal proteins into prion proteins (hence its infectivity). ↑PrPSc leads to spongiform changes (tiny cavities) in the brain. Most cases are ***sporadic***.

Variant CJD

(vCJD; only 183 cases worldwide by 2006) is transmitted via meat contaminated by CNS tissue affected by bovine spongiform encephalopathy BSE; see BOX). In ***inherited*** forms (incidence: 1 per 10^6/yr, worldwide,[4] eg as the Gerstmann-Sträussler syndrome), the 'normal' protein is abnormally unstable and readily transforms to PrPSc.

Iatrogenic

causes may include: contaminated neurosurgical/dental instruments, corneal transplants, hormones from human pituitaries (eg growth hormone) and ?blood products. Prion protein is resistant to sterilisation.

Signs:

Progressive dementia, focal CNS signs, myoclonus, depression, eye signs (diplopia, supranuclear palsies, complex visual disturbances, homonymous field defects, hallucinations cortical blindness).[5]

Tests:

Tonsil/olfactory biopsy;[6] CSF gel electrophoresis.

Treatment:

None proven. Death occurs within 6 months in sporadic and iatrogenic forms.

Prevention:

Regulations aimed at limiting the spread of BSE, the transmission of BSE prions to humans, and iatrogenic transmission, will hopefully limit the spread of this disease.[7]

Crigler-Najjar syndrome

An inherited cause of unconjugated hyperbilirubinaemia presenting in the first days of life with jaundice ± CNS signs. Cause: mutation leading to abolition of bilirubin UDP-glucuronosyltransferase (UGT) activity.

[prescription take]:

Liver transplant before irreversible kernicterus (OHCS p115) develops. Phototherapy can keep bilirubin levels down while awaiting transplant.[8]

The fine line between fame and infamy

After his neurological experiments. Charles Brown-Séquard 1817-94 proclaimed that he had discovered the secret of perpetual youth after injecting himself with a concoction of testicular blood, seminal fluid, and testicular extracts from dogs and guinea pigs. In the 1880s over 12,000 doctors were queuing up for his special extracts, which they used on their patients in various ways. He gave the extracts away free, provided that results of their use were reported back to him. 314 out of 405 cases of tabes were improved, and his own urinary flow rate improved by 25%. Endocrinologists never forgave him for bringing their science into disrepute—but, to this day, no one really knows whether he discovered anything of any practical use.[9]

Signs which may distinguish variant CJD from sporadic CJD (SCJD)

- An earlier age at presentation (median 29yrs vs 60yrs in sporadic CJD).
- Longer survival (median 14 months vs 4 months in sporadic CJD).
- Psychiatric features are an early sign (anxiety, withdrawal, apathy, agitation, a permanent look of fear in the eyes, depression, personality change, lack of awareness of surroundings, insomnia). Hallucinations and delusions may occur—before akinetic mutism.
- Painful sensory symptoms are commoner (eg foot pain hyperaesthesia).
- Dementia is often delayed (occurs early in sporadic CJD).
- Normal EEG (sporadic CJD has a characteristic spike and wave pattern).
- MRI *may* show a characteristic signal in the posterior thalamic area. CT is normal in both forms of the illness, and CSF tests detecting 14-3-3 protein cannot be relied on (may be +ve in both variant and sporadic CJD).
- Mean CSF tau-pT181/tau protein ratio is 10-fold higher in vCJD than in sCJD.[10]
- Homozygosity for methionine at codon 129 of the PRP gene is typical.
- NB: as the incubation period may be up to several decades, predictions of incidence of vCJD may be underestimations.

Curtis-Fitz-Hugh syndrome

is inflammation of the liver capsule (perihepatitis) due to chlamydial or gonococcal infection, often with pelvic inflammatory disease (in women). Right upper quadrant pain occurs.

Devic's syndrome (neuromyelitis optica)

This is a variant of multiple sclerosis (with distinguishing features on MRI). There is demyelination of the optic nerves, chiasm, and the cord.

Treatment:

Azathioprine is often used to suppress attacks, as opposed to treatments such as ß-interferon in MS.

Prognosis

is variable, and complete remission may occur.

Dressler's syndrome

This develops 2-10wks after an MI or heart surgery. It is thought that myocardial necrosis stimulates the formation of autoantibodies against heart muscle.

The Patient:

He or she may suffer recurrent fever and chest pain ± pleural or pericardial rub (from serositis). Cardiac tamponade may occur, so avoid anticoagulants.

[prescription take]:

Aspirin, NSAIDs or steroids.

Dubin-Johnson syndrome

An autosomal recessive disorder, causing defective hepatocyte excretion of conjugated bilirubin. It is caused by a point mutation in a gene coding for a canalicular transport protein. There is intermittent jaundice with pain in the right hypochondrium. There is no hepatomegaly.

Tests:

Alk phos ↔; bilirubinuria on dipstick. Liver biopsy: diagnostic pigment granules.[11]

Dupuytren's contracture

Palmar fascia contracts so that the fingers (often 5th finger) cannot extend. There is nodular thickening of the connective tissue over the 4th & 5th fingers.

Prevalence:

~10% of ♂ >65yrs (↑ if +ve family history).

Associations:

Smoking, alcohol use, heavy manual labour, trauma, DM, phenytoin, HIV. Peyronie's may co-exist (p700). It is thought to be caused by local hypoxia: ischaemia (the primary event) → increased xanthine oxidase activity → reduced oxygen → superoxide free radicals → fibroblast proliferation → Type III collagen → palmar fibrosis. Surgery may be needed.

Ekbom's syndrome

(Restless legs) There is an irresistible desire to move the legs when in bed, ± unpleasant leg sensations. The mechanism is unclear. It is usually idiopathic; secondary causes include iron deficiency, uraemia, pregnancy, DM, polyneuropathy and rheumatoid arthritis.

Treatment:

Dopamine agonists are commonly used; benzodiazepines eg clonazepam (1-4mg PO nocte) may also help. Ekbom also described delusional parasitosis: 'I am invaded by parasites'.[12]

Fabry's disease

An X-linked recessive disorder of glycolipid metabolism, due to ↓levels of lysosomal α-galactosidase A. There is accumulation of glycosphingolipids in the skin (angiokeratoma corporis diffusum), eyes (lens opacities), heart (LVH, conduction defects, infarction), kidneys (progressive renal failure), CNS (stroke) and peripheral nerves (neuropathy). Most die in the 5th decade due to renal failure, stroke or MI.

Treatment:

Biweekly infusions of recombinant human α-galactosidase A are safe: long term data are awaited.[13]

Fanconi anaemia

is an autosomal recessive disorder with defective stem cell repair, leading to aplastic anaemia (with increased susceptibility to acute myeloid leukaemia), skin pigmentation, skeletal malformation (eg absent radii, short stature, microcephaly, syndactyly), neurological deficits (congenital deafness, IQ↓), and cryptorchidism. Several genes have been implicated.[14]

Felty's syndrome

Rheumatoid arthritis + splenomegaly + WCC↓. There is hypersplenism (anaemia ± platelets↓), recurrent infections, also skin ulcers and lymphadenopathy. Rh factor: ↑↑. Splenectomy may improve neutropenia.

Foster Kennedy syndrome

Optic atrophy of one eye with papilloedema of the other, due respectively to optic nerve compression and ↑ICP from a mass (eg meningioma, hydatid, plasmacytoma) on the side of the optic atrophy.

Friedreich's ataxia

This is an autosomal recessive disorder, with expansions of the trinucleotide repeat GAA in the X25 (frataxin) gene. There is degeneration of many nerve tracts: spinocerebellar tracts degenerate causing cerebellar ataxia, dysarthria, nystagmus, and dysdiadochokinesis. Loss of corticospinal tracts occurs

(weakness and plantars ↑↑) with peripheral nerve damage, so tendon reflexes are paradoxically depressed (differential diagnosis p459). There is also dorsal column degeneration, hence loss of positional and vibration sense. Pes cavus and scoliosis occur. Cardiomyopathy may cause CCF. Typical age at death: ~50yrs.

[prescription take]:

There is no cure; surgery may provide symptomatic relief for musculoskeletal problems.

Features distinguishing Devic's disease from multiple sclerosis[15]

	Devic's disease	Multiple sclerosis
Course	May be monophasic or relapsing	Relapsing usually; see p488
Attack severity	Usually severe	Often mild
Respiratory failure	~30% of cases, due to cervical myelitis	Rare
MRI head	Usually normal	Many periventricular whitematter lesions
MRI cord	Multiple, small, peripheral lesions	Extensive central lesions
CSF oligoclonal bands	Absent	Present
Permanent disability	Usually attack-related	Usually in late progressive disease
Co-existent autoimmune disease	Present in up to 50%	Uncommon

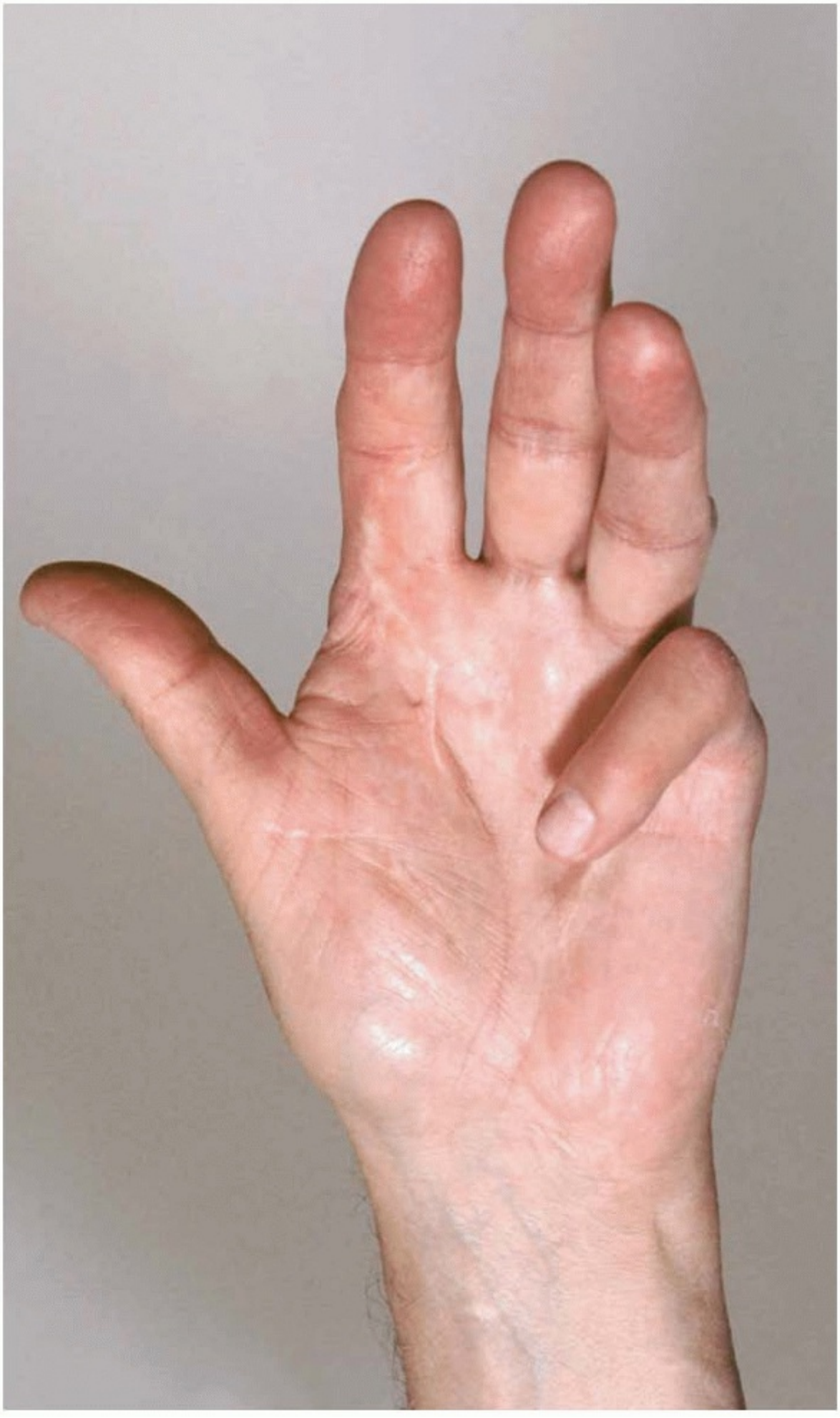


Fig 1. Dupuytren's contracture of the 5th finger

Froin's syndrome

CSF protein↑ and xanthochromia with normal cell count, a sign of blockage in CSF flow in the spine, eg from a spinal tumour. *[Georges Froin, 1874]*

Gardner's syndrome

(Autosomal dominant) Variant of familial adenomatous polyposis, caused by mutations in the APC gene (5q21). Features include hundreds of malignant colon polyps (which 'inevitably', given time, become malignant— typically before 40yrs old),[16] benign bone osteomas, epidermal cysts, dermoid tumours, fibromas, and neurofibromas.

Fundoscopy:

Black spots (congenital hypertrophy of retinal pigment epithelium); this helps detect carriers of the gene before symptoms develop.

Onset:

2-70yrs, eg mass effect (eg obstructed ureters) or bloody diarrhoea. Careful follow-up is needed. Subtotal colectomy + removal of polyps may prevent malignancy. Endoscopic polypectomy with long-term sulindac therapy has been tried to postpone prophylactic colectomy.[17] *[EJ Gardner 1950]*

Gélineau's syndrome (narcolepsy)

The patient, usually a young man, succumbs to irresistible attacks of inappropriate sleep ± vivid hallucinations, cataplexy (sudden hypotonia), and sleep paralysis (paralysis of speech + willed movement on waking, while fully alert, OHCS p393).

Putative mechanism:

Genetic mutations lead to loss of hypothalamic hypocretin-containing neurones, possibly via autoimmune destruction.[18] 95% are +ve for HLA DR2.

[prescription take]:

Stimulants (eg methylphenidate, OHCS p211, 10mg PO after breakfast and lunch) may cause dependence ± psychosis. Modafinil (~200mg PO as a single daily dose before noon) may be better. SE: anxiety, aggression, dry mouth, euphoria, insomnia, BP↑, dyskinesia, alk phos↑.

Gerstmann's syndrome

Finger agnosia (inability to identify fingers by name), left/right disorientation, agraphia (inability to write), acalculia (to calculate) & alexia (to read). These symptoms together suggest a dominant parietal lesion.

Gilbert's syndrome

This inherited metabolic disorder is a common cause of *unconjugated* hyperbilirubinaemia, due to decreased bilirubin UDP-glucuronosyltransferase activity. Prevalence is estimated at 1-2%. The onset is shortly after birth, but it may be unnoticed for many years. Jaundice occurs during intercurrent illness, and bilirubin rises on fasting. Liver biopsy is normal, but should rarely be required clinically. It is a benign condition. *[Nicolas Gilbert, 1901]*

Gilles de la Tourette syndrome

Presentation:

(♂:♀≈4:1) Waxing and waning motor and phonic tics (p460; mean age of onset: 6yrs), blinking, nodding, stuttering ± irrepressible, explosive, occasionally obscene verbal ejaculations ± anger control problems and attention-deficit disorder. There may be a witty, innovatory, phantasmagoric picture, 'with mimicry, antics, playfulness, extravagance, impudence, audacity, dramatizations, surreal associations, uninhibited affect, speed, 'go', vivid imagery and memory, and hunger for stimuli'; also grunting, sniffing, throat-clearing, twirling, nipping people, obscene gestures (copropraxia), repeating self and others (palilalia, echolalia), repeating others' movements (echopraxia). More prosaic forms are commoner.

Pathogenesis:

Probably an inherited developmental disorder of basal ganglia disinhibition. Group A ß-haemolytic streps may trigger these symptoms, as in Sydenham's chorea (p128; unproven, see BOX).

MRI:

Large left thalamus.[19]

Associations:

Obsessive-compulsive/attention-deficit disorder.

[prescription take]:

Haloperidol ~1.5mg/8h PO, pimozide, olanzapine, or risperidone—if the patient wants help.

Goodpasture's syndrome

Acute glomerulonephritis + lung symptoms (haemoptysis/diffuse pulmonary haemorrhage) caused by antiglomerular basement membrane antibodies (binding kidney's basement membrane and alveolar membrane).

Tests:

CXR: infiltrates due to pulmonary haemorrhage, often in lower zones. Kidney biopsy: crescentic glomerulonephritis.

Treatment:

▸▸Treat shock. Vigorous immunosuppressive treatment and plasmapheresis; see p288. *[Ernest Goodpasture, 1919]*

Cataplexy is highly specific for narcolepsy/Gélineau's syndrome

Daytime sleepiness has many causes, but if it occurs with catalepsy the diagnosis 'must' be narcolepsy. Cataplexy is bilateral loss of tone in antigravity muscles provoked by emotions such as laughter, startle, excitement, or anger. Associated phenomena include: falls, mouth opening, dysarthria, mutism, and phasic muscle jerking around the mouth. Most attacks are brief, but injury can occur (eg if several attacks per day). It is comparable to the atonia of rapid eye movement sleep *but without loss of awareness*. ΔΔ: Bradycardia, migraine, atonic/akinetic epilepsy,[20][21] delayed sleep phase syndrome, conversion disorder, malingering, and psychosis.[22]

Don't confuse capa***plex***y with cata***leps***y—a waxy flexibility where involuntary statue-like postures are effortless maintained (frozen) despite looking most uncomfortable (this motor-perceptual dissociative phenomenon may be induced by hypnosis, psychosis, antipsychotics, or a thalamic lesion).[23] Catalepsy is one of the signs of ***catatonia***[24] —a neuropsychiatric syndrome of catalepsy, negativism, mutism, muscular rigidity, mannerisms, autonomic instability, and fever.[25]

Post-streptococcal autoimmune CNS disorders (eg Tourettism)

Group A streptococci can (rarely) induce autoimmune diseases of the heart, joints, and brain, eg movement disorders (chorea, tics/Tourettism, dystonia, and Parkinsonism), emotional disorders, and sleep disorders. MRI and pathological studies suggest that the most vulnerable CNS region is the basal ganglia. Immunopathogenesis is poorly understood: there is some support for autoantibody-mediated disease, but studies are conflicting.[26]

The lung and its various vasculitides (eg Goodpasture's)

Lung vasculitis is most commonly seen with the primary idiopathic, small-vessel or ANCA (p539) associated vasculitides (Wegener's granulomatosis, microscopic polyangiitis, and Churg-Strauss syndrome).[27] Medium-vessel vasculitis (classic polyarteritis nodosa), large-vessel vasculitis (Takayasu arteritis), primary immune complex-mediated vasculitis (Goodpasture's syndrome), and secondary vasculitis (SLE) can all affect the lung.

Guillain-Barré syndrome

Incidence:

1-2/100,000/yr.

Signs:

A few weeks after 'flu vaccine, gastroenteritis or URTI, a symmetrical ascending muscle weakness occurs. Common triggers are *Campylobacter jejuni*, CMV, mycoplasma, zoster, HIV, EBV. The pathogen causes antibody formation, which attack nerve cells. In 40%, no cause is found. It may advance quickly, affecting all limbs at once, and can lead to paralysis. There is a progressive phase of up to 4 weeks, followed by recovery. Unlike other neuropathies, *proximal* muscles are more affected, and trunk, respiratory, and cranial nerves (esp. VII) may be involved. Pain is common (eg back, limb) but sensory signs may be absent. Autonomic dysfunction may occur eg sweating, ↑HR, BP changes, dysrhythmias. Progressive respiratory involvement is the chief danger.

Tests:

Nerve conduction studies: slowing of conduction. CSF: protein↑ (often >5.5g/L), normal CSF white cell count.

Treatment:

Respiratory involvement requires transfer to ITU. Check forced vital capacity (FVC) 4 hourly. ▸*Ventilate sooner rather than later*, eg if FVC <1.5L, P_aO_2 <10kPa, P_aCO_2 >6kPa. Specific treatment is with IV immunoglobulin 0.4g/kg/24h for 5d or plasma exchange; they are equally effective. Corticosteroids have no role.

Prognosis:

Good; ~85% make a complete or nearly complete recovery. 10% are unable to walk alone at 1yr. *Complete paralysis is compatible with complete recovery.*

Mortality:

10%.

Henoch-Schönlein purpura (HSP)

is a small vessel vasculitis, which presents with purpura (purple nodules which do not disappear on pressure—signifying intradermal bleeding) often over buttocks and extensor surfaces, typically affecting young ♂. There may be glomerulonephritis (p288), joint involvement, abdominal pain (±intussusception), which may mimic an 'acute abdomen'.

Horner's syndrome

Pupil constriction (*miosis*), sunken eye (*enophthalmos*), *ptosis* and ipsilateral loss of sweating (*anhidrosis*) due to interruption of the face's sympathetic supply, eg at the brainstem (demyelination, vascular disease), cord (syringomyelia), thoracic outlet (Pancoast's tumour, p700), or on the sympathetic nerves' trip on the internal carotid artery into the skull (carotid aneurysm), and thence to the orbit. *[Johann Horner, 1869]*

Huntington's chorea

is an autosomal dominant condition (gene on chromosome 4) with full penetrance, due to expansions of a CAG trinucleotide repeat. Onset is usually in middle age, so the child of an affected parent lives under a Damocles' sword, having a 50% chance of becoming affected. Genetic tests are available. Signs are insidious, then progressive: chorea → irritability → dementia ± seizures → death.

Pathology:

Cerebral atrophy with loss of corpus striatum GABA-nergic & cholinergic neurones.

Treatment:

(p54) None prevents progression. Offer counselling to patient and family.[28] *[George Huntington, 1872]*

Jervell-Lange-Nielsen syndrome

An autosomal recessive inherited disorder of ventricular repolarization, causing a prolonged QTc interval (p82), associated with bilateral deafness. There is predisposition to syncope, seizures, Torsade de pointes, sudden death. Mutations in a K+ channel subunit may be responsible.[29]

Kaposi's sarcoma (KS)

This sarcoma is derived from capillary endothelial cells or from fibrous tissue, and is associated with a serologically identifiable human herpes virus (KSHV = HHV-8). It presents as purple papules or plaques on skin and mucosa (any organ). It metastasizes to lymph nodes. 3 types: **1** Classic, especially elderly Mediterranean or Jewish males. **2** Endemic (Central Africa). In these two forms, peripheral, slow-growing skin lesions are found, visceral involvement is rare, and lymph node involvement may lead to oedema. **3** KS in immunosuppression eg HIV, organ transplant recipients. This can be aggressive, with multiple skin lesions and visceral involvement (eg lungs, bowel). In HIV, KS occurs particularly in homosexual men, where it is diagnostic of AIDS (p396), and carries a poor prognosis. Pulmonary KS may present as breathlessness. Bowel KS may cause nausea, abdominal pain.

Diagnosis

is by biopsy.

[prescription take]:

Skin lesions are treated with radiotherapy or intralesional TNF-α. Chemotherapy is used for widespread disease. *[Moricz Kaposi, 1887]*

Diagnostic criteria in typical Guillain-Barré polyneuritis[1]

Features required for diagnosis:

Progressive weakness of all 4 limbs Areflexia

Features excluding diagnosis:

Purely sensory symptoms Diagnosis of:

- Myasthenia
- Botulism
- Poliomyelitis
- Diphtheria
- Porphyria
- Toxic neuropathy

Features supporting diagnosis:

Progression over days, up to 4wks

Near symmetry of symptoms

Sensory symptoms/signs only mild CN involvement (eg bilateral facial weakness)

Recovery starts ~2wks after the period of progression has finished

Autonomic dysfunction

Absence of fever at onset

CSF protein ↑ with CSF WCC $<10\times10^6$/L

Typical electrophysiological tests

Variants of Guillain-Barré syndrome include:

- *Chronic inflammatory demyelinating polyradiculopathy:* (CIDP) characterized by a slower onset and recovery.
- *Miller-Fisher syndrome* which comprises of ophthalmoplegia, ataxia and areflexia. Associated with anti-GQ1b antibodies in the serum.

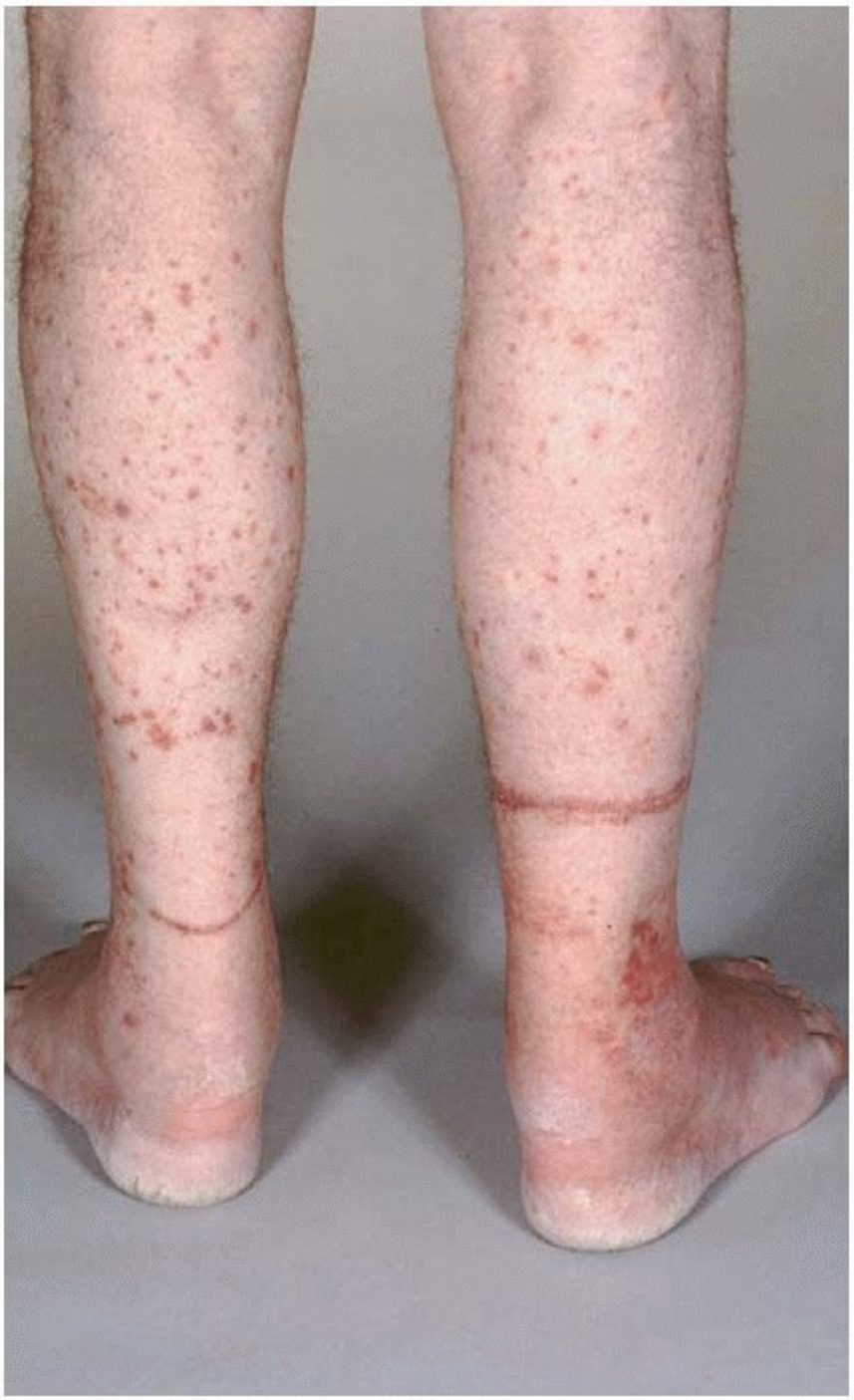


Fig 1. Vasculitic rash in Henoch-Schönlein purpura

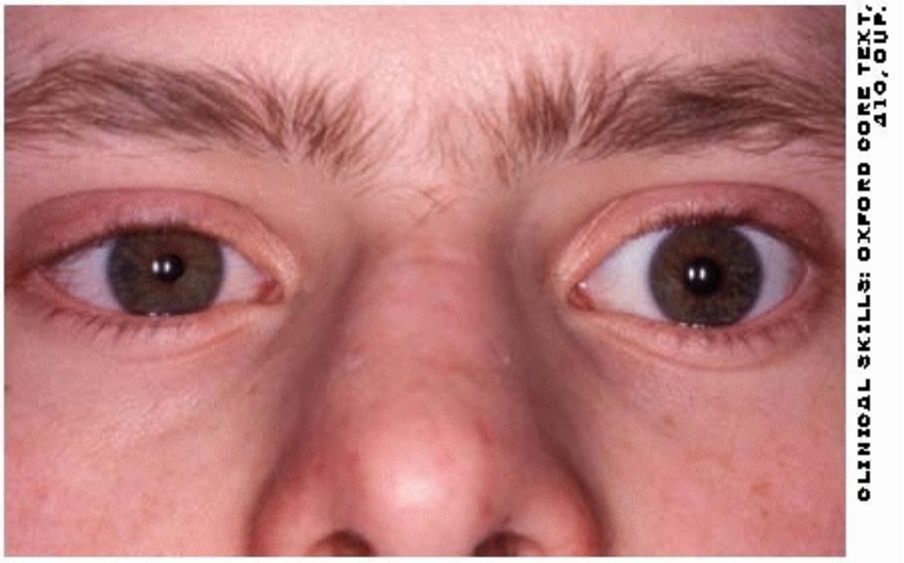


Fig 2. Miosis in Horner's syndrome, affecting the patient's right eye.

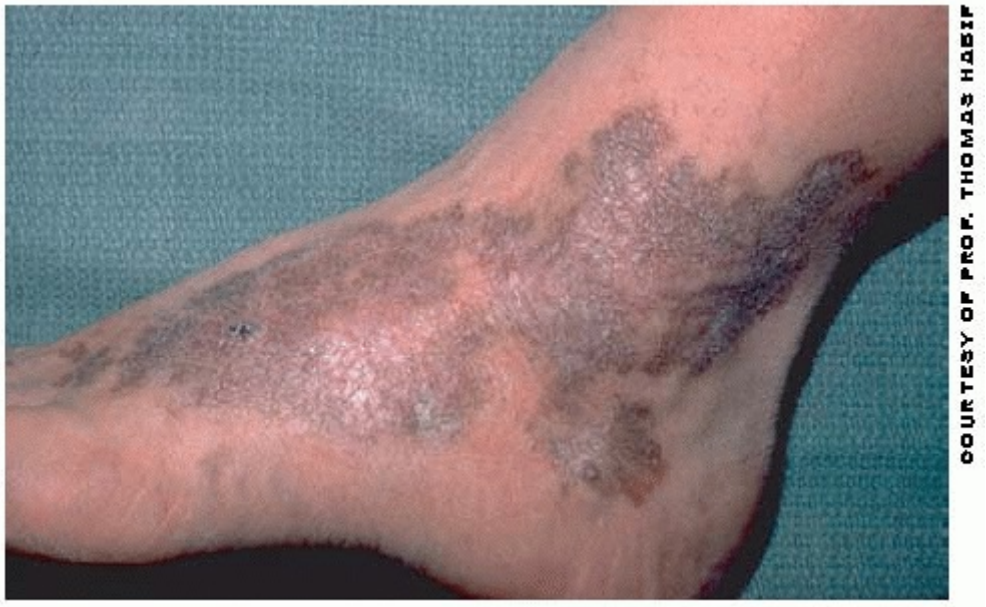


Fig 3. Kaposi's sarcoma.[31]

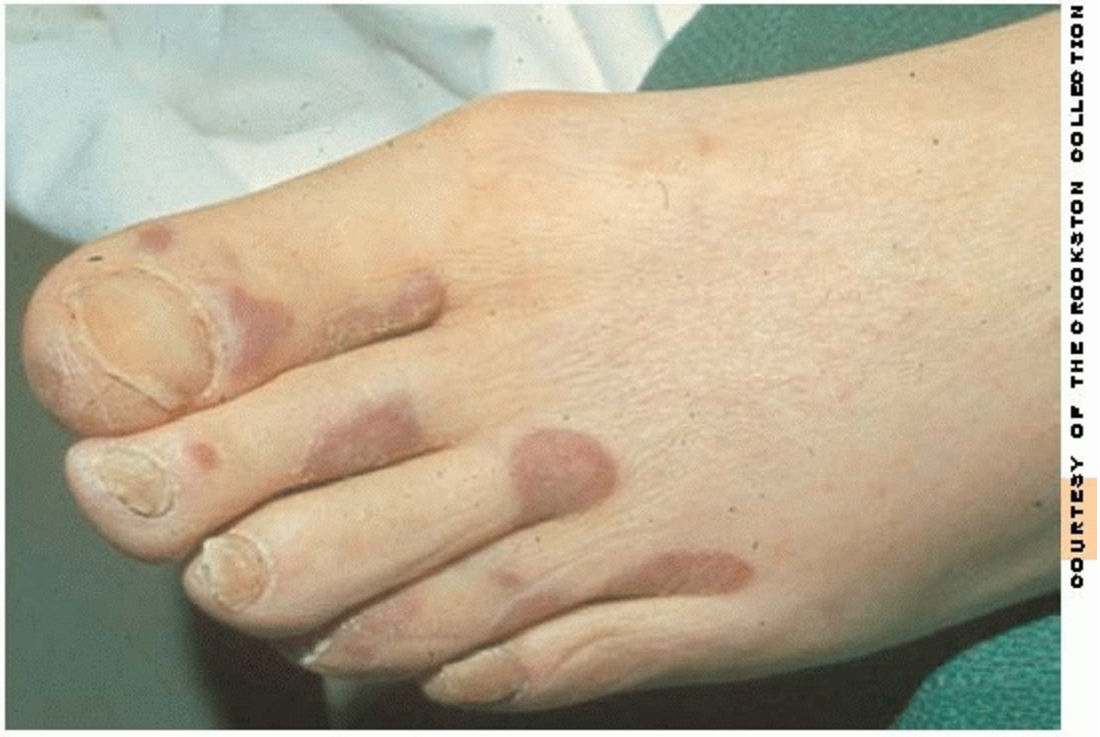


Fig 4. Another patient with Kaposi's sarcoma.[30]

Klippel-Trénaunay syndrome

A triad of port-wine stain, varicose veins, and limb hypertrophy, due to vascular malformation. Usually sporadic, though a few families exhibiting autosomal dominant inheritance have been reported.[32]

Korsakoff's syndrome

↓Ability to acquire new memories, eg after Wernicke's encephalopathy, due to thiamine deficiency (eg in alcoholics). The patient may have to relive his grief each time he hears of the death of a friend. He confabulates to fill in gaps in his memory owing to retrograde amnesia.

[prescription take]:

See *Wernicke's*, p706. Donepezil [1] may have a role.[33] *[Sergei Korsakoff (more accurately transliterated Korsakov), 1887]*

Langerhans'-cell histiocytosis (Histiocytosis X)

A group of disorders involving single- or multi-organ infiltration by granulomatous lesions containing dendritic (Langerhans') cells. Lung and bone involvement is most common; skin, pituitary, thyroid, liver, spleen and lymph nodes may be affected. Lung disease is associated with smoking, and causes interstitial fibrosis. CXR shows nodular changes or honeycomb pattern.

Diagnosis:

Biopsy (eg skin, lung) shows characteristic Birbeck granules on electron microscopy.

Treatment:

This involves local excision or steroids, vinblastine ± etoposide in severe disease. OHCS p644.[34]

Leriche's syndrome

Absent femoral pulses, intermittent claudication of buttock muscles, pale cold legs, and erectile dysfunction due to distal aortic occlusive disease (eg a saddle embolus at its bifurcation); surgery may help.[35] *[René Leriche, 1940]*

Löffler's eosinophilic carditis

Restrictive cardiomyopathy + eosinophilia (eg 120 × 10^9/L). It may be an early stage of tropical endomyocardial fibrosis and overlaps with idiopathic hypereosinophilic syndrome (HES), but is distinct from eosinophilic leukaemia.

Signs:

increasing heart failure (75%) ± mitral regurgitation (49%) ± heart block.

Treatment:

Digoxin + diuretics often only help if the eosinophilia is suppressed, eg by prednisolone or hydroxycarbamide (=hydroxyurea).[36]

Löffler's syndrome (pulmonary eosinophilia)

An allergic infiltration of the lungs by eosinophils. Allergens include: *Ascaris lumbricoides*, *Trichinella spiralis*, *Fasciola hepatica*, *Strongyloides*, *Ankylostoma*, *Toxocara*, *Clonorchis sinensis*,[37] sulfonamides, hydralazine, and nitrofurantoin. Often symptomless with incidental CXR (diffuse fan-shaped shadows), or cough, T°↑, eosinophilia (in ~20%) & larval migrans (p430).

[prescription take]:

Eradicate cause (eg p433). If idiopathic, steroids are effective. *[Wilhelm Löffler, 1887-1972]*

Lown-Ganong-Levine syndrome

A pre-excitation syndrome, similar to Wolf-Parkinson-White (WPW, p112), characterized by a short P-R interval (<0.12 sec), a normal QRS complex (as opposed to the δ-waves of WPW), and risk of supraventricular tachycardia (but not AF/flutter). The cause is not completely understood, but may be due to paranodal fibres that bypass all or part of the atrioventricular node. The patient may complain of intermittent palpitations.[38]

McArdle's glycogen storage disease (Type V)

Caused by the absence of a glycolytic enzyme, muscle phosphorylase. Inheritance: autosomal recessive. Fatigue and cramps follow exercise. Strenuous exercise may provoke rhabdomyolysis and myoglobinuria. Muscle biopsy is diagnostic, showing necrosis and atrophy.

[prescription take]:

Moderate aerobic exercise is beneficial, but avoid heavy exertion. Creatinine supplements and pre-exercise sucrose have been tried.[39]

Mallory-Weiss tear

Vomiting *causes* haematemesis via an oesophageal tear.

Marchiafava-Bignami syndrome

Alcohol-induced corpus callosum necrosis (±extrapontine myelinolysis) causing left-handed deficit of constructional ability, agraphia, mutism, ataxia, poor bimanual co-ordination, gaze apraxia/pseudohallucinated look, dysarthria, epilepsy, paucity of vocal and facial expression modulation,[40] ↓consciousness, coma.

Δ:

MRI.[41]

[prescription take]:

as *Wernicke's*, p706.

Marchiafava-Micheli syndrome (paroxysmal nocturnal haemoglobinuria, PNH)

an acquired clonal expansion and of a multi-potent stem cell carrying a somatic mutation in the X-linked PIG-A gene. Glycosylphosphatidylinositol (GPI)-anchored proteins are lacking on blood cells derived from these mutated stem cells, predisposing to haemolysis, thrombosis, sepsis, and marrow failure.[42]
See p324.

Fatal effects of alcohol on the CNS

- Inhibitions↓ (unsafe sex↑ etc etc)
- Wernicke's encephalopathy
- Hepatic encephalopathy
- Cerebral atrophy (dementia)
- Central pontine myelinolysis
- Cerebellar atrophy (falls etc)
- Stroke (all varieties)
- Seizures
- Marchiafava-Bignami syndrome

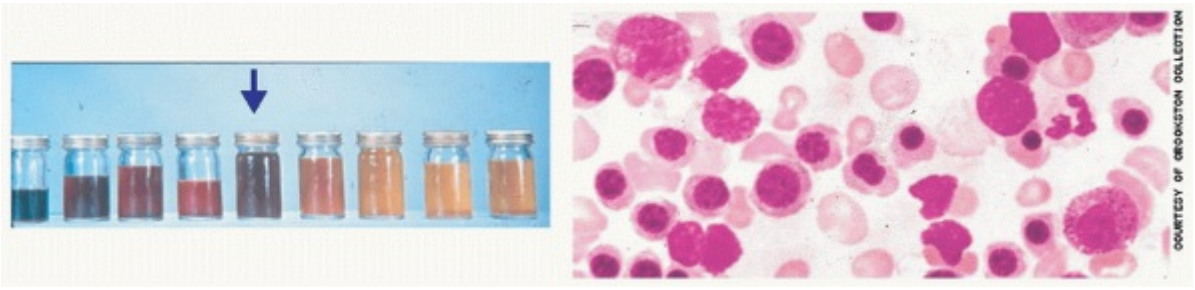


Fig 1. PNH. As always, the darkest hour is before dawn (in this 24h urine sample).[43] NB: this phenomenon is not all that reliable. A much better test even than a marrow biopsy (Fig 1, right, showing a clone of PNH cells) is flow cytometric analysis of GPI anchored proteins on peripheral blood cells. This can determine the size of the PNH clone and type of GPI deficiency (complete or partial). [prescription take]: Most benefit from supportive measures—but allogeneic stem cell transplantation is the only cure.[44]

Marfan's syndrome

is an autosomal dominant connective tissue disease. It is caused by fibrillin-1 (15q21.1) gene mutations, which ↓extracellular microfibril formation, normally required to maintain elastic fibres.[45] NB: ~25% of cases occur with no family history.

Major criteria

(diagnostic if >2): Lens dislocation (*ectopia lentis*); aortic dissection or dilatation; dural ectasia; skeletal features: arachnodactyly (long spidery fingers), armspan > height, pectus deformity, scoliosis, pes planus.

Minor signs:

Mitral valve prolapse, high-arched palate, joint hypermobility. Diagnosis is clinical; MRI for dural ectasia (enlargement of the neural canal) may be helpful.

[prescription take]:

The danger is aortic dissection: beta-blockers are used to slow dilatation of the aortic root. Annual echocardiogram should be performed, with elective surgical repair when maximal aortic diameter is >5cm. In pregnancy, the risk of dissection rises. Homocystinuria has similar skeletal deformities:

***Marfan's* autosomal dominant**	***vs***	***Homocystinuria* cystathione ß-synthetase deficiency; autosomal recessive with early vasculopathy**
• Upwards lens dislocation		• Downwards lens dislocation
• Aortic valve incompetence		• Heart rarely affected
• *Normal* intelligence		• Mental retardation
• Scoliosis, flat feet, herniae		• Recurrent thromboses, osteoporosis

- Life expectancy is reduced from cardiovascular risks
- +ve urine cyanide-nitroprusside test
- Response to pyridoxine

Meckel's diverticulum

Prevalence:

≤2%. ≤2 inches long, and >2 feet from the ileocaecal valve, it contains gastric and pancreatic tissue. There may be gastric acid secretion, causing occult GI pain and bleeding.

Diagnosis:

Radionucleotide scan; laparotomy. Acute inflammation may present like appendicitis.

Meigs' syndrome

The association of a pleural effusion (transudate, usually right sided) + benign ovarian fibroma (or thecoma) + ascites. *[Joseph Meigs, 1937]*

Ménétrier's disease

consists of giant gastric mucosal folds up to 4cm high, mainly involving the fundus, with atrophy of the glands and increased mucosal thickness. The cause is unknown; CMV infection and *H. pylori* have been suggested. There is excess mucous secretion, hyposecretion of gastric acid, and protein loss from the stomach, causing peripheral oedema. There may be epigastric pain, vomiting, and weight loss. It is a premalignant disease.

Treatment:

May respond to *H. pylori* eradication therapy. Some require surgery if intractable symptoms or concern over malignant change. *[Pierre Ménétrier, 1859]*

Meyer-Betz syndrome (Paroxysmal myoglobinuria)

This idiopathic condition causes necrosis of exercising muscles. There is muscle pain, weakness, and discoloured urine: pink→brown (as ↑myoglobin is excreted). Acute renal failure can result from myoglobinuria (p299). DIC is associated.

Tests:

WCC↑, LFT↑, LDH↑, CPK↑, urine myoglobin↑.

Diagnosis:

Muscle biopsy. Exertion should be avoided.

Mikulicz's syndrome

A variant of Sjögren's syndrome, with symmetrical enlargement of lacrimal and salivary glands, and blocking of ducts, with dry eyes/mouth. It may feature with TB, sarcoidosis or lymphoproliferative disease, or occur as a primary autoimmune disease. *[Johann von Mikulicz-Radecki, 1892]*

Milroy's syndrome (Lymphoedema praecox)

An inherited malfunction of the lymphatics causing asymmetric swelling of the legs (usually in young girls).

Management:

- Reassure (it is benign; ≤10% progress to the other leg).
- Treat any cellulitis actively.
- Good foot hygiene.
- If support stockings do not help, try a Lymphapress® device for active compression at night. Surgery with skin grafts is very rarely needed for ‘elephantiasis leg’.

Münchausen's syndrome

The patient gains hospital admissions via deception, feigning illness, hoping for a laparotomy (*laparotimophilia migrans*), or by bleeding (*haemorrhagica histrionica*) or with curious fits (*neurologica diabolica*) or false heart attacks (*cardiopathia fantastica*). Munchausen-by-proxy entails injury to a dependent person by his or her carer (eg mother) to gain medical attention. Covert video surveillance is an ethically problematic tool which may be necessary for diagnosis.

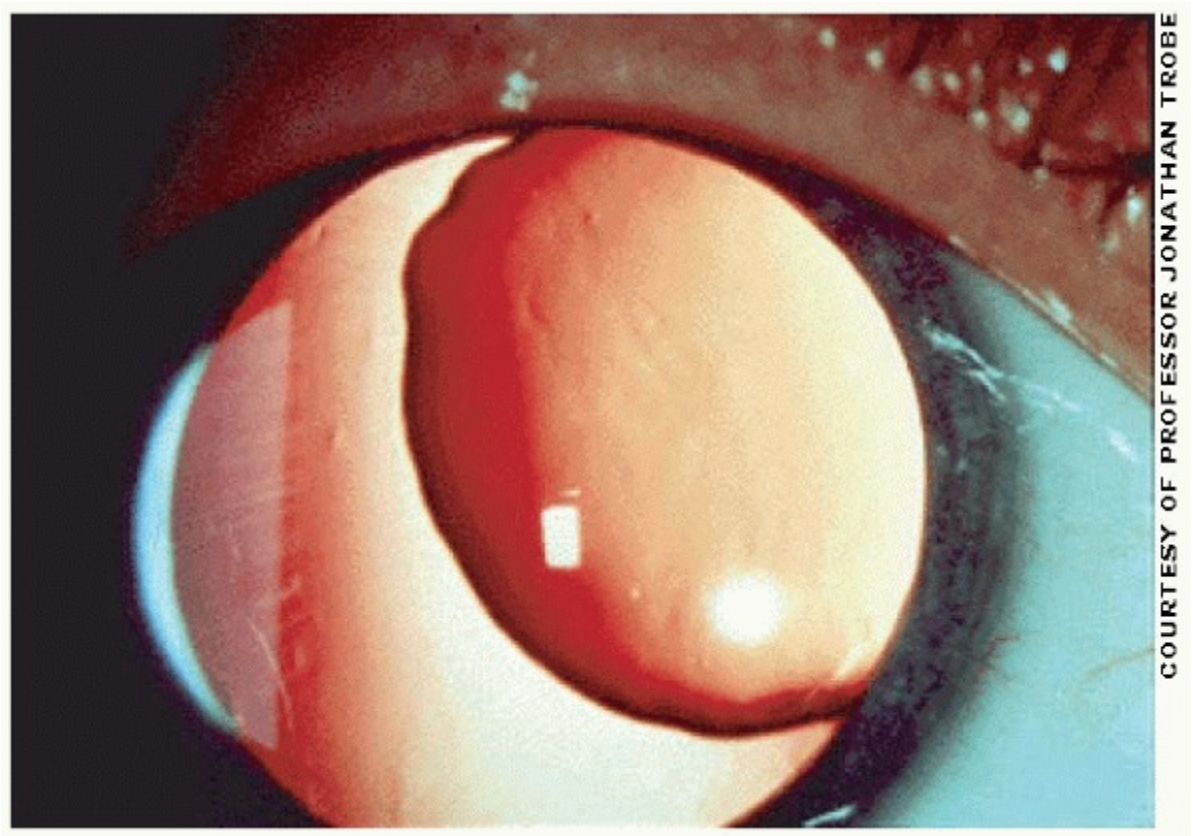


Fig 1. Lens dislocation in Marfan's syndrome: here the lens is dislocated superiorly and medially.[46]

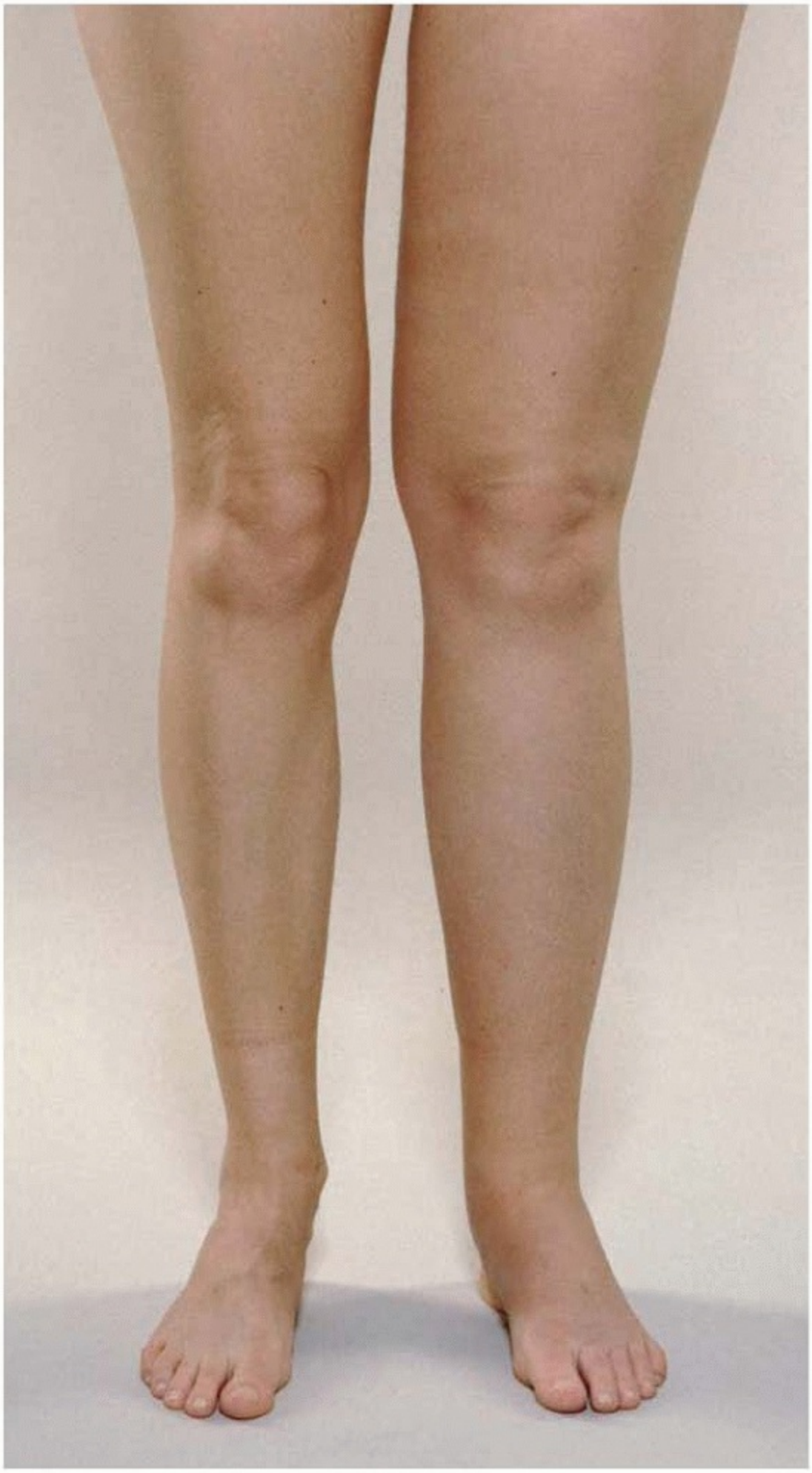


Fig 2. Milroy's syndrome.

Nelson's syndrome

↑skin pigmentation due to excess ACTH from an enlarging pituitary tumour, after bilateral adrenalectomy removes -ve feedback, p208.

Ogilvie's syndrome

Acute functional ('pseudo') colonic obstruction caused by: malignant retroperitoneal infiltration, spine fracture, or electrolyte imbalance.

[prescription take]:

Correct U&E, conservative measures. Contrast enema or colonoscopy allows decompression, and excludes mechanical causes. Neostigmine is also effective, suggesting parasympathetic suppression is to blame.[47] Surgery is rarely needed.

Ortner's cardiovocal syndrome

Recurrent laryngeal nerve palsy from a large left atrium (eg from mitral stenosis) or aortic dissection.

Osler-Weber-Rendu syndrome (Hereditary haemorrhagic telangiectasia)

Telangiectasia on the skin and mucous membranes, which may cause epistaxis or chronic GI bleeds, with iron deficiency anaemia. It is associated with pulmonary, hepatic and cerebral AVMs. Inheritance: autosomal dominant.[48]

Paget's disease of breast

is intra-epidermal spread of an intraductal cancer. Any red, scaly lesion around the nipple should suggest Paget's disease: do a biopsy. ▸Never diagnose eczema of the nipple without a biopsy.

Treatment:

Mastectomy + lymph node clearance. *[Sir James Paget, 1874]*

Pancoast's syndrome

Apical lung cancer + ipsilateral Horner's (p694), from invasion of the cervical sympathetic plexus. Also shoulder/arm pain (brachial plexus invasion C8-T2) ± hoarse voice/bovine cough (unilateral recurrent laryngeal nerve palsy and vocal cord paralysis). *[Henry Pancoast, 1932]*

Parinaud's syndrome (Dorsal midbrain syndrome)

Upward gaze palsy + pseudo-Argyll Robertson pupils (p70). Causes: hydrocephalus, pineal tumours, stroke.

Peutz-Jeghers' syndrome

Germline mutations of gene LKB1 cause mucocutaneous dark freckles on lips, oral mucosa, palm and soles ± GI polyps (hamartomas), causing obstruction or bleeds.

Malignant change:

≤3%, typically duodenal polyps.

[prescription take]:

Usually conservative or local excision.

NB: hamartomas are excessive focal overgrowths of normal cells in an organ, composed of the same cell type.

Peyronie's disease

Penile fibrosis leads to angulation, making coitus most inconvenient.

Associations:

Dupuytren's (p690); atheroma. Erectile dysfunction occurs in ~50%.

Treatment:

Surgery and prostheses aid penetration. Shock wave therapy, vitamin E, tamoxifen, colchicine, and intra-lesional verapamil or interferon α2α, have been used with variable success in early disease.[49]

Pott's syndrome

(spinal TB). Rare in the West, this is usually spread from an extraspinal source, most often the lungs.

Features:

Back pain, and stiffness of *all* back movements. Fever, night sweats and weight loss may occur. Progressive bone destruction leads to vertebral collapse and gibbus (sharply angled curvature of the spine). Abscess formation may lead to cord compression, causing paraplegia, and bowel and bladder dysfunction (p458).

X-rays:

narrow disc spaces and vertebral osteoporosis early, leading to destruction with wedging of vertebrae. Lesions in the thoracic spine often lead to kyphosis. Abscess formation in the lumbar spine may track down to the psoas muscle, and erode through the skin.

[prescription take]:

Anti-TB drugs (p386). *[Sir Percival Pott, 1779]*

Prinzmetal (variant) angina

Angina from coronary artery spasm: ECG: ST *elevation*.

[prescription take]:

Use Ca^{2+} channel-blockers (see angina p102) but not ß-blockers.[50] Association: Circle of Willis occlusion from intimal thickening (moyamoya disease).

Raynaud's syndrome

This is peripheral digital ischaemia due to vasospasm, precipitated by cold or emotion. Fingers or toes ache and change colour: pale → blue → red. It may be idiopathic (Raynaud's *disease*—prevalence: 3-20%; ♀:♂ >1:1), or have an underlying cause (Raynaud's *phenomenon*).

Tests:

Exclude an underlying cause (see BOX).

[prescription take]:

Keep warm (eg electrically heated mittens); stop smoking. Nifedipine 5-20mg/8h PO helps, as may losartan, prazosin, or fluoxetine. Sympathectomy may help in those with severe disease. Iloprost, as a nebulized solution, may salvage digits with ulcers ± near-gangrene; effects last up to 16 weeks. Relapse is common.

Prinzmetal angina and vascular hyperreactivity

Coronary spasm plays an important role not only in Prinzmetal angina but also coronary heart disease in general, including acute coronary syndromes, especially in some populations (eg Japanese).[51] Coronary spasm can be induced by a variety of stimuli with different mechanisms of action, including ergonovine, acetylcholine, and methacholine (the former is used diagnostically).[1] These cause vasodilatation by endothelium-derived relaxing factor when vascular endothelium is functioning normally, whereas they cause vasoconstriction if the endothelium is damaged. In the light of these facts, patients with coronary spasm are thought to have a disturbance in endothelial function as well as local hyperreactivity of the coronary arteries.

If full anti-anginal therapy does not reduce symptoms, intracoronary radiation (20Gy brachytherapy) to vasospastic segments may be tried.[52]

Prognosis is good (especially if non-smoker, no past MI, and no diabetes); there is some evidence that prognosis may be better with the new calcium channel blockers such as benidipine.[53]

Prinzmetal angina is associated with vascular hyper-reactivity/vasospastic disorders such as Raynaud's phenomenon and migraine.

ß-blockers and large doses of aspirin are contraindicated.

[1] Since Prinzmetal angina is not a 'demand-induced' symptom, but a supply (vasospastic) abnormality, exercise treadmill stress testing is of no diagnostic value. The most sensitive and specific test is IV ergonovine. 50µg at 5min intervals is given in a specialist lab until a +ve result or 400µg is given. When positive, the symptoms and ↑ST should be present. Nitroglycerin rapidly reverses the effects of ergonovine if refractory spasm occurs.

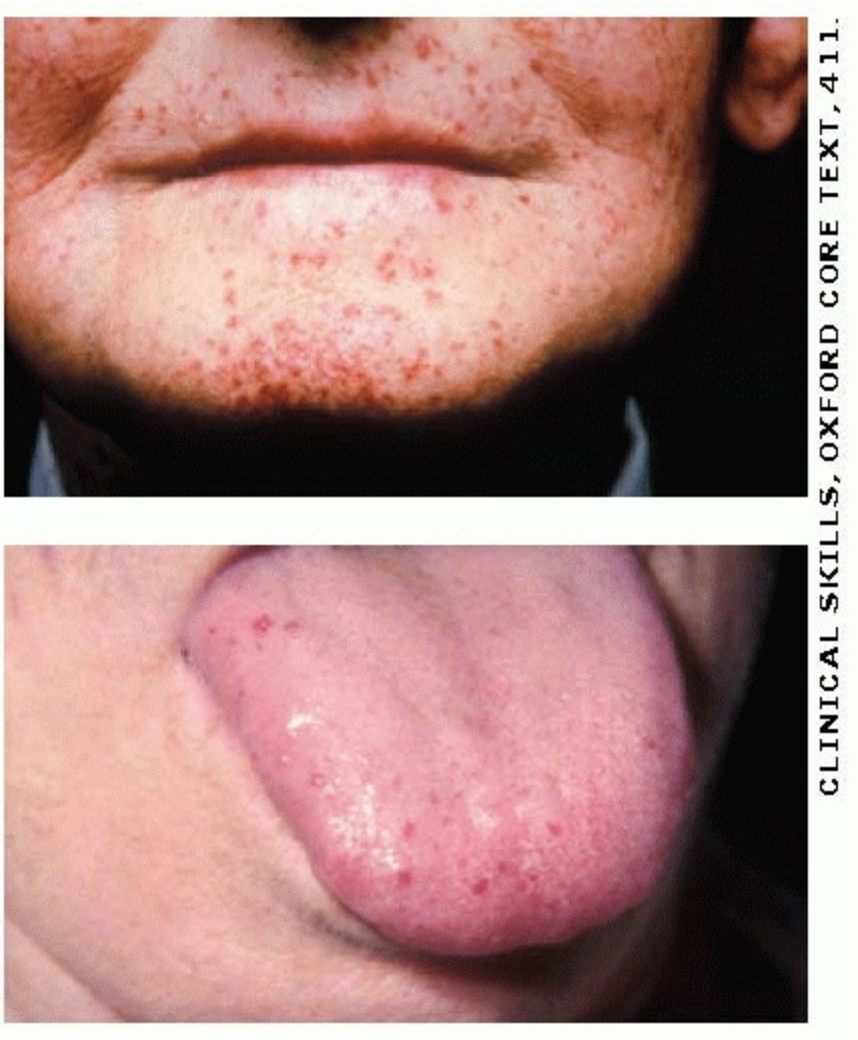


Fig 1. Telangiectasia in Osler-Weber-Rendu syndrome.

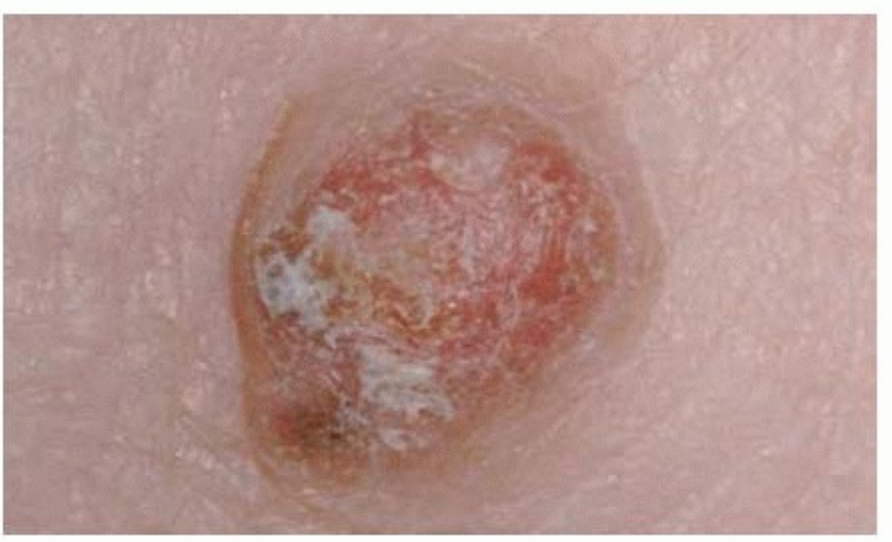


Fig 2. Paget's disease of the breast.

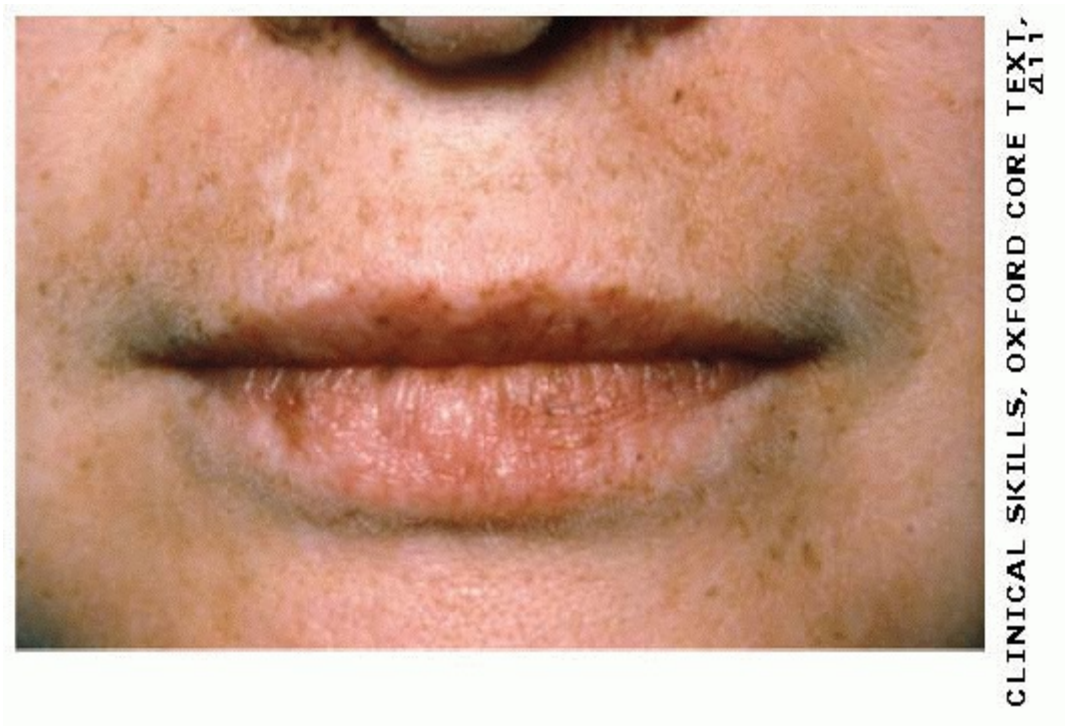


Fig 3. Perioral pigmentation, seen in Peutz-Jegher's syndrome.

Conditions in which Raynaud's phenomenon may be exhibited[2]

- *Connective tissue disorders:* Systemic sclerosis, SLE, rheumatoid arthritis, ermatomyositis/polymyositis.
- *Occupational:* Using vibrating tools.
- *Obstructive:* Thoracic outlet obstruction, Buerger's disease, atheroma.
- *Haematological:* Thrombocytosis, cold agglutinin disease, polycythaemia rubra vera (p350), monoclonal gammopathies.
- *Drugs:* ß-blockers.
- *Others:* Hypothyroidism.

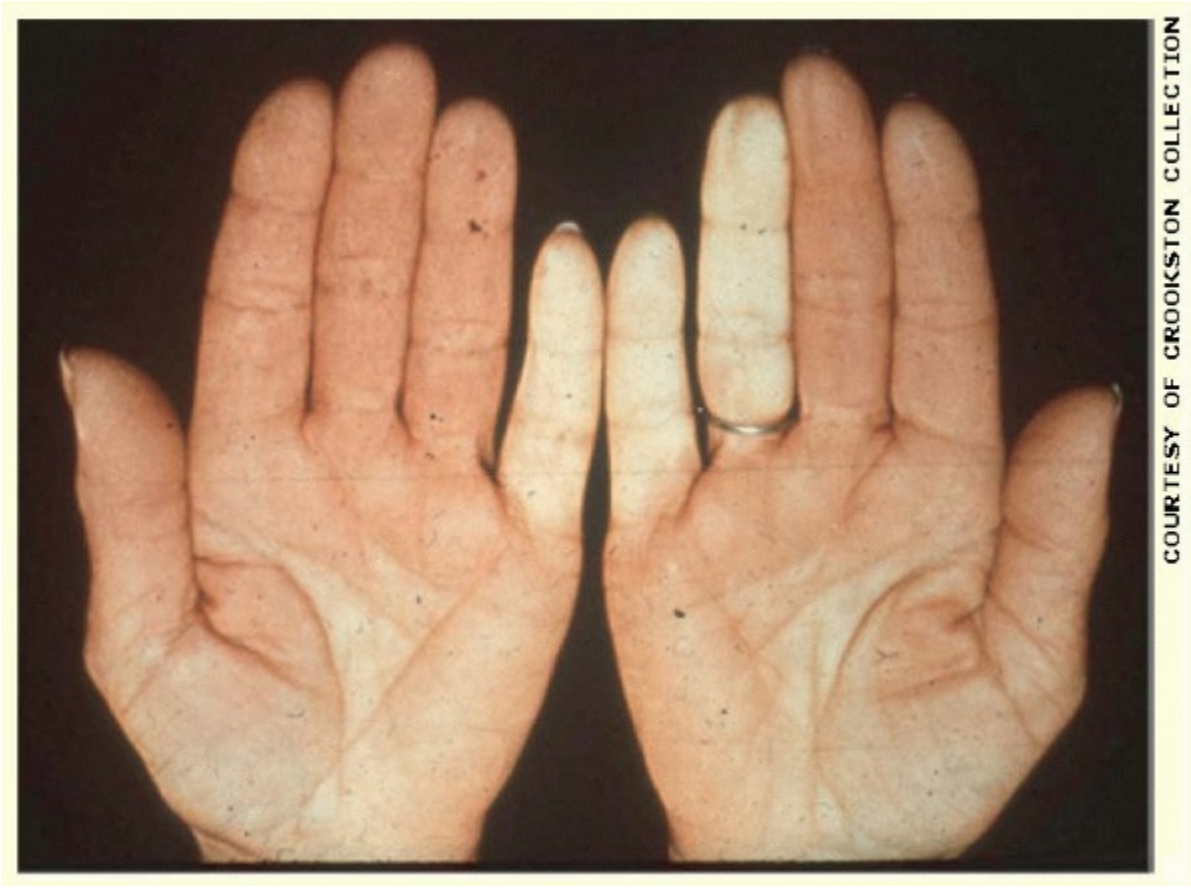


Fig 4. Raynaud's phenomenon in SLE.[54]

Refsum's syndrome

is an autosomal recessive disorder where there is accumulation of phytanic acid in tissues, due to a mutation of the gene coding for the peroxisomal enzyme phytanoyl-CoA hydroxylase. This leads to a sensorimotor polyneuropathy, nerve deafness, night blindness (retinitis pigmentosa), cerebellar ataxia, ichthyosis, anosmia, and can cause cardiomyopathy.

Tests:

Plasma phytanic acid↑. ↑CSF protein with normal cell count.

Treatment:

Restrict foods containing phytanic acid (animal fats, dairy products, green leafy vegetables); plasmapheresis is used for severe or rapidly deteriorating clinical symptoms.

Romano-Ward syndrome

(autosomal dominant) A mutation in a K^+ channel subunit causes congenital long QT syndrome, and a predisposition towards ventricular tachyarrythmias, torsades de pointes, syncope, and sudden death.

Rotor syndrome

Defective excretion of conjugated bilirubin, producing cholestatic jaundice. Inheritance is probably autosomal recessive.

Sister Mary Joseph nodule

An umbilical nodule, caused by a metastatic deposit from an intra-abdominal malignancy.

Sjögren's syndrome

is a chronic inflammatory autoimmune disorder. It may be primary (♀:♂ 9:1, onset 4^{th}-5^{th} decade) or secondary, associated with connective tissue disease (eg RA, SLE, systemic sclerosis). There is lymphocytic infiltration and fibrosis of exocrine glands, especially lacrimal and salivary glands.

Features:

↓tear production (dry eyes, keratoconjunctivitis sicca), xerostomia (↓salivation—dry mouth, dental caries), parotid gland swelling. Other glands are affected causing vaginal dryness, dyspareunia, dry cough and dysphagia. Systemic features include polyarthritis/arthralgia, Raynaud's, lymphadenopathy, vasculitis, lung, liver and kidney involvement, peripheral neuropathy, myositis and fatigue. It is associated with other autoimmune diseases (eg thyroid disease, autoimmune hepatitis, PBC) and an ↑risk of non-Hodgkin's B-cell lymphoma.

Tests:

Measure conjunctival dryness using Schirmer's test: put a strip of filter paper under the lower lid and measure the distance along the paper that tears are absorbed; <5mm in 5min is +ve. Rose Bengal staining may show keratitis on slit-lamp examination. Anti-Ro (SSA) and anti-La (SSB) antibodies may be present. Rheumatoid factor is usually +ve; there may be +ve ANA and hypergammaglobulinaemia. Gland biopsy shows focal lymphocytic aggregation.

[prescription take]:

Treat sicca symptoms: eye drops eg hypromellose (artificial tears), gels, ointment, frequent drinks, sugar free pastilles/gum or pilocarpine. NSAIDs and hydroxychloroquine are used for arthralgia, and immunosuppressants may be indicated in severe systemic disease.[55] *[Henrik Sjögren, 1933]*

Stevens-Johnson syndrome

A severe form of erythema multiforme (p546), and a variant of toxic epidermal necrolysis. It is caused by a hypersensitivity reaction, usually to drugs (eg salicylates, sulfonamides, penicillin, barbiturates, carbamazepine, phenytoin), but is also seen with infections or cancer. There is ulceration of the skin and mucosal surfaces (eg mouth, urethra, lungs, conjunctivae). Typical target lesions develop, often on the palms or soles with blistering in the centre. There may be a prodromal phase with fever, malaise, arthralgia, myalgia ± vomiting and diarrhoea.

Treatment:

The disease is usually self-limiting, so removing any precipitant and supportive care (eg calamine lotion for the skin) will usually suffice. Steroids (systemic and eye-drops) were used, but trials have been variable, so ask a dermatologist and ophthalmologist. Ciclosporin and thalidomide have been used, but IV immunoglobulin is not helpful.[56]

Prognosis:

Mortality ~5%. The illness may be severe for the first 10d before resolving over 30d. Damage to the eyes may persist and at worst, blindness may result.[57]

Sturge-Weber syndrome (Encephalotrigeminal angiomatosis)

The association of a port wine stain on the face (often in trigeminal distribution) with contralateral focal fits, due to a corresponding haemangioma in the brain. There may be glaucoma, hemiplegia and learning impairment.

Tests:

Skull X-ray shows cortical calcification, angiography is usually normal. MRI may show the angioma.

[prescription take]:

Laser therapy can remove facial port wine stains. Anticonvulsants are indicated for seizures; hemispherectomy may be required if seizures are intractable.

Causes of a long QT interval (eg Romano-Ward)

Many conditions and drugs (check BNF) cause a long QT interval—and Brugada syndrome, p687, is a similar syndrome predisposing to sudden cardiac death.

Congenital:

Jervell-Lange-Nielsen syndrome: autosomal recessive with associated deafness.[58] (Romano-Ward syndrome is autosomal dominant).

Cardiac:

Myocardial infarction or ischaemia; mitral valve prolapse.

HIV:

May be a direct effect of the virus or from protease inhibitors.

Metabolic:

$K^+\downarrow$; $Mg^{2+}\downarrow$; $Ca^{2+}\downarrow$; starvation; hypothyroidism; hypothermia.

Toxic:

Organophosphates.

Anti-arrhythmic drugs:

Quinidine; amiodarone; procainamide; sotalol.

Antibiotics et al:

Erythromycin; levofloxacin; pentamidine; halofantrine.

Antihistamines:

Terfenadine; astemizole.

Motility drugs:

Domperidone; droperidol in doses >1.25mg (also cisapride).

Psychoactive drugs:

Haloperidol; risperidone; tricyclics; SSRIs.

Connective tissue diseases:

anti-Ro/SSA antibodies (p538).

Herbalism:

Ask about Chinese folk remedies (may contain unknown amounts of arsenic).[59][60] Cocaine, quinine and artemisinins (and other antimalarials) are examples of herbalism-derived products which can prolong the QT interval.

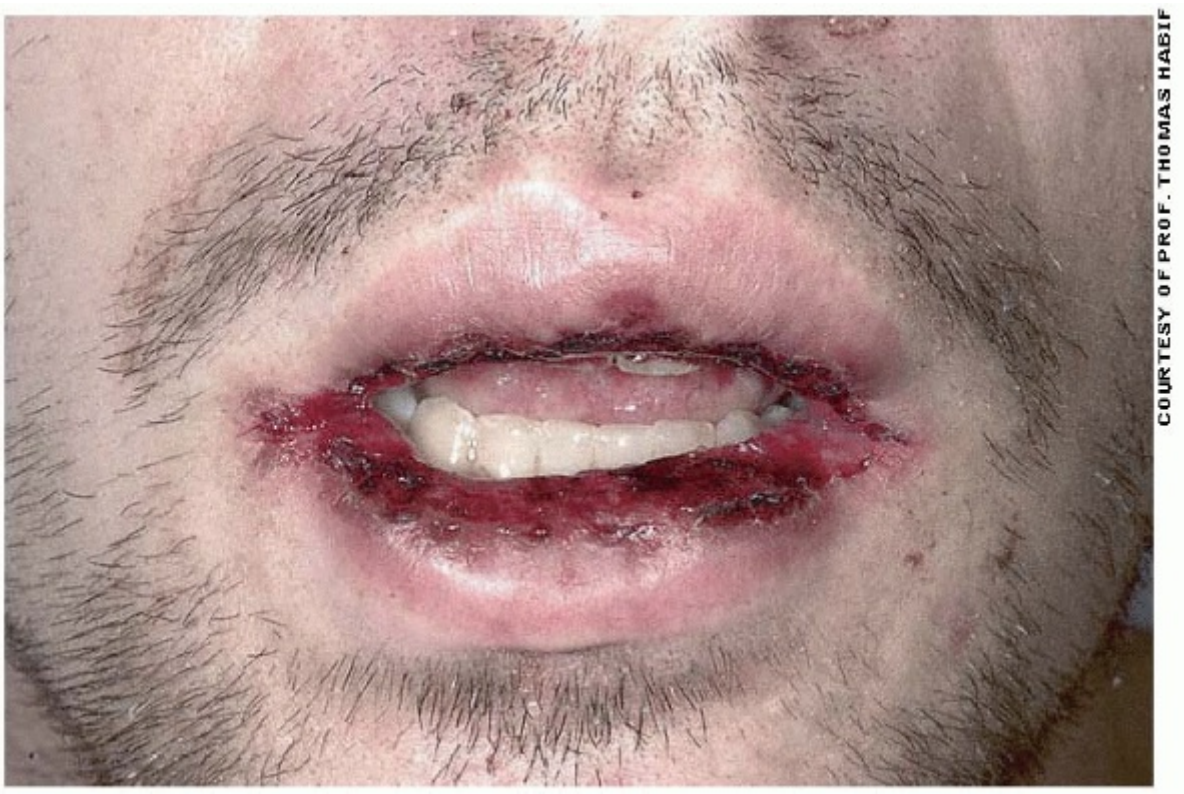


Fig 1. Stevens-Johnson syndrome.[61]

Takayasu's arteritis (Aortic arch syndrome, pulseless disease)

Rare outside of Japan, this systemic vasculitis affects the aorta and its major branches, causing stenosis and thrombosis. Acute inflammation causes dilatation and aneurysms. It often affects ♀, 20-40yrs old. Symptoms depend on the arteries involved. The aortic arch is often affected, with cerebral, ophthalmological and upper limb symptoms eg dizziness, visual changes, weak arm pulses. Systemic features are common—eg fever, weight loss and malaise. ↑BP is often a feature, due to renovascular involvement. Complications include aortic valve regurgitation, aortic aneurysm and dissection; ischaemic stroke (↑BP and thrombus); and ischaemic heart disease.

Diagnosis:

↑ESR & CRP; angiography of the aorta (invasive or CT/MRI).

[prescription take]:

Prednisolone (1mg/kg/day PO). Methotrexate or cyclophosphamide have been used in resistant cases. BP control is essential to ↓risk of stroke. Angioplasty ± stenting, or bypass surgery are done for vascular complications.

Prognosis:

~95% survival at 15 years. *[Mikito Takayasu, 1908]*

Tietze's syndrome (Idiopathic costochondritis)

Localized pain/tenderness at the costosternal junction, enhanced by motion, coughing, or sneezing. The 2nd rib is most often affected. The diagnostic key is *localized* tenderness which is marked (flinches on prodding).

Treatment:

Simple analgesia, eg aspirin, NSAIDs. Its importance is that it is a benign cause of what at first seems to be alarming, eg cardiac pain. In lengthy illness, local steroid injections may be used.

Todd's palsy

Limb weakness (eg hemiplegia) following a seizure. The patient seems to have had a stroke, but recovers in <24h. *[Robert Todd, 1856]*

Vincent's angina

Mouth infection with ulcerative gingivitis from *Borrelia vincentii* (a spirochaete) + fusiform bacilli, often affecting young male smokers with poor oral hygiene. Try penicillin V 250mg/6h and metronidazole 400mg/8h PO, with chlorhexidine mouthwashes.

Von Hippel-Lindau syndrome

is an autosomal dominant disorder, with germ-line mutation of a tumour suppressor gene on chromosome 3p (also implicated in sporadic renal cell carcinoma). It predisposes to bilateral renal cell carcinoma, retinal and cerebellar haemangioblastoma, and phaeochromocytoma. It may present with visual impairment or cerebellar signs (eg ataxia).

Von Willebrand's disease (VWD)

Von Willebrand's factor (vWF) has 3 roles in clotting: to bring platelets into contact with exposed subendothelium, to make platelets bind to each other, and to bind to factor VIII protecting it from destruction in the circulation. There are >22 types of vWD, the commonest are:

- *Type I:* (commonest) Autosomal dominant deficiency (↓levels) of vWF.
- *Type II:* Abnormal vWF, with lack of high molecular weight multimers.
- *Type III:* Undetectable vWF levels (autosomal recessive with gene deletions).
- *Type Normandy:* Impaired vWF-factor VIII binding (mutations in VIII-binding domains of vWF; causes an *autosomal recessive* mimic of haemophilia A).

Signs

are of a platelet type disorder (p330): bruising, epistaxis, menorrhagia, ↑bleeding post-tooth extraction. Symptoms are mild in Type I and II disease.

Tests:

APTT↑, bleeding time↑, Factor VIIIC↓ (clotting activity), vWF Ag↓; INR & platelets ↔.

[prescription take]:

Get expert help. Vasopressin is used in mild bleeding, vWF rich Factor VIII concentrate for surgery or major bleed. Avoid NSAIDs.

Wallenberg's lateral medullary syndrome

This relatively common syndrome comprises lesions to multiple CNS nuclei, caused by posterior inferior cerebellar artery occlusion leading to brainstem infarction.

Features:

- dysphagia, dysarthria (IX and X nuclei)
- vertigo, nausea, vomiting, nystagmus (vestibular nucleus)
- ipsilateral ataxia (inferior cerebellar peduncle)
- ipsilateral Horner's syndrome (descending sympathetic fibres)
- loss of pain and temperature sensation on the ipsilateral face (V nucleus) and contralateral limbs (spinothalamic tract). There is no limb weakness as the pyramidal tracts are unaffected.

In the rarer *medial medullary syndrome*, vertebral or anterior spinal artery occlusion causes ipsilateral tongue paralysis (XII nucleus) with contralateral limb weakness (pyramidal tract, sparing the face) and loss of position sense.

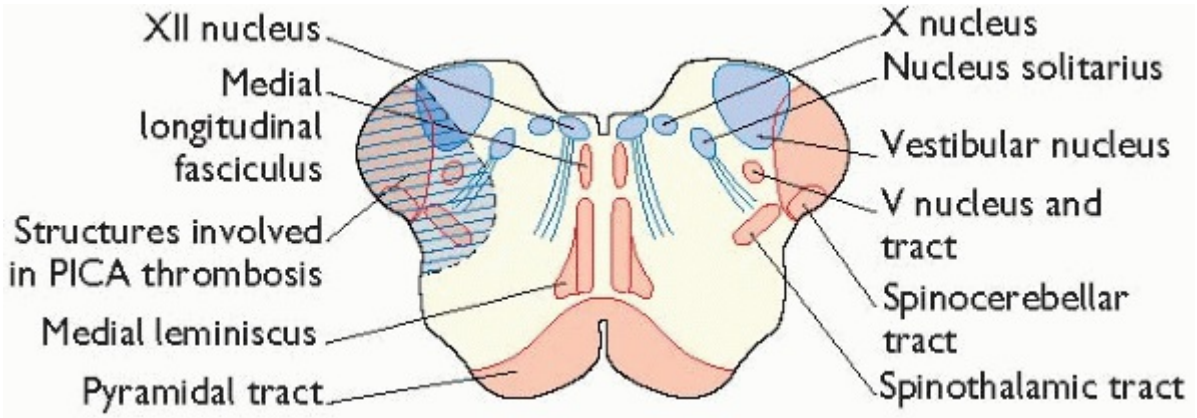


Fig 1. Cross section of the medulla showing structures involved in Wallenberg's lateral medullary syndrome (posterior inferior cerebellar artery thrombosis).

Waterhouse-Friderichsen's (WhF) syndrome

Bilateral adrenal cortex haemorrhage, often occurring in rapidly deteriorating meningococcal sepsis, alongside widespread purpura, meningitis, coma, and DIC. The meningococcal endotoxin acts as a potent initiator of inflammatory and coagulation cascades. Other causes include *H. influenzae*, pneumococcal, streptococcal, and staphylococcal sepsis. Adrenal failure causes shock, as normal vascular tone requires cortisol to set activity of alpha and beta adrenergic receptors, and aldosterone is needed to maintain extracellular fluid volume.

Treatment:

▸▸Antibiotics eg ceftriaxone 2g/12h IV (p806) and hydrocortisone 200mg/4h IV for adrenal support. ICU admission is usually indicated.

Weber's syndrome

Ipsilateral 3rd-nerve palsy with contralateral hemiplegia, due to infarction of one half of the midbrain, after occlusion of the paramedian branches of the basilar artery (which supply the cerebral peduncles).

Wegener's granulomatosis

is a multisystem disorder of unknown cause characterised by necrotizing granulomatous inflammation and vasculitis of small and medium vessels. It has a predilection for the upper respiratory tract, lungs and kidneys.

Features:

Upper airways disease is common, with nasal obstruction, ulcers, epistaxis, or destruction of the nasal septum causing a characteristic 'saddle-nose' deformity[1]. Sinusitis is often a feature. Renal disease causes rapidly progressive glomerulonephritis with crescent formation, proteinuria or haematuria. Pulmonary involvement may cause cough, haemoptysis (severe if pulmonary haemorrhage) or pleuritis. There may also be skin purpura or nodules, peripheral neuropathy, mononeuritis multiplex, arthritis/arthralgia or ocular involvement eg keratitis, conjunctivitis, scleritis, episcleritis, uveitis, proptosis.

Tests:

cANCA, confirmed with a raised PR3 in the majority (p539). Urinalysis should be performed to look for proteinuria or haematuria. If these are present, consider a renal biopsy. Do a CXR to look for evidence of pulmonary haemorrhage. Cytology from sputum/BAL may show atypical cells that can be confused with bronchial carcinoma.[62]

Treatment:

Depends on the extent of disease. Severe disease (eg biopsy-proven renal disease) should be treated with corticosteroids and cyclophosphamide. Continuous oral cyclophosphamide may be more effective than pulsed IV regimens at inducing sustained remission, but may have more side effects. Co-trimoxazole may be given as prophylaxis against *Pneumocystis carinii* and *Staphylococcal* colonisation. Patients with severe renal disease (eg creatinine> 500µmol/L) may benefit from plasma exchange in addition. Azathioprine and methotrexate are used as maintenance therapies.

Wernicke's encephalopathy

Thiamine (vitamin B_1) deficiency with a classical triad of ophthalmoplegia (nystagmus, lateral rectus or conjugate gaze palsies), ataxia (wide-based gait) and confusion. Always consider this diagnosis in alcoholics: it may also present with memory disturbance, hypotension, hypothermia, or reduced consciousness. Focal areas of brain damage occur, including periaqueductal punctate haemorrhages.

Recognised causes:

Alcoholism, eating disorders, malnutrition, prolonged vomiting eg with chemotherapy, GI malignancy, hyperemesis gravidarum.

Tests:

Red cell transketolase↓, (rarely done).

Treatment:

Urgent thiamine to prevent irreversible Korsakoff's syndrome (p696). Give IV thiamine (Pabrinex®) if there are any of the above features, 2-3 pairs of high-potency ampules/8h IV over 10min for up to 5d, then convert to oral thiamine. An IM (gluteal) preparation is available. Anaphylaxis may occur so have resuscitation facilities to hand. If there is co-existing hypoglycaemia (often the case in this group of patients), make sure thiamine is given *before* glucose, as Wernicke's can be precipitated by glucose administration to a thiamine-deficient patient.

Prognosis:

Untreated, death occurs in 20%, and Korsakoff's psychosis occurs in 85%, a quarter of whom will require long-term institutional care. *[Karl Wernicke, 1875]*

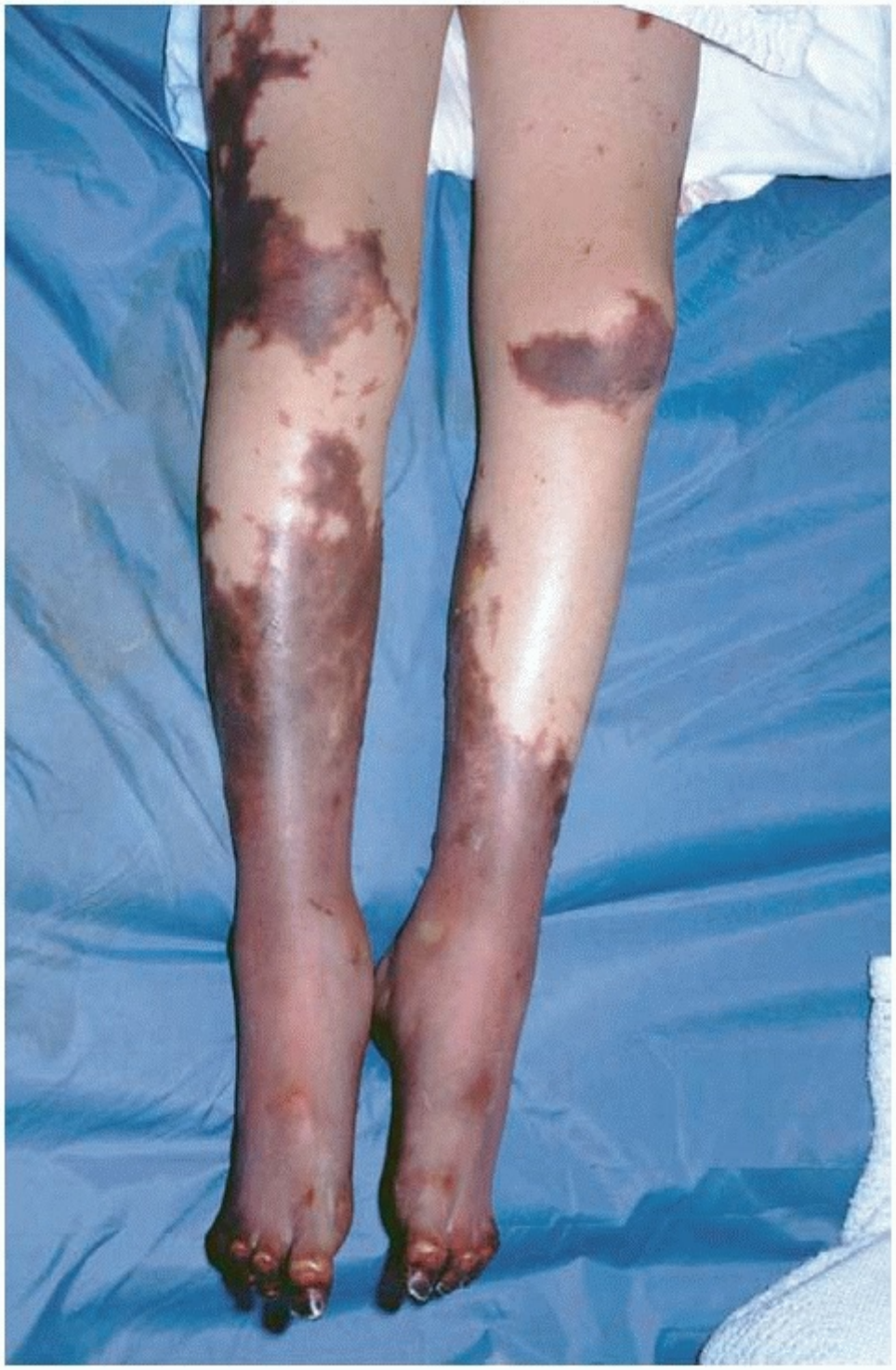


Fig 1. Meningococcal sepsis with purpura.

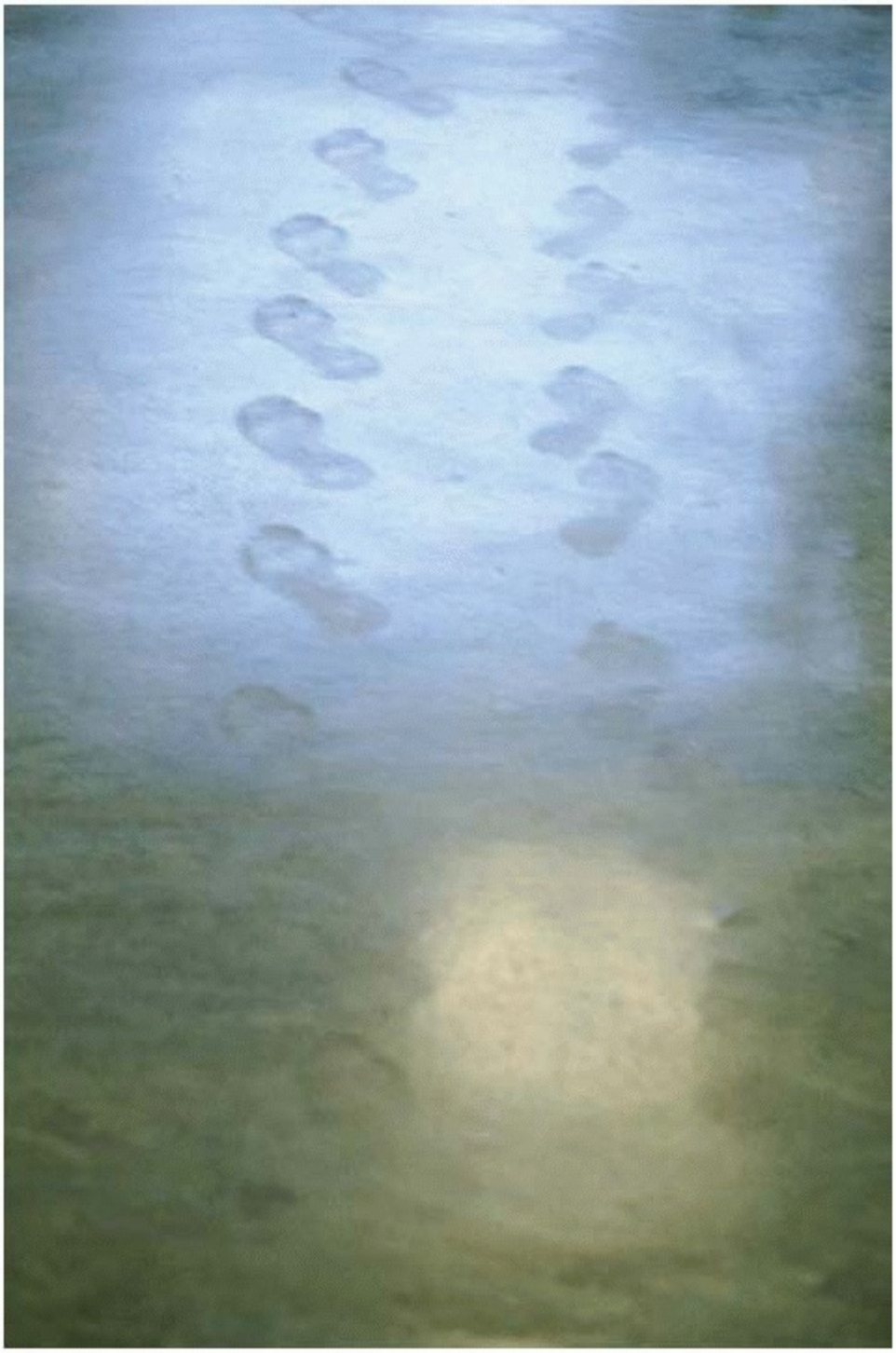


Fig 2. Wide based gait (footprints), seen in Wernicke's encephalopathy.

Whipple's disease[1]

A rare cause of GI malabsorption which usually occurs in middle-aged white males, most commonly in Europe. It is caused by *Tropheryma whippelii*, which produces a systemic disease.

Features:

often starts insidiously with arthralgia (chronic, migratory, seronegative arthropathy affecting mainly peripheral joints). GI symptoms commonly include weight loss, diarrhoea or colicky abdominal pain, leading to malabsorption (p272). Systemic symptoms such as fever, sweats, lymphadenopathy and skin hyperpigmentation also occur. Cardiac involvement may lead to endocarditis, which is typically blood culture negative. CNS features include a reversible dementia, ophthalmoplegia, and facial myoclonus (if all together, they are highly suggestive)—also hypothalamic syndrome (Hyperphagia, polydipsia, insomnia). NB: CNS involvement may occur without GI involvement.

Tests:

Jejunal biopsy shows stunted villi. There is deposition of macrophages in the lamina propria containing granules which stain positive for periodic acid-Schiff (PAS). Similar cells may be found in affected samples eg CSF, cardiac valve tissue, lymph nodes, synovial fluid. The bacteria may be seen within macrophages on electron microscopy. MRI may demonstrate CNS involvement.

[prescription take]:

should include antibiotics which cross the blood-brain barrier. Current recommendations are IV ceftriaxone (or penicillin plus streptomycin) for 2wks then oral co-trimoxazole for 1yr. Shorter courses risk relapse with CNS features. A rapid improvement in symptoms usually occurs. *[George Whipple, 1907]*

Zellweger syndrome (cerebrohepatorenal syndrome)

A rare autosomal recessive disorder characterized by absent peroxisomes. Peroxisomes are intracellular organelles, required for many cellular activities, including lipid metabolism. The syndrome is a severe form of infantile Refsum's syndrome, and exhibits similar biochemical abnormalities (p703). Clinical features include craniofacial abnormalities, severe hypotonia and mental retardation, glaucoma, cataracts, hepatomegaly and renal cysts. A number of causative genes (eg PEX1*)* have been identified. Life expectancy is usually a few months only.

Zollinger-Ellison syndrome

This is the association of peptic ulcers with a gastrinsecreting adenoma (gastrinoma). Gastrin excites excessive gastric acid production, which may produce multiple ulcers in the duodenum and stomach. The adenoma is usually found in the pancreas, although it may arise in the stomach or duodenum. Most cases are sporadic; 20% are associated with Multiple Endocrine Neoplasia, type 1 (MEN1, p207). 60% are malignant, metastases are found in local lymph nodes and the liver.

Symptoms:

Include abdominal pain and dyspepsia, from the ulcer(s), and chronic diarrhoea due to inactivation of pancreatic enzymes (also causes steatorrhoea) and damage to intestinal mucosa.

Incidence:

~0.1% of patients with peptic ulcer disease. Suspect in those with multiple peptic ulcers, ulcers distal to the duodenum, or a family history of peptic ulcers (or of islet cell, pituitary, or parathyroid adenomas).

Tests:

Raised fasting serum gastrin level (>1000pg/mL). Hypochlorhydria (reduced acid production eg in chronic atrophic gastritis) should be excluded as this also causes a raised gastrin level: gastric pH should be <2. The secretin stimulation test is useful in suspected cases with only mildly raised gastrin levels (100-1000pg/mL). The adenoma is often small and difficult to image; a combination of somatostatin receptor scintigraphy, endoscopic ultrasound and CT is used to localise and stage the adenoma.

[prescription take]:

High dose proton pump inhibitors (PPIs), eg omeprazole: start with 60mg/d and adjust according to response. Measuring intragastric pH helps determine the best dose (aim to keep pH at 2-7). Surgical resection of the adenoma with lymph node clearance is generally recommended if >2cm in size, as this indicates malignant potential. Surgery is usually avoided in MEN1, as adenomas are often multiple, and metastatic disease is rare. Metastatic disease is treated with combination chemotherapy ± interferon α. Selective embolization may be undertaken for hepatic metastases.

Prognosis:

5-year survival: 80% if single resectable lesion, ~20% with hepatic metastases. All patients should be screened for MEN1.

Editors: Longmore, Murray; Wilkinson, Ian B; Turmezei, Tom; Cheung, Chee Kay
Title: *Oxford Handbook of Clinical Medicine, 7th Edition*

18

Radiology

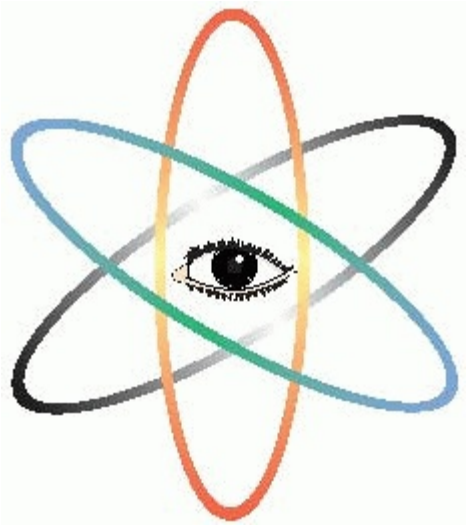


Fig 1. As in the natural world, so it is in the physical: decay brings about new matter through a seemingly endless cycle. Yet the fragility of the human body reminds us that our own part in the cycle is fleeting. So how do we benefit? As humans, the answer may lie in the realm of the metaphysical rather than physical, but as doctors, at the nucleus of our work, we are given a vision not only into the inner workings of the body, but also into the colourful lives of those we treat.

Typical effective doses

The effective dose of an examination is calculated as the weighted sum of the doses to different body tissues. The weighting factor for each tissue depends on its sensitivity. The effective dose thus provides a single dose estimate related to the total radiation risk, no matter how the radiation dose is distributed around the body. This table is certainly not to be learnt; rather it serves as a reminder of the relative exposures to radiation that we prescribe in practice.

Procedure	Typical effective dose (mSv)	CXR equivalents	Approx. equivalent period of background radiation[1]
X-ray examinations			
Limbs and joints	<0.01	<0.5	<1.5 days
Chest (PA)	0.02	1	3 days

Abdomen	1	50	6 months
Lumbar spine	1.3	65	7 months
CT head	2.3	115	1 year
IVU	2.5	125	14 months
Barium meal	3	150	16 months
Barium enema	7	350	3.2 years
CT chest	8	400	3.6 years
CT abdo/pelvis	10	500	4.5 years
Radionuclide studies			
Lung ventilation	0.3	15	7 weeks
Lung perfusion	1	50	6 months
Thyroid	1	50	6 months
Bone	4	200	1.8 years

PET head	5	250	2.3 years
Dynamic cardiac	6	300	2.7 years

After Making the Best Use of a Department of Clinical Radiology, 5e RCOR; with permission

Justifying exposure to ionising radiation

The very nature of ionising radiation that gives us vision into the human body also gives it lethal properties. The decision to expose patients to radiation must be made with the risks in mind, and even with strict guidelines we still have a tendency to over-exposure in medical practice. So when requesting an examination, the clinical benefits should far outweigh the risks of radiation sensitivity, cancer induction and genetic mutation.

The responsibility lies with us not to rely too heavily on radiological examinations and to restrain from the temptation of requesting examinations to comfort patients, or replace a lost film, or when the result will have no effect on management or clinical outcome. To give an idea of the relative doses involved, a CT examination of the abdomen and pelvis gives a typical effective dose of 500 times as much radiation as a CXR (see TABLE above). This important factor also tells us about the preference of ultrasound over CT when investigating abdominal and pelvic complaints such as acute appendicitis, especially given its youthful demographics.

▸Unwitting exposure of the unborn fetus to radiation is inexcusable at any stage of gestation—unless the mother's life is in immediate danger—and it is the responsibility of the referring clinician to ensure that this is avoided. Discuss beforehand with the patient that you would like to do a pregnancy test, explaining why, being broad in your suppositions and tactful in your inquisitions.

The art of the request

One of the most nerve-wracking moments that you can encounter as a recently qualified doctor might be having to request a radiology investigation face-to-face with a seasoned consultant radiologist. Imagine that you have been asked by your team to request an ultrasound examination of the renal tract for one of your patients who has a newly raised creatinine of 300 ?mol/L. You explain that you aren't quite sure what to write on the request form, however they have already moved on to the next patient on the busy post-take ward round. What do you write? How much do you write? Who do you ask? Below are some pointers that will aid you in making a successful request for a radiological investigation.

Before you start…

- Ensure that the investigation has not been done already or recently.
- *Is the patient fit to have the investigation?* An agitated or confused individual is unlikely to stay still for a claustrophobic CT head examination!

The request form

- Include all relevant clinical information, blood tests and recent radiology findings on the request form. This is especially important given that there has been an increase in e-based request systems combined with a decrease in direct communication between the radiologist and the requesting clinician. Remember that the aim of radiology is to provide information in order to alter the management of the patient and the outcome of the disease. Think, therefore, what do I need to know?—see MINIBOX, Radiology can help.
- Include how the investigation will help resolve the clinical problem facing you.
- Include '± intervention' on the request form if you think it may take place (eg CT abdomen ± drainage, for an abdominal collection).

Radiology can help:

- **Confirm** a suspected diagnosis
- **Exclude** something important
- **Define** the extent of a disease
- **Monitor** the progress of a disease

The verbal request

- Always **request** and never order an investigation.
- Know the case as fully as possible, but keeping your request brief and accurate.
- Know what you need to confirm, exclude, monitor progress of or define.
- 'I was hoping to get your opinion about this interesting case…' is a potentially successful opener to a request.
- Pre-empt by saying how the investigation will change your management (which you will be invariably asked).
- Have any previous radiology of relevance with you when you make the request eg a CXR if requesting a CT pulmonary angiogram (CTPA) or ventilation/perfusion ([V with dot above]/[Q with dot above]) scintigram.
- Inquire of the radiologist what he thinks is the correct investigation for the case.
- You may have an easier time requesting an investigation from a radiologist who specialises in that particular technique (eg CT) or who is linked to your clinical team (eg he may lead your clinical x-ray meeting).

Stuck in the middle?

You may find yourself a go-between, with your team on one side eagerly awaiting the investigation before the next move and the radiology department on the other side trying to prioritise and fit the investigation into their already overscheduled timetable. It is in these situations it is important to remember that the patient is also caught in the middle, completely unaware of the goings-on around him. Take a few moments to lay out the progress plan and air expectations—it will make the experience of being swept away to the radiology department without warning a far less scary experience!

Interpreting an image

It is not always possible to rely on a radiologist for the interpretation of an investigation, especially in an emergency or in the middle of the night. Remembering the following points may help hone your own interpreting skills:

- Take every passing opportunity to peruse examinations so that spotting both normal and abnormal variations comes more easily—the old idiom *practice makes perfect* is very apt here.
- Getting to grips with the science behind radiology makes interpretation easier and will explain the suitability of modalities to different clinical scenarios. Knowing how an investigation is done will also give practical clues to the result produced—eg a routine CXR is performed in the posteroanterior (PA) direction (the source posterior, the cassette anterior) so that the cardiac shadow is minimised.
- Use a systematic approach so that you don't pass anything unnoticed. Don't worry, though—some things can be notoriously difficult to spot.
- Virtually all investigations yield a 2D image from a 3D structure, though there have been recent developments in 3D imaging (**fig 4**, p719). A basic understanding of anatomical relationships of the area in question will help reconstruct the images in your mind into a clear representation of the reality before you.
- The standard orientation of all axial cross-sectional imaging is as if you are looking up at the supine patient from his feet. For images with non-conventional orientations (eg MRCP) look on the image for clue markings, or rely on your knowledge of anatomy—it can be tricky to visualise oblique sections!
- Don't rely solely on the investigation, but use it as part of the clinical work-up to help make an informed management decision.
- Go back to see the patient after looking at the investigation and reading the radiologist's report: you might picture them in a different light and notice something that you didn't before.

Presenting an image

Everyone has their own method for presenting, and the right way is **your own way**. As long as you cover everything systematically—because we all get 'hot-seat amnesia' at some point—the particulars will take care of themselves. Continue to polish your own method and remember a few extra tips for when an image is presented expectantly by your consultant/examiner and the floor is yours:

- A brief pensive silence with a thoughtful expression as you analyze the image is allowed—but not too long, otherwise it might look like you have been thrown!
- State the written details such as name, date of birth, where and how the imaging was taken. Look for clues: weighting of an MRI, a '**+ c**' indicating that contrast medium has been used, the phase of the investigation (arterial/venous/portal), or even the name of the organ printed on an ultrasound.
- State the type, mode and technical quality of investigation—not always easy!

Going through the above also gives you a bit of thinking time. Then:

- It is acceptable to start with any obvious abnormalities—they may be life-threatening —provided afterwards you move on systematically.
- Just like the bedside clues in a physical examination, there are clues in radiology examinations. Note oxygen masks, ECG leads, venous access, infusion apparatus, and invasive devices. Identifying what they are also helps you to look through what may otherwise appear to be a cluttered mess.
- Not everything on the image is inside the subject—some things may be on the surface/outside or not there at all, eg ring artefacts or 'stair-stepping' on CT.
- Stating a differential diagnosis is good practice, as not all findings are diagnostic.
- If there is additional clinical information that would help you to make a diagnosis, don't be afraid to ask. After all, we treat patients and not images!

Remember:	X-ray=***radiodensity*** (lucency/opacity)	CT=***attenuation***
	US=***echogenicity/reflectivity***	MRI=***signal intensity***

Chest x-ray (CXR) Enlarged images: p836

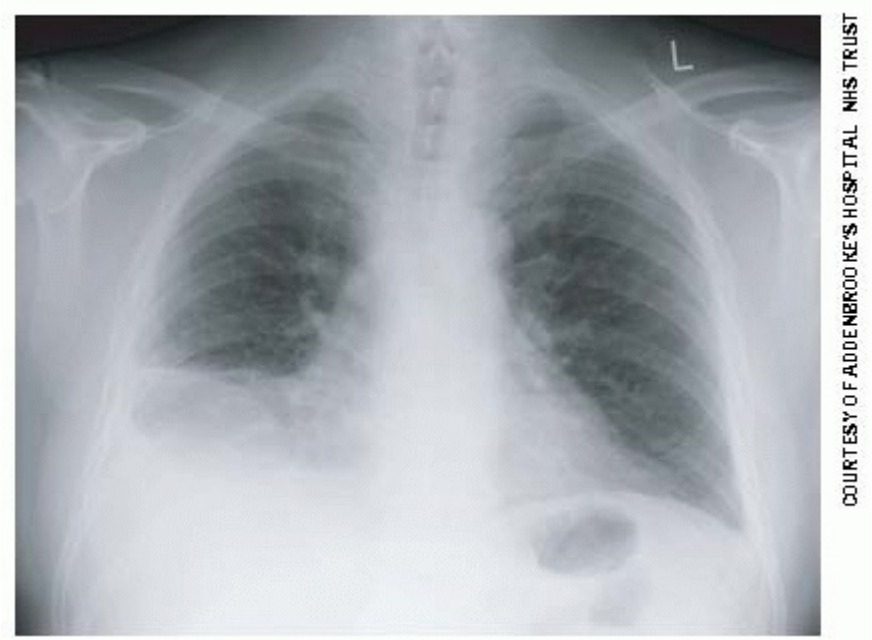


Fig 1. Middle lobe consolidation and a right pleural effusion. (see color image)

Principles

Images are usually taken on inspiration with the patient standing in front of the cassette and the x-ray source behind (postero-anterior, ie PA). Emergency images may be the other way (antero-posterior, AP), which magnifies heart size, and supine, which alters the distribution of air and fluid in the lungs and pleural cavities. There are 4 radiographic densities: **air**, **fat**, **water/soft tissue**, and **bone**. A border is only seen at an interface of 2 densities, eg heart (soft tissue) and lung (air); the 'silhouette' is lost if air in the lung is replaced by consolidation (water). The silhouette sign localizes pathology (eg middle lobe pneumonia or collapse causing loss of clarity of the right heart border, **fig 1**). When interpreting a radiograph use a systematic approach that works for you—eg from outside to inside, or inside-out—but start by assessing the technical qualities of the image:

- ***Rotation:*** The sternal ends of the clavicles should symmetrically overlie the transverse processes of the 4th or 5th thoracic vertebrae.
- ***Inspiration:*** There should be 5 to 7 ribs visible anteriorly (or 10 posteriorly). Hyperinflation can be abnormal, eg COPD.
- ***Exposure:*** An under-exposed image will be too white and an over-exposed image will be too black. Both cause a loss of definition and quality.
- ***Position:*** The entire lung margins must be visible, especially the costophrenic angles.

Trachea

Should be central or just to the right. Deviated by collapse (towards the side of the lesion), tension (away from the side of the lesion), or rotation of the film. Also check heart position (below).

Mediastinum

May be widened in many disorders: retrosternal thyroid; lymph node enlargement (sarcoidosis, lymphoma, metastases, TB); tumour (thymoma, teratoma, neurogenic tumours); aortic aneurysm; cysts (bronchogenic cyst, pericardial cyst); paravertebral mass (TB); oesophageal dilatation (achalasia, hiatus hernia). There are 4 'moguls' normally visible on the left border of the mediastinum that may help identify pathology if abnormal. From superior to inferior they are: **1** Aortic knuckle; **2** Pulmonary outflow tract; **3** Left auricle; **4** Left ventricle.

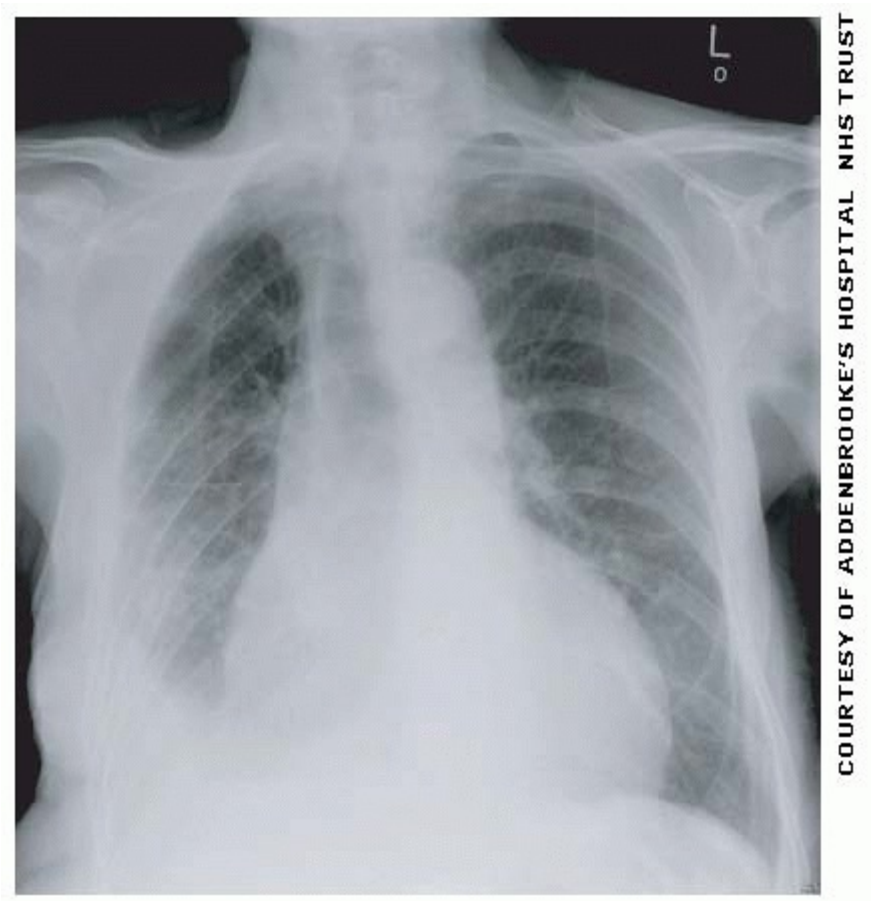


Fig 2. Cardiomegaly and loss of the right costophrenic angle from a pleural effusion: consistent with heart failure.(see color image)

Hila

The left hilum is higher than the right, but they should be the same size and density. May be pulled up or down by fibrosis or collapse. **1** ***Enlarged hila:*** Nodes; pulmonary arterial hypertension (± an enlarged second 'mogul'); bronchogenic carcinoma. **2** ***Calcification:*** Previous TB; silicosis; histoplasmosis (p428). Sarcoidosis, TB and lymphoma can give bilateral hilar + right paratracheal lymphadenopathy.

Heart

Normally <15cm across—approximately 50% of the width of the thorax. À should lie to the right of the vertebral column, 2/3 to the left. It may appear elongated if the chest is hyperinflated (COPD) or enlarged if the image is AP, there is failure (**fig 2**), or a pericardial effusion. Are there calcified valves?

The diaphragm

The right side is usually slightly higher.

Causes of a raised hemidiaphragm:

Lung volume loss; stroke; phrenic nerve palsy (from: trauma; MND, p498; cancer); hepatomegaly; subphrenic abscess. Subpulmonic effusion and diaphragm rupture give apparent elevation. **NB:** Bilateral palsies (polio, muscular dystrophy) cause hypoxia.

Lungs

Shadowing is described as nodular, reticular (network of fine lines, interstitial), or alveolar (fluffy). A single nodule can be described as an SOL.

Nodules:[1]

- Neoplasia: lung carcinoma, adenoma, hamartoma, metastases—often missed if small.
- Infections (varicella pneumonia, hydatid, septic emboli). An abscess can also appear as an SOL.

- Granulomas (miliary TB, sarcoidosis, histoplasmosis, Wegener's granulomatosis, p706).
- Pneumoconioses (except asbestosis), Caplan's syndrome (p688).

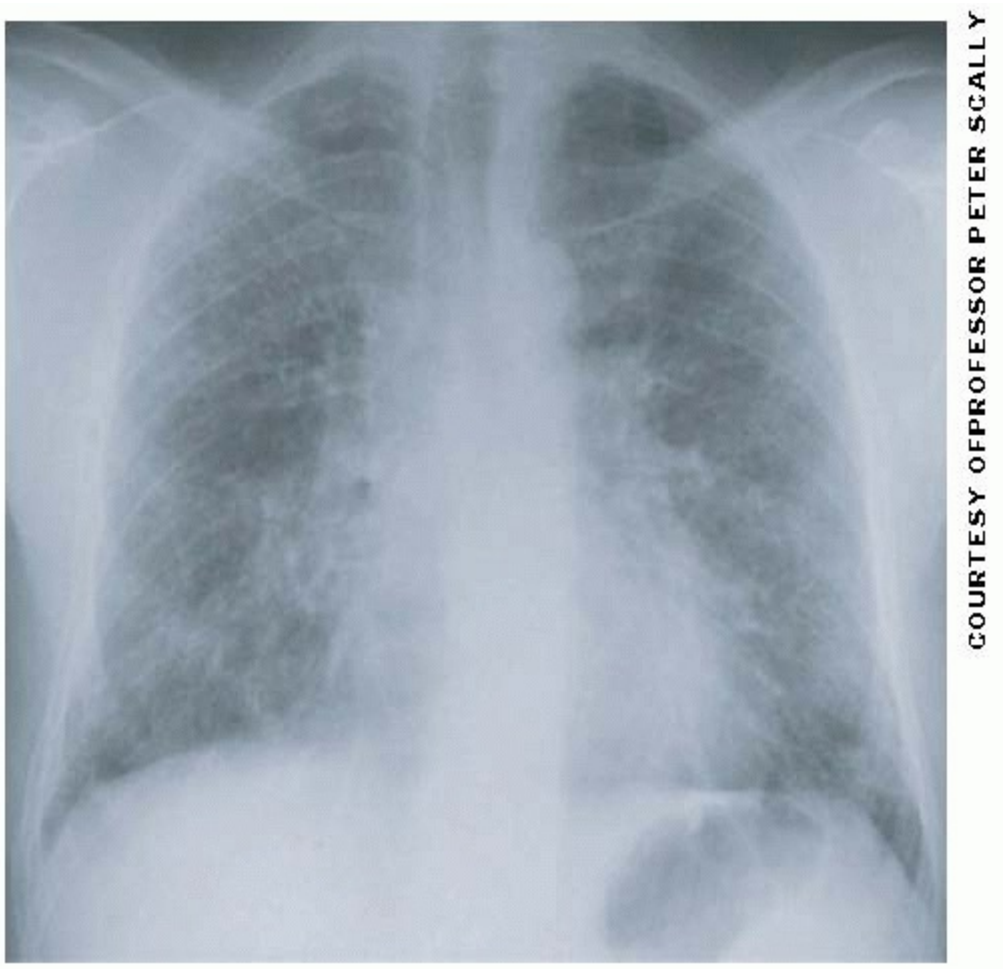


Fig 3. Diffuse reticular shadowing secondary to interstitial lung disease. The diagnosis was fibrosing alveolitis (UIP). (see color image)

Reticular shadows:

(**fig 3**) Usually acute interstitial changes (cardiac or noncardiac pulmonary interstitial oedema; atypical pneumonia, eg viral; or:

- Fibrosis; TB; histoplasmosis
- Sarcoidosis; silicosis; asbestosis
- Usual interstitial pneumonitis (UIP)
- Neoplasia (lymphangitis carcinomatosa)
- Fibrosing alveolitis; rheumatoid (p532)
- Wegener's (p706); SLE; PAN; CREST (p538)

Alveolar shadows:

Usually pulmonary oedema from LVF (p786). Also:

- Pneumonia
- Haemorrhage
- Drugs (heroin, cytotoxics, p516)
- Smoke inhalation (p831)
- O_2 toxicity

- Fat emboli, ~7 days post-fracture
- Renal or liver failure (p294 & p250)
- ARDS (p170); DIC (p336)
- Head injury, or after neurosurgery
- Alveolar proteinosis
- Near-drowning (OHCS p724)
- Heat stroke (p778).

'Ring' shadows:

Either airways seen end-on (airbronchograms; bronchiectasis), or cavitating lesions, eg abscess (bacterial, fungal, amoebic), tumour, or pulmonary infarct (triangular with a pleural base).

Linear opacities:

Septal lines (Kerley B lines, ie interlobular lymphatics seen with fluid, tumour, or dusts); atelectasis; pleural plaques (asbestosis). *White-out* of an entire hemithorax can occur in pneumonia, massive pleural effusion, ARDS, or after pneumonectomy (**fig 4**).

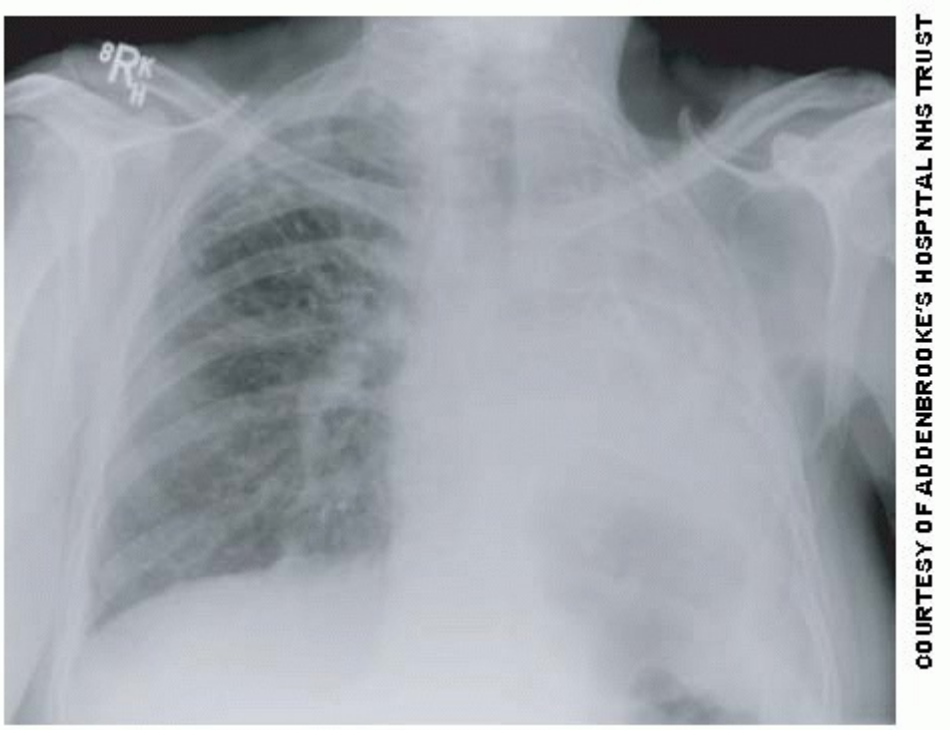


Fig 4. Complete opacification of the left hemithorax after pneumonectomy; note the mediastinum is shifted to the left.

Air outside the lungs:

Check for a pneumothorax (difficult to spot if apical or in a supine image), surgical emphysema (trauma, iatrogenic) and gas under the diaphragm (perforated viscus, trauma, surgery).

Bones

Check the ***clavicles*** for bone density (loss of cortex in osteoporosis) or fracture, the ***ribs*** for fractures, notching, absence (surgery) and lesions (eg metastases), the ***vertebral column*** for collapse or destruction and the ***shoulders*** for fracture and arthritis.

An apparently normal CXR?

Check for tracheal compression, absent breast shadow (mastectomy), double left heart border (left lower lobe collapse, **fig 1**), fluid level behind the heart (hiatus hernia, achalasia), and paravertebral abscess (TB). ▸Remember to check old images for comparison: **fig 3** could be acute interstitial oedema, but comparison with a previous image showed that the changes were chronic.

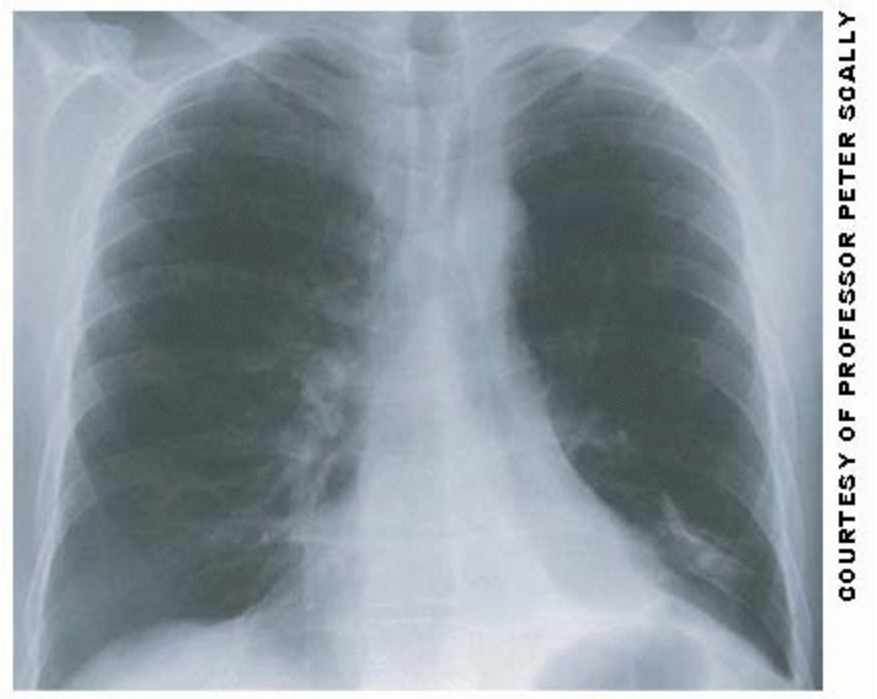


Fig 5. Collapse of the left lower lobe—the triangular opacity behind the heart. Also, the left main bronchus has been pulled down. ▸Enlarged versions of these CXRs appear before the index. (see color image)

Plain abdominal x-ray (AXR) Enlarged images: p838

These are rarely diagnostic, and are non-contributory in most mild or moderate instances of abdominal pain. Indications for AXR with acute abdominal symptoms are:

- Acute abdominal pain warranting admission or surgery
- Suspicion of perforation or obstruction
- Acute exacerbation of inflammatory bowel disease
- Haematuria, renal failure, or renal colic
- Ingestion of a sharp or poisonous foreign body (eg lithium battery)
- Blunt or penetrating injury to the abdomen
- Intussusception in paediatrics.

Erect AXRs are rarely done, since bowel gas pattern is best seen on supine images and free intraperitoneal gas (signifying perforation) is best seen on an erect CXR (**fig 1**, p581). The following routine covers most of the important aspects:

- **Gas patterns: Look for:** An abnormal quantity of gas in the stomach, small intestine, or colon. Deciding whether you are looking at small or large bowel:

  The small bowel's diameter is normally ~2.5cm, the colon ~5cm, and the caecum up to 10cm. Dilated small bowel occurs in obstruction and paralytic ileus. Dilated large bowel ($\gtrsim$6cm) occurs with both these, and also in toxic dilatation in someone who is really sick, and, in the elderly, benign hypotonicity. Grossly dilated segments of bowel occur in sigmoid and caecal volvulus. Loss of normal mucosal folds, irregular mucosal islands, and bowel wall thickening can be seen in inflammatory colitis (eg IBD)—**fig 4**. 'Thumbprinting' is protrusion of rounded indentations of thickened mural folds into the lumen and is seen in large bowel ischaemia.

- **Gas outside the lumen:** You must explain any gas outside the lumen of the stomach, small intestine, and colon. It could be: **1** Pneumoperitoneum; signs visible on the supine AXR include: gas on both sides of the bowel wall (Rigler's sign), a triangle of gas in the RUQ trapped beneath the falciform ligament, and a football-shaped distribution of gas beneath the anterior abdominal wall. **2** Gas in the urinary tract—eg in the bladder from a fistula. **3** Gas in biliary tree (pneumatobilia—see MINIBOX), or rarely **4** Intramural gas, found in bowel

  necrosis, clostridial infection, necrotizing enterocolitis (neonates) and pneumatosis cystoides intestinalis (a rare and benign condition).[2]

- **Local peritoneal inflammation** can cause localized ileus (a sentinel loop of intraluminal gas), giving a clue to the site of pathology. Roughly: **RUQ** ≈ cholecystitis, **LUQ** ≈ pancreatitis, ***RLQ*** ≈ appendicitis, ***LLQ*** ≈ diverticulitis.

- **Biliary tree Look for:** Pneumatobilia (see MINIBOX) and calcification in the gall bladder (only ~10% of gallstones are visible on plain AXR). Calcification of the gallbladder wall (porcelain gallbladder) is a result of chronic inflammation secondary to gallstones or adenocarcinoma in 22% of cases.[3]

- **The urinary tract** The kidneys normally have an equivalent length of 2½-3½ vertebral bodies and slope inferolateraly, with the left sitting higher than the right. Their outlines can usually be discerned because they have a surrounding layer of perinephric fat—if this is or has been inflamed (eg perinephric abscess) then the outline is obliterated. The ureters pass near the tips of the lumbar transverse processes, cross the sacroiliac joints, down to the ischial spines, and turn medially to join the bladder. Check the kidneys and ureteric courses for calculi (visible in 90% of cases)—this

requires practice! See p730 for intravenous urography (IVU).

- **Other soft tissues: Look for:** Size/position of: liver, spleen and bladder. A grossly enlarged liver will push the bowel to the left side of the abdomen, spleen to the right, bladder superiorly. The liver and spleen should not extend below the level of the 12th rib on a correctly aligned image.
- **Other calcification:** Calcification can be seen in the abdominal aorta, splenic artery, pancreas (chronic pancreatitis), mesenteric lymph nodes (**fig 5**), and granulomas in the liver and spleen. Phleboliths, recognised by their rounded shape and radiolucent centre, are harmless calcifications found in the perivesical veins.
- **Medical devices:** Double-J and biliary stents, nephrostomy and gastrostomy tubes, intrauterine devices (eg coil), laparoscopic sterilisation clips, and chronic ambulatory peritoneal dialysis (CAPD) catheters (**fig 6**) can all be seen on AXR.
- **Bones and joints:** In the lumbar spine, look for scoliosis and degenerative disease (osteophytes, joint space narrowing). Identify and compare the vertebral bodies, spinous processes (lack of arch closure in spina bifida), pedicles (can be destroyed in malignancy), facet joints, and transverse processes (**fig 5**). Be on the lookout for metastatic deposits (osteolytic or osteosclerotic) and Paget's disease (unusual patterns of bone expansion, sclerosis and/or lysis). Although not the preferred view, the sacroiliac joints can also be seen (sclerotic in early ankylosing spondylitis). In renal osteodystrophy (p294) there is a 'rugger jersey' spine of alternating bands of sclerosis (opacity) and osteopenia (lucency).

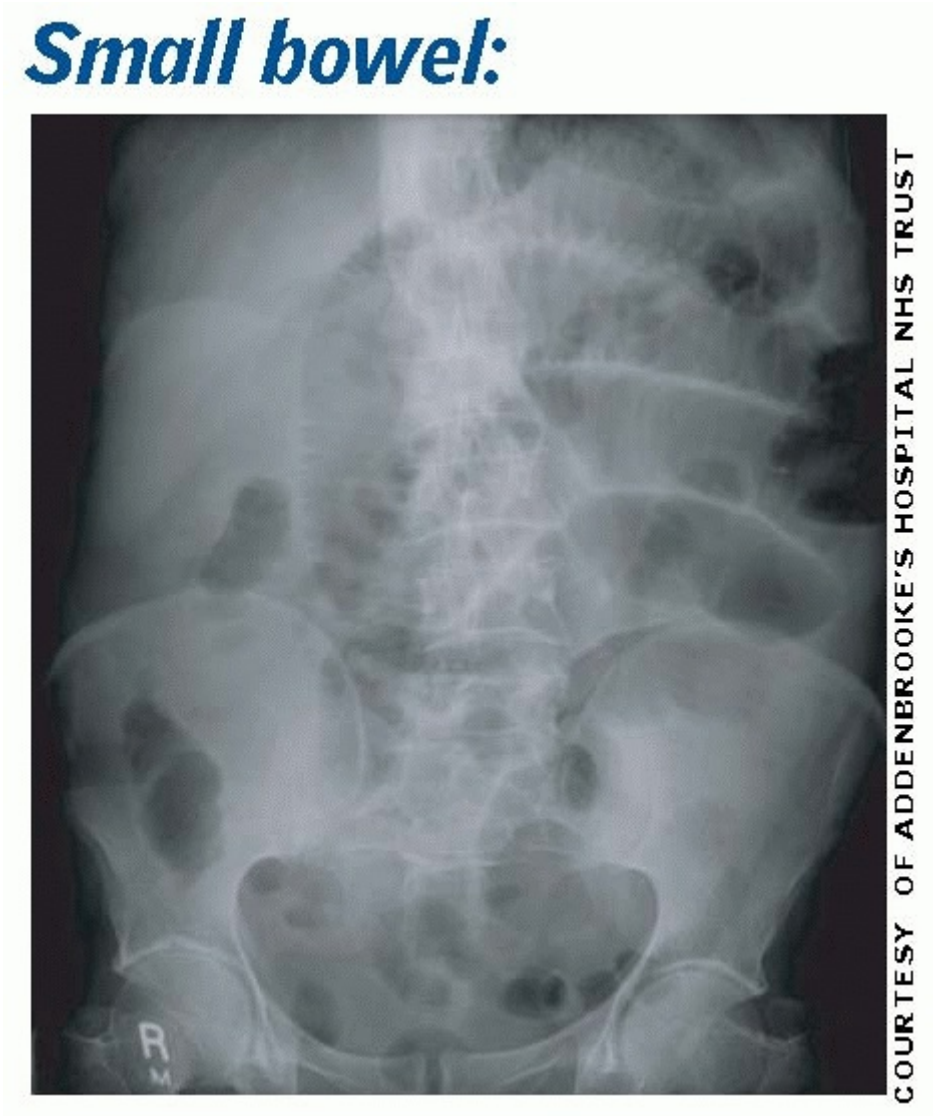


Fig 1. The pattern seen in small bowel obstruction. (see color image)

- Smaller calibre
- Central; multiple loops
- *Valvuli conniventes:* folds that go from wall to wall, all the way across the lumen; more regular than *haustra*
- Grey (contains air & fluid)

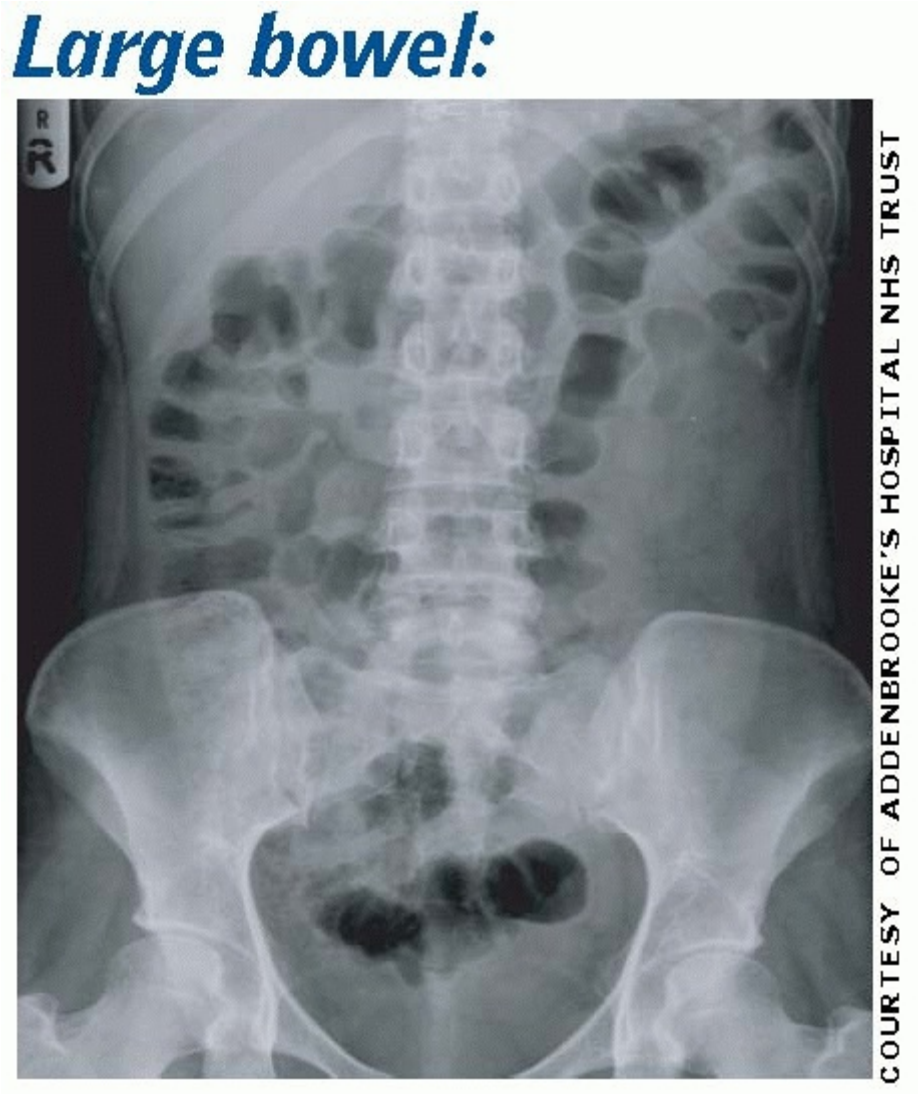


Fig 2. Normal large bowel gas pattern. (see color image)

- Larger calibre
- Peripheral
- *Haustra:* do not go all the way across the lumen, but may appear to do so if viewed from an angle
- Blacker (contains gas)[1]

Ileus:

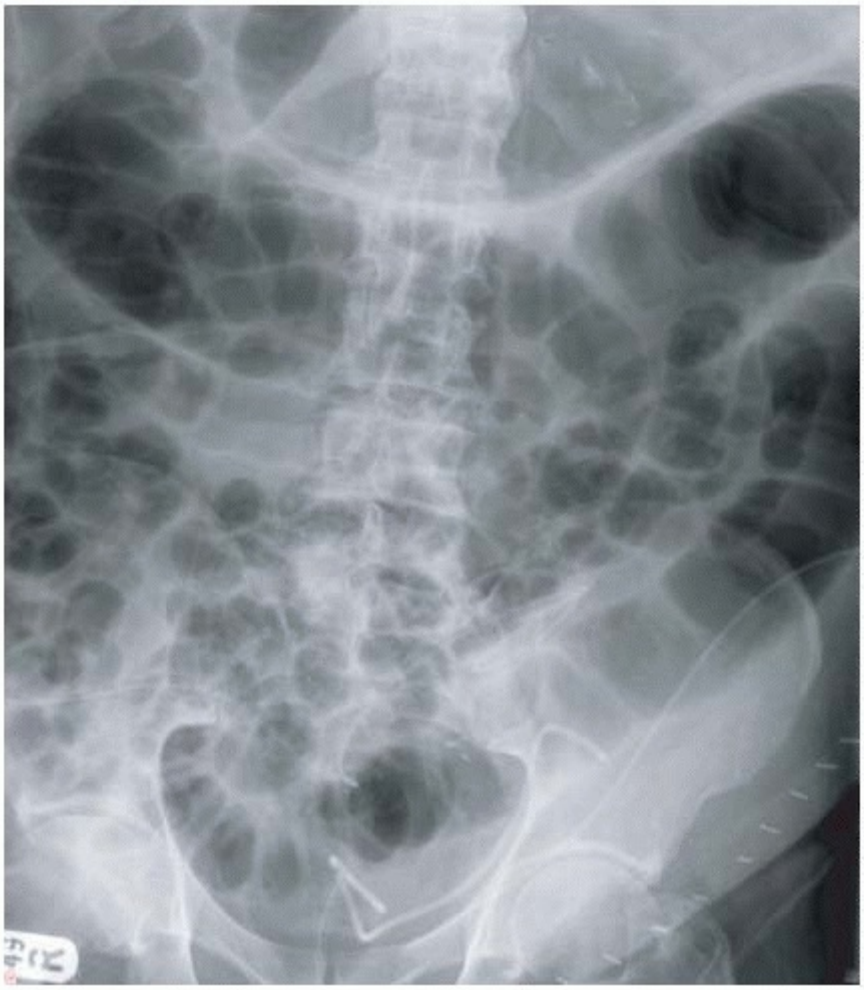


Fig 3. Multiple dilated air filled loops of large and small bowel. This pattern is seen in ileus.

- Both small and large bowel visible
- There is no clear transition point that corresponds to an obstructing lesion

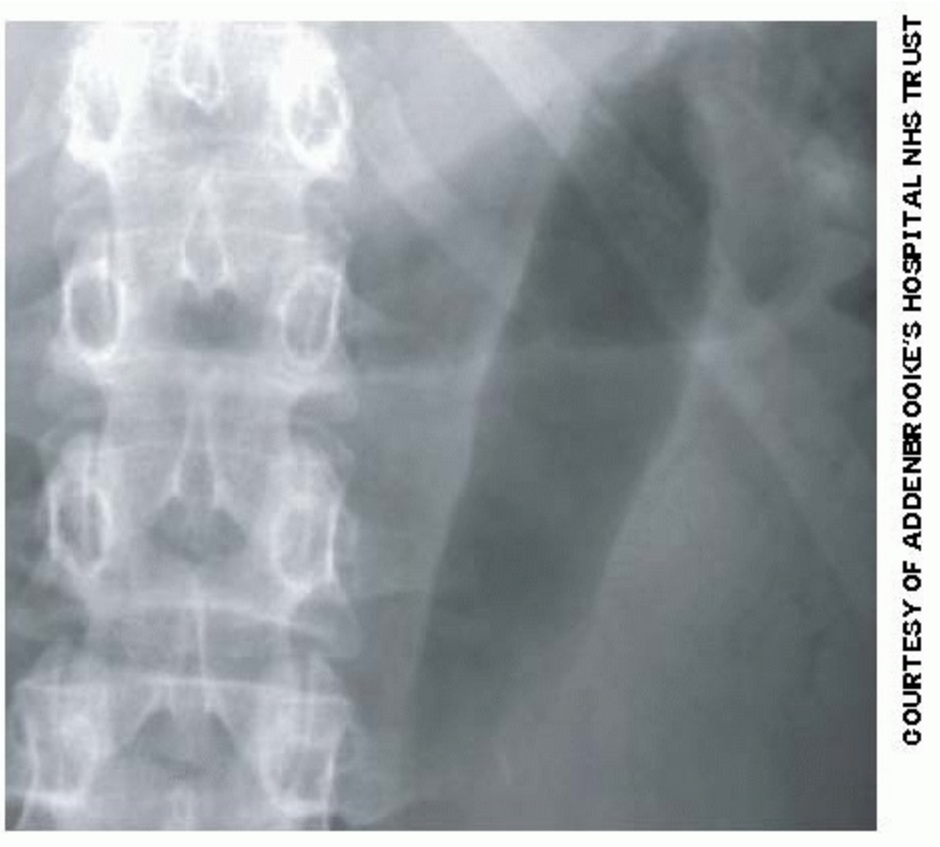


Fig 4. Part of the descending colon with mucosal thickening and loss of normal haustral pattern; seen in colitis (see color image)

Pneumatobilia:

- Post-ERCP
- Post-surgery
- Anaerobic cholangitis
- Recent stone passage
- Gallbladder-bowel fistula

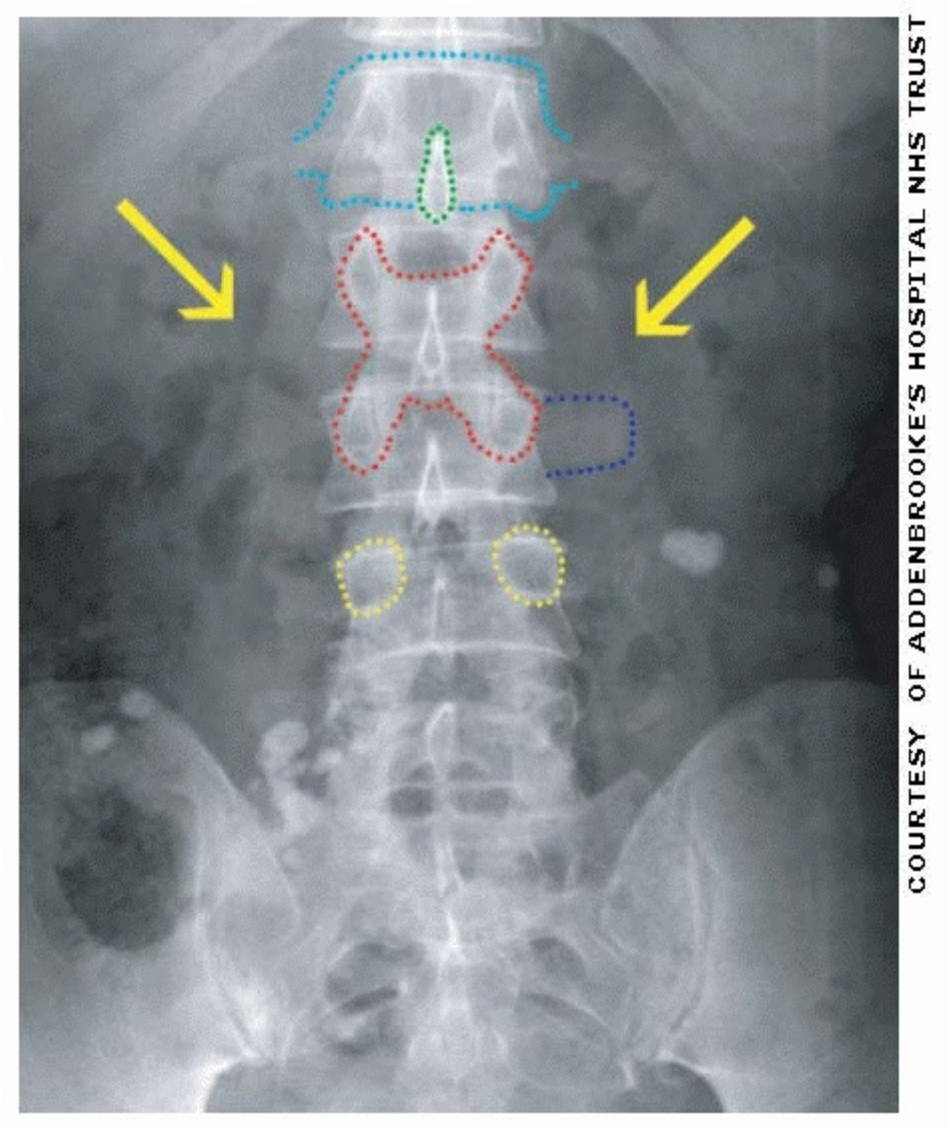


Fig 5. AXR showing calcified mesenteric lymph nodes. Also note; psoas lines (arrows); spinous process (green); transverse process (blue); pedicles (yellow): facet joint processes (outline in red); vertebral body (cyan). (see color image)

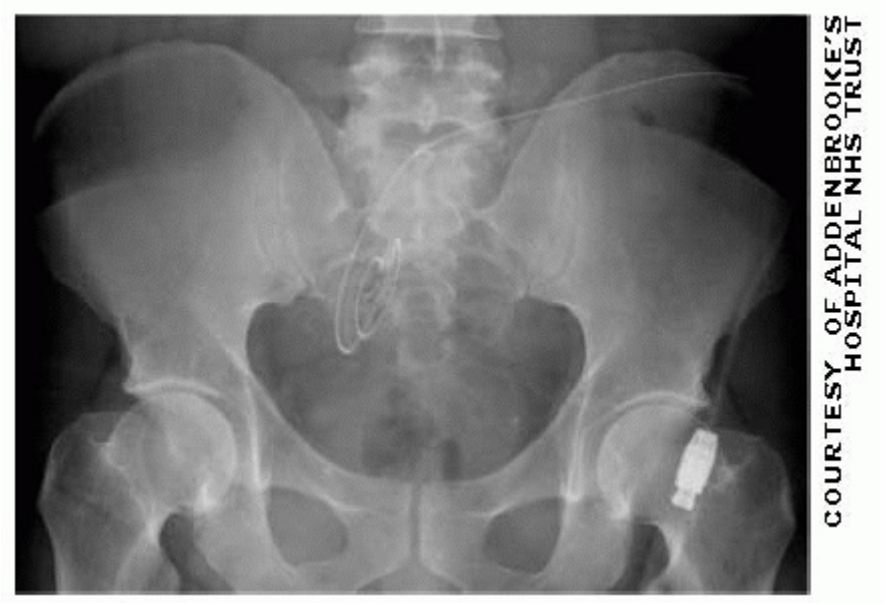
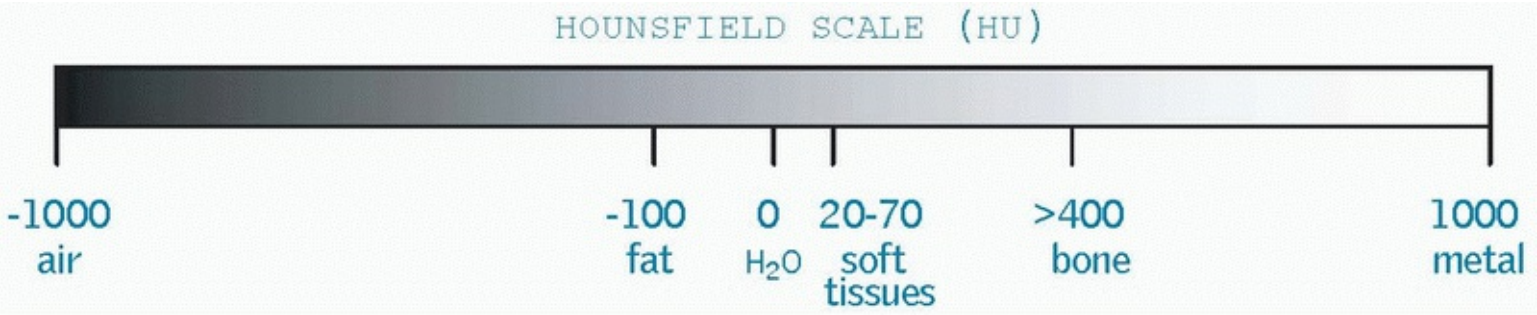


Fig 6. A CAPD catheter (for continuous ambulatory peritoneal dialysis). ▸Enlarged images p839

▸Don't expect too many answers from plain abdominal images! Develop and rely on your clinical skills. At the end of the day the most common diagnosis for abdominal pain is abdominal pain of unknown origin: think of major pathologies.

Computed tomography (CT)

Since its first use in Atkinson Morley Hospital in 1972,[4] CT has become a speedy and accurate aid to the clinician, with new systems producing whole body images in under one breath (thanks to continuous, helical rather than sequential, axial data acquisition). Within a single slice (eg 2-5mm thick) CT records the **attenuation**[1] of different tissues to ionising radiation and calculates a mean value for a given volume of tissue, called a **voxel**, in a process called **volume averaging**. This value is represented in greyscale as a single point, called a **pixel**, in the final 2D image, usually 512 by 512 pixels. The greyscale of the image is measured on the Hounsfield scale relative to the attenuation of water, which has a value of 0 Hounsfield units (HU) and ranges from less than -1000 HU (low attenuation) to more than +1000 HU (high attenuation).



Because our eyes cannot pick up the subtle variation in attenuation of the tissues that CT can, there are different **windows** that can be used to look at tissues of different density, eg bone or lung (**fig 1**).

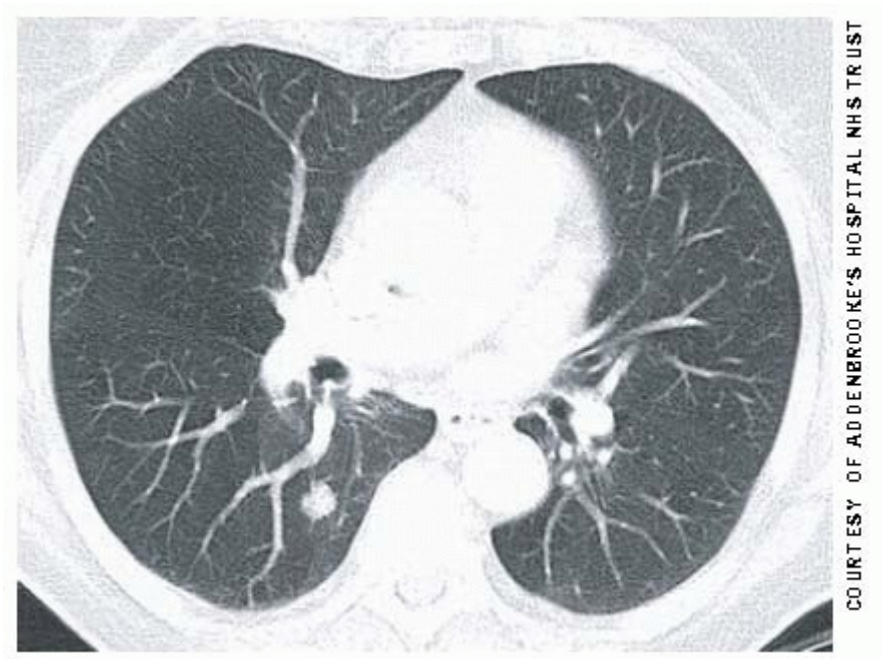


Fig 1. Axial CT chest on a lung window algorithm showing a solitary pulmonary metastasis.

CT with intravenous iodinated contrast medium

gives the ability to image vascular anatomy and vascular structures in arterial, venous and delayed phases after the injection of contrast medium (**fig 2**). Contrast medium is usually given IV for examinations of the chest, abdomen and pelvis. CTs of the brain, spine, and musculoskeletal system are normally done without IV contrast. Enhancement of the colonic lumen can be achieved with oral contrast medium given 24h beforehand, or by rectal administration. Air is insufflated for CT colonography or 'virtual colonoscopy'—**fig 6**, p729). Oral contrast or water is administered 1h before an examination for definition of the stomach and small bowel. Also see **Contrast in imaging**, p734.

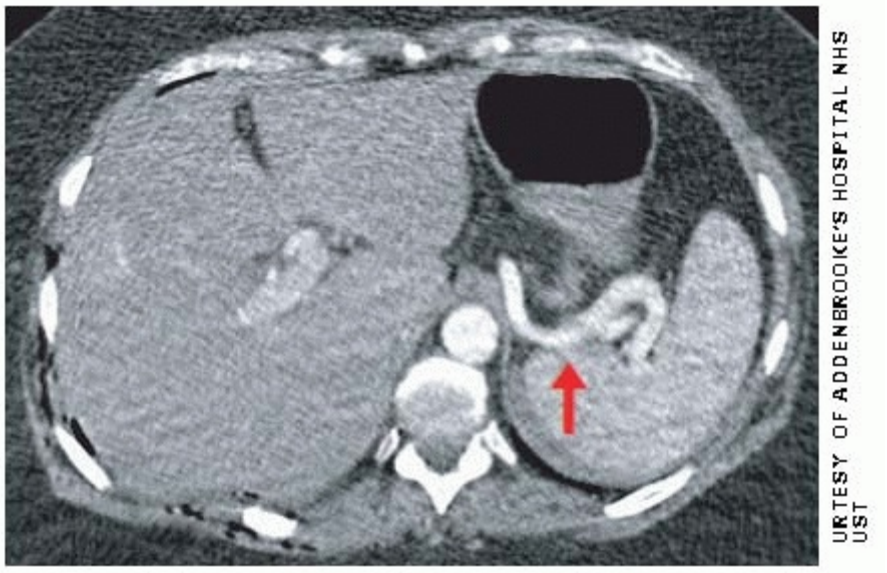


Fig 2. Axial CT of abdomen post IV contrast. The tortuous splenic artery is well seen (arrow).

CT as the examination of choice:

Staging and monitoring malignant disease; intracranial pathology, eg CVA, trauma, ↑ICP, and SOLs (especially when calcified, eg oligodendroglioma); trauma; pre-operative assessment of complex masses; obese patients (US in thinner individuals); most post-operative complications; visualisation of anatomy for drainage, biopsy and nerve blocks.

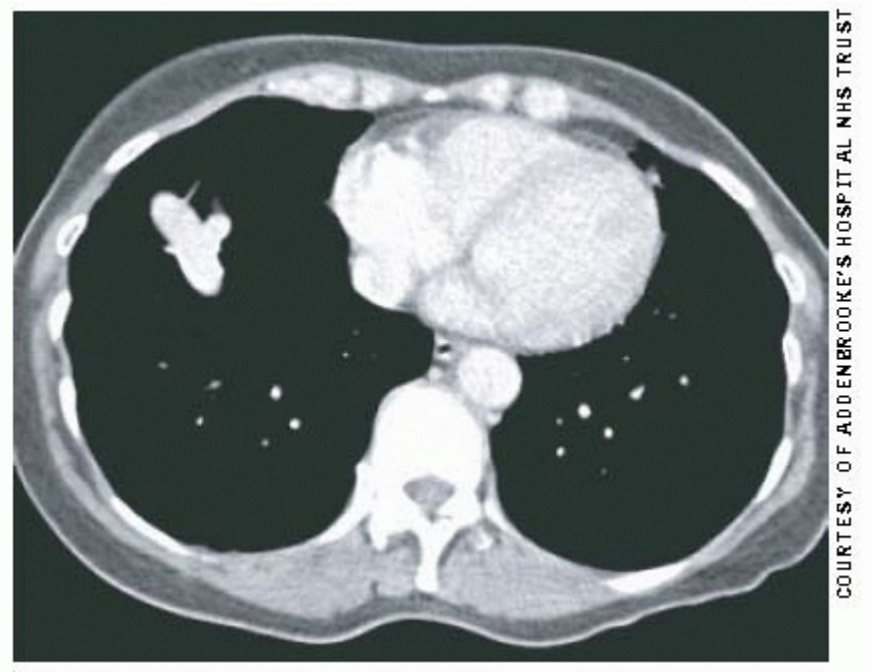


Fig 3. Axial CT of chest post IV contrast. The avidly enhancing middle lobe lesion was an arterio-venous malformation.[2]

Artefacts and interference

Remember that the CT slice image is a matrix representation of the attenuation produced by rotating the system around the patient—this explains some of the artefacts that can be produced. High attenuation items such as metal fillings, clips and prostheses (and even bone) can cause interference. This is one reason why the posterior cranial fossa was not well imaged on CT—it is better now. 'Stair-stepping' and poorly defined edges are caused by volume averaging (the partial volume effect) and can be overcome by reducing the slice width for the desired sections.

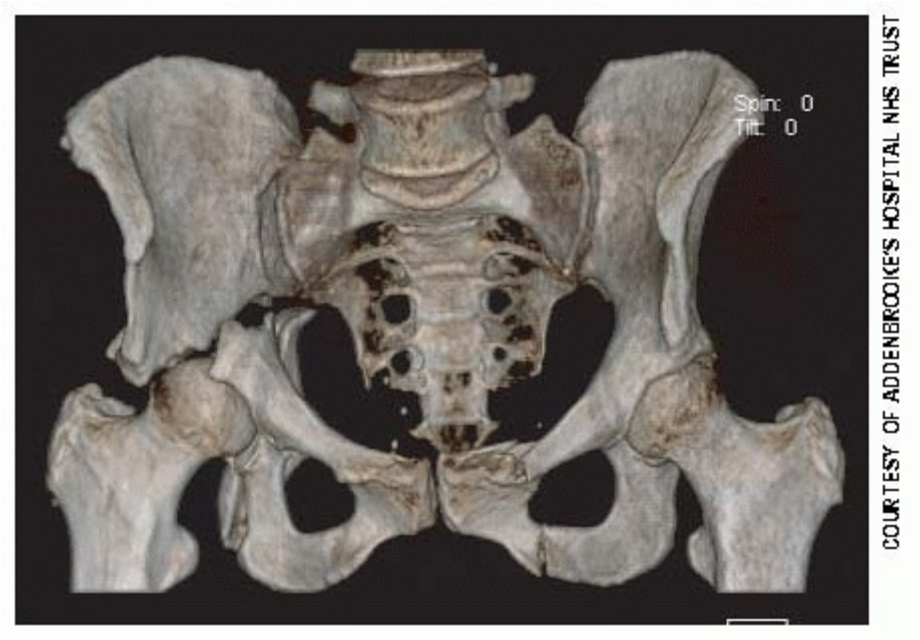


Fig 4. Surface rendered 3D CT reconstruction of the pelvis. There is a fracture through the superior acetabulum.

The future of CT

Multi-detector CT (MDCT) systems (see BOX [V with dot above]/[Q with dot above] vs CTPA, p725) are an important advance. They image a volume of tissue, rather than individual slices. Also by decreasing the thickness of a slice, they increase volume averaging and thus increase resolution and reduce artefact. Multiplanar (not just axial) slices can be retrieved from one 'sweep', giving thousands of images that are stored digitally and reconstructed, eg into a 3D image (**fig 4**). CT angiography uses MDCT and digital modulation technology to enable 3D colour reconstructions. CT urography is rapidly becoming the investigation of choice for the urinary tract. Perfusion CT scanning is a developing technique that maps cerebral blood flow by acquiring images over a period after a rapid IV bolus of contrast medium. Its role is yet to be established in the investigation of acute stroke, though it does have the advantages of being less invasive than angiography and more available than MRI.[5] CT combined with PET (see p730) has and increased sensitivity and specificity over each alone.

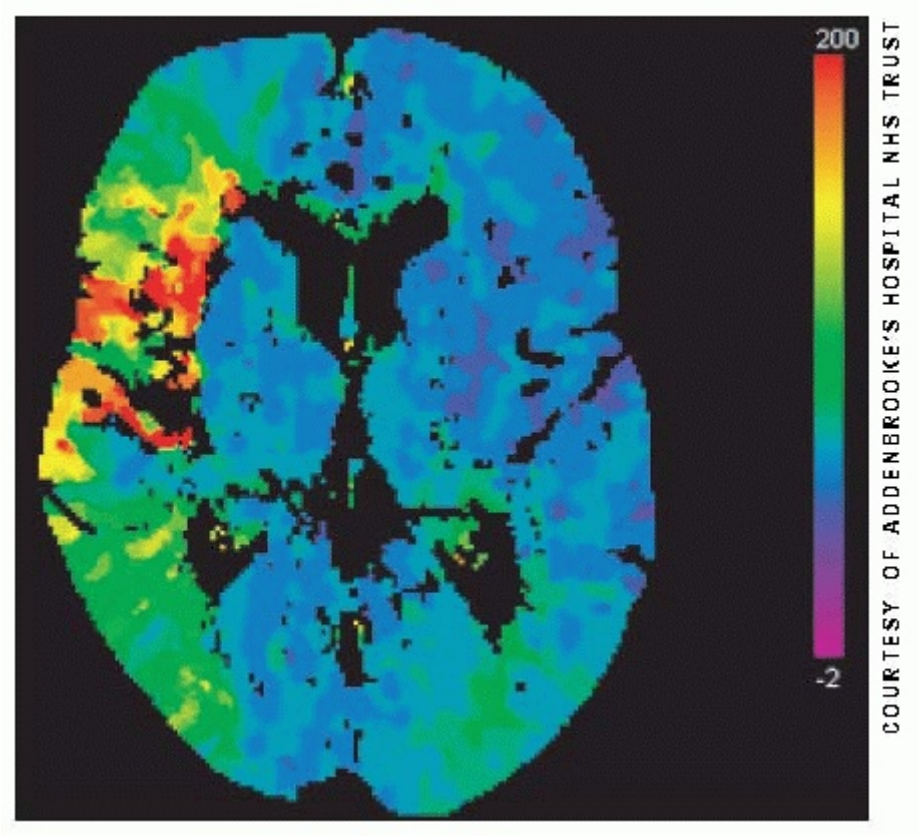


Fig 5. Head perfusion CT, with signs of ischaemia in the right middle cerebral artery territory.

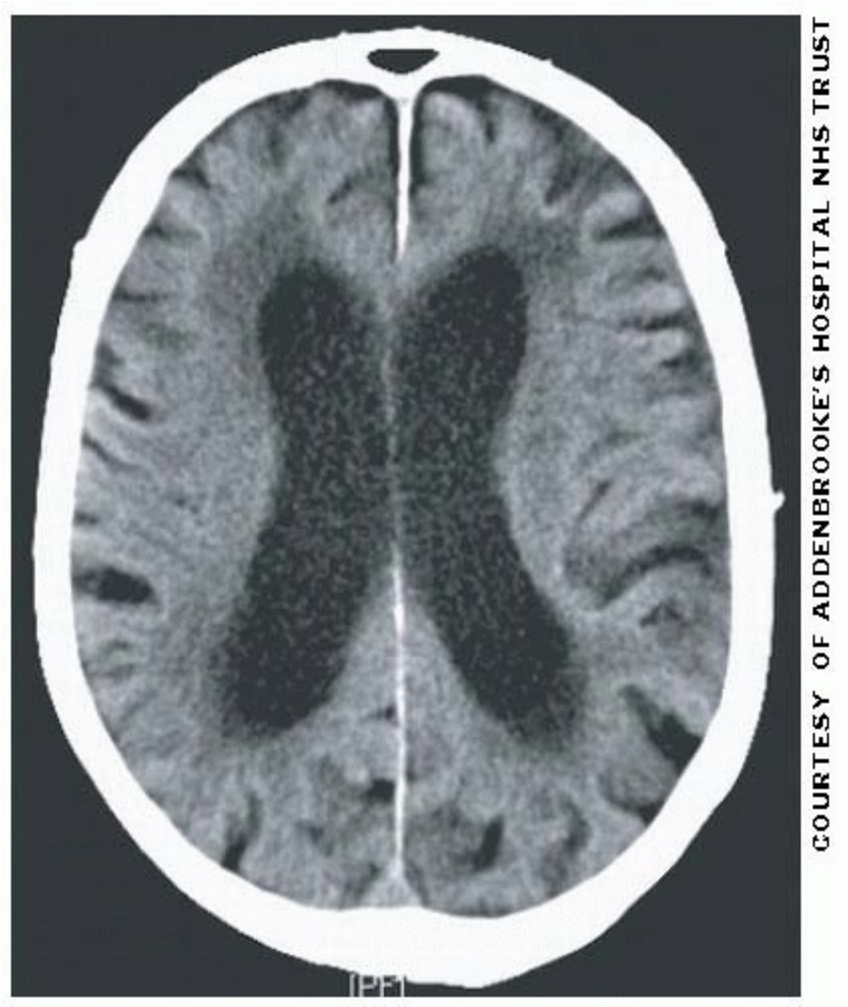


Fig 6. Axial non-enhanced CT of the brain. There is ventricular dilatation with prominent cerebral sulci indicating cerebral atrophy. But the degree of atrophy is often not well-correlated with clinical symptoms—a reminder that morphology does not reflect function.

Too many CTs?

It is tempting to think that we might be overusing such a valuable resource. Given that CT examinations account for perhaps 40% of iatrogenic radiation exposure it is sensible to consider if usage is appropriate. Yet in one review, the auditors were unable to account for any substantial group of patients that were undergoing unnecessary CT examination.[6]

When deciding to request a CT, it is still important to consider the need and the benefit of CT over other imaging investigations. MRI is becoming more suitable as an alternative, especially in younger patients, and is even preferable in circumstances where we regularly use CT because of its greater availability (eg imaging the liver). Ultrasound may also be an accurate and appropriate alternative. To get the best result, discuss the options with a radiologist.

Magnetic resonance imaging (MRI)

1 A large proportion of the human body is fat or water (~80%).

2 Fat and water contain a large number of hydrogen nuclei (unpaired protons).

3 The spin of a positively charged hydrogen nucleus gives it magnetic polarity.

Thus…

- Placing the human body in a magnetic field (clinically from 0.2-3 Tesla) aligns its hydrogen nuclei either with (parallel) or against (anti-parallel) the field.
- A radiofrequency (RF) pulse at the resonant frequency flips nuclei away from their original alignment by an angle depending on the amount of energy they absorb.
- When the RF pulse stops, the nuclei flip back (or **relax**) into their original alignment, emitting the energy (called an **echo**) that was absorbed from the RF field.
- Measuring and plotting the energy of the returning signal according to location (provided the nuclei haven't moved) gives a picture of fat, tissue, and water as distributed throughout the body.

- The hydrogen nuclei in flowing blood move after receiving the RF pulses. The echo is not detected, and so the vessel lumen appears black.

Rather than radiodensity or attenuation, the correct descriptive terminology for the greyscale seen in MRI is **signal intensity**: high signal appears white and low signal black (see below). **Weighting** is a quality of MRI that is dependent on the length of the period between the RF pulses (**repetition time**, **TR**) and the time between an RF pulse and the echo (**echo time**, **TE**). MR images are most commonly T1-weighted (good for visualising anatomy) or T2-weighted (good for visualising disease) but can also be a mixture of both, called **proton density** (PD) weighting. **FLAIR** sequences produce heavily T2-weighted images. A good way to determine the weighting of an MR image is to look for water—eg in the aqueous humour of the eye, CSF, or synovial fluid (see TABLE).

	T1-WEIGHTED	**T2-WEIGHTED**
TR	short (<1000ms)	long (>2000ms)
TE	short (<30ms)	long (>80ms)
LOW SIGNAL ▪	**water** flowing Hb fresh Hb haemosiderin	bone flowing Hb deoxyHb haemosiderin melanin
HIGH SIGNAL □	bone fat cholesterol gadolinium (p734) metHb	**water** cholesterol fresh Hb metHb

Advantages

MRI's great bonus is that it does not involve ionising radiation. It has no known long term adverse effects, though power is limited by controls on energy deposition into tissue. It is excellent for imaging soft tissues (water-and hence proton-dense). It is preferred over CT for intracranial, head and neck, spinal, and musculoskeletal disorders. Multiplanar acquisition of images can provide multiple views and 3D reconstruction from one examination.

Disadvantages

include poor imaging of lung parenchyma and GI mucosa, being more claustrophobic and noisy than CT, and current high cost combined with poor availability.

Contraindications

Absolute:

- Cardiac pacemakers and other cardiac electrical devices.
- Intra-ocular metallic foreign bodies. (You may need to request an X-ray of the orbits to exclude a foreign body)

Relative:

- Intracranial aneurysm clips.
- Certain types of artificial heart valves.
- If unable to complete the pre-scan questionnaire.
- 1st trimester of pregnancy (not currently approved.)
- Cochlear implants. **NB:** Orthopaedic prostheses and extracranial metallic clips are generally safe.

▸If uncertain, discuss with a radiologist.

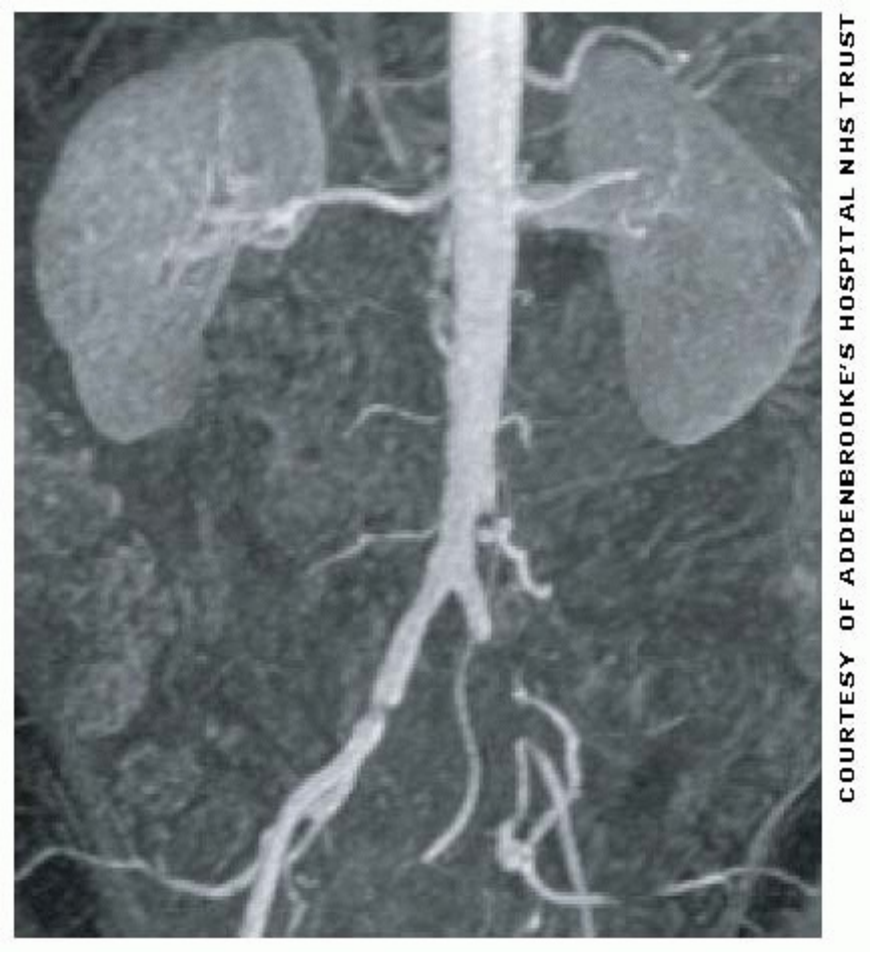


Fig 1. One of the many successful developments in MRI has been magnetic resonance angiography (MRA). It can accurately reconstruct vascular anatomy with or without IV gadolinium. This makes it a valuable in the assessment of vascular disease in patients with nephropathy. This also precludes the need for femoral puncture (the usual point of entry for conventional contrast angiography), which can have complications of haemorrhage, pseudoaneurysm formation and arterial thrombosis. This MRA shows complete occlusion of the left common iliac artery and focal stenosis of the right common iliac artery.

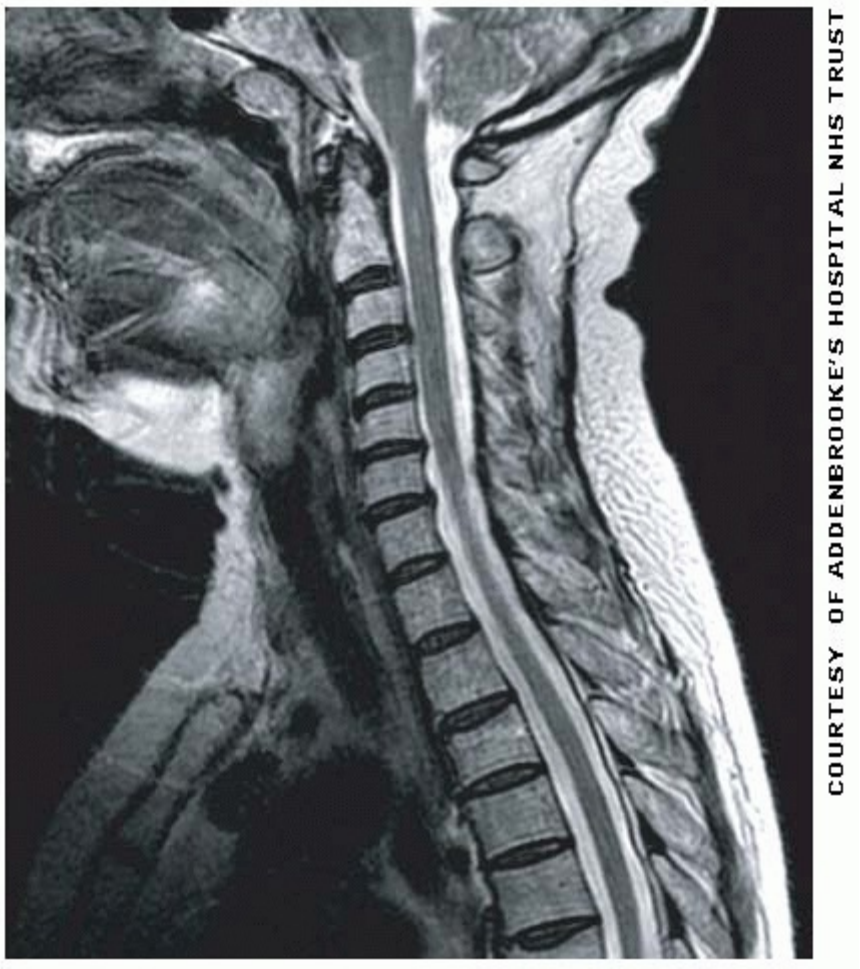


Fig 2. T2 weighted sagittal MRI of the cervical spine. There is impingement of the spinal cord at the C5/6 and C6/7 levels caused by degenerative disease. C2 (axis) is identifiable from the odontoid peg, that is embryologically derived from the body at C1 (atlas).

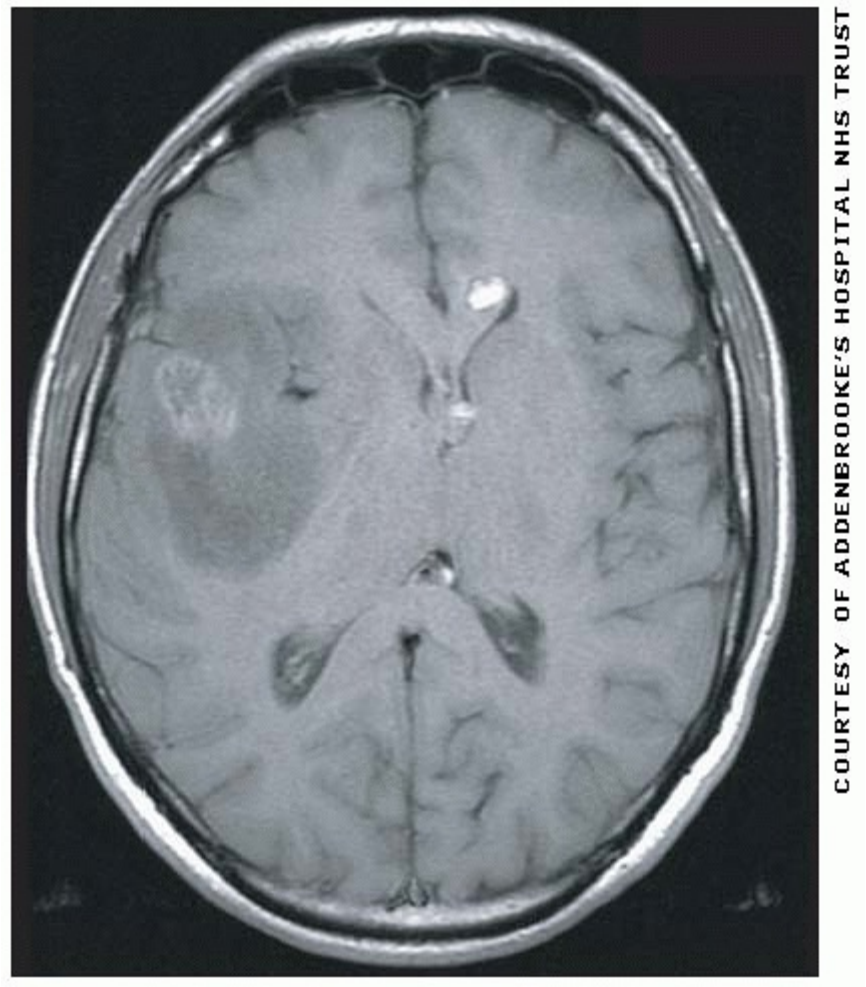


Fig 3. Axial T1 weighted MRI of the brain post IV gadolinium. In the right tempro-parietal region there is an area of low signal with a more central area of high signal. This is causing mass effect with effacement of the sulci and adjacent right frontal horn of the lateral ventricle. There is midline shift.

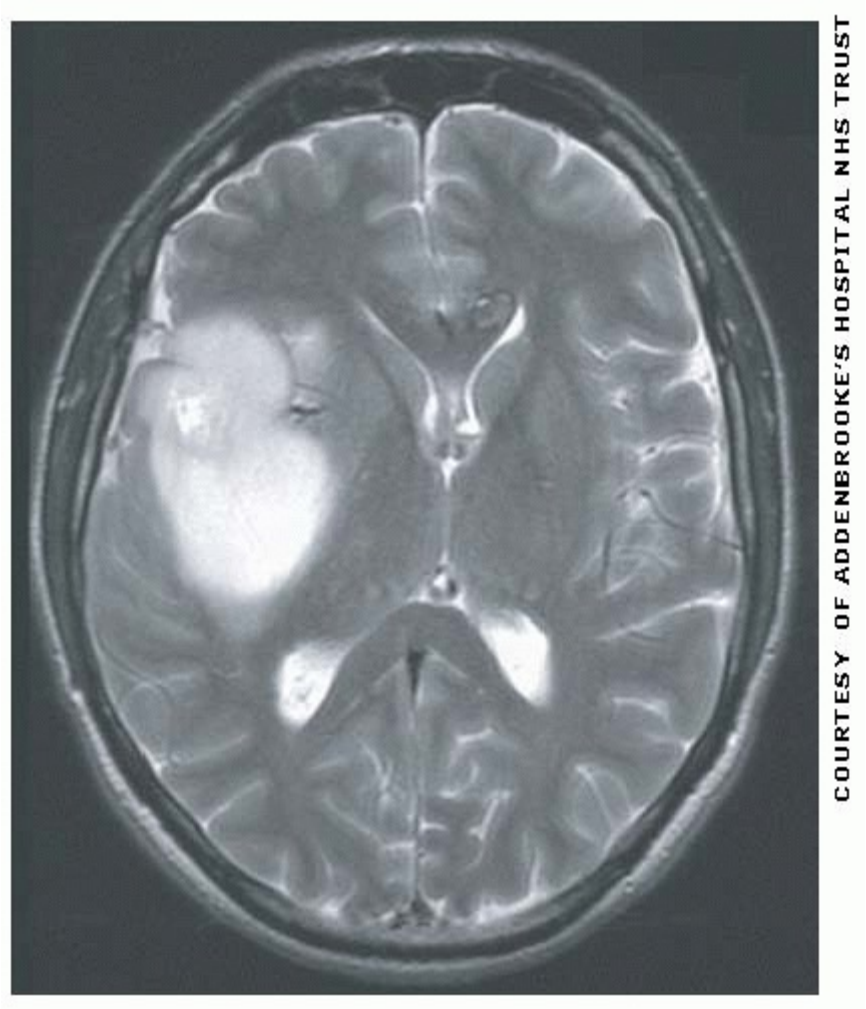


Fig 4. Axial T2 weighted MRI of the same patient at the same level. The high signal in the temporo-parietal region with more central focal high signal again shows mass effect. The diagnosis was of a cystic tumour. Note that on this T2 weighted image the cerebrospinal fluid within the ventricles and cortical sulci are of high signal due to their high water content.

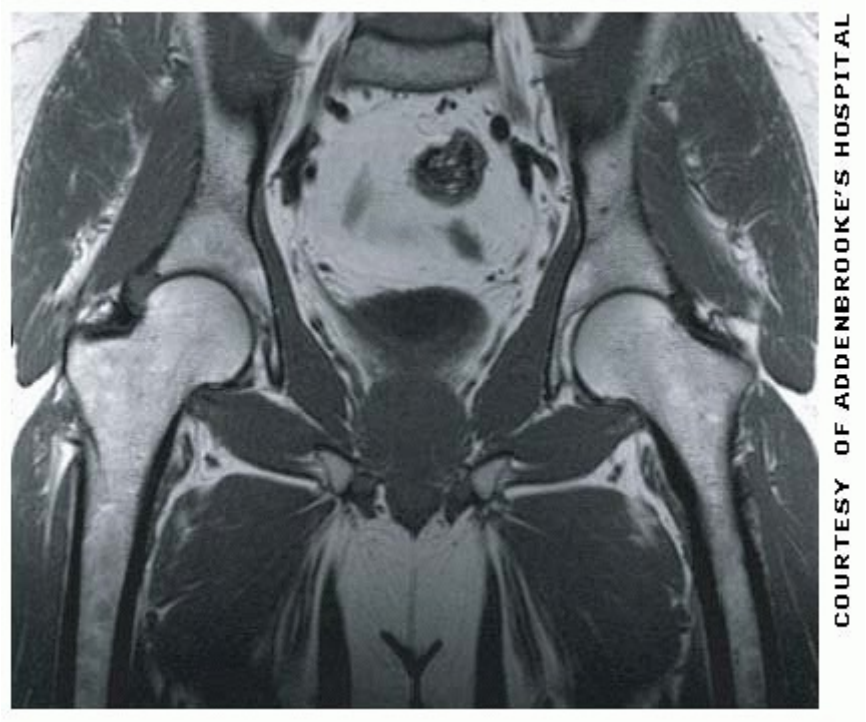


Fig 5. Coronal T1 weighted MRI of the hips. On T1 weighted imaging the normal adult bone marrow is high signal due to fatty yellow marrow, whilst red marrow gives a lower signal. MRI gives remarkable soft tissue contrast definition.

Ultrasound (US)

Unlike the other methods of imaging, ultrasound does not use electromagnetic radiation. Instead, it relies on the properties of longitudinal sound waves. This has made it a popular and safe form of diagnostic imaging. High frequency sound waves (3-15MHz) are produced from a piezo-electric quartz crystal, the size, shape and resonant frequency of which are important in determining tissue penetration and image quality. One if the interesting characteristics of ultrasound is that the transducer acts as both transmitter and receiver because of the piezo-electric properties of quartz crystal.[1]

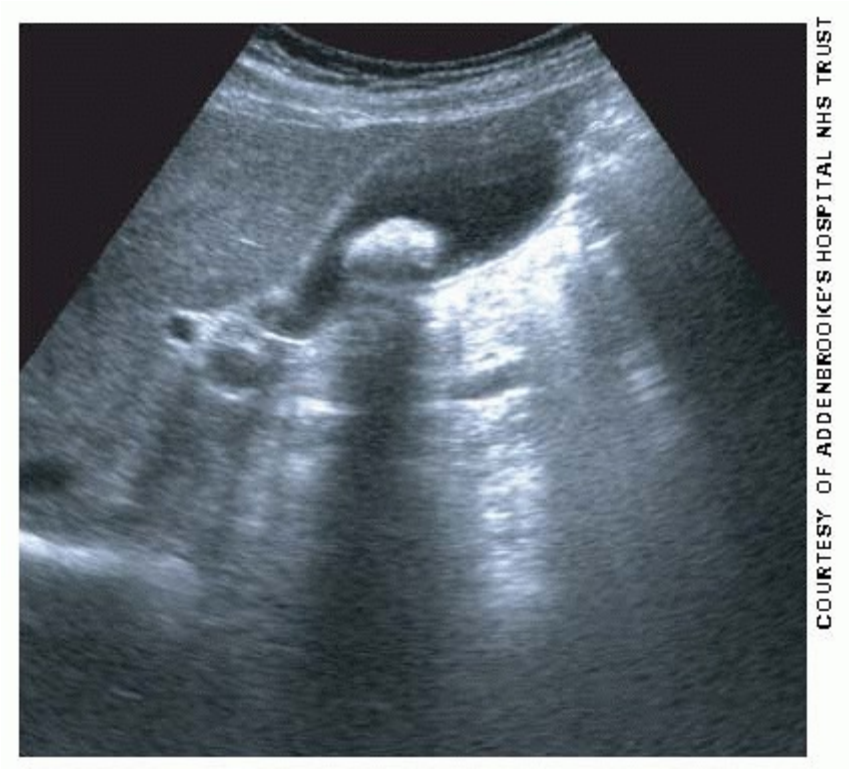


Fig 1. Abdominal US showing a hyperechoic calcified gallstone causing a dense acoustic shadow (black) posteriorly. The hypoechoic gallbladder (bile) as a fluid structure has echobright acoustic enhancement (white). Different tissues have different acoustic impedance values and therefore affect the velocity of the ultrasound wave as it travels through a tissue.

The passage of sound waves through tissue is affected by **attenuation** and **reflection**. Attenuation disperses the waves out of the range of the receiver, whereas it is the waves reflected to the receiver that determine the image derived. The quality of this image is closely dependent on the difference in **acoustic impedance** between adjacent soft tissues.

With the help of software a real-time 2D image is produced. During processing an average attenuation value is assumed throughout the depth of the tissue examined. This means that if a higher-than-average attenuation structure is in the superficial tissues, then everything deep to it will be in a low intensity (black) **acoustic shadow**. If a lower-than-average attenuation object is in the superficial tissues then everything deep to it will be high intensity (white) or **enhanced**; see MINIBOX. If a tissue interface is strongly disparate, then all the waves are reflected back, making it impossible to image beyond it.

Acoustic shadow

- Fibrous tissue
- Calcification
- Gas

Acoustic enhancement

- Fluid-filled and cystic structures

Ultrasound techniques

A-mode

(standing for amplitude) gives a 1D trace that depicts the depth of an interface and the strength of the reflected signal.

B-mode

(standing for brightness) is the most common technique, and gives 2D slices that map the different magnitudes of echo in greyscale.

M-mode

(standing for movement) displays a trace of the movement of structures within the line of the sound beam. It is used to effect in imaging eg heart valves (p98).

Duplex ultrasonography (flow and morphology)

By combining the Doppler effect (the shift in wavelength caused by movement of a source or reflecting surface) with B-mode ultrasound technology it is possible to determine flow characteristics of the circulation (**fig 2**). This is extremely useful in arterial and venous studies, and echocardiography.

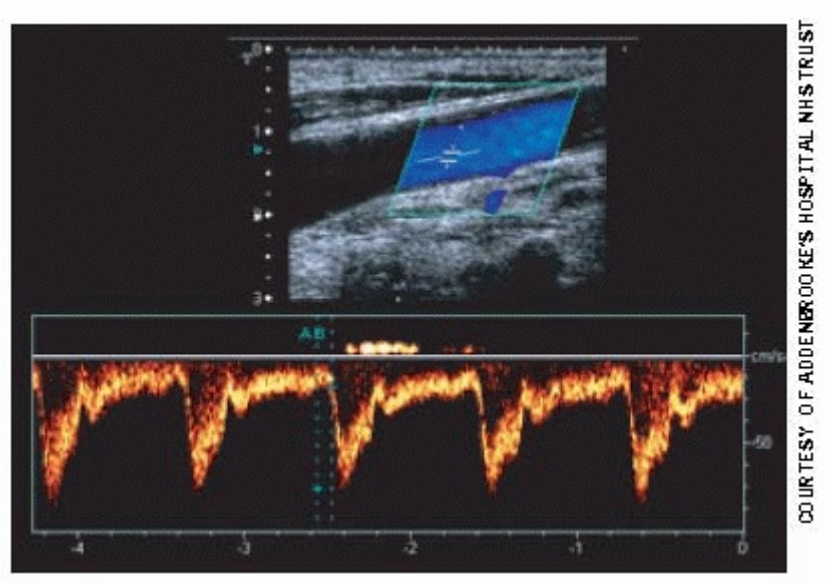


Fig 2. A normal Duplex US of the right common carotid artery. It can measure the flow rate in the artery (here 76cm/s). The Doppler trace (orange) is displayed below the main image.

Advantages of US

Portable; quick; cheap; nonionising; real-time; can be used with intervention; can enter organs, eg anorectum, vagina, GI tract.

Disadvantages of US

Inter-performer variance; poor quality in obese subjects; interference from bone, bowel gas, calculi and other superimposed structures.

Endoscopic US

can be used to image structures from within the body. It is most commonly done as transoesophageal echocardiography (TOE, p98), but is also used to assess the depth of invasion of carcinomas eg pancreas, stomach.[7]

Structures commonly imaged with ultrasound

The following structures should always be considered for imaging with ultrasound, given that it is non-invasive, non-ionising investigation:

Abdominal	Pelvic		Vascular	Other
Gall bladder	Uterus	Fetus	Carotid arteries[1]	Pleural effusion

Liver	Ovaries	Bladder	Abdominal aorta	Thyroid
Spleen	Salpinges		Portal system	Lumps & bumps
Appendix	Cervix		Peripheral arteries	Testes
Pancreas	Adnexae		Leg veins	Fistulae
Ascites	Appendix!			Musculoskeletal

[1] Indicated in: those with full recovery from stroke in whom endarterectomy is considered; suspected dissection; young patients with ischaemic stroke, and all patients with TIA.

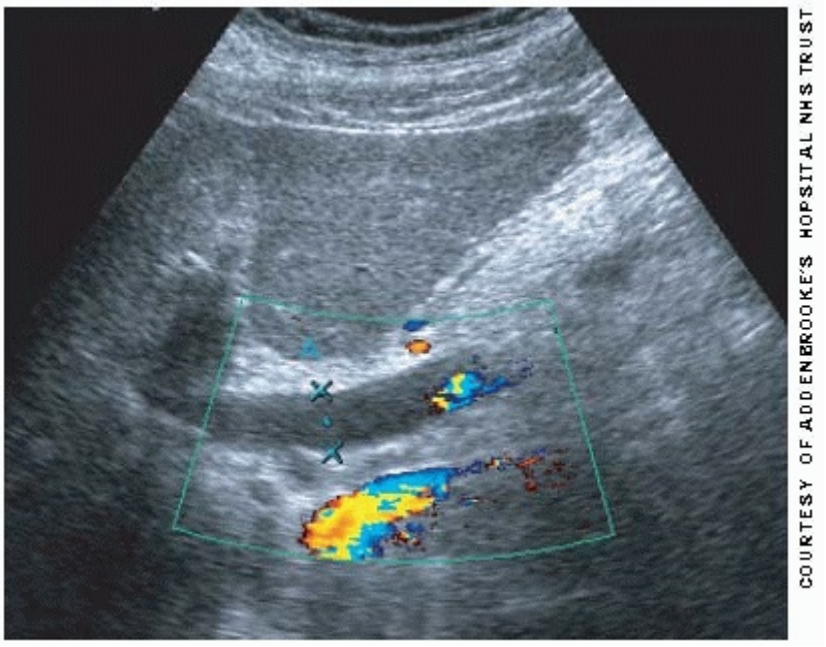


Fig 3. Ultrasound of the liver showing the common bile duct to be dilated proximal to a presumed obstruction (a width >6mm if <60yrs old is abnormal). Duplex mode shows flow in the portal vein that lies (along with the hepatic artery) posterior to the duct in the lesser omentum's free edge. The next questions are 'what is causing the obstruction?' and 'where can I get that information?'.

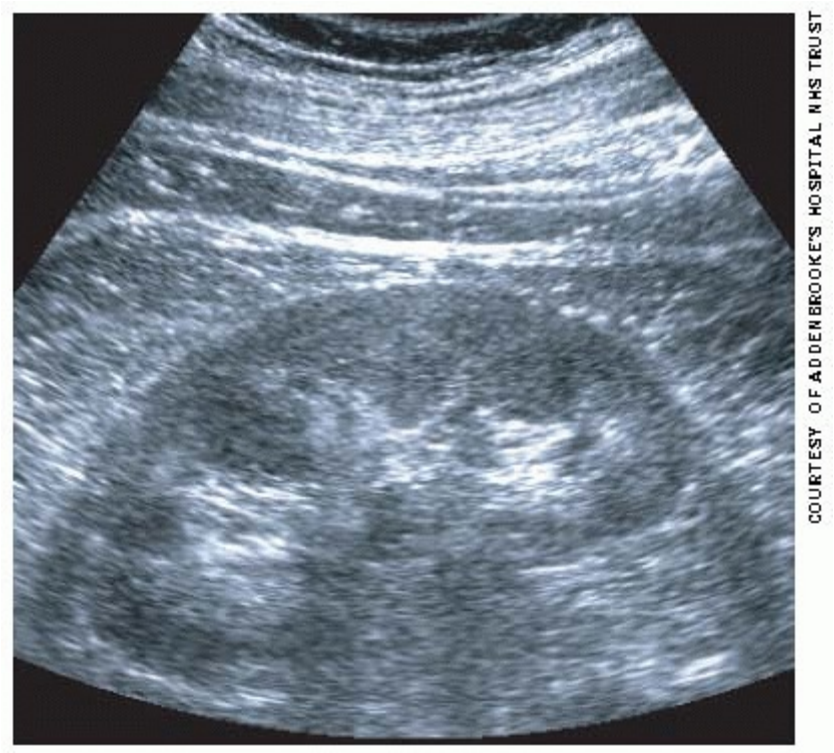


Fig 4. Ultrasound of the kidney. On first inspection the image may appear normal but there is increased echogenicity predominantly within the medulla and some posterior acoustic shadowing associated with this. This is nephrocalcinosis of which there are many causes.

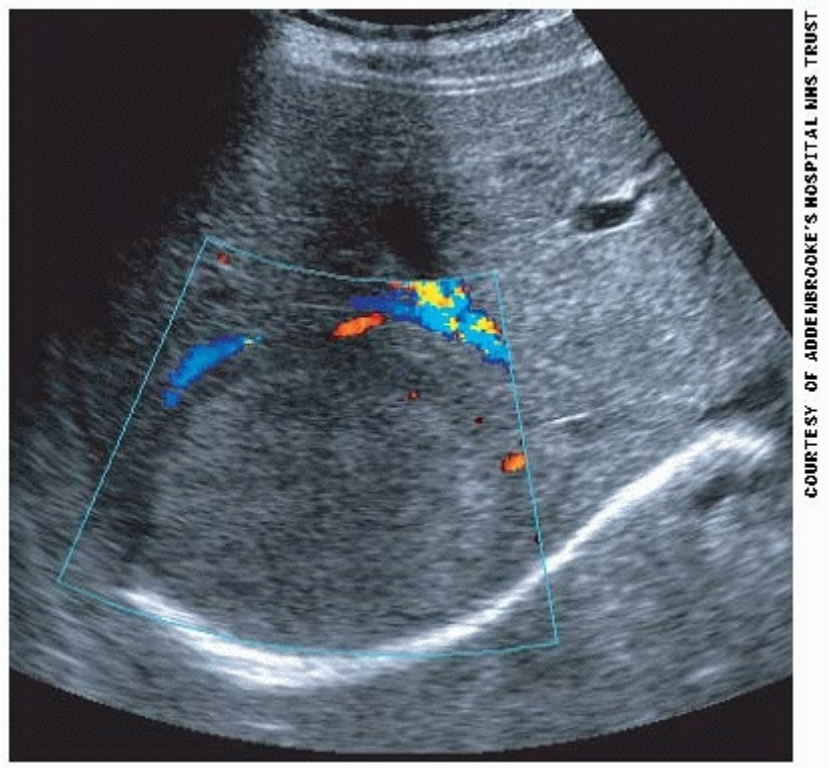


Fig 5. Ultrasound of the liver showing a solitary round mass in the posterior aspect of the right lobe of the liver. This was a primary liver tumour. Duplex imaging shows a leash of vessels surrounding the lesion but not within it, suggesting it is not a highly vascular tumour.

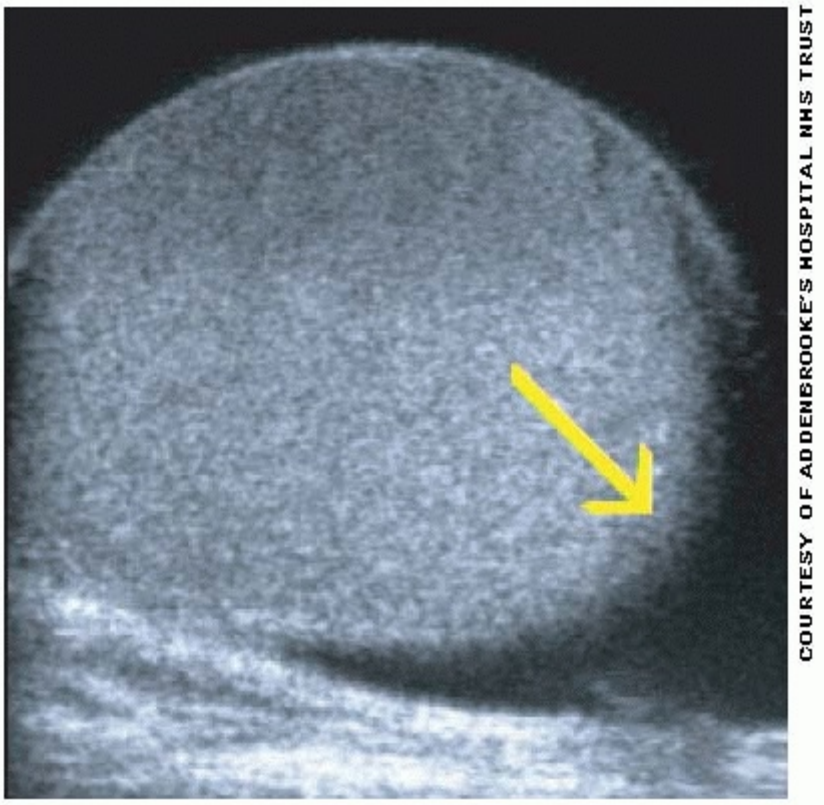


Fig 6. Ultrasound of the testis showing a hydrocele (arrow). On of the great advantages of ultrasound that it does not use radiation, and so is ideal for imaging radiosensitive tissues such as the testis, thyroid, and fetus.

Nuclear medicine

Nuclear medicine is a growing field with both diagnostic and therapeutic applications. The latter is developing rapidly, but here we are mostly concerned with its diagnostic capabilities. The use of molecules labelled with a radioisotope means that there is exposure to ionising radiation, though doses are usually less than those from a CT abdomen (see TABLE, p711).

Positron emission tomography (PET)

maps glucose metabolism in the body. F-18-fluorodeoxyglucose (FDG), a short half-life glucose analogue (λ=110min), is taken up by metabolically active tissues. It decays rapidly to produce a positron that, after travelling a few mm through tissue, annihilates with an electron to produce a pair of high energy photons (γ rays), which are subsequently detected. Neoplasms have a high uptake of FDG, but so do benign inflammatory and granulomatous lesions —if one is considering false +ves, consider sarcoidosis and TB. Non-pathological high uptake of FDG in brain, liver, kidney, bladder, larynx and lymphoid tissue of pharynx can interfere with interpretation leading to falsely -ve scans. Resolution of lesions can be down to 4mm. 3D analysis greatly increases sensitivity compared to 2D. *Cancer:* PET has a role when combined with MRI and CT. It is used in a colorectal cancer for evaluation of local recurrence, treatment of liver metastases and in looking for extrahepatic metastases when considering hepatic resection. Also indicated for staging of: non-small cell lung cancer; lymphoma; melanoma; oesophageal cancer. *Dementia:* PET of no proven value, but is used in research.

Radionuclide imaging in cardiology: p726.

Ventilation ([V with dot above]) scintigraphy

(**fig 1**) uses technetium (Tc) or xenon-133 (^{133}Xe). Requires a CXR within last 24h for comparison. You can sometimes discern it from a perfusion image by the presence of radioisotope in the upper airway.

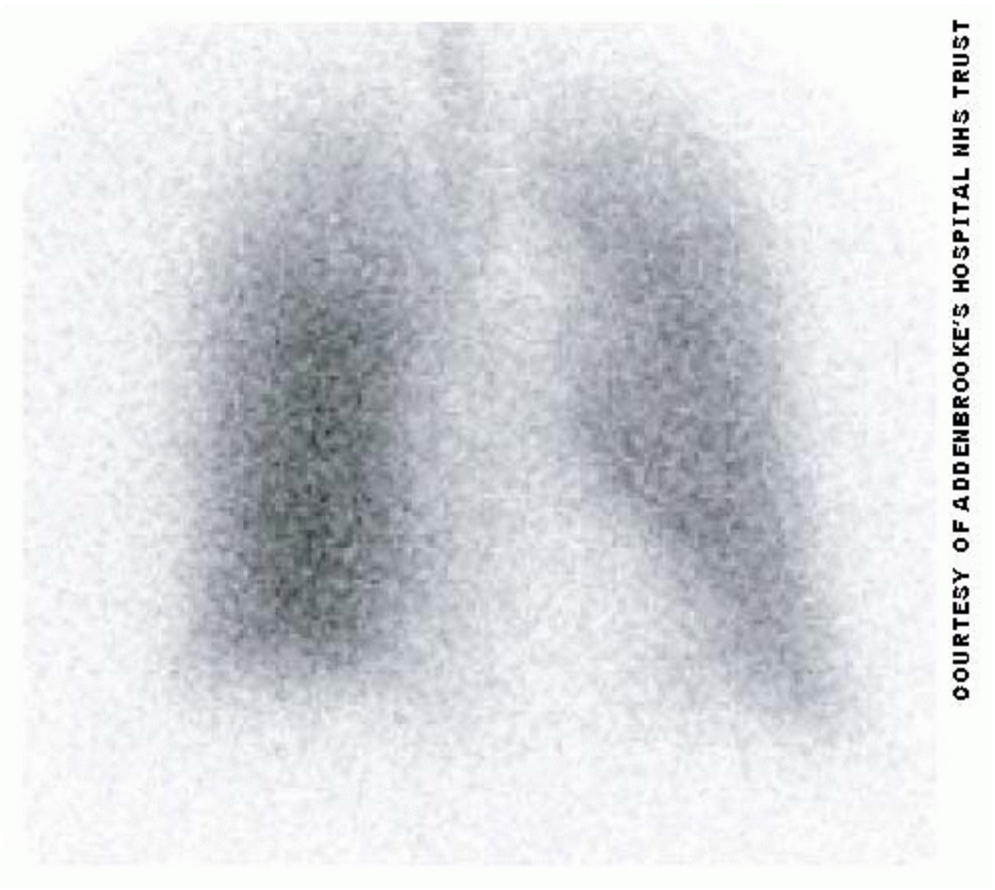


Fig 1. Ventilation scintigram.

Perfusion ([Q with dot above]) scintigraphy

(**fig 2**) uses 99mtechnetium-labelled (^{99m}Tc) macroaggregates that block a small proportions of lung capillaries and thus lodge in the pulmonary circulation. Reported as high, intermediate, low probability, or normal according to findings. A normal perfusion scintigram excludes PE, hence its high sensitivity.

Bone scintigraphy

Important for primary and secondary bone tumours (often -ve in myeloma) and bone disorders such as osteomalacia, stress fractures, avascular necrosis, and the arthropathies. Uses bisphosphonates labelled with ^{99m}Tc. More sensitive than X-ray for finding metastases because some lesions may not appear on X-ray if less than 50% of the bone matrix has been destroyed.

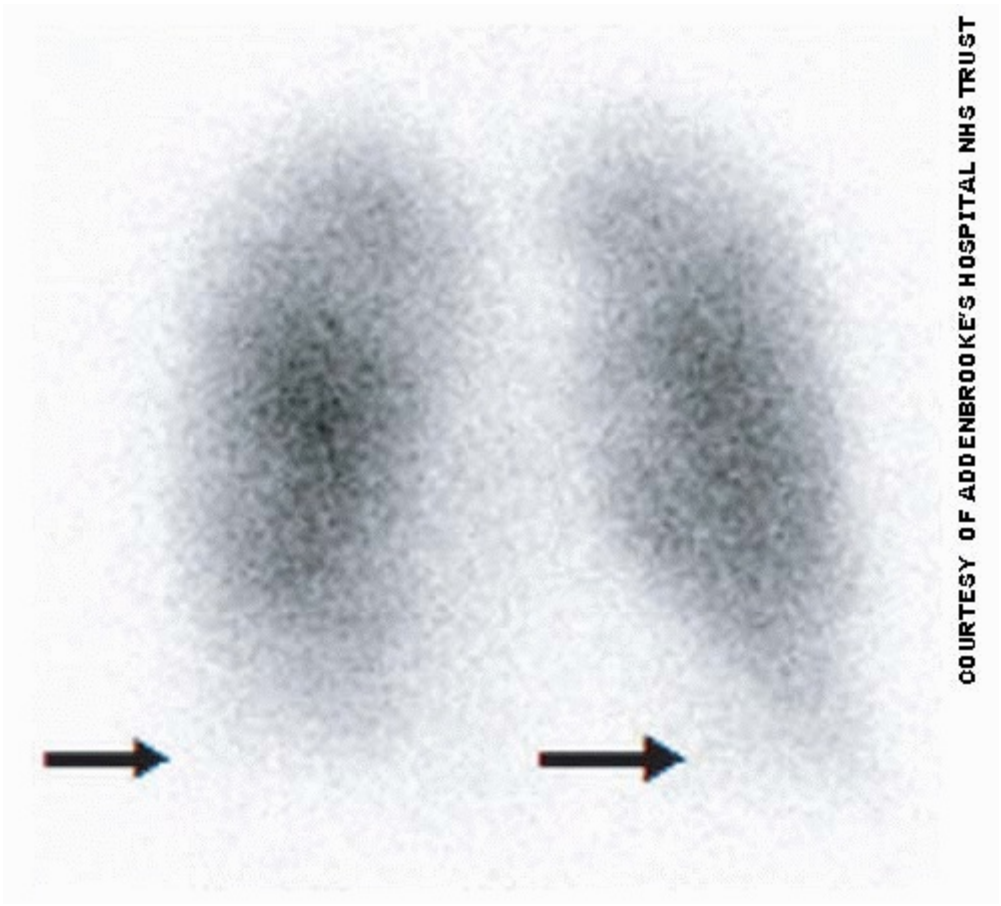


Fig 2. Perfusion scintigram showing mismatches with **fig 1**.

Thyroid disease

TcO_4 is commonly used. Studies can differentiate between Graves' disease, toxic multinodular goitre, and subacute thyroiditis (**fig 3** and also **fig 1**, p623). Excellent for identifying ectopic tissue and functioning nodules, and also indicated for detecting residual or recurrent thyroid tissue after surgery. 10% of cold (non-functioning) nodules are malignant, whereas hot nodules are normally toxic adenomas. Iodine-131 (^{131}I) is used for therapeutic intervention in thyrotoxicosis.

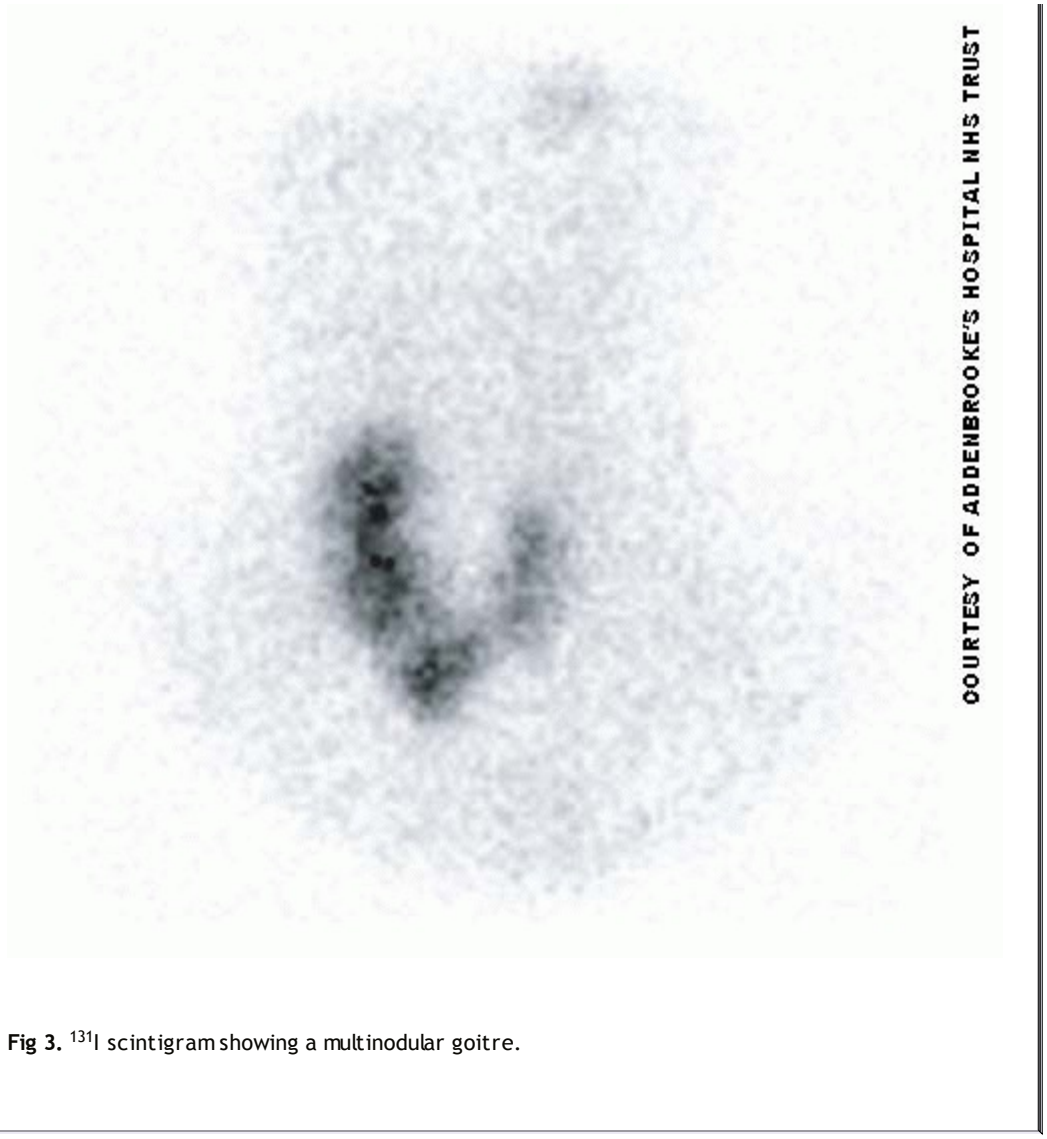


Fig 3. ^{131}I scintigram showing a multinodular goitre.

Phaeochromocytoma

Iodine-123 (^{123}I) metaiodobenzylguanide (MIBG) is taken-up by sympathetic tissues, and indicates functioning, ectopic, and metastatic adrenal medullary (and other neural crest) tumours. ^{123}I-MIBG is also used for treatment.

Hyperparathyroidism

^{99m}Tc-methoxyisobutyl isonitrile (MIBI) scans can detect parathyroid adenomas (**fig 4**).

Adrenal cortical disease

Radionuclide imaging is used to differentiate adenoma from diffuse hyperplasia.

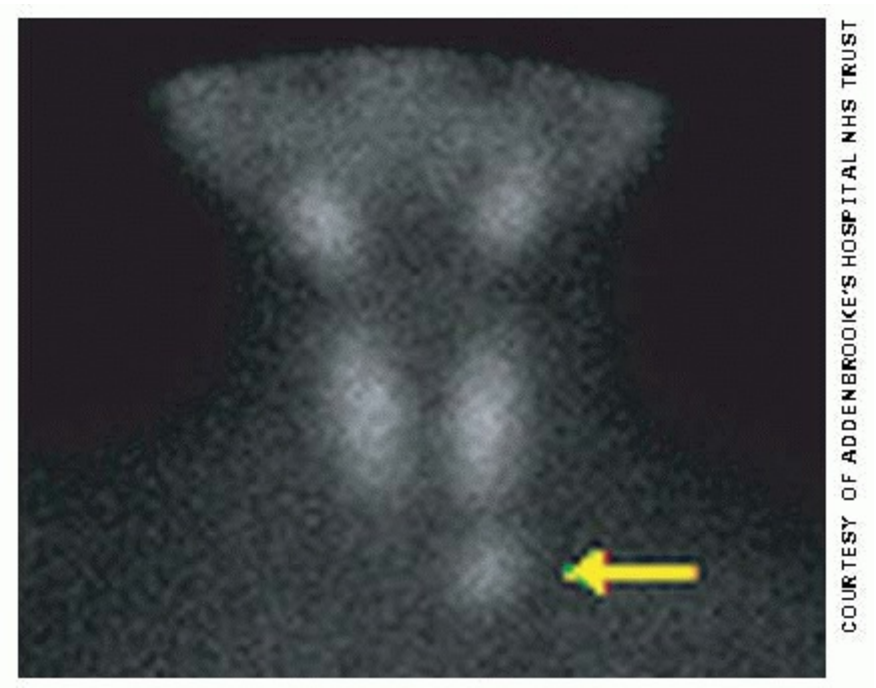


Fig 4. MIBI study showing a parathyroid adenoma.

GI haemorrhage

Scans performed after endoscopy and CT for ***acute bleeding***. Uses a red cell-labelled technique. More sensitive than angiography and useful in cases of intermittent GI bleeding. In ***chronic bleeding***, done when all other investigations are negative, using red cell (^{99m}Tc-pertechnetate) techniques if ectopic gastric mucosa or a Meckel's diverticulum is suspected.

Crohn's disease

White cell-labelled technique (indium-111) can pinpoint areas of small bowel activity and extent of disease in conjunction with barium studies. Also indicated to assess acute flare-up of colonic disease for Crohn's and UC.

Renal studies

Chromium-51 (^{51}Cr) EDTA or DTPA (^{99m}Tc, p182) is used to assess GFR. ^{99m}Tc-mercaptoacetyltriglycine (MAG3) technique assesses relative renal function and renal transit time (eg in obstructive nephropathy or renovascular disease). Dynamic renal mapping gives quantifiable information about renal function and the degree of obstruction which is not available from other modalities. ^{99m}Tc-dimercaptosuccinic acid (DMSA) scanning (**fig 5**) is the gold standard for evaluation of renal scarring that occurs eg in reflux nephropathy.

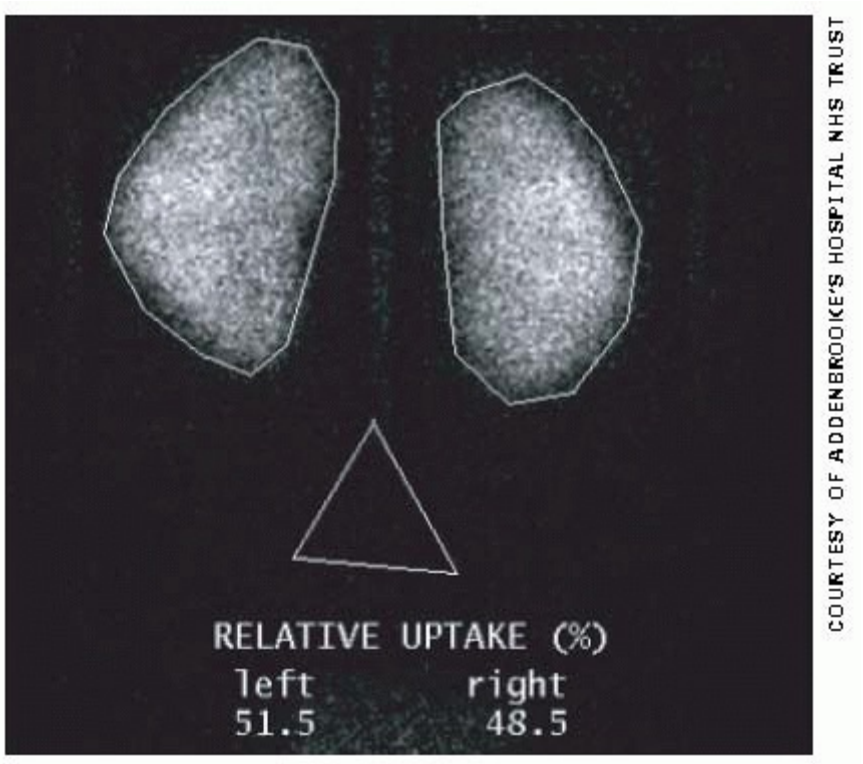


Fig 5. DMSA showing relative renal function of each kidney.

[V with dot above]/[Q with dot above] scintigram or CTPA?[1]

This question continues to leave us without a definite answer. Standard investigation has been CXR then [V with dot above]/[Q with dot above] scintigraphy: PPV of 96% if high probability, and reliable to exclude PE if 'normal'. CTPA (**fig 6**) is sensitive and specific (reported >90%) if the embolus lies in the pulmonary arteries, but its bane has been the subsegmental PE (making CTPA only 60% sensitive and 70% specific if included in total lung analysis). New multidetector CT (MDCT) systems have up to 64 detectors, giving thinner slices (0.6-1.25mm) and a faster scanning time that reduces respiratory motion artefacts and gives better subsegmental imaging. Faster data acquisition also requires less IV contrast medium, beneficial for patients with renal and cardiac impairment. Preliminary results from the PIOPED II trial (an ongoing multicentre prospective study) gave CTPA alone a sensitivity and specificity of 83% and 96% respectively.[8] The completion of the trial is awaited, but first-line investigation may be recommended as CTPA and venous phase CT of the leg veins and pelvis.[9] CTPA's advantages are that it is more readily available and that it can demonstrate other lesions.

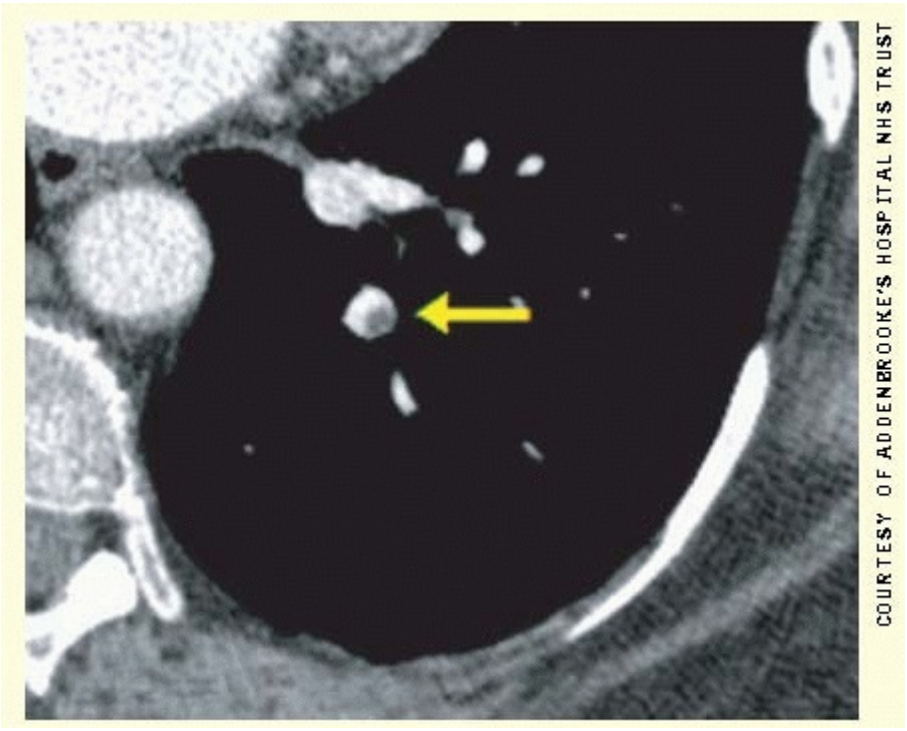


Fig 6. CT pulmonary angiogram (CTPA) showing a filling defect consistent with an embolus within a branch of a left pulmonary artery.

Radionuclide imaging in cardiology

Myocardial perfusion imaging

A non-invasive method of assessing regional myocardial blood flow and the cellular integrity of myocytes. The technique uses radionuclide tracers which cross the myocyte membrane and are trapped intracellularly. Thallium-201 (^{201}Th), a K^+ analogue, is distributed via regional myocardial blood flow and requires cellular integrity for uptake. Newer technetium-99 (^{99}Tc) based agents are similar to ^{201}Th but have improved imaging characteristics, and can be used to assess myocardial perfusion and LV performance in the same study. Myocardial territories supplied by unobstructed coronary vessels have normal perfusion whereas regions supplied by stenosed coronary vessels have poorer relative perfusion, a difference that is accentuated by exercise. For this reason, exercise tests are used in conjunction with radionuclide imaging to identify areas at risk of ischaemia/infarction. Exercise scans are compared with resting views: ***reperfusion*** (ischaemia, see BOX, 'Cardiac perfusion scintigraphy') or ***fixed defects*** (infarct) can be seen and the coronary artery involved reliably predicted. Drugs (eg ***adenosine***, ***dobutamine*** and ***dipyridamole***) can also be used to induce perfusion differences between normal and underperfused tissues.

Myocardial perfusion imaging adds information in patients presenting with acute MI (to determine the amount of myocardium salvaged by thrombolysis) and in diagnosing acute chest pain in those without classical ECG changes (to define the presence of significant perfusion defects).

Positron emission tomography (PET)

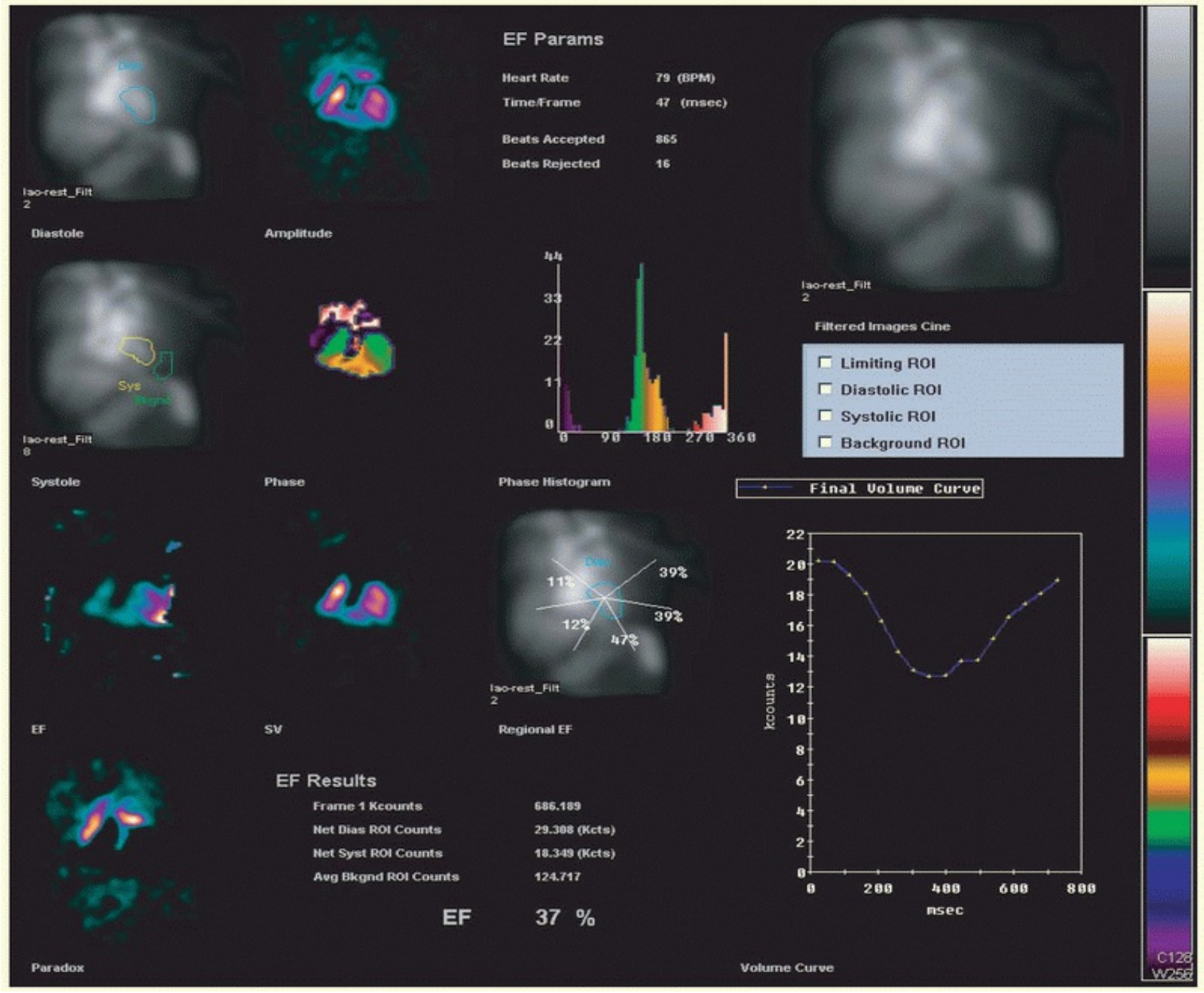
Severely underperfused tissues, such as those supplied by a critically stenotic coronary artery, switch from fatty acid metabolism to glycolytic metabolism. Such altered cellular biochemistry may be imaged by PET using 18F-labelled fluorodeoxyglucose (FDG), which identifies the glycolytically active tissue that is viable. This phenomenon, severe resting ischaemia, occurs in up to 40% of fixed defects seen on ^{201}Th scans.

Cardiac CT and MRI

CT Recent improvements in CT technology have made routine cardiac imaging possible. 16 or 64 slice CT, because of its speed and resolution, can image coronary arteries and exclude significant disease with a NPV of 97-99%. It can also visualise CABG patency, provide coronary artery Ca^{2+} scoring (a risk factor for coronary artery disease), demonstrate cardiac anatomy including congenital anomalies, and estimate ventricular function. With undiagnosed significant chest pain, CT will increasingly be used for the 'triple rule out', an enhanced study of the chest to simultaneously exclude coronary artery occlusion, pulmonary emboli, and aortic dissection. This comes at the cost of radiation exposure.

MRI has less resolution than CT but its lack of ionising radiation make it a good choice for congenital heart disease in children and adults. MRI is superior to CT for functional assessment although resolution limits its imaging of coronary artery disease. Flow velocities can be measured and because the flow is proportional to the pressure differences, degrees of stenosis and regurgitation across heart valves can be calculated. Myocardial infarction, perfusion and viability can also be imaged with the use of IV gadolinium contrast medium. Both CT and MR use ECG-gating to acquire the imaging data and relate it to the position in the cardiac cycle, thus minimising the movement artefact. This only works when the patient is in sinus rhythm.

Cardiac ^{99m}technetium MUGA scintigram

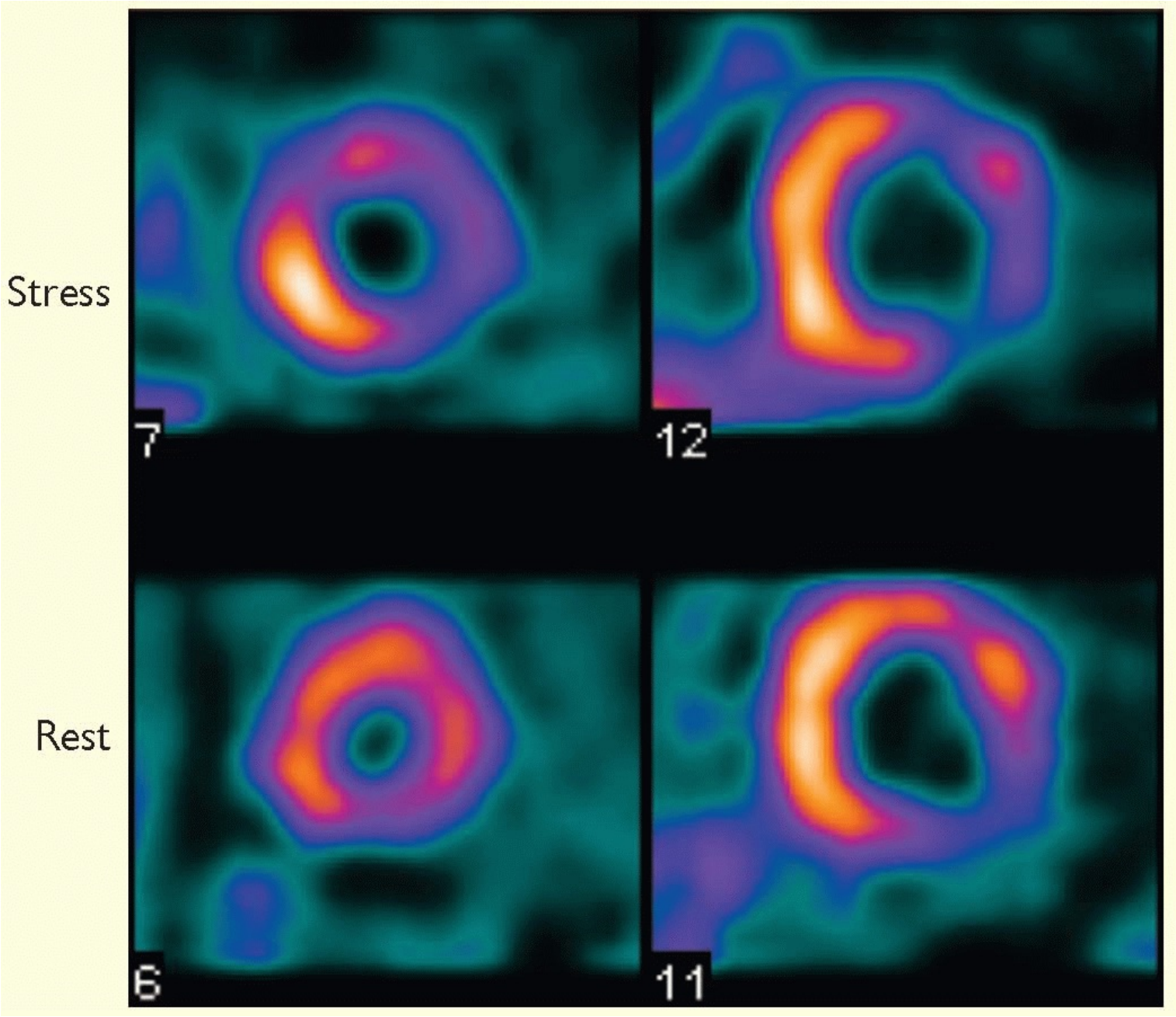


Cardiac MUGA scintigram 'Courtesy of Addenbrooke's Hospital NHS Trust.

Multiple gated acquisition (MUGA)

scanning is a non-invasive method of measuring left ventricle ejection fraction (EF, 37% in the study shown above). After injection of ^{99}Tc, a dynamic image of the left ventricle is obtained over several hundred heartbeats by gamma camera. A widespread use for MUGA scanning has been in the pre-operative assessment of patients for vascular surgery. However one review suggested it was an accurate predictor of long-term prognosis but not of operative risk. Stress echocardiography and perfusion scintigraphy may have more clinical relevance in this role.

Cardiac perfusion scintigraphy



^{99}Tc perfusion study showing perfusion defect in the left ventricle anterior & lateral walls at stress which is reversible (difference between stress and rest images).

Radiological GI procedures and imaging

Abdominal ultrasound (US)

(**fig 1**) is used for the investigation of abdominal pain, abnormal LFT, jaundice, hepatomegaly and abdominal masses. Patients should be nil by mouth for 4h before the scan in order to allow visualization of the gall bladder (**fig 1**, p722). Pelvic ultrasound requires the bladder to be full. Ultrasound may also be used to guide diagnostic biopsy or therapeutic aspiration.

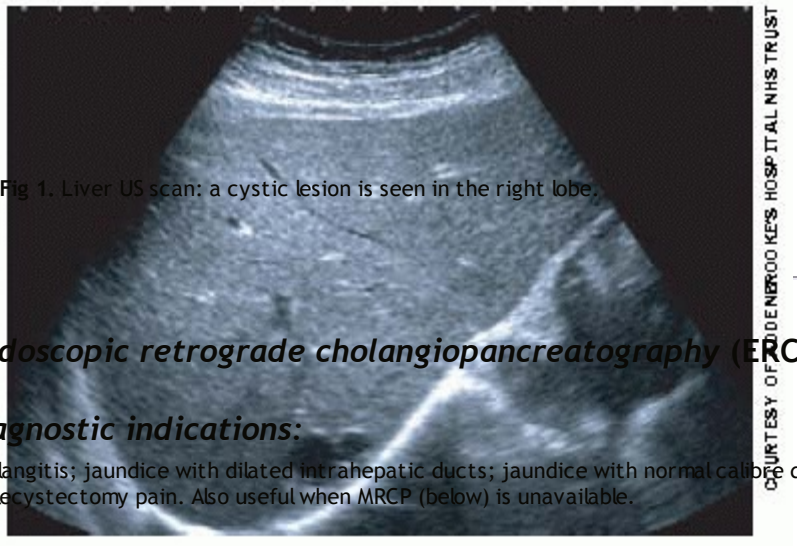


Fig 1. Liver US scan: a cystic lesion is seen in the right lobe.

Endoscopic retrograde cholangiopancreatography (ERCP, fig 2)

Diagnostic indications:

Cholangitis; jaundice with dilated intrahepatic ducts; jaundice with normal calibre ducts and a non-diagnostic liver biopsy; recurrent pancreatitis; post-cholecystectomy pain. Also useful when MRCP (below) is unavailable.

Therapeutic indications:

Sphincterotomy for common bile duct stones; stenting of malignant strictures.

Pre-procedure:

Check LFT, clotting and platelet count. Prescribe antibiotic prophylaxis (eg ***ciprofloxacin*** 750mg PO 2h before), analgesia (eg ***morphine*** 5mg and ***metoclopramide*** 10mg IV 1h before) and sedation (eg ***midazolam*** 2.5-10mg IV).

Procedure:

A catheter is advanced from a side-viewing duodenoscope via the ampulla into the common bile duct. Contrast medium is injected and x-rays taken to show lesions in the biliary tree and pancreatic ducts.

Complications:

Pancreatitis; bleeding; cholangitis; perforation. Mortality <0.2% overall; 0.4% if performing stone removal.

Fig 2. The ERCP shows dilated intra- and extrahepatic ducts. The multiple filling defects relate to calculi within and obstructing the ducts. Note the cholecystectomy clips. (see color image)

Contrast swallows

(**fig 3**) can help in dysphagia (p232). Real-time fluoroscopic imaging studies are used to assess swallowing function.

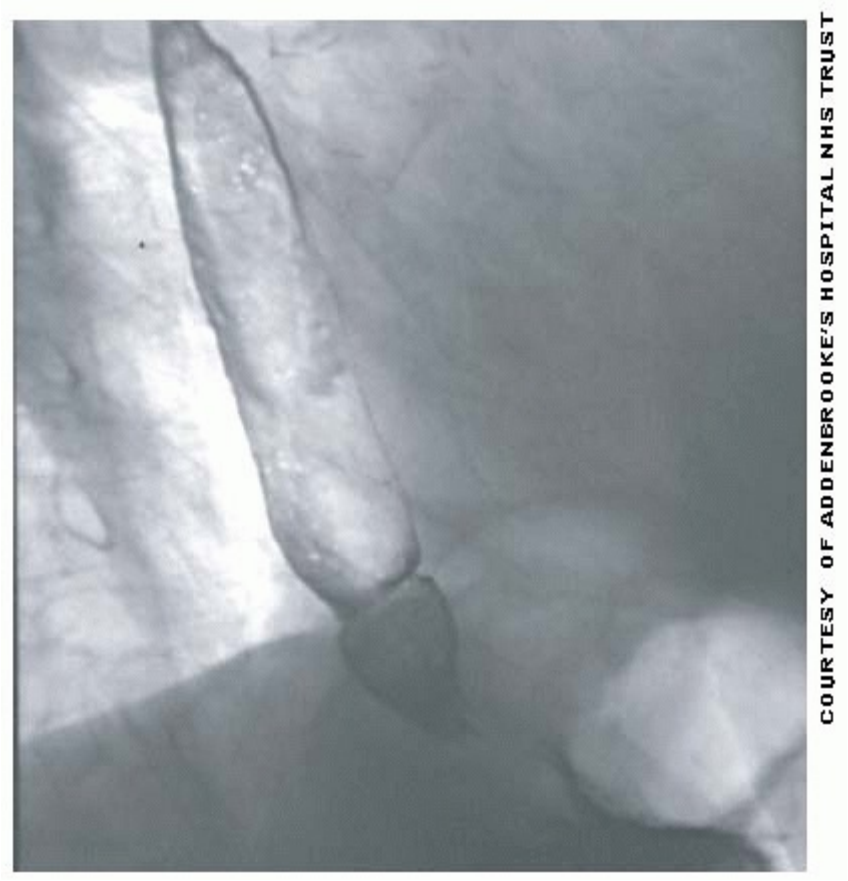


Fig 3. Double contrast swallow showing a Schatski or B ring. It is a benign circumferential stricture pathognomonic of a hiatus hernia, as it marks the junction between squamous & columnar epithelium.

Small bowel follow through

(**fig 4**) After bowel prep, barium is ingested and images taken every ~½h until barium reaches the caecum. Spot images are taken of areas of interest, eg the terminal ileum.

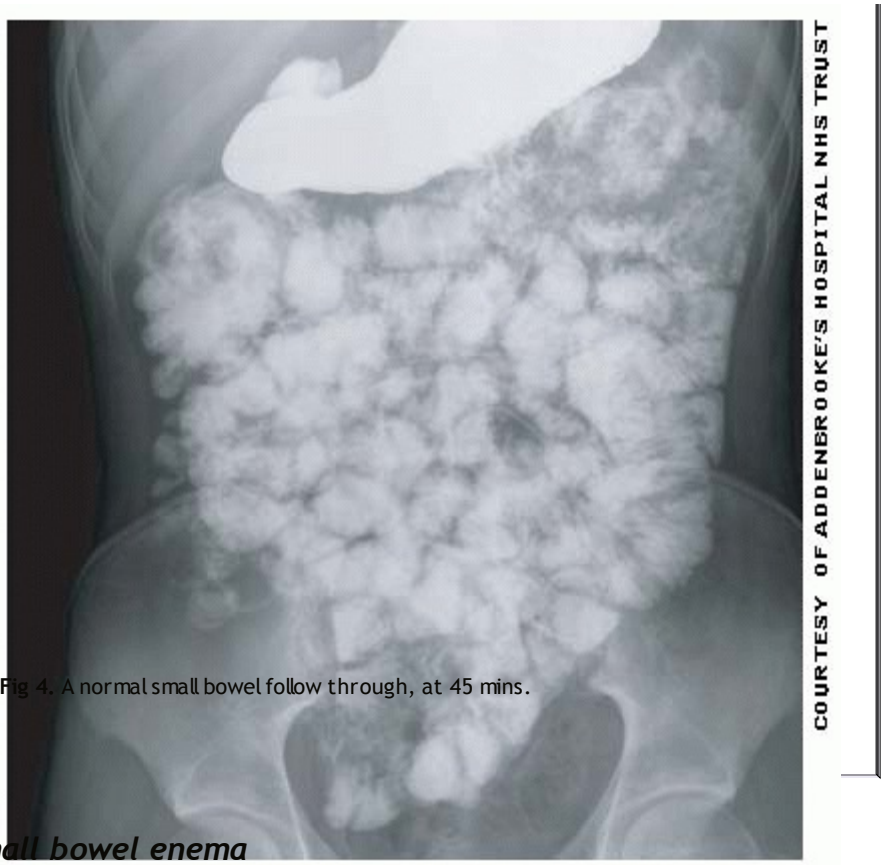


Fig 4. A normal small bowel follow through, at 45 mins.

Small bowel enema

After bowel prep, the duodenum is intubated and barium is introduced. Although technically more demanding than barium follow-through, it gives better mucosal definition.

Barium enema

Always do a PR first ± rigid sigmoidoscopy and biopsy. Preparation is as in colonoscopy (p248). For a double contrast barium enema (**fig 5**), barium and air or CO_2 are introduced per rectum. Iodinated contrast medium may be used instead of barium in suspected colonic obstruction. The enema may show diverticular disease or cancers (eg an irregular 'apple-core' narrowing of the lumen). In Crohn's disease, look for 'cobblestoning', 'rose thorn' ulcers, and colonic strictures with rectal sparing. *Disadvantages:* Significant radiation dose; no biopsy possible.

Computed tomography (CT)

(**figs 6** & **7**) is indicated if ultrasound is difficult or nondiagnostic. It allows better visualization of the GI tract retroperitoneal structures. Oral or IV contrast medium enhances definition (p734). The big disadvantage is the high radiation dose. CT colonography ('virtual colonoscopy') is being used increasingly: it gives excellent mucosal definition but interpretation takes time and has inter-observer variability.[10] For polyps >9mm specificity is 97% but sensitivity is 85% and drops to 48% if <6mm.[11]

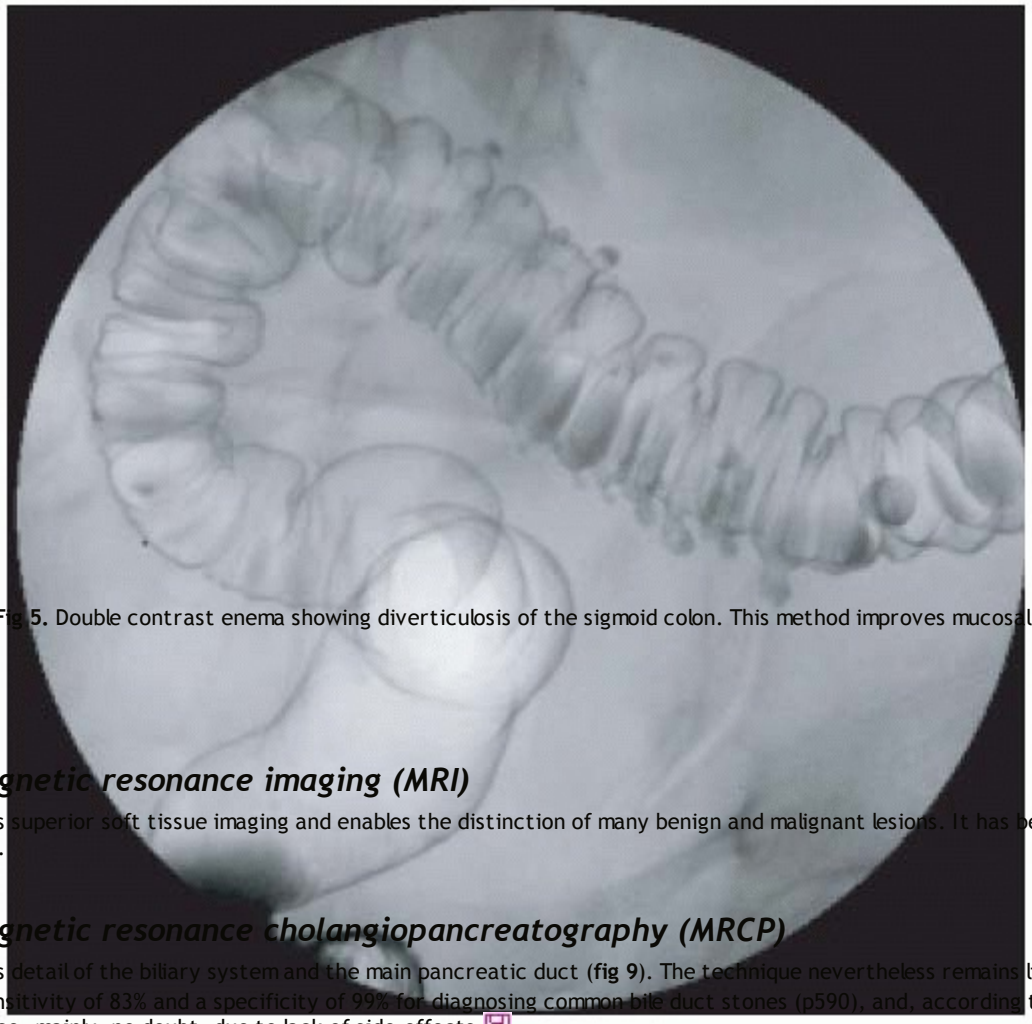


Fig 5. Double contrast enema showing diverticulosis of the sigmoid colon. This method improves mucosal definition.

Magnetic resonance imaging (MRI)

gives superior soft tissue imaging and enables the distinction of many benign and malignant lesions. It has become increasingly popular for imaging of the liver.

Magnetic resonance cholangiopancreatography (MRCP)

gives detail of the biliary system and the main pancreatic duct (**fig 9**). The technique nevertheless remains limited by poor spatial resolution.[12] MRCP had a sensitivity of 83% and a specificity of 99% for diagnosing common bile duct stones (p590), and, according to some authorities, is the investigation of choice—mainly, no doubt, due to lack of side-effects.[13]

Wireless capsule endoscopy

(See p248).

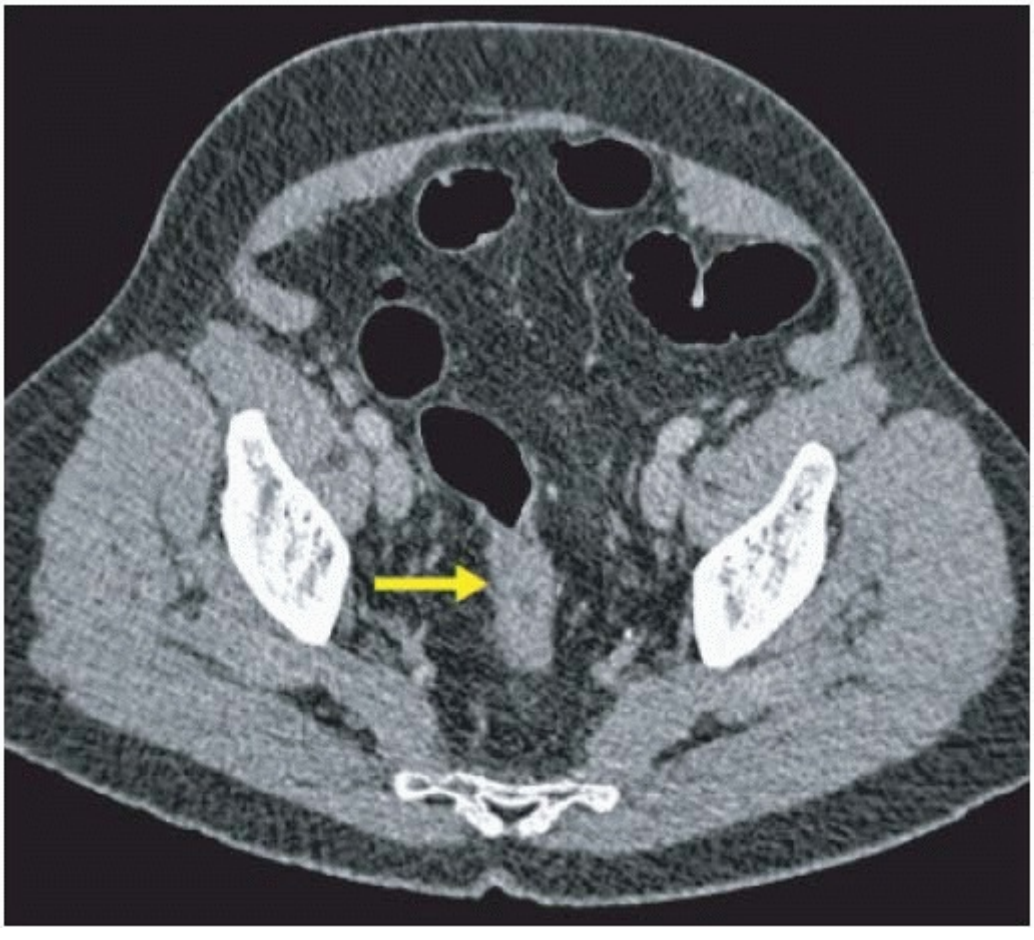


Fig 6. Axial CT colonogram: rectal thickening & stenosis (arrow) consistent with a rectal tumour.

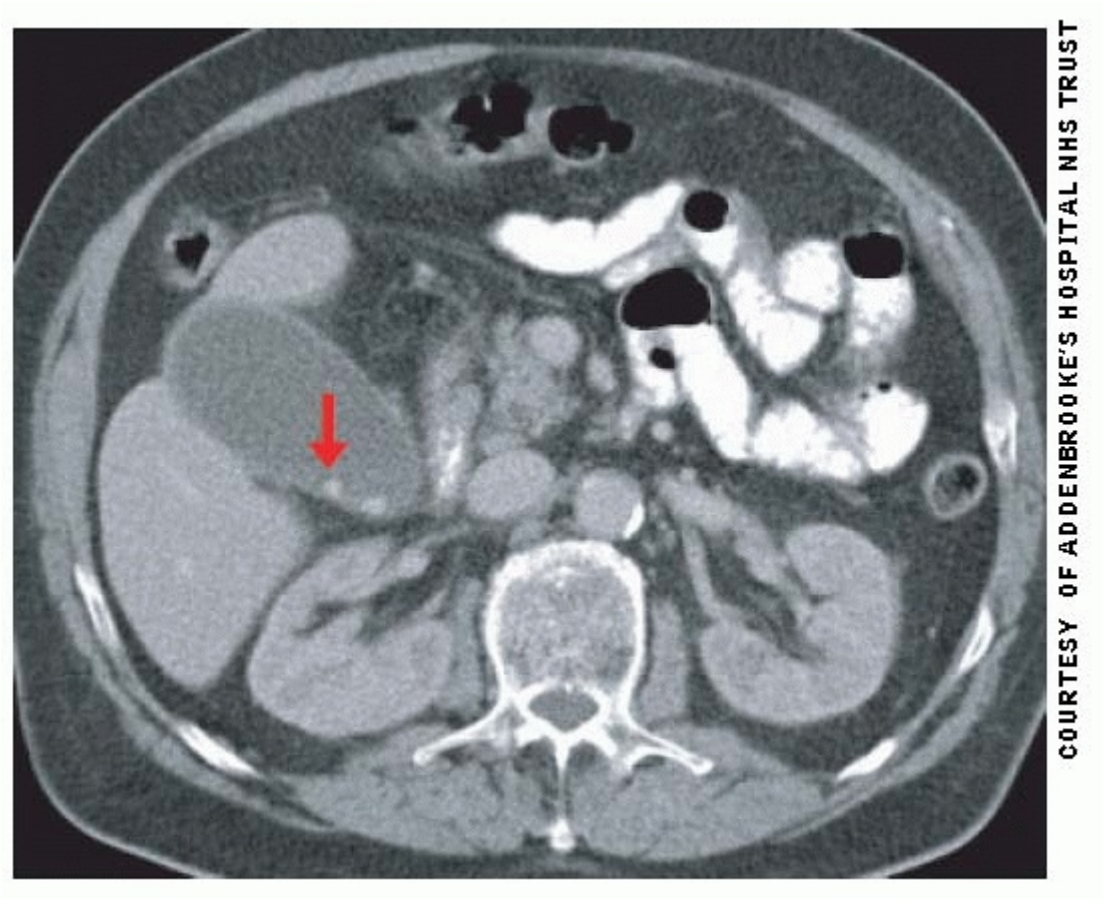
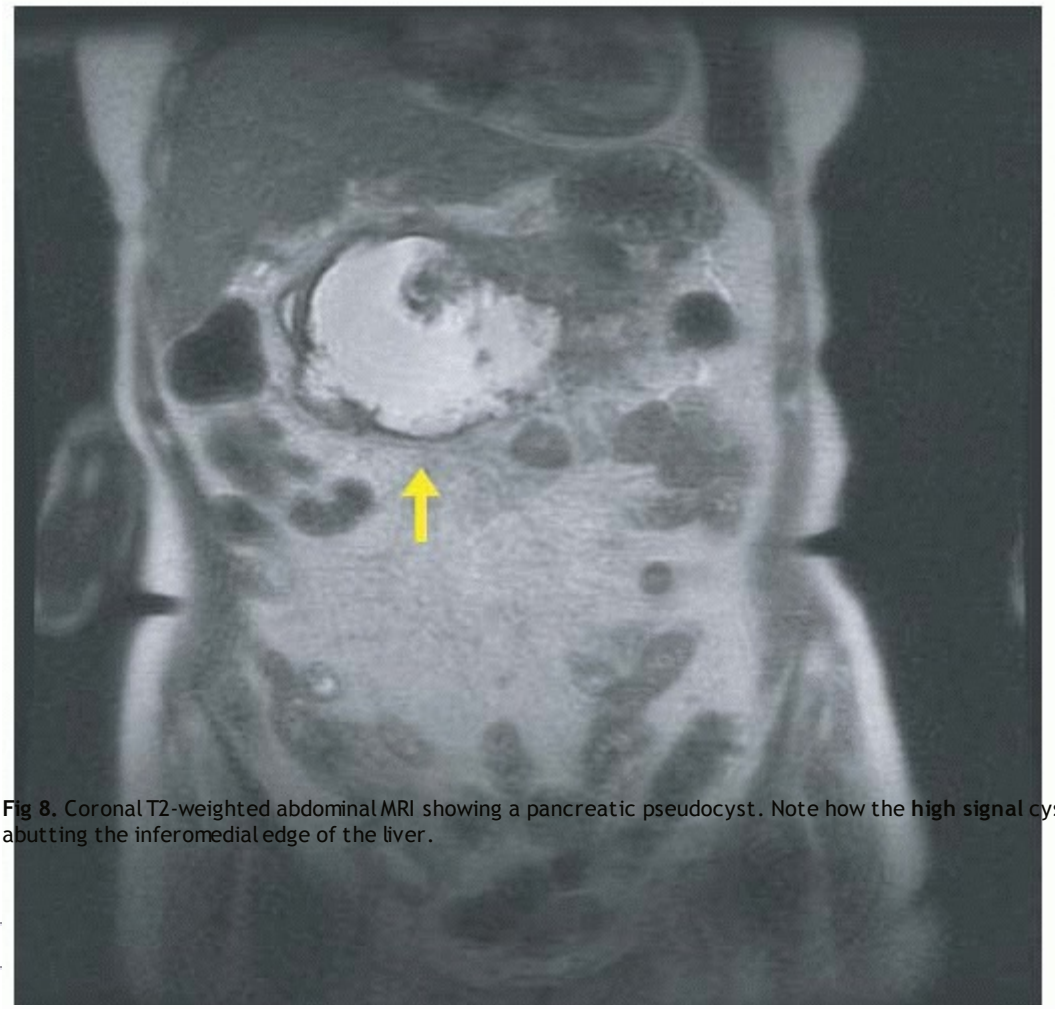
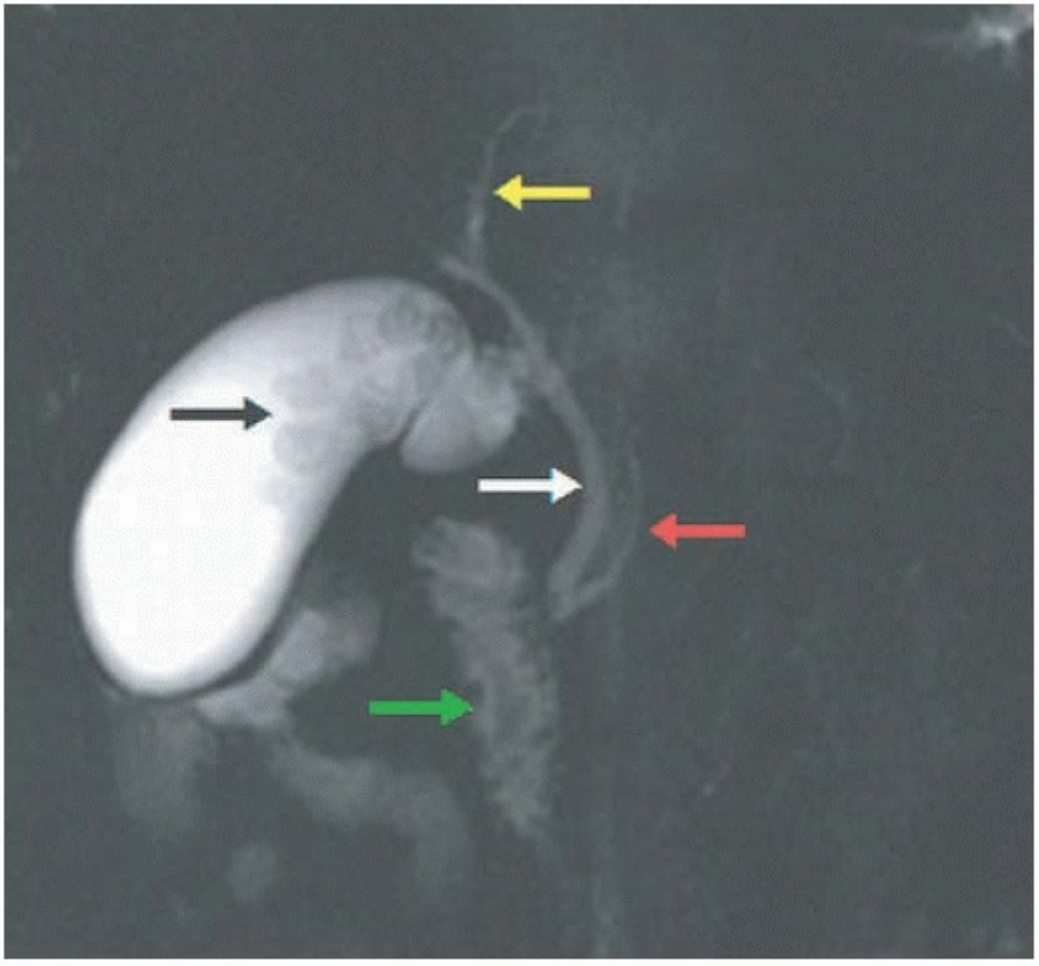


Fig 7. Axial CT of the abdomen post IV and oral contrast medium. The gallbladder contains gallstones (arrow). Oral contrast medium is seen within the small bowel but not the large bowel. Lateral to the vertebral column are the psoas muscles and the kidneys. Anterior to the vertebrae are the IVC and the aorta. Anterior to the IVC is the uncinate process of the pancreas.



COURTESY OF DR. STEPHEN GOLDING

Fig 8. Coronal T2-weighted abdominal MRI showing a pancreatic pseudocyst. Note how the **high signal** cyst occupies the lesser sac (arrow), abutting the inferomedial edge of the liver.



COURTESY OF ADDENBROOKE'S HOSPITAL NHS TRUST

Fig 9. Normal MRCP of the biliary system showing: left hepatic duct (yellow arrow); multiple gallstones in the gallbladder (black arrow); common bile duct (white arrow); pancreatic duct (red arrow); duodenum (green arrow). (see color image)

Urinary tract imaging

AXR

Look at kidneys, paths of the ureters, and bladder. Note any abnormal calcification—related to which of these 3 processes?

1 Calculi; only 90% are seen on plain films.

2 Dystrophic calcification, eg in carcinomas or TB.

3 Nephrocalcinosis (parenchymal, rare, **fig 4**, p723).

Ultrasound

is best initial image, showing:

- Renal size—**small** in chronic renal failure, **large** in renal masses, benign cysts,[1] hypertrophy if other kidney missing, polycystic kidney disease (**fig 1**), and rarities such as amyloidosis (p354).[14]
- Hydronephrosis, which may indicate ureteric obstruction or reflux (**fig 1**, p683).
- Perinephric collections (trauma, post-renal biopsy).
- Transplanted kidneys (collections, obstruction, perfusion—**fig 1**, p625).
- Bladder residual volume: useful in assessment of the need to catheterise.
- Prostate: transrectal ultrasound enables US-guided biopsy of focal lesions. **NB:** Prostate size does not correlate with symptoms.

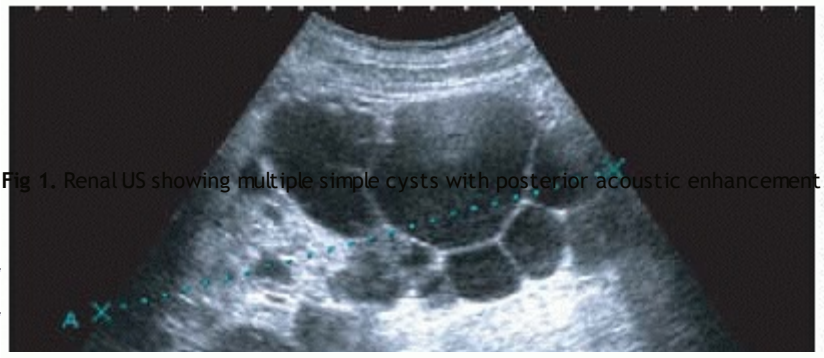


Fig 1. Renal US showing multiple simple cysts with posterior acoustic enhancement.

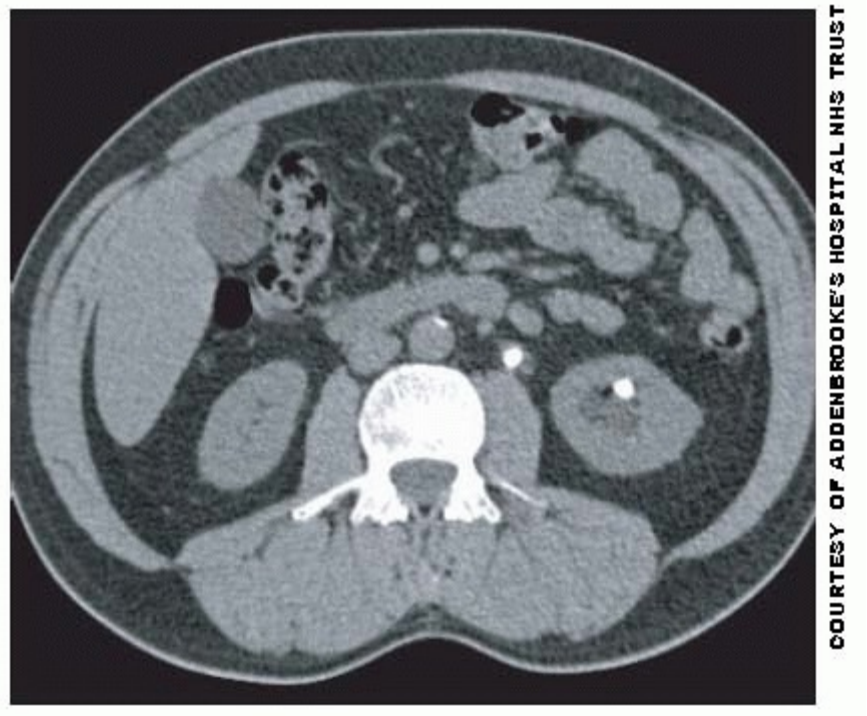


Fig 2. Axial unenhanced CT of the abdomen. There is a left proximal ureteric calculus (anterior to the left psoas) and a left calyceal calculus. The left ureteric calculus is causing mild obstruction of the left kidney. A bone window algorithm may help highlight calcium dense objects within the abdomen. If <7mm diameter, a calculus is likely to pass spontaneously.

Advantages:

Fast; cheap; independent of renal function; no iv contrast medium or radiation risk.

Disadvantages:

Intraluminal masses (eg transitional cell carcinomas) in the upper tracts may not be seen; not a functional study; only suggests obstruction if there is dilatation of the collecting system (~5% of obstructed kidneys have non-dilated systems).

Computed tomography (CT)

has revolutionized renal colic imaging. Unenhanced images are 97% sensitive for calculi, and show many other pathologies (**fig 2**). CT has a similar radiation dose to IVU. CT allows detailed delineation of: masses (solid or cystic, contrast enhancement, calcification, local/ distant extension, renal vein involvement); renal trauma (2 kidneys, haemorrhage, devascularization, laceration, urine leak); retroperitoneal lesions.

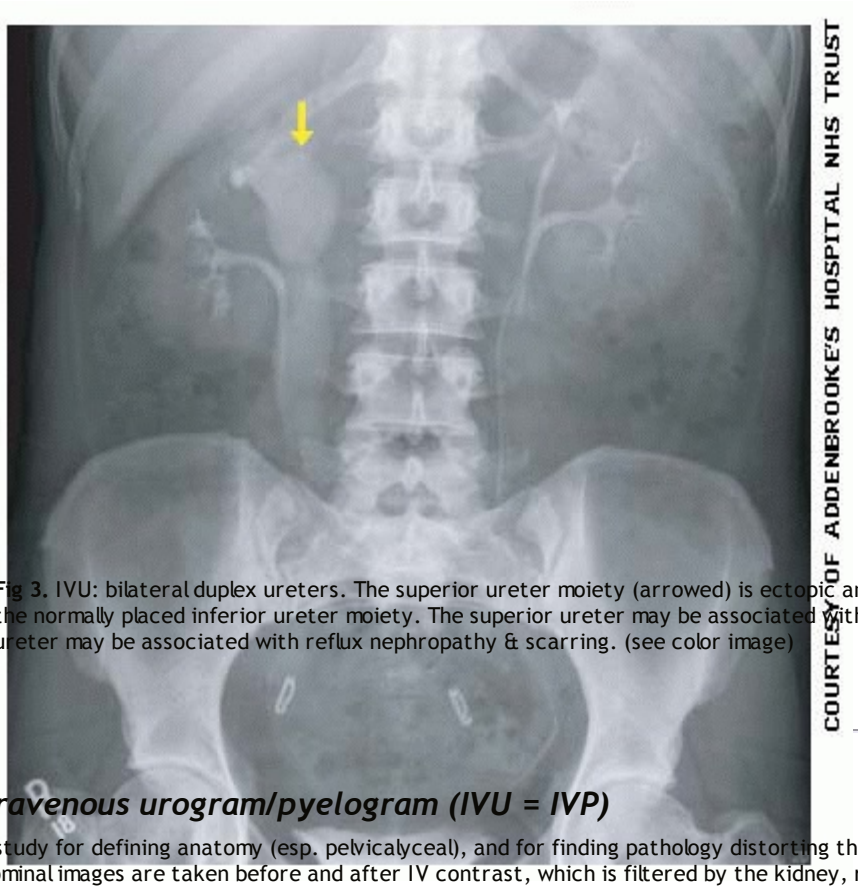


Fig 3. IVU: bilateral duplex ureters. The superior ureter moiety (arrowed) is ectopic and enters the bladder, urethra or vagina more inferiorly than the normally placed inferior ureter moiety. The superior ureter may be associated with a ureterocele and is more likely to obstruct. The inferior ureter may be associated with reflux nephropathy & scarring. (see color image)

Intravenous urogram/pyelogram (IVU = IVP)

is a study for defining anatomy (esp. pelvicalyceal), and for finding pathology distorting the collecting system.[2] It yields some functional information. Abdominal images are taken before and after IV contrast, which is filtered by the kidney, reaching the renal tubules at ~1min (***nephrogram phase***). At this stage look for indentations (scarring) and protrusions (cysts, tumour). Try to decide which kidney is normal if there is a difference in size or a delay in the nephrogram. The smaller kidney may be normal (other side enlarged) or abnormal (chronic disease). The larger kidney may be normal (compensatory) or abnormal (eg tumour, cysts, obstruction). Later

images show contrast medium in the pelvis (pyelogram), ureters, and bladder. Look for filling defects (**fig 7**) and evidence of obstruction (**fig 8**).

Retrograde pyelography

is good at showing pelvicalyceal and ureteric anatomy, and at detecting pathology such as transitional cell carcinoma (TCC). Contrast is injected via a ureteric catheter.

Percutaneous nephrostomy

The renal pelvis is punctured with imaging guidance. Diagnostic images are obtained following contrast injection (antegrade pyelogram, **fig 4**). A nephrostomy tube may then be placed to allow drainage.

Renal arteriography

(**fig 5**) Still the final arbiter of renal artery stenosis. Therapeutic indications: angioplasty; stenting and selective embolization (bleeding tumour, trauma, or AV malformation).

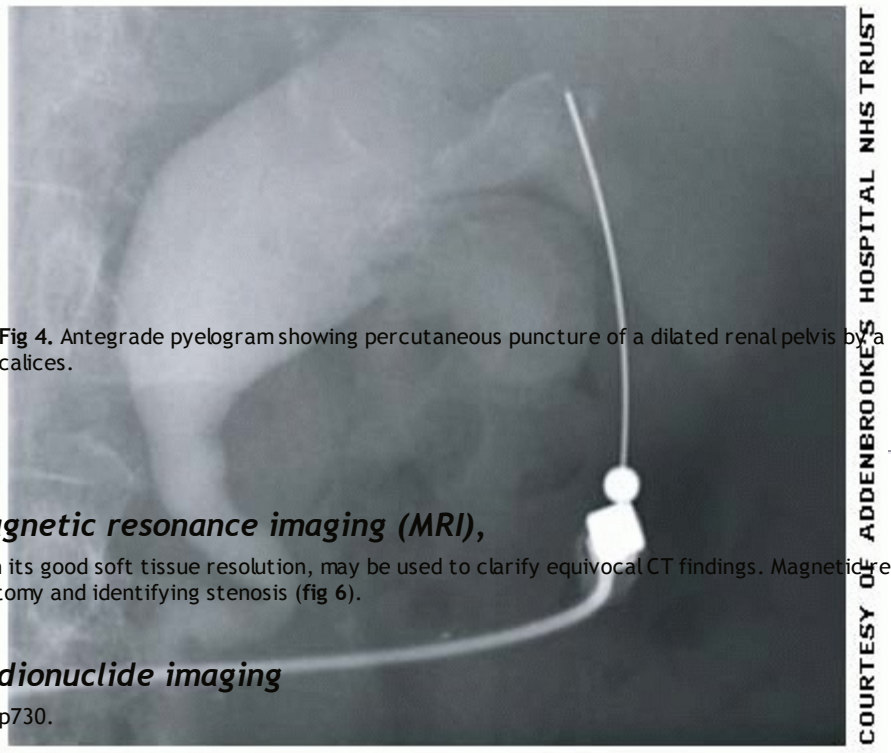


Fig 4. Antegrade pyelogram showing percutaneous puncture of a dilated renal pelvis by a fine co-axial needle. Contrast is injected to outline the calices.

Magnetic resonance imaging (MRI),

with its good soft tissue resolution, may be used to clarify equivocal CT findings. Magnetic resonance angiography (MRA) is useful in imaging renal artery anatomy and identifying stenosis (**fig 6**).

Radionuclide imaging

See p730.

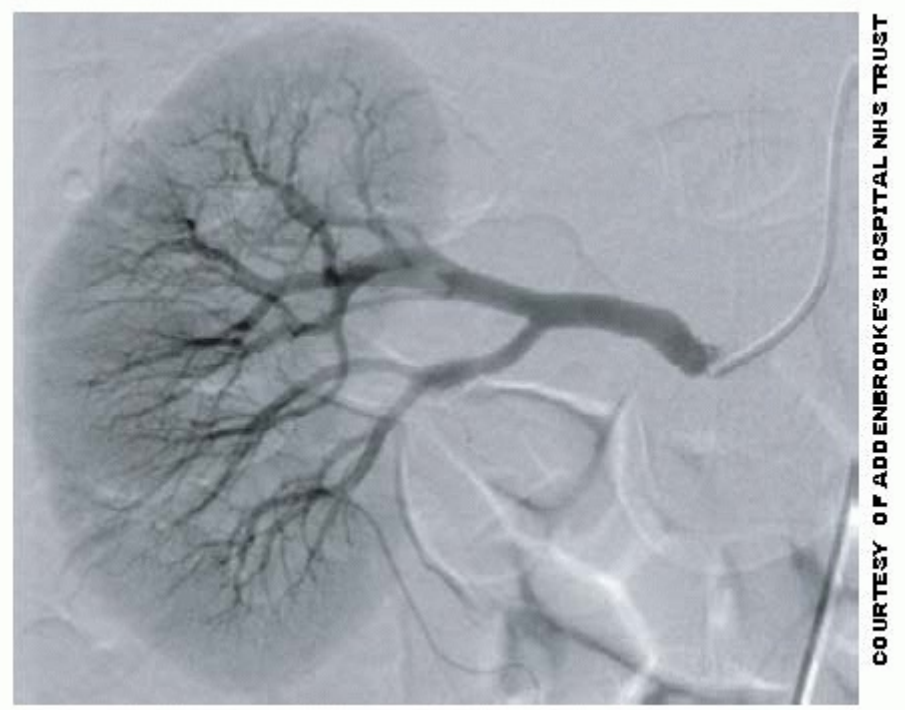


Fig 5. Normal renal artery digital subtraction angiogram (DSA). It is possible to tell that this is a DSA as no other structure has any definition or contrast in the image. There is, however, some interference from overlying bowel gas, which is not an uncommon problem. GI tract peristalsis can be diminished during the examination by using IV ***buscopan*** or ***glucagon***.

Fig 6. Coronal 3D MRA of the kidneys showing an anomalous left renal artery (arrow) arising from the same level as the IMA. This is important information pre-transplant. Anomalous renal arteries are common and, like the normal renal arteries, are end arteries, hence the consequence of infarction if tied at surgery.

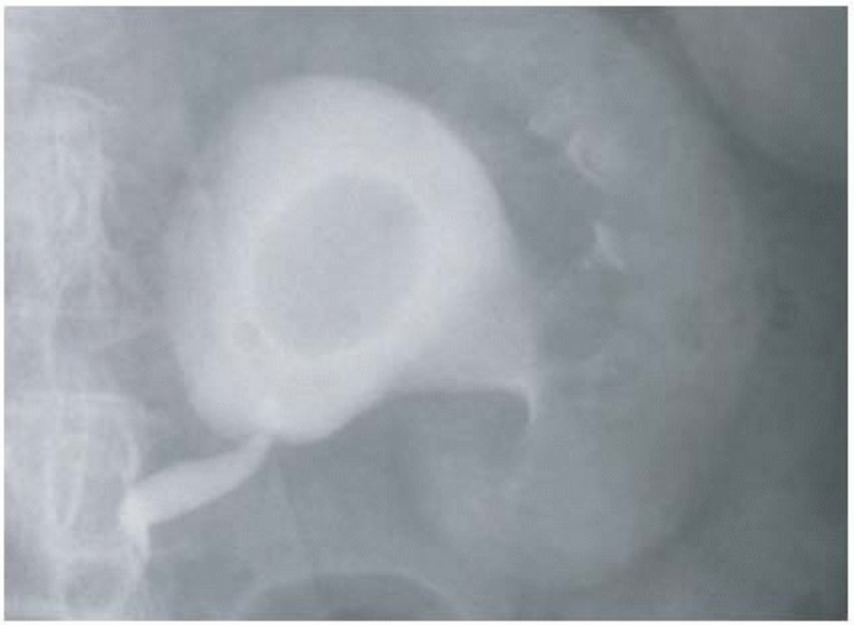


Fig 7. IVU showing a filling defect in the centre of the renal pelvis corresponding to a renal calculus. Filling defects can also be caused by tumour, haematoma, fungal balls or sloughed papillae from renal papillary necrosis. The filling defect can sometimes have the impressive multi-faceted appearance of a staghorn calculus that can occupy the entire pelvicalyceal system.

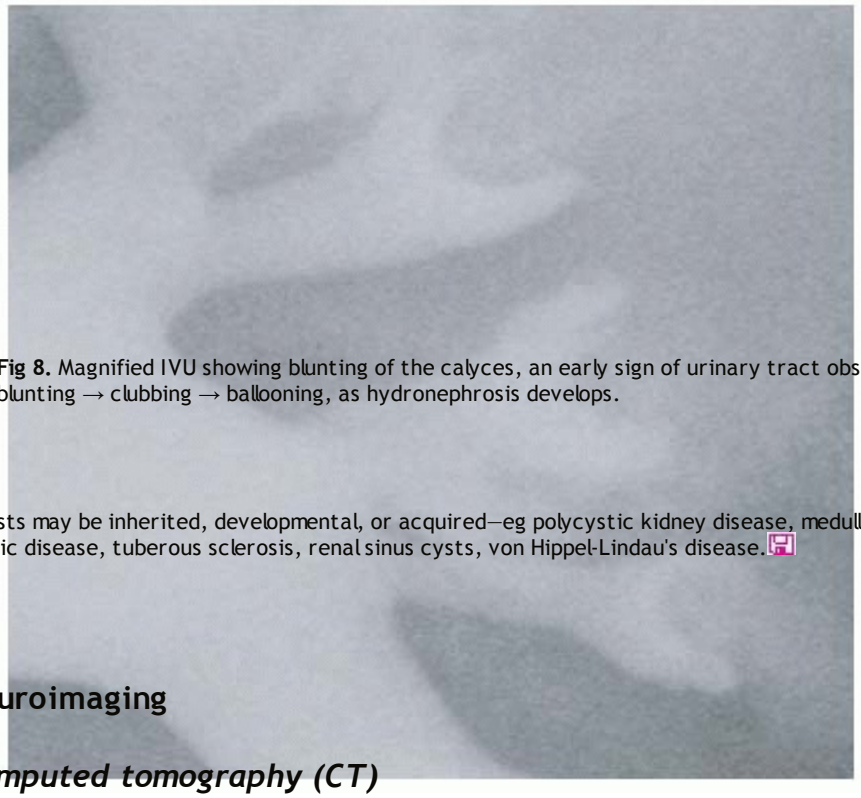


Fig 8. Magnified IVU showing blunting of the calyces, an early sign of urinary tract obstruction. Sequentially in obstruction there is calyceal blunting → clubbing → ballooning, as hydronephrosis develops.

[1] Cysts may be inherited, developmental, or acquired—eg polycystic kidney disease, medullary sponge kidney, multicystic dysplastic kidney, medullary cystic disease, tuberous sclerosis, renal sinus cysts, von Hippel-Lindau's disease.

Neuroimaging

Computed tomography (CT)

The attenuation of biological soft tissues is in a narrow range from about +80 for blood and muscle, to 0 for CSF, and down to -100 for fat (see p718 for the Hounsfield scale). IV contrast medium may be given, initially demonstrating an angiographic effect as the high attenuation contrast in the vessels makes them appear white. Later, if there is a defect in the blood-brain barrier, as with neoplasms or infection, contrast medium will opacify the margins of a lesion, giving an enhancing, white area in the cerebrum or cerebellum. Some intracranial components do not have a blood-brain barrier and enhance normally: eg pituitary gland and choroid plexus.

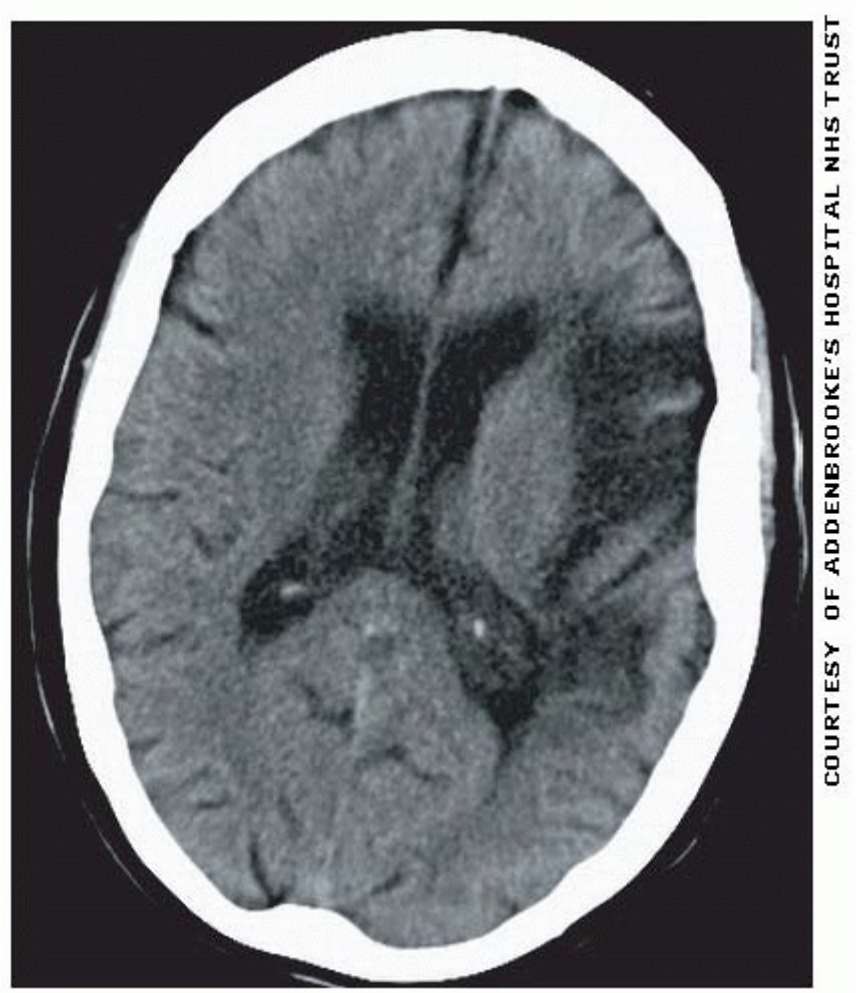


Fig 1. Unenhanced axial CT head: note the old stroke in the left middle cerebral artery territory.

Compared with MRI, CT is good at showing acute haemorrhage and fractures, and is much easier to do in ill or anaesthetized patients, and so is valuable in emergencies. Fresh blood is of higher attenuation (∴ whiter) than brain tissue. Attenuation of haematomas declines as Hb breaks down so that a subacute subdural haematoma at 2wks may have an attenuation the same as adjacent brain, making it difficult to detect. A chronic subdural haematoma will be of relatively low attenuation.

CT is commonly performed in acute stroke to exclude haemorrhage (eg preanticoagulation). The actual area of infarction/ischaemia will not show up for a day or so, and will be low-attenuation **cytotoxic oedema** (intracellular oedema including both white and grey matter—look for loss of grey matter definition).

Tumours and abscesses can have common features, eg a ring enhancing mass, surrounding vasogenic oedema, and mass effect. **Vasogenic oedema** is extracellular and spreads through the white matter. Mass effect causes compression of the sulci and ipsilateral ventricle, and may also cause herniation, (subfalcine, transtentorial, or tonsillar). ▸On p475 there are images of this.

One indication for CT is acute, severe headache. If there is concern about subarachnoid haemorrhage, a non-contrast CT may show acute blood. Even if it does not, it will show if the basal cisterns are normal and therefore lumbar puncture is probably safe.

Cranial* CT *perfusion is a developing technique that assesses cerebral blood flow without the need for invasive angiographic techniques (**fig 5**, p719). ***3D* CT *angiography*** gives excellent mapping of the cerebral circulation (**fig 4**).

Magnetic resonance imaging (MRI)

See p720. Example of stroke on MRI: p463. The chief image sequences are:

- ***T1-weighted images:*** Give good anatomical detail to which the T2 image can be compared. Fat is brightest (signal intensity↑); other tissues are darker to varying degrees. Flowing blood is low signal. Gadolinium-DTPA contrast medium (p734) usually results in an increase in signal intensity.
- ***T2-weighted images:*** These provide the best detection of most lesions as they usually contain some oedema fluid and therefore appear white (eg **fig 4**, p721). Fat and fluid appear brightest. Flowing blood is again low signal.

Magnetic resonance angiography (MRA*)* can map the carotid, vertebrobasilar and cerebral arterial circulations. ***Functional* MRI**

can image regional blood flow.

Contrast angiography

(**fig 4**) is less common as a diagnostic tool since the advent of MRA and CT angiography and perfusion techniques, though it has the advantage of being therapeutic—eg coil embolization of saccular aneurysms.

Radionuclide imaging

See p724. PET is mostly used as a research tool in dementia, but perfusion scintigraphy can be used in the assessment of Alzheimer's disease, other dementias (**fig 5**), and localising epileptogenic foci. Dopamine scintigraphy can be used to assess local cerebral uptake in Parkinson's disease.

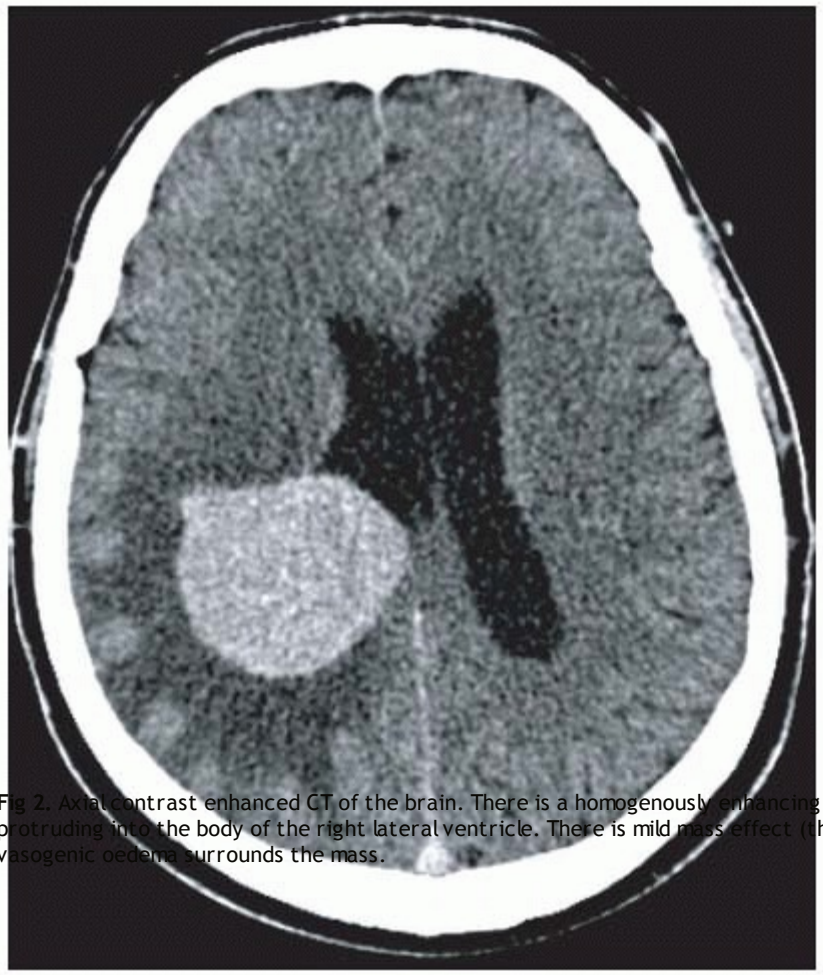


Fig 2. Axial contrast enhanced CT of the brain. There is a homogenously enhancing well defined mass in the right cerebral hemisphere that is protruding into the body of the right lateral ventricle. There is mild mass effect (the corpus callosum is displaced to the left), and low attenuation vasogenic oedema surrounds the mass.

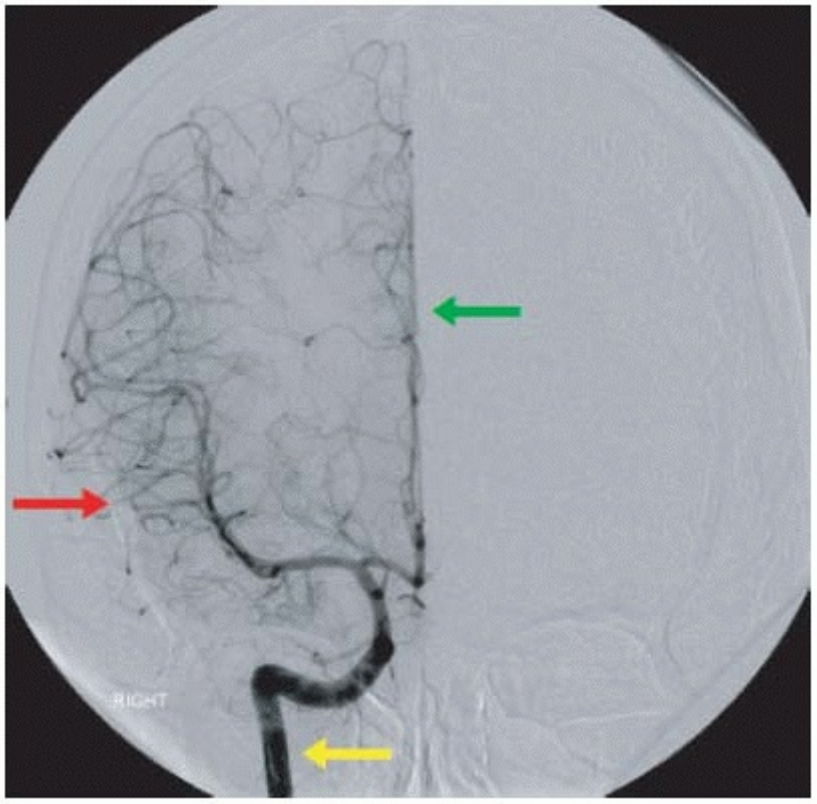


Fig 3. Digital subtraction angiogram (DSA). The right internal carotid artery (yellow arrow), anterior cerebral artery (green arrow) and middle cerebral artery (red arrow) are shown.

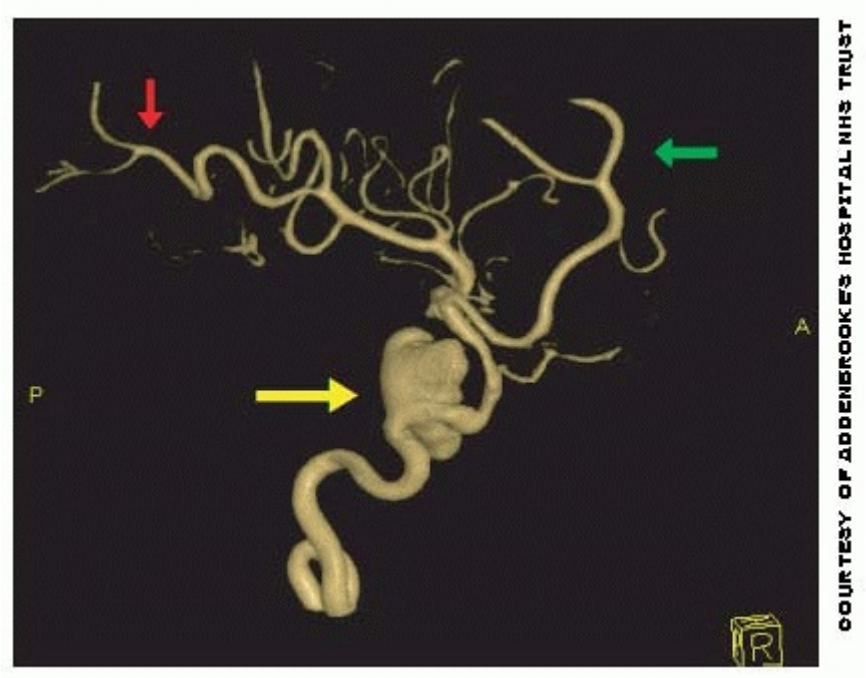


Fig 4. 3D DSA showing an internal carotid artery aneurysm (yellow arrow) viewed from the right. The anterior cerebral artery circulation is marked by the green arrow and the middle cerebral artery circulation by the red arrow.

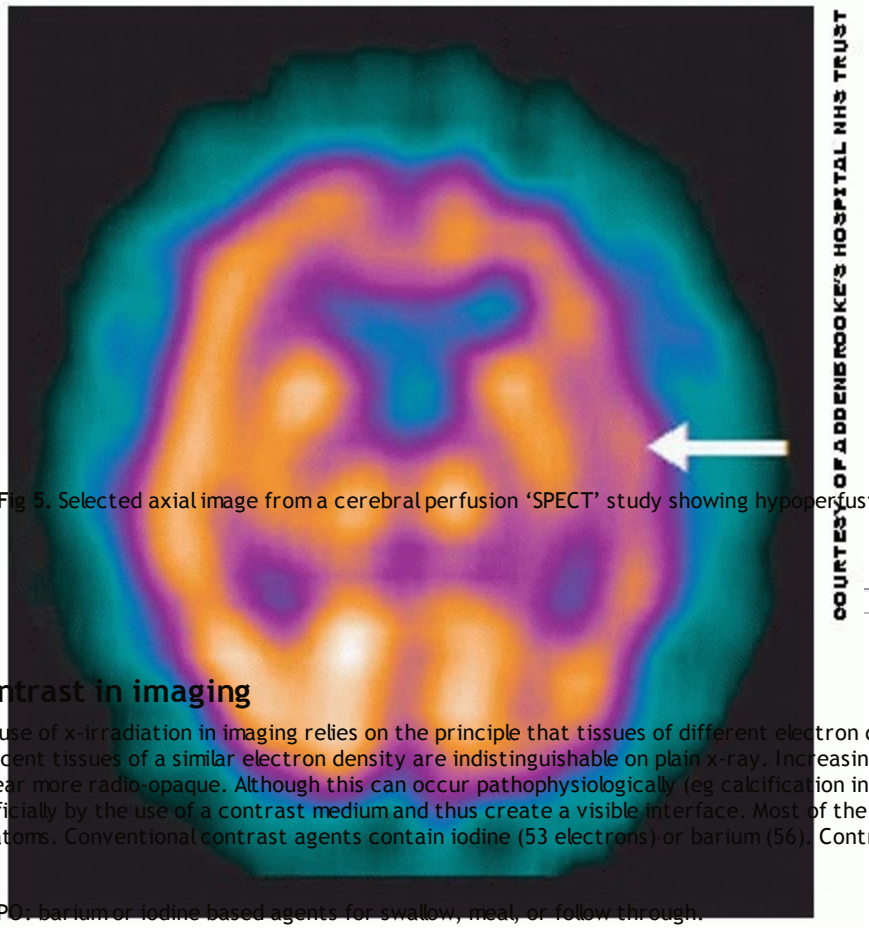


Fig 5. Selected axial image from a cerebral perfusion 'SPECT' study showing hypoperfusion in the left parietal frontal lobes.

Contrast in imaging

The use of x-irradiation in imaging relies on the principle that tissues of different electron densities produce different degrees of attenuation. Two adjacent tissues of a similar electron density are indistinguishable on plain x-ray. Increasing electron density increases attenuation and makes tissues appear more radio-opaque. Although this can occur pathophysiologically (eg calcification in chronic pancreatitis or malignancy) it can be induced artificially by the use of a contrast medium and thus create a visible interface. Most of the body consists of hydrogen (1 electron), oxygen (8), and carbon (6) atoms. Conventional contrast agents contain iodine (53 electrons) or barium (56). Contrast medium is usually administered by the following routes:

- PO: barium or iodine based agents for swallow, meal, or follow through.
- PR: eg barium or iodine based agent enema.
- Inhaled: technetium or xenon used in ventilation scintigraphy.
- IV: iodine or gadolinium based contrast agents.

IV contrast medium has the most widespread clinical application. The ideal intravenous contrast medium should be non-ionic, hydrophilic, iso-osmolar and nonchemotoxic and should have no adverse reactions.

Iodine based contrast agents

Iodine is used because of its relatively high electron density and good physiological tolerance. When used with CT, the examination is said to be **contrast enhanced**—look for '**+ c**' amongst the scan details. Caution should be taken in patients with the following because of the increased risk of adverse reactions (have latest renal function to hand): renal or cardiac impairment; atopy; myeloma; diabetes; sickle cell disease; the elderly and infants; a history of allergy. Minor reactions include nausea, vomiting and a sensation of warmth. Moderate reactions include urticaria, bronchospasm, angioedema and ↓BP (1:250); theoretical risk of death for 1:150 000 ▸***Metformin*** must be withheld before and for 48hrs after IV contrast administration because of risk of lactic acidosis. ▸Avoid iodine-based agents in patients with active hyperthyroidism.

Barium sulphate

is the most common contrast medium used in examination of the GI tract. Water-insoluble particles of 0.6-1.4?m diameter are mixed with large organic molecules such as pectin and gum to promote good flow, mucosal adherence and high density in thin layers. Risks: chemical pneumonitis or peritonitis.

Water-soluble **iodine based** contrast agents (eg Gastrografin®) are used instead of barium where there is a risk of peritoneal contamination (eg fistula, megacolon, ulceration, diverticulitis, bowel anastomosis, acute intestinal haemorrhage). It is high osmolarity. ▸Contains iodine so establish allergy history and thyroid status.

Air

In a double contrast enema, air (or CO2) is insufflated as a **negative contrast medium** after barium administration to enhance mucosal definition (**fig 5**, p729).

Gadolinium

is a lanthanide series element with paramagnetic qualities that is administered intravenously (as gadolinium-DTPA) to enhance the contrast of certain structures in MRI. It works by reducing the time to relaxation (TR) of hydrogen nuclei in its proximity and appears as high signal on T1 weighted scans. It does not cross the blood-brain barrier and is therefore useful in enhancing isointense extraaxial tumours such as meningiomas. It can also highlight areas where the blood brain barrier has broken down secondary to inflammatory or neoplastic processes. It is renally excreted and well tolerated, because only small doses are used. Adverse reactions do include headache, nausea and local irritation at the site of injection, with idiosyncratic reaction reported in less than 1%.

Imaging the acutely unwell patient

Asking yourself '*Does this investigation need to be done right now?*' will often yield the answer '***no!***', yet there are a few

occasions when early imaging can provide vital diagnostic information and influence the prognosis for a patient:

- Acute cauda equina syndrome (p458): ▸▸MRI lumbar spine.
- Suspected thoracic aorta dissection (p586): ▸▸CT thorax + IV contrast medium, MRI or TOE. The mediastinum is rarely widened on CXR.
- Acute renal failure (p292 & p820): ▸▸US of renal tract should be performed to exclude an obstructive (∴ easily treatable) cause.
- Acute pulmonary oedema: ▸▸A portable CXR will help the clinical picture but should not delay definitive treatment (p786).
- Acute abdomen with signs of peritonism: ▸▸Erect CXR should be performed looking for intraperitoneal free gas (**fig 1**, p581), a sign of intestinal perforation. Remember that a patient who has had surgery will have gas (air/CO2) in the abdominal cavity, detectable on plain radiography as late as day 10 post-op.[15] Early CT (<6h after onset of symptoms) in addition to plain radiography appears not to provide additional diagnostic information in gastroduodenal perforation.[16] In one study performing an US technique (the **scissors** manoeuvre) to look for sub-diaphragmatic free air had 94% sensitivity and 100% specificity.[17]
- Any patient with post-traumatic midline cervical spine tenderness—not just for the emergency department! ▸▸Hard collar and backboard immobilisation followed by a lateral C-spine x-ray, then full C-spine series. All the vertebrae down to the top of T1 must be visualised and cleared before it is safe to take the collar off. CT may be required if the plain radiographs are inadequate or inconclusive.
- Sudden onset focal neurology, **worst ever** headache, deteriorating GCS: ▸▸CT head, then LP if no evidence of ↑ICP. Once an examination has been reported as normal, the nursing team can take a rest from work-intensive 'neuro' observations.

Remember that imaging—or re-imaging for a poor quality film—should never delay the definitive treatment of an emergency condition, eg:

- Tension pneumothorax (p798 and **fig 1**): ▸▸decompression **not** CXR.
- Intra-abdominal haemorrhage or viscus rupture (p580): ▸▸laparotomy.
- High clinical suspicion of torsion of testis (p600): ▸▸surgery **not** Doppler US.
- Collapse, acute abdomen, shock, moribund: ▸▸laparotomy. A ruptured aneurysm has an extremely poor prognosis that tails off by the minute (p586).

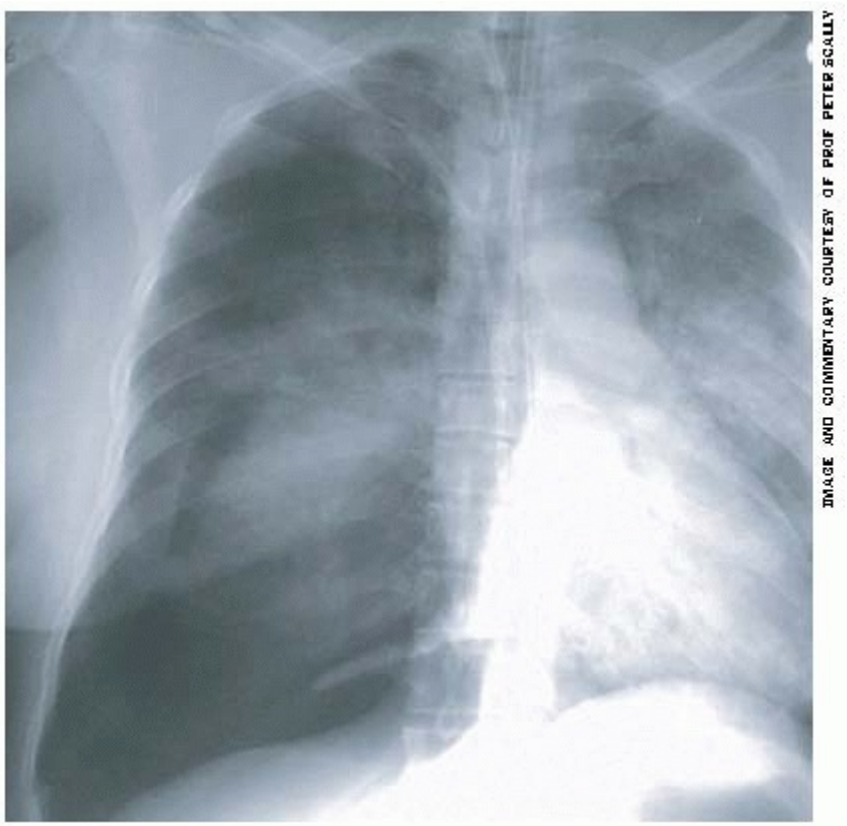


Fig 1. This is a great educational film from the intensive care unit. The inexperienced doctor could be distracted by the poor quality, badly centred film: the technicians do the best they can under difficult conditions. To ask for a new film here would be a mistake. There is adequate information to make a life-saving decision. After checking the name of the patient, see that the tubes and lines are well positioned— the endotracheal (ET) and NG tubes and the right subclavian venous line. **Lungs:** The left lung shows consolidation. The right is too black and the right hemidiaphragm is depressed. **Pleura:** The pleural recess is seen at the right base. **Mediastinum:** Left-shifted, obstructing venous return—so cardiac output↓, and a threat to life. Is it being pushed or pulled? Check **hila**, **bones** and **soft tissues**. Is the ET tube down the right main bronchus, inflating the right lung and collapsing the left? No. Is the right lung collapsed? Yes. ▸▸Right tension pneumothorax. Needle thoracocentesis decompression and a chest tube are needed now. The left lung consolidation could be a result of any of the causes of ARDS (p170). If intubated, consolidation/collapse often occurs at the left base: suction catheters pass down the ET tube and preferentially into the right main bronchus.

Acknowledgements

We thank Professor Peter Scally who is our Specialist Reader for this chapter.

Editors: Longmore, Murray; Wilkinson, Ian B; Turmezei, Tom; Cheung, Chee Kay
Title: *Oxford Handbook of Clinical Medicine, 7th Edition*

19

Reference Intervals, etc.

The Gaussian ('Normal') distribution

Once upon a time, in a famous hospital named R— in the middle of England, there lived a crusty old surgeon and a brilliant young house officer. The surgeon issued infallible and peremptory edicts such as 'all my patients with a haemoglobin less than 10 must be transfused'. Everyone did as the surgeon said (this was a long time ago) except for the wily house officer who understood statistics, sampling error, and the play of chance. One day she was rung up by the haematologist who asked her "Why have you requested 3 blood counts on Mrs Wells today? One is enough. You are wasting our resources!" "Not so," said the house officer. "The first Hb was 9.8; the second was 9.7 and the third was 10.1g/dL. I knew if I was persistent, I stood a good chance of preventing an unnecessary transfusion. She is a patient of Mr X." The two conspirators smiled at each other down the telephone, and no more was said. Of course the right way of dealing with this problem is through clinical governance, and dialogue with the surgeon. But the point remains: numbers are elastic, despite, on occasion, being given to 3 decimal places. Don't believe in them as absolute entities, and don't believe that the normal range is anything other than arbitrary; think before you act: think statistically. *Think like Gauss*.

Fig 1. Carl Friedrich Gauss (1777-1855) and his Gaussian ('Normal') distribution. This bell-shaped graph is the theoretical basis of reference intervals (normal values—see below). In some ways Gauss would have made an ideal handbook author: he left behind him a tiny notebook of just 19 pages which solved 146 problems in mathematics including non-euclidean geometry—his motto being *pauca sed matura* (few but ripe). His messages were brief and perhaps *too* much to the point (not surprisingly, since he invented the first telegraph in 1833)—on being disturbed during deep thought to be told that his wife was dying it is reported that he replied "Tell her to wait a moment until I'm through…"[1]

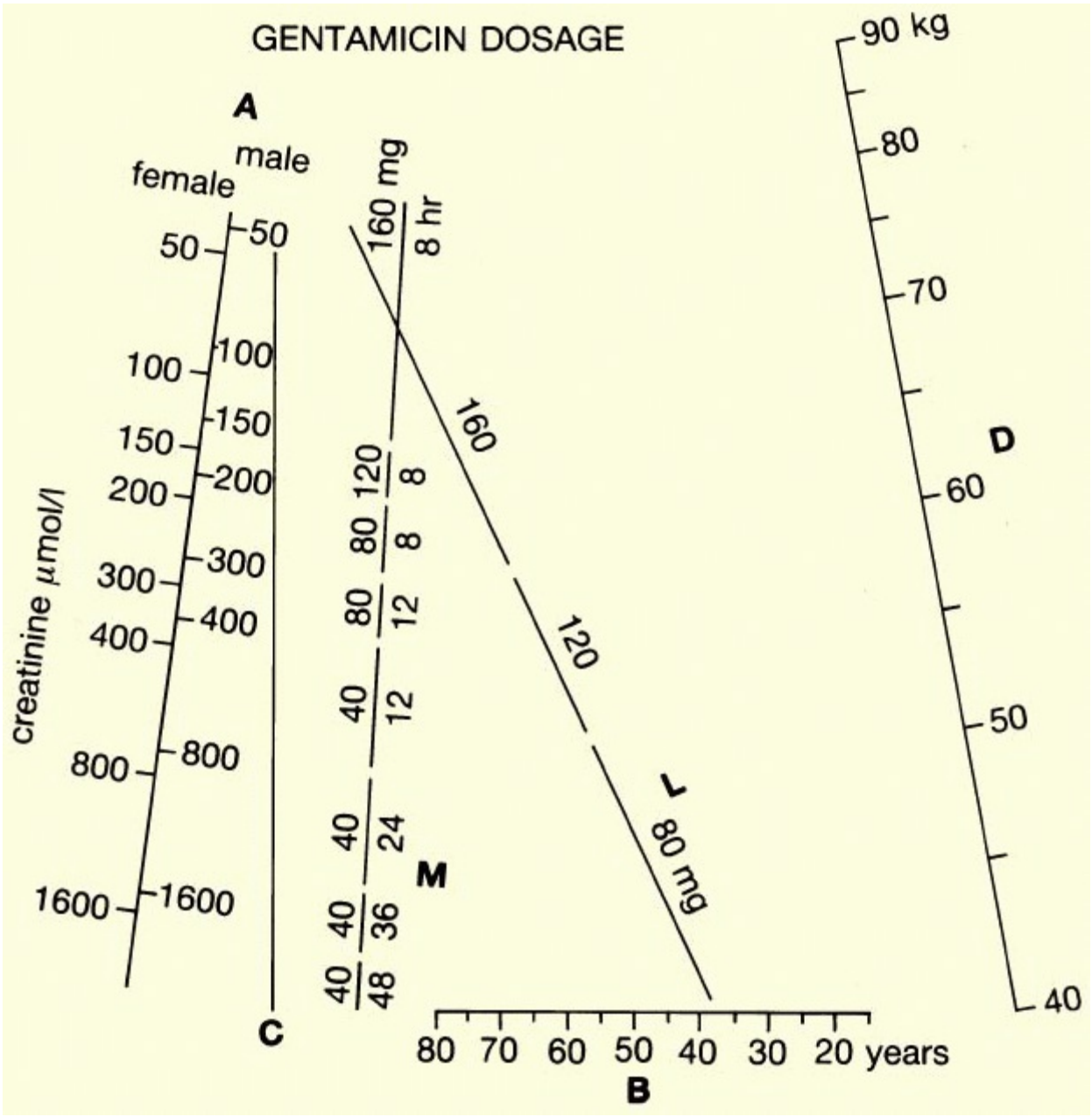
Some definitions

- ***Range:*** The lowest and highest value of all observations in the set being studied.
- ***Arithmetic mean:*** The sum of all observations , by the number of observations.
- ***Median:*** The median is the middle value (eg 9 data points are higher and 9 are lower). If their distribution is Normal, then the median co-insides with the mean.
- ***Standard deviation (SD):*** The square root of the variance (the average of the square of the distance of each data point from the mean). When the distribution of the observations is Normal, 95% of observations are located in the interval 'mean ± 1.96SD'. This is the basis of the reference interval.[2]
- ***Standard error of the mean:*** This is the SD divided by the square root of the number of observations. Suppose a population mean of serum urate is 5.4mg per 100mL and the standard deviation is 1. If you drew 100 samples of 25 people in each sample and calculated 100 sample means, how many of those means would you expect to fall within the range 5.4-1.96×1 to 5.4+1.96×1? Answer: 95.[3]

Gentamicin

The potential for oto- and nephro-toxicity is great if gentamicin is used inappropriately, so use local expert advice/guidelines Although historically given twice or 3-times daily, many now favour **once daily dosing**—fewer SEs, ± better bactericidal activity. Meta-analyses back this, provided there is no increase in cardiac output (eg anaemia; Paget's disease), and the context is not ascites, burns, children, or pregnancy. The big problem is lack of information on calculating and monitoring once-a-day regimens. The *Cooke & Grace* regimen provisionally recommends, for feverish neutropenic adults with serum creatinine <300µmol/L, a starting dose of gentamicin 5mg/kg IVI over 30min. Measure serum trough ~24h later. If <1mg/L, then do twice weekly monitoring. If trough is 1-2mg/L, halve dose, and check trough after 24h. If trough >2mg/L, stop and switch drug. Other regimens also exist (D Nicolau 1995 *Antimicrob Agents Chemoth* **39** 650).

Nomogram for repeated dosing of gentamicin



The above allows for thrice daily doses.

1. Join with a straight line the serum creatinine concentration appropriate to the sex on scale A and the age on scale **B**. Mark the point at which this line cuts line **C**.
2. Join with a line the mark on line **C** and the body weight on line **D**. Mark the points at which this line cuts lines **L** and **M**, to get the loading and maintenance doses, respectively.
3. Confirm the appropriateness of this regimen at an early stage by measuring serum levels, especially in severe illness and renal impairment.
4. Adjust **dose** if peak concentration (1h after IM dose; ½ after IV dose) outside the range 5-10mg/L. A trough concentration (just before dose) above 2mg/L indicates the need for a longer **dosage interval**.

Drug therapeutic ranges in plasma

▸ Ranges should only be used as a guide to treatment.

A drug in an apparently too low concentration may still be clinically useful. Some patients require (and tolerate) levels in the 'toxic' range.

* ***Amikacin*** peak (1h post IV dose): 20-30mg/L. Trough: <10mg/L.

* ***Carbamazepine*** Optimal concentration: 20-50µmol/L [4-12mg/L].

* ***Clonazepam*** trough: 0.08-0.24µmol/L [0.025-0.075mg/L].

* ***Digoxin***[1] (6-12h post dose) 1-2.6nmol/L [0.8-2µg/L]. <1.3nmol/L may be toxic if there is hypokalaemia. Signs of CVS toxicity: arrhythmias, heart block. CNS: confusion, insomnia, agitation, seeing too much yellow (xanthopsia), delirium. GI: nausea.

* ***Ethosuximide*** trough: 300-700µmol/L [40-100mg/L].

* ***Gentamicin***[1] For single-dose regimen, see opposite. Peak—1h post IV dose: 9-18µmol/L [5-10mg/L; 3-5mg/L in IE]. Trough (just before dose): <4.2µmol/L (<2mg/L; <1mg/L in IE). Toxic signs: tinnitus, deafness, nystagmus, vertigo, renal failure. See OPPOSITE.

Lithium[1]

(12h post dose). Guidelines vary: 0.4-0.8mmol/L is reasonable. ***Early*** signs of toxicity (Li^+ ≤1.5mmol/L): tremor, agitation, twitching. ***Intermediate:*** lethargy. ***Late:*** (Li^+ >2mmol/L) spasms, coma, fits, arrhythmias, renal failure (haemodialysis may be needed). See OHCS p354.

Netilmicin

peak—1h post IV dose: 7-12mg/L. Trough <2mg/L.

* ***Phenobarbital*** Trough: 60-180µmol/L [15-40mg/L].

* ***Phenytoin***[1] trough: 40-80µmol/L [10-20mg/L]. Signs of toxicity: ataxia, nystagmus, sedation, dysarthria, diplopia.

Theophylline

10-20mg/mL (55-110µmol/L). (▸ see p795) Take sample 4-6h after starting an infusion (which should be stopped for ~15min just before the specimen is taken). Signs of toxicity: arrhythmias, anxiety, tremor, convulsions.

Tobramycin

peak (1h post IV dose): 11-21µmol/L [5-10mg/L]. Trough: ≤4.3µmol/L [<2mg/L].

[*]***Vancomycin***

trough: 5-10 mg/L (initiate monitoring 48 hr after first dose). In SBE/IE, the trough level is 10-15mg/L. Peak levels are now rarely checked.

The time since the last dose should be specified on the form.

Some important drug interactions ▸see *BNF* www.bnf.org

Note: '↑' means the effect of the drug in italics is increased (eg through inhibition of metabolism or renal clearance). '↓' means that its effect is decreased (eg through enzyme induction).

Adenosine

↓ by: aminophylline. ↑ by dipyridamole.

Aminoglycosides

↑ by: loop diuretics.

Anti-diabetic drugs

(any) ↑ by: alcohol, ß-blockers, monoamine oxidase inhibitors, bezafibrate. ↓ by: corticosteroids, diazoxide, diuretics, contraceptive steroids, (possibly also lithium).

Sulfonylureas ↑ by: azapropazone, chloramphenicol, bezafibrate, co-trimoxazole, miconazole, sulfinpyrazone.

Sulfonylureas ↓ by: rifampicin (nifedipine occasionally).

Metformin ↑ by: cimetidine. With alcohol: lactic acidosis risk.

Antiretroviral agents (HIV):

See p402.

Angiotensin-converting enzyme (ACE) inhibitors

↓ effect by: oestrogens NSAIDs.

Antihistamines

Avoid anything which ↑concentrations and risk of arrhythmias, eg erythromycin, other macrolides (eg azithromycin), antifungals, halofantrine, tricyclics, antipsychotics, SSRIs (p442), protease inhibitors (p402), diuretics, ßblockers, antiarrhythmics.

Azathioprine

↑ by: allopurinol.

ß-blockers

Avoid verapamil; ↓: NSAIDs. Lipophilic ß-blockers (eg propranolol) are metabolized by the liver, and concentrations are ↑ by cimetidine. This does not happen with hydrophilic ß-blockers (eg atenolol).

Carbamazepine

↑ by: erythromycin, isoniazid, verapamil.

Cimetidine:

theophylline↑, warfarin↑, lidocaine↑, amitriptyline↑, propranolol↑, pethidine↑, phenytoin↑, metronidazole↑, quinine↑.

Contraceptive steroids

↓ by: antibiotics, barbiturates, carbamazepine, phenytoin, rifampicin.

Ciclosporin

↑ by: erythromycin, nifedipine, grapefruit juice. ↓ by: phenytoin.

Digoxin

↑ by: amiodarone, carbenoxolone and diuretics (as K^+ levels lowered), quinine, verapamil.

Diuretics

↓ by: NSAIDs—particularly indometacin.

Ergotamine

↑ by: erythromycin (ergotism may occur).

Fluconazole:

Avoid concurrent astemizole .

Lithium

↑ by: thiazide diuretics.

Methotrexate

↑ by: aspirin, NSAIDs. Many antibiotics (check BNF).

Phenytoin

↑ by: chloramphenicol, cimetidine, disulfiram, isoniazid, sulfonamides. ↓ by: carbamazepine.

Potassium-sparing diuretics with ACE-inhibitors:

Hyperkalaemia.

Theophyllines

↑ by: cimetidine, ciprofloxacin, erythromycin, contraceptive steroids, propranolol. ↓ by: barbiturates, carbamazepine, phenytoin, rifampicin. See p795.

Valproate

↓by: carbamazepine, phenobarbital, phenytoin.

Warfarin and nicoumalone

(=acenocoumarol) ↑ by: alcohol, allopurinol, amiodarone, aspirin, chloramphenicol, cimetidine, ciprofloxacin, co-trimoxazole, danazol, dipyridamole, disulfiram, erythromycin (and broad-spectrum antibiotics), gemfibrozil, glucagon, ketoconazole, metronidazole, miconazole, nalidixic acid, neomycin, NSAIDS, phenytoin, quinidine, simvastatin (but not pravastatin), sulfinpyrazone, sulfonamides, tetracyclines, thyroxine.

Warfarin and nicoumalone

↓ by: aminoglutethimide, barbiturates, carbamazepine, contraceptive steroids, dichloralphenazone, griseofulvin, rifampicin, phenytoin, vitamin K.

Zidovudine (AZT)

↑ by: paracetamol (increased marrow toxicity).

IVI solutions to avoid Dextrose:

Avoid furosemide, ampicillin, hydralazine, insulin, melphalan, phenytoin, and quinine.

0.9% saline IVI:

Avoid amphotericin, lignocaine, nitroprusside.

Haematology—reference intervals

(For B_{12}, folate, Fe, and TIBC, see p742-3)

Measurement		Reference interval	Your hospital
White cell count (WCC)		4.0-11.0 × 10^9/L	
Red cell count	♂	4.5-6.5 × 10^{12}/L	
	♀	3.9-5.6 × 10^{12}/L	
Haemoglobin	♂	13.5-18.0g/dL	
	♀	11.5-16.0g/dL	
Packed red cell volume (PCV) or haematocrit	♂	0.4-0.54L/L	
	♀	0.37-0.47L/L	
Mean cell volume (MCV)		76-96fL	
Mean cell haemoglobin (MCH)		27-32pg	

Mean cell haemoglobin concentration (MCHC)		30-36g/dL
Neutrophils		2.0-7.5 × 10^9/L;
		40-75% WCC
Lymphocytes		1.3-3.5 × 10^9/L;
		20-45% WCC
Eosinophils		0.04-0.44 × 10^9/L;
		1-6% WCC
Basophils		0.0-0.10 × 10^9/L;
		0-1% WCC
Monocytes		0.2-0.8 × 10^9/L;
		2-10% WCC
Platelet count		150-400 × 10^9/L
Reticulocyte count		0.8-2.0%[1] 25-100×10^9/L

Erythrocyte sedimentation rate		Depends on age (p356)
Prothrombin time (factors I, II, VII, X)		10-14s
Activated partial thrombo- plastin time (VIII, IX, XI, XII)		35-45s
D-dimers[2]		<0.5mg/L

Proposed therapeutic ranges for prothrombin time: See p335

[1] Only use percentages as reference interval if red cell count is normal; otherwise, use the absolute value. Express as a ratio *vs* control.

[2] D-dimer assay may be useful as a screening test for thromboembolic disease see *Lancet* 1999 **353** 190. However, the reference range depends on the assay—**check** with your haematology lab.

Reference intervals (RI)—*biochemistry*

See p652 for the *philosophy of the normal range*; see OHCS p222 *for children*. Drugs (and other substances) may interfere with any chemical method; as these effects may be method dependent, it is difficult for the clinician to be aware of all the possibilities. If in doubt, discuss with the lab.

Substance	Specimen	Reference interval (labs vary, so a guide only)	Your hospital
Adrenocorticotrophic hormone	P	<80ng/L	
Alanine aminotransferase (ALT)	P	5-35iu/L	
Albumin	P[1]	35-50g/L	
Aldosterone	P[2]	100-500pmol/L	

Alkaline phosphatase	P	30-150u/L (adults)
α-amylase	P	0-180 Somogyi u/dL
α-fetoprotein	S	<10ku/L
Angiotensin II	P[2]	5-35pmol/L
Antidiuretic hormone (ADH)	P	0.9-4.6pmol/L
Aspartate transaminase	P	5-35iu/L
Bicarbonate	P[1]	24-30mmol/L
Bilirubin	P	3-17μmol/L
BNP (see p665)	P	<50ng/L
Calcitonin	P	<0.1μg/L
Calcium (ionized)	P	1.0-1.25mmol/L
Calcium (total)	P[1]	2.12-2.65mmol/L
Chloride	P	95-105mmol/L
[3]Cholesterol (see p682)	P	<5.0mmol/L

VLDL (see p682)	P	0.128-0.645mmol/L
LDL	P	<2.0mmol/L
HDL	P	0.9-1.93mmol/L
Cortisol	P	A.M. 450-700nmol/L midnight 80-280nmol/L
Creatine kinase (CK)	P	♂ 25-195iu/L
		♀ 25-170iu/L
Creatinine (∝to lean body mass)	P[1]	70-≤150µmol/L
Ferritin	P	12-200µg/L
Folate	S	2.1µg/L
Follicle-stimulating hormone (FSH)	P/S	2-8u/L in ♀ (luteal); >25u/L in menopause
Gamma-glutamyl	P	♂ 11-51iu/L
transpeptidase		♀ 7-33iu/L
Glucose (fasting)	P	3.5-5.5mmol/L

Growth hormone	P	<20mu/L
HbA_{1c} (= glycosylated Hb)	B	<5.5%; <6.5≈good control in DM
Iron	S	♂ 14-31µmol/L ♀ 11-30µmol/L
Lactate dehydrogenase (LDH)	P	70-250iu/L
Lead	B	<1.8mmol/L
Luteinizing hormone (LH) (premenopausal)	P	3-16u/L (luteal)
Magnesium	P	0.75-1.05mmol/L
Osmolality	P	278-305mosmol/kg
Parathyroid hormone (PTH)	P	<0.8-8.5pmol/L
Prolactin	P	♂ <450u/L; ♀<600u/L
Prostate specific antigen (PSA)	P	0-4µg/ml, age specific, see p681
Protein (total)	P	60-80g/L
Red cell folate	B	0.36-1.44µmol/L (160-640µg/L)

Renin (erect/recumbent)	P[2]	2.8-4.5/ 1.1-2.7pmol/mL/h
Sodium	P[1]	135-145mmol/L
Thyroid-binding globulin (TBG)	P	7-17mg/L
Thyroid-stimulating hormone (TSH) widens with age, p200	P	0.5-5.7mu/L
Thyroxine (T4)	P	70-140nmol/L
Thyroxine (free)	P	9-22pmol/L
Total iron-binding capacity	S	54-75µmol/L
Triglyceride	P	0.55-1.90mmol/L
Tri-iodothyroinine (T_3)	P	1.2-3.0nmol/L
Troponin T (see p104)	P	<0.1µg/L
Urate	P[1]	♂ 210-480µmol/L
		♀ 150-390µmol/L
Urea	P[1]	2.5-6.7mmol/L
Vitamin B_{12}	S	0.13-0.68nmol/L (>150ng/L)

[1] See *OHCS* p15 for reference intervals in pregnancy.

[2] The sample requires special handling: contact the laboratory.

[3] Desired upper limit of cholesterol would be <6mmol/L. In some populations, 7.8mmol/L is the top end of the distribution.

P=plasma (eg heparin bottle); **S**=serum (clotted; no anticoagulant); **B**=whole blood (edetic acid EDTA bottle)

*Arterial blood gases—**reference intervals***

pH: 7.35-7.45 P_aCO_2: 4.7-6.0kPa

P_aO_2: >10.6kPa Base excess: ±2mmol/L

Note: 7.6mmHg = 1kPa (atmospheric pressure ≈ 100kPa)

Urine reference intervals	Reference interval	Your hospital
Cortisol (free)	<280nmol/24h	
Hydroxyindole acetic acid	16-73µmol/24h	
Hydroxymethylmandelic acid (HMMA, VMA)	16-48µmol/24h	

Metanephrines	0.03-0.69µmol/mmol creatinine (or <5.5µmol/day)
Osmolality	350-1000mosmol/kg
17-oxogenic steroids	♂ 28-30µmol/24h
	♀ 21-66µmol/24h
17-oxosteroids (neutral)	♂ 17-76µmol/24h
	♀ 14-59µmol/24h
Phosphate (inorganic)	15-50mmol/24h
Potassium	14-120mmol/24h
Protein	<150mg/24h
Sodium	100-250mmol/24h

Useful addresses (for those in the UK)

For ***addresses of disease-specific organizations***, see the Health Information Line (below, or www.patient.org.uk/); for ***poisons information services*** see p822

Diabetes UK

10 Queen Ann St, London W1M 0BD (020 7323 1531)

British Medical Association (BMA)

BMA House, Tavistock Square, London WC1H 9JP (020 7387 4499)

Bureau of Hygiene and Tropical Medicine

Keppel St, London WC1E 7HT (020 7636 8636)

Central Public Health Lab

61 Colindale Av, London NW9 5HT (020 8200 4400)

Committee on Safety of Medicines

(part of the MHRA) freepost, London SW8 5BR

Communicable Disease Surveillance Centre

(for up-to-date advice on travel health needs) 61 Colindale Avenue, London NW9 5HT (020 8200 6868)

Disabled Living Foundation

(Advice on aids and equipment to help the disabled) 380-384 Harrow Rd, London W9 2HU (020 7289 6111)

Evidence-based medicine

Cochrane Centre (01865 516300) NHS Centre for Reviews and Dissemination (01904 433707)

Central Health Outcomes Unit DoH (020 7972 2000)

Centre for Health Economics (01904 433645)

Centre for Evidence-based Medicine (01865 221321)

Bandolier (01865 226863); INTERNET: www.jr2.ox.ac.uk/Bandolier

UK clearing house—Health Outcomes (0113 233 3940)

General Medical Council

178 Great Portland St, London W1W (020 7580 7642)

Health Information Line

(for a wide range of information for doctors and patients, and addresses of disease-specific organizations) 0800 665544

Liverpool School of Tropical Medicine

Pembroke Place, Liverpool L3 5QA (0151 708 9393)

Malaria Reference Laboratory

(for advice on malaria prophylaxis) 020 7636 8636 (for advice on treatment ring 020 7387 4411)

Medic-Alert Foundation

12 Bridge Wharf, 156 Caledonian Rd, London N1 9UD (020 7833 3034)

Medical Defence Union (UK)

3 Devonshire Place, London W1N 2EA (020 7486 6181 and 0800 716376, fax 0161 491 1420)

Medical & Dental Defence Union

144 West George St, Glasgow (0141 332 6646)

Medical Foundation for the Care of Victims of Torture

96-98 Grafton Rd, Kentish Town, London NW5 3EJ (020 7813 7777) www.torturecare.org.uk

Medical Protection Society

50 Hallam St, London W1N 6DE (020 7637 0541)

Multiple Sclerosis Society

25 Effie Road, London SW6 1EE (020 7736 6267)

National Counselling Service for Sick Doctors

(0870 241 0535)

NHS direct

0845 46 47

The Patients' Association

(an advice service for patients) PO Box 935, Harrow (0845 608 4455)

Transplant service (UK)

(Can these organs be used?) 0117 9507 777. To make your own organs available, add your name online at uktransplant.org.uk

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Internet addresses, and becoming a Knowledge Information Officer

The internet is older than most doctors, being of the same vintage as, say, penicillin—is used more often than penicillin, and is having just as profound effects on medicine. During the time it takes you to read this page, your betterconnected patients may have checked out your latest prescription and be wondering why it does not tally with the recommendations of Guatemalan Guidelines on Gynaecomastia, or the National Institute for Health and Clinical Excellence's Treatise on Toxoplasmosis. Our patients have time and motivation, whereas we have little time and our motivation may be flickering. This can seem threatening to the doctor who sees himself/herself as a dispenser of wisdom and precious remedies. It is less threatening if we consider ourselves to be in partnership with our patients. The evidence is that those who use the internet to question their therapy receive a better service.

If all this makes you depressed don't give up. The chances are that someone in your team is more familiar with the technology than you. Ask her if she will be your Knowledge Information Officer for a while. The answer will probably be 'Yes'. If everyone says 'No', then you are probably ahead of your team. So go to your local librarian, and ask his advice, get some training, and then offer yourself as your team's Knowledge Information Officer.[4] If no one asks you any questions, your team is either sleeping or dead (all organisms and organizations have information needs)—or you are not available at the right time: get yourself an e-mail address and teach the team to send you messages.

How to use a Knowledge Information Officer

Their role is to answer your clinical questions. Can tetanus toxoid cause purpura? Is there a connection between knee pain and constipation? Frame your questions as simply as possible. You are not asking him whether it is likely that this patient's purpura is due to last week's tetanus vaccine, just if it is a reported happening. You maintain clinical responsibility and use the knowledge you are given to frame appropriate management.

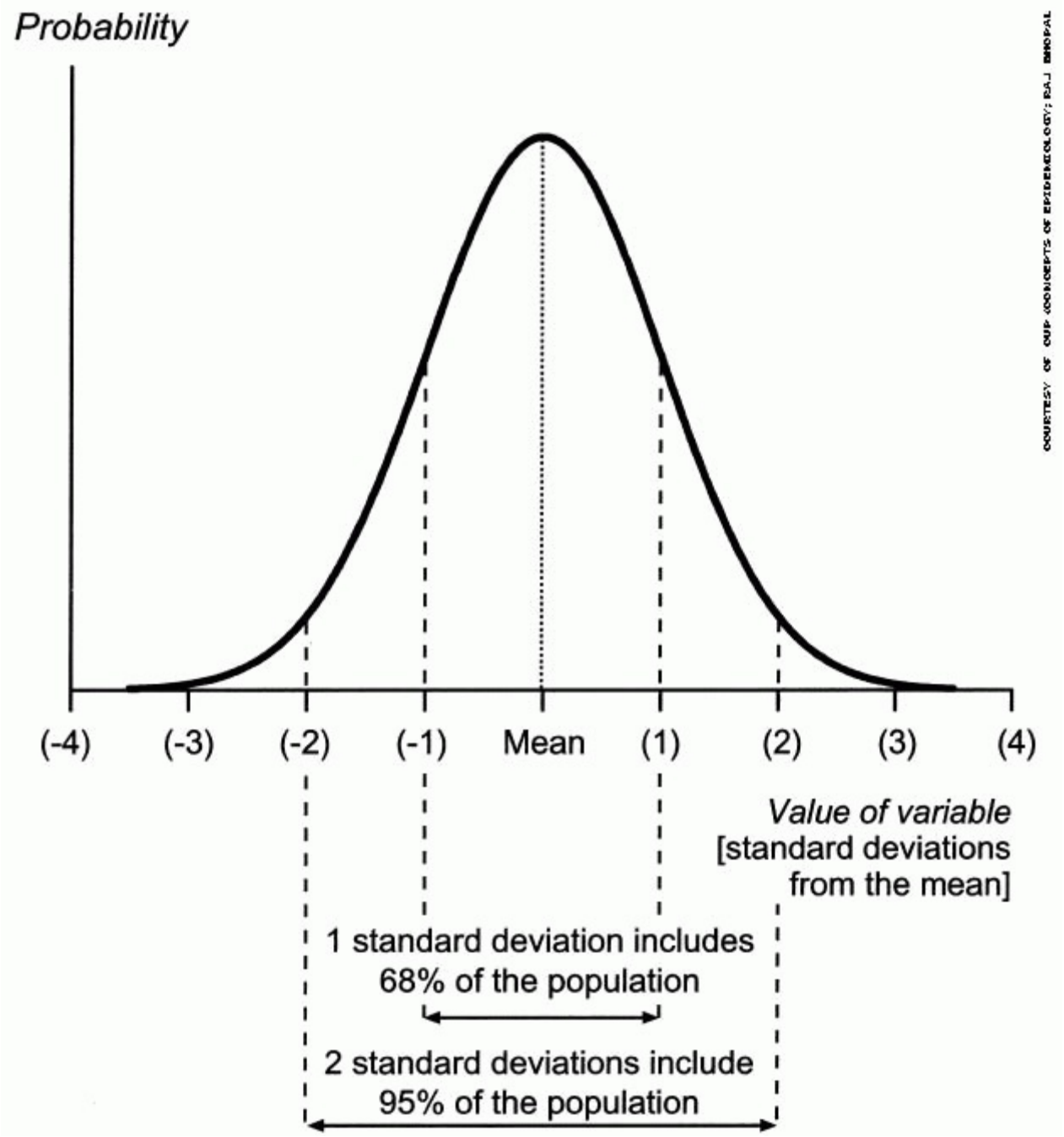
Useful sources for Knowledge Information Officers

A basic starter kit:

1. ***Drugs:*** e*MIMS* (more up to date than *eBNF*, but see the *What's new* section at www.bnf.org); *eMIMS* contains many Data-sheets; free and updated monthly.
2. ***Differential diagnoses*** (eg what causes chest pain, knee pain, and urea↑?) and *rare diseases*—try Mentor (www.webmentorlibrary.com)
3. ***Research:*** Medline is free at www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed. Searches can be limited with nested commands: eg angina [therapy] **AND** (2005 [PDAT] **OR** 2004 [PDAT]) **AND** (new eng j med [JOURNAL] or lancet [JOURNAL]) **AND** human **AND** hasabstract **AND** randomized controlled trial [PTYP] Note use of upper case AND/OR, and no space in the phrase 'hasabstract'. This search yields 6 results, for example. Adding 'AND buck g [AUTHOR]' narrows it down to one. For advanced advice on using Medline, see OHCS p504. Be careful. Missing out a close-bracket ')' before 'and human' gives 2220 results. Also, check your spelling carefully.
4. ***Meta-analyses:*** www.update-software.com (eg Cochrane library).

If you *are* your team's Knowledge Information Officer, decide how to categorize, store, and retrieve knowledge you import and export. Time-management gurus tell us that the main time-waster is, for most organizations, chasing items known to exist but currently lost. Manual systems and bursting filing cabinets are not the answer: linked hard disks and searchable databases are.

Acknowledgements



Editors: Longmore, Murray; Wilkinson, Ian B; Turmezei, Tom; Cheung, Chee Kay
Title: *Oxford Handbook of Clinical Medicine, 7th Edition*

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Practical Procedures

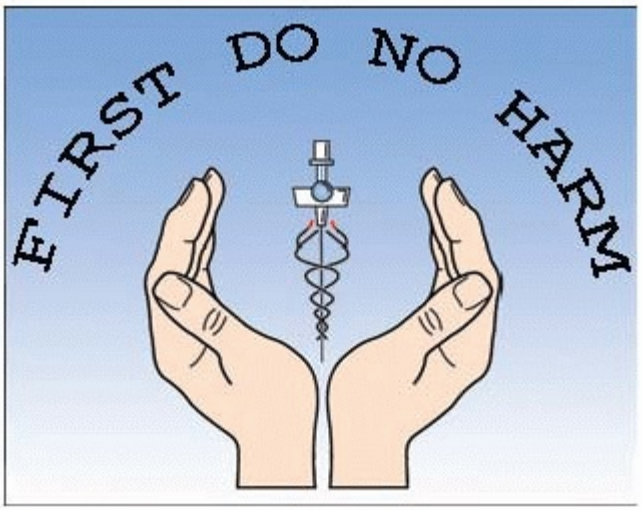


Fig 1. Hands-on experience is a vital part of the learning process in medicine—without it we could never hope to improve our skills, and they would gently drift away from us on a current of inadequacy. But a golden rule to remember is: ▸*first do no harm*. We must know when we are out of our depth. A call for senior help may be one of the most important that you ever make.

Nasogastric (Ryle's) tubes

These tubes are passed into the stomach *via* the nose—orogastric if *via* the mouth—and drain externally. Sizes: 16 = large, 12 = medium, 10 = small.

Uses:

- To empty the stomach: eg pre-op, acute pancreatitis, intestinal obstruction, paralytic ileus, gastric outflow obstruction, risk of aspiration.
- Intra-operatively: eg to inflate/deflate the stomach to give easier access to the upper abdomen, to decompress the bowel or to test an anastomosis.
- For irreversible dysphagia: eg motor neurone disease.
- For feeding ill patients: use a special fine-bore tube.

Passing the tube

Nurses are experts and will ask you (who may never have passed one) to do so only when they fail—so the first question to ask is: 'Have you asked the charge-nurse from the ward next door?'

- Wear non-sterile gloves and an apron to protect from those 'rich encrustations' so often found on our clothes after a few days on the wards.[1]
- Explain the procedure. Take a new, cool (hence less flexible) tube. Have a cup of water to hand. Lubricate well with aqueous gel.
- Use the tube, by holding it against the patient's head, to estimate the length required to get from the nostril to the back of the throat.
- Place lubricated tube in nostril with its natural curve promoting passage down, rather than up. The right nostril is often easier than the left. Advance directly backwards (not upwards).
- When the tip is estimated to be entering the throat, rotate the tube by ~180° to discourage passage into the mouth.
- Advance the tube into the oesophagus during a swallow and thence into the stomach. It may be easier to swallow with a sip of water and easier to advance if rotating rather than pushing. **If this fails:** Try the other nostril, then oral insertion.
- The tube should have distance markings along it: the stomach is at ~35-40cm in an adult, so advance to at least this distance, preferably 10-20cm beyond.
- Secure with tape to the nose. Use litmus paper to test that you are in the stomach—the gastric contents will be acidic. Alternatively listen over the stomach for bubbling (=*borborygmi*) with a stethoscope whilst pushing 5- 10mL of air down the tube. Using a CXR to check positioning is generally now regarded as an unnecessary exposure to radiation, though some may require it (eg fine bore tubes).
- Either spigot the tube, or allow to drain into a dependent catheter bag secured to the patient's clothing (zinc oxide tape around tube to form a flap, safety pin through flap).

▸Do not pass a tube nasally if there is any suspicion of a facial fracture.

▸Get senior help if the patient has recently had upper GI surgery—it is not good news to have pushed the tube through a fresh anastomosis!

Complications:

• Pain, or, rarely: • Loss of electrolytes • Oesophagitis • Tracheal or duodenal intubation • Necrosis: retro- or nasopharyngeal • Perforation of the stomach.

Weaning

When thinking about removing a nasogastric tube that is *in situ* for decompression or relief of obstruction, it is a good idea to wean it so that the patient manages well without it:

- First it should be on free drainage with eg 4hrly aspirations;
- Then spigot with 4hrly aspirations;
- Then spigot only. If this is tolerated along with oral intake then it is probably safe to remove the tube;
- If progression is not tolerated then take a step backwards.

Placing IV cannulae (drips)

▸Although siting a cannula has almost become *de rigueur* for hospital admissions, try to avoid IVIs, as infections/MRSA at the IVI site can cause real problems, especially in the elderly. Insertion skill is best shown at the bedside by an expert:

1. **Set up a tray** Swab to clean skin; cannula(e); syringe + 1mL 1% ***lidocaine***; cotton-wool/gauze swab to stop bleeding from unsuccessful attempts; tape/Tegaderm® to fix cannula; elastoplast; saline flush; portable sharps bin: **▸need-lestick injuries do happen**. Take multiple items for brave but failed attempts.
2. **Set up a drip-stand** with first bag of fluid (carefully checked with a nurse); 'run through' a giving-set (a nurse will show you how).
3. **Ask a nurse to help** until you are experienced. Nurses prefer helping rather than changing the bed clothes because of spilt blood.
4. **Explain** the procedure to the patient, including that only the tube and **not** the needle remains in the arm. Place the tourniquet around the arm.
5. **Have the patient lying down** This prevents most faints and further problems when they do occur.
6. **Search hard for the best vein** (palpable, not merely visible). Don't be too hasty. Rest the arm below the level of the heart to aid filling. Ask them to clench and unclench their fist. Feel with your most sensitive finger—a golden touch will come with practice.
7. **▸Stay away from** arms with AV dialysis fistulae and the ipsilateral side to axillary surgery. Also avoid sites crossing a joint, if possible.
8. **Get comfortable** It makes all the difference when learning.
9. **Place a paper towel** under arm to soak up any blood.
10. **Tap the vein** to make it prominent.
11. **Clean the skin** Use local anaesthetic (or ***Emla®*** cream or **tetrcaine** 4% gel[MET 2]): it is kinder, it **does** work, but takes ~¾h to work. Consider using a fine needle to raise a bleb of ***lidocaine***, like a nettle sting, just to the vein's side. Wait 15s.

After it is in:

1 Take blood with a syringe or adapter, if you are going to. **2** Remove the tourniquet. **3** Flush the cannula. **4** Fix cannula firmly with tape; check flow. **5** Connect fluid tube. **6** Bandage a loop of the tube to the arm. If the drip is across a joint, use a splint. **7** Check the flow speed. Write a fluid chart (p656). **8** When the drip comes down, remove the cannula. (A patient once asked at follow-up if he still needed 'this green plastic thing in my hand'.) **NB:** Adding heparin to the IVI has not been shown to maintain patency (unlike arterial lines).[MET 3]

If you fail after 3 attempts

▸Shocked patients need fluid quickly: if you are having trouble putting in a drip, call your senior. The advice below assumes that the drip is not immediately life-saving. ▸▸If it is, see EMERGENCY BOX.

Experienced doctors can forget they had to learn. Ask to be taught and for help when you need it. Is this the right needle for the right job? What is the drip for? If the patient may need blood quickly, use a large size (eg grey; green is suitable for slow IVIs—or even pink if the veins are fragile, see TABLE). Other measures:

- Explain to the patient that veins can be difficult. Take a break…
- Try submerging the arm in a bowl of warm water for 2min.
- Use a blood pressure cuff at 80mmHg as a tourniquet.
- Try putting a small amount of GTN paste over the vein.

If you still cannot get the drip in

You are now downcast, so call your senior— it may hurt your pride but perhaps this was not your time. Calling him could make him, you and your patient happy and not many things do that! If you are afraid to ask your senior, ask another house officer—they are much more likely to succeed than you at this juncture. If you cannot find anyone to help, have a coffee and return an hour later. Veins are capricious: they come and go.

Resiting

Inflamed drip sites need prompt resiting of the drip. If site is healthy, gently infuse a 5mL syringe of 0.9% saline through the cannula. If resistance and/or pain prevents this, the drip needs resiting. If the drip has 'tissued' (subcutaneous leakage), resiting is also required (see BOX).

'The drip has tissued'

If you are called about the above, ask yourself: • Is there fluid in bag and givingset? • Inspect the cannula: take bandage off. • Is the drip still needed? • Are the control taps open? • Are there kinks in the tube? • Is a venous valve blocking the cannula end?

Intravenous cannulae sizes and UK colour conventions

Gauge	Colour	Diameter (mm)	Length (mm)	Flow rate (mL/min^{V})
14G	▪▪	2	45	250
16G	▪	1.7	42	170
18G	▪	1.2	40	90
20G	▪	1	32	55
22G	▪	0.28	25	25
24G	▪	0.7	19	24

V=Maximum flow rate under gravity.

According to Poiseuille's law[1] the flow rate (Q) of a fluid through a tubular structure is inversely proportional to viscosity (η) and length (l) and proportional to the pressure difference across it (Pi - Po) and the radius to the power of 4. Hence: $Q \propto \frac{(Pi - Po)\, r^4}{\eta\, l}$

[1] Poiseuille's law is a neat piece of physiology and worth remembering—it is applicable in some form to almost every system in the body.

A last throw of the dice

Just once it may come down to you. For some, this is one of the challenges and thrills in medicine. There may be no one else available to help when there is an absolute and urgent indication for IV drugs/fluids/blood—and all of the above measures have been tried, and have failed. Think of lonesome night shifts, overrun emergency departments, a disaster scene, war, or medicine in the field. The following measures are not recommended for non-life threatening scenarios.

▸▸ Don't worry. Have a good look again. Feet? Inside of the forearm? Upper arm?

▸▸ Have you really exhausted all of your options for help from a colleague? Maybe the ITU registrar is approachable—they do have remarkable skills.

▸▸ Is the patient familiar with his/her own veins (eg previous IV drug abuser)?

▸▸ If there is only a small amount IV medication required and a small, short vein, you may be able to gain access with a carefully placed butterfly needle that is taped down. Some drugs cannot be passed this way (eg amiodarone, K^+).

▸▸ The external jugular vein may become prominent when the patient is head down (Trendelenberg) by 5-10° (▸not in situations of fluid overload, LVF, ↑ICP) Only attempt cannulation of this vein if you are not going to jeopardise future central line insertion, and if you can clearly determine the surrounding anatomy.

Only do the following if you have had the appropriate training/experience:

▸▸ Options in children: 1 Inserting an intraosseous needle 2-3cm inferior and just medial to the tibial tuberosity (indicated after 2 failed peripheral cannulations in an emergency). This is not generally done in adults (off the battle-field)[4] as the bone is far less forgiving and far more painful. 2 Cannulating a scalp vein.

▸▸ Central venous catheterisation (p762). This may be just as hard in a profoundly hypovolaemic arrest patient, and a good knowledge of local anatomy and of the procedure (± ultrasound guidance) will be invaluable.

NB: A cut down to the long saphenous vein may (must!) be attempted, in extremis,[5] *even if you have no prior experience* (at this site you won't kill by being ham-fisted). ▸▸Make a transverse incision 1-2cm anterior and superior to the medial malleolus ▸▸Free the vein with forceps ▸▸Cannulate it under direct vision.

▸Here, **'first do no harm'** is trumped by **'nothing ventured, nothing gained'**.

Hopefully, it shouldn't ever have to come to these measures, but one day…

Catheterizing bladders

Catheters

Size:

(in French gauge): 12=small; 16=large; 20=very large (eg 3-way). Use the smallest you can. Latex is soft (▸ask about allergy); simplastic firmer. A silastic (silicone) catheter may be used long term, but costs more.

Shape:

Foley is typical (**fig 1**); ***coudé* (elbow)** catheters have an angled tip to ease around prostates but are more risky; **Teeman** catheters have tapered ends for a similar reason; **3-way** catheters are used in clot or debris retention and have an extra, separate lumen for irrigation fluid that is attached to the irrigation set via an extra port on the distal end (**fig 2**)—call the urology ward for advice on how to set this up. **Condom** (Conveen®) catheters♂ (Paul's tubing) have no indwelling parts, and are preferred by nurses and patients (less pain) even though they may leak and fall off.[6]

Catheter problems:

• ***Infection*** (don't use antibiotics unless systemically unwell—discuss treatment with a microbiologist). Consider bladder irrigation, eg 0.9% saline or chlorhexidine 0.02% (may irritate). • ***Bladder spasm*** may be painful —try reducing the water in the balloon or an anticholinergic drug eg ***oxybutinin***.

Methods of catheterizing bladders

1. ***Per urethram:*** This route is used to relieve urinary retention, to monitor urine output in critically ill patients, or to collect urine for diagnosis uncontaminated by urethral flora. ▸It is contraindicated in urethral injury (eg pelvic fracture) and acute prostatitis. Catheterization introduces bacteria into the bladder, so **aseptic technique is vital**.[1] Women and men are often catheterized by nurses; you too should be able to catheterize both.

   - Explain the procedure, and consider analgesia. If you don't have a catheterisation pack, make up your own (see BOX).
   - Lie the patient supine in a well-lit area: women with knees flexed and hips abducted with heels together. Use a gloved hand to prep urethral meatus in a pubis-to-anus direction, holding the labia apart with the other hand. With uncircumcised men (ask the patient beforehand if they have been circumcised to make sure), retract the foreskin to 'prep' the glans; use a gloved hand to hold the penis still and off the scrotum. The hand used to hold the penis or labia should not touch the catheter (use forceps if needed). A sterile drape with a hole in the middle may help asepsis. **Remember:** left hand dirty, right hand sterile.
   - Put sterile ***lidocaine*** 1-2% gel on the catheter tip and ≤10mL into the urethra (≤5mL if ♀). In men, stretch the penis perpendicular to the body to eliminate any urethral folds that may lead to false passage.
   - Use steady **gentle** pressure to advance the catheter. ▸**Never force the catheter**. In men, mild resistance in the first ~10cm may be from a urethral stricture from previous catheterisation. Insert to the hilt; wait until urine emerges before inflating the balloon. Remember to check the balloon's capacity before inflation (written on the outer end). Collect a sterile specimen and attach a drainage bag. Pull the catheter back so that the balloon comes to rest at the bladder neck.
   - If you are having trouble getting past the prostate try: more lubrication; a larger catheter; a *coudé* catheter—or call the urologists, who may use a guide-wire.

   ▸ Remember to reposition the foreskin in uncircumcised men after the catheter is inserted to prevent massive oedema of the glans and paraphimos (see p66).

2. ***Suprapubic catheterization*** Ensure the bladder is distended so that there is no risk of peritoneal penetration; you may have to wait for it to fill up. Clean the skin, infiltrate with local anaesthetic down to the bladder, nick the skin, and then insert trocar down vertically above the symphysis pubis. When urine is draining, advance the catheter over the trocar and tape it down securely.

▸Have all the kit ready beforehand and a helping hand as it can get messy!

Checklist:

- Gloves
- Catheter
- ***Lidocaine*** jelly
- 10mL 0.9% saline
- Prep, eg Savlon®
- Drape
- Kidney dish
- Gauze swabs
- Forceps
- Drainage bag
- Specimen container

Self-catheterisation

This is a good, safe way of managing chronic retention from a neuropathic bladder (eg in multiple sclerosis, diabetic neuropathy, spinal tumour or trauma). Never consider a patient in difficulties from a big residual volume to be too old, young, or disabled to learn. 5-yr-old children can learn the technique, and can have their lives transformed—so motivation may be excellent. There may be fewer UTIs as there is no residual urine—and less reflux obstructive uropathy. Assessing suitability entails testing sacral dermatomes: a 'numb bum' implies ↓ sensation of a full bladder; higher sensory loss may mean catheterization will be painless. Get help from your continence adviser who will be in a position to teach the patient or carer that catheterizations must be gentle (the catheter is of a much smaller calibre), particularly if sensation is lacking, and must number >4/d ('always keep your catheter with you; don't wait for an urge before catheterizing'). See **fig 3**.

Fig 1. A size 14F latex Foley catheter with the balloon inflated *via* the topmost port of the outer end (green).[1] **NB:** These images are not to scale.

Fig 2. The external end of a size 20F 3-way catheter. The lowest port is for the bladder irrigation fluid and the uppermost port (yellow) is for balloon inflation.

Fig 3. A size 10F catheter for self-catheterisation. They are usually much smaller than indwelling catheters eg 10F compared to 14F. Note that this catheter also has no balloon.

"The catheter is not draining…"

You will be asked to check catheters that are not draining. Possibilities are:

- The catheter is bypassing: a condom catheter may be more appropriate.
- The catheter is blocked: with aseptic technique flush and withdraw 20mL of sterile 0.9% saline with a bladder syringe. This may get the flow going again. A 3-way catheter may be needed if there is clot or debris retention.
- The catheter has slipped into the proximal (prostatic♂) urethra, possible even if the balloon is fully inflated. This is may be the case if a flush enters but cannot be withdrawn: with aseptic technique deflate the balloon, advance and reinflate, then flush and withdraw again.
- Renal hypoperfusion: in a dehydrated/post-op patient a fluid challenge of 250mL Gelofusine® STAT (or slower if renal/cardiac co-morbidity) may help. Check all other parameters (eg pulse, BP, CVP) and increase rate of IV fluids if appropriate.

  ▸▸ Acute renal failure (p820): this is unlikely, though most probably from renal hypoperfusion (ie pre-renal failure), but there may be other factors involved causing acute tubular necrosis, eg nephrotoxic drugs.

  ▸▸ The catheter has perforated the lower urinary tract on insertion and is not lying in the bladder or urethra. If suspected, call the urologists

immediately.

Remember: urine output should be >400mL in 24h or >0.5mL/kg/h (see p562).

Trial without catheter (TWOC)

When it is time to remove a catheter, the possibility of urinary retention must be considered. If very likely, arrange for a urology outpatient TWOC in 2 weeks; otherwise remove the catheter first thing one morning. If retention does occur, insert a long-term catheter (eg silicone) and arrange urology clinic follow-up.

Tapping ascites

Ascites may be sampled to provide a cytological or bacterial diagnosis, eg to exclude spontaneous bacterial peritonitis (SBP, see p252). Before starting ensure that you know the patient's platelets + clotting times. If they are abnormal, seek help before proceeding.

- Place the patient flat and tap out the ascites, marking a point where fluid has been identified, avoiding vessels, stomas and scars (adhesions to the anterior abdominal wall). The left side may be safer (less chance of nicking liver/spleen).
- Clean the skin. Infiltrate some local anaesthetic, eg 1% ***lidocaine*** (see p559).
- Insert a 21G needle on a 20mL syringe into the skin and advance while aspirating until fluid is withdrawn.
- Remove the needle and apply a sterile dressing.
- Send fluid for ***microscopy***, ***culture***, ***chemistry*** (protein, see p176), and ***cytology***. Call microbiology to forewarn them if urgent analysis of the specimen is required.

Diagnostic aspiration of a pleural effusion

- If not yet done, a CXR may help evaluate the side and size of the effusion.
- Percuss the upper border of the pleural effusion and choose a site 1 or 2 intercostal spaces below it (usually posteriorly or laterally).
- Mark the spot and then clean the area with an antiseptic solution.
- Infiltrate down to the pleura with 5-10mL of 1% ***lidocaine*** (see p559).
- Attach a 21G needle to a syringe and insert it just above the upper border of the rib below the mark to avoid the neurovascular bundle (see BOX). Aspirate whilst advancing the needle. Draw off 10-30mL of pleural fluid.

Send fluid to the lab for ***chemistry*** (protein, glucose, pH, LDH, amylase); ***bacteriology*** (microscopy and culture, auramine stain, TB culture); ***cytology*** and, if indicated, ***immunology*** (rheumatoid factor, ANA, complement).

Pleural biopsy

This is usually performed in patients with a pleural effusion when analysis of pleural fluid has not provided an underlying diagnosis. It should not be performed on the ward in patients without an effusion as this requires a different approach. This procedure requires some practice, so if you are inexperienced, ask a senior doctor to assist you.

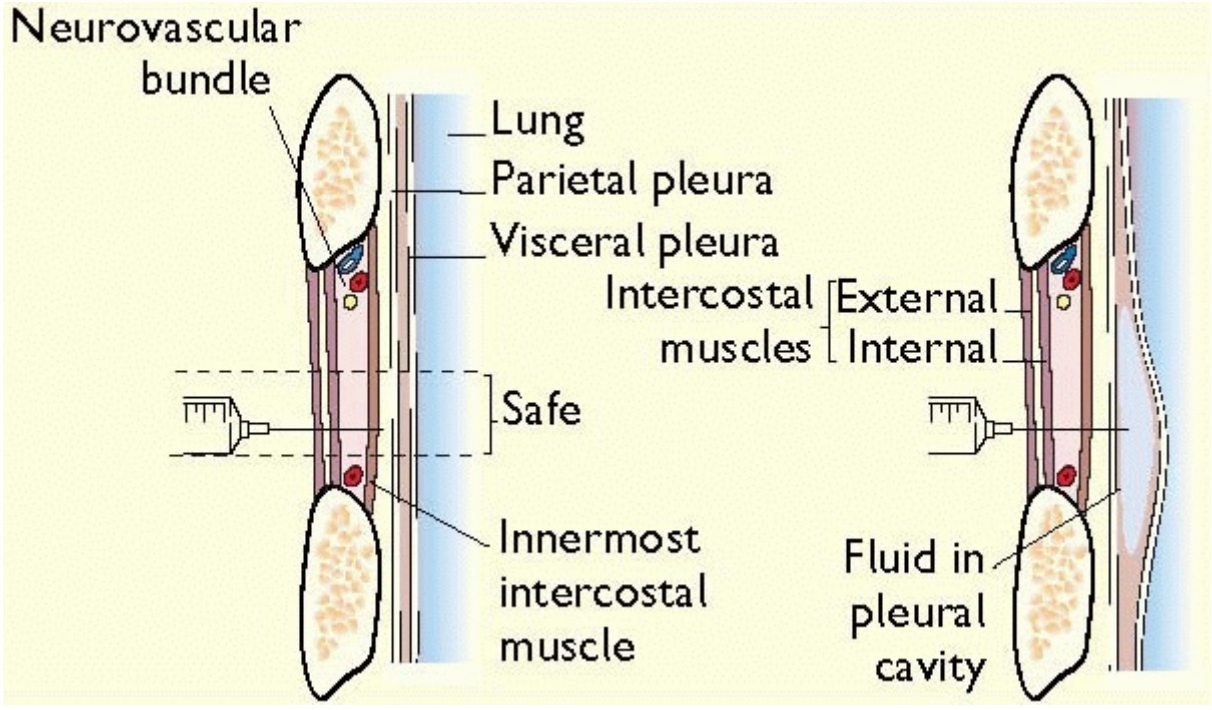
- Place the patient in an upright position on the edge of the bed, arms resting on a pillow on a bed-table to provide support.
- Identify the upper border of the pleural effusion posteriorly or laterally and mark an intercostal space 1-2 ribs below this.
- Clean the skin with an antiseptic solution and apply sterile drapes.
- Infiltrate down to the pleura with 5-10mL of 1% ***lidocaine*** (see p559).
- Check that you are in the correct space by aspirating pleural fluid.
- Make a deep skin incision 0.5cm wide immediately above the upper border of the rib below the chosen intercostal space (avoids neurovascular bundle).
- Carefully advance the Abrams' needle through the incision until a ‘give’ is felt as you enter the pleural space.
- Open the needle by twisting the trocar. Check that fluid can be aspirated.
- Manoeuvre the open needle so that the cutting notch is pointing inferiorly (to avoid the neurovascular bundle) and caught on the pleura—pull the needle back slightly at an angle to the chest wall—then close the needle and withdraw. A slight tug may be required at this stage.
- Withdraw the needle in expiration and repeat.
- Place the tissue samples in the appropriate media for histological and microbiological examination. Send to the lab for *microscopy*, *culture*, and *histology*.
- Withdraw the needle, and apply a sterile dressing, occasionally a single suture may be required. Perform a post-procedure CXR.

Abdominal paracentesis

For patients with tense, refractory or recurrent ascites that is symptomatic, it is possible to drain the ascites using a Bonnano® catheter (initially designed for suprapubic catheterisation). Paracentesis in such patients even in the presence spontaneous bacterial peritonitis may be safe.[7] The procedure is best done supervised before attempting it alone. ***Contraindications:*** End-stage cirrhosis; coagulopathy; hyponatraemia (≤126mmol/L); sepsis. The main complication of the procedure is severe hypovolaemia secondary to reaccumulation of the ascites, so intravascular replenishment with a plasma expander is required—eg 100mL 20% ***human albumin*** IV for each litre of ascites drained.[8] You may need to call the haematology lab to request this in advance.

- Ensure you have good IV access—eg 18G cannula in the antecubital fossa.
- Examine the abdomen carefully, evaluating the ascites and checking for organomegaly. Mark where you are going to enter. Approach from the left side unless previous local surgery/stoma prevents this—call a senior for support and advice if this is the case.
- Prepare the patient as if for an ascitic tap (see OPPOSITE), taking extra care to keep the procedure aseptic (use a sterile drape). Infiltrate the local anaesthetic.
- Perform an ascitic tap first so that you know you are in the correct place.
- Carefully thread the catheter over the (large and long) needle using the guide so that the pig-tail has been straightened out. Remove the guide.
- With the left hand hold the needle ~1 inch from the tip—this will stop it from advancing too far (and from performing an aortic biopsy!). With the right hand, hold the other end.
- Gently insert the needle perpendicular the skin at the site of the ascitic tap up to your hold with your left hand—ascites should now drain easily. If necessary advance the needle and catheter a short distance until good flow is achieved.
- Advance the catheter over the needle with your left hand, keeping the needle in exactly the same place with your right hand. ▸Do not re-advance the needle because it will go through the curled pig-tail and do not withdraw it because you won't be able to thread in the catheter.
- When fully inserted, connect the catheter to a drainage bag (keep it below the level of the abdomen) and tape it down securely to the skin.
- The patient should stay in bed as the ascites drains.
- Replenish intravascular volume with human albumin (see above).
- Ask the nursing staff to remove the catheter after 6h or after a pre-determined volume has been drained. (Up to 20L can come off in 6 hours!)
- Send a sample of ascitic fluid to the lab for MC+S.
- Check U&E after the procedure and re-examine the patient.

Safe approach to entering the pleura by the intercostal route



Inserting a chest drain

Indications:

- Pneumothorax: ventilated; tension; persistent/recurrent (eg <24h after 1st aspiration); large 2nd spontaneous pneumothorax if >50yrs old)
- Malignant pleural effusion
- Empyema or complicated parapneumonic effusion
- Traumatic haemopneumothorax;

- Air transfer
- Post-operatively: eg thoracotomy; oesophagectomy; cardiothoracic surgery.

Sterile procedure: [9]

- Have the x-rays or CT scans available to confirm location for chest drain insertion..
- Preparation: Trolley with dressing pack; iodine; needles; 10mL syringe; 20mL 1% ***lidocaine***; scalpel (*N*°15); suture; chest drain (eg 10-14F, if trauma or haemothorax larger gauge eg 28-30F); underwater drainage bottle; connection tubes; sterile H_2O; tape. Incontinence pad under patient. Swab extensively.
- Choose insertion site:[10] 4th-6th intercostal space, anterior- to mid-axillary line— the 'safe triangle' (see BOX). A more posterior approach eg the 7th space posteriorly may be required to drain a loculated effusion, and occasionally the 2nd intercostal space in the mid-clavicular line may be used for apical pneumothoraces—however, both approaches tend to be less comfortable.
- Infiltrate down to pleura with 10-20mL of 1% ***lidocaine***. Check that either air or fluid can be aspirated from the proposed insertion site—if not **do not** proceed. Wait 3min.
- Make a 2cm incision above 6th rib, to avoid neurovascular bundle under rib 5. **Bluntly** dissect down to the pleura. Puncture pleura with scissors or forceps. If large bore tube (>24F), then sweep a finger inside chest to clear adherent lung and exclude (eg in blunt abdominal trauma) stomach in the chest! **NB:** Some new kits use a Seldinger technique for insertion.

▸ Before inserting the drain, remove the metal trochar completely; introduce the drain **atraumatically** using forceps to advance it.

- Advance the tip upwards to the apex (or base if draining an effusion). Stop on meeting resistance. Then attach the drain via the tubing to the underwater seal. Ensure that the longer tube within the bottle is underwater and bubbling with respiration. If the patient is to be moved to another hospital, substitute Heimlich flutter valve or drainage bag with flap valve for underwater drain.

▸ You should never clamp chest drains inserted for pneumothoraces. Clamping is occasionally used when pleural effusions are being drained to control the rate of drainage and prevent expansion pulmonary oedema.[11]

- With large/medium bore tubes, the incision should be closed with a mattress suture or suture across the incision. Purse string sutures are no-longer recommended as they may lead to increased scarring and wound pain.
- Fix the drain with a second suture tied around the tube like a 'Roman gaiter'. Secure the drain with tape (eg 'Sleek®') to prevent it from slipping.
- Request a CXR to check the position of the drain.

Complications:

- Thoracic or abdominal organ injury
- Lymphatic damage ∴ chylothorax
- Damage to long thoracic nerve of Bell ∴ wing scapula
- Rarely, arrhythmia.[12]

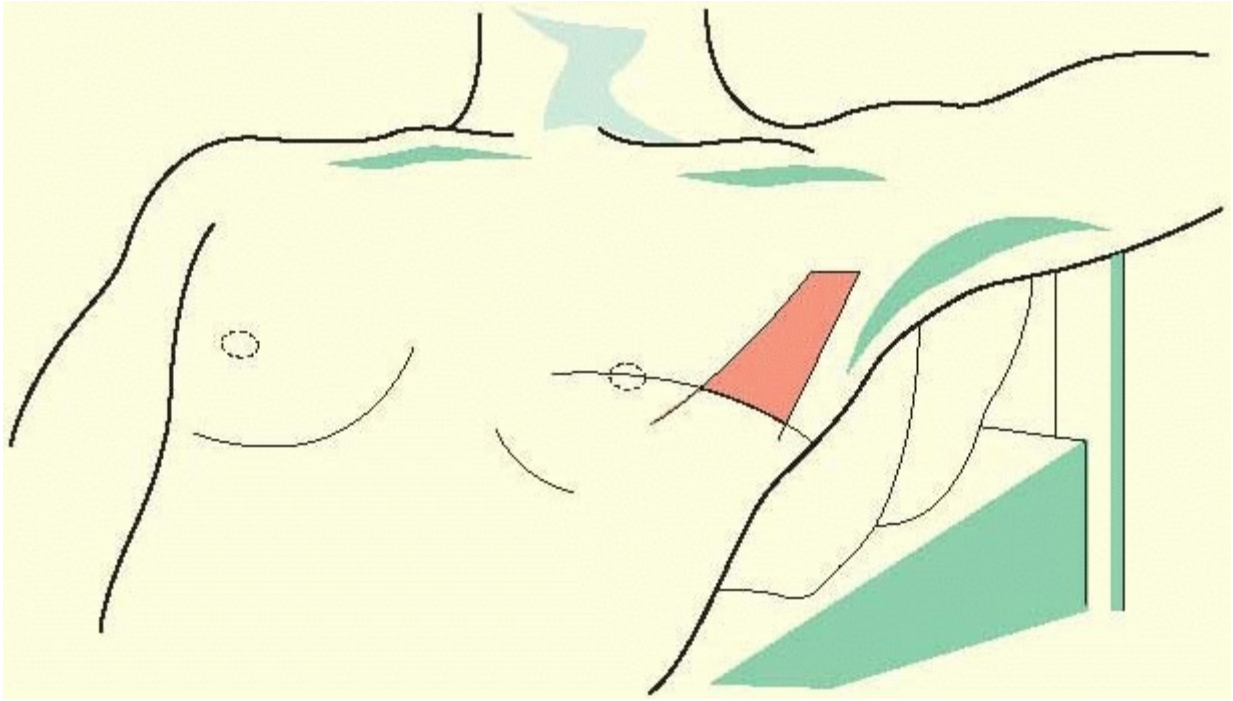
Watch out for:

- Retrograde flow back into the chest
- Persistent bubbling—there may be a continual leak from the lung
- Blockage of the tube from clots or kinking—no swinging or bubbling
- Malposition—check position with CXR.

Removal (in pneumothorax)

should be considered when the drain is no-longer bubbling and the CXR shows reinflation. Smartly withdraw during expiration or Valsalva manoeuvre and close the hole immediately with the pre-placed suture. There is no need to clamp the drain beforehand as the for need reinsertion is unlikely.[RCT][13] Give analgesia beforehand, eg ***morphine*** or a strong NSAID.[14]

The 'safe triangle' for insertion of a chest drain



Redrawn from Thorax 2003 58 suppl II; ii55, with permission.

Relieving a tension pneumothorax

Symptoms:

Acute respiratory distress, chest pain, ▸▸respiratory arrest.

Signs:

Hypotension; distended neck veins; asymmetrical lung expansion; trachea and apex deviated away from side of reduced air entry and hyperresonance to percussion. ▸▸There is no time for a CXR (but see **fig 1**, p735).

Aim:

To release air from the pleural space. In a tension pneumothorax air is drawn into the intra-pleural space with each breath, but cannot escape due to a valve-like effect of the tiny flap in the parietal pleura. The increasing pressure progressively embarrasses the heart and the other lung.

▸▸100% oxygen.

▸▸ Insert a large bore IV cannula (eg Venflon®) usually through the 2nd intercostal space in the mid-clavicular line or the 'safe triangle' for chest drain insertion (see BOX). Remove the stylet, which will allow the trapped air to escape, usually with an audible hiss. The tension pneumothorax has now been converted to an open pneumothorax. Tape securely. ▸Don't recover the cannula as tensioning will recur.

▸▸ Proceed to formal chest drain insertion (see OPPOSITE).

Aspiration of a pneumothorax

Identify the 2nd intercostal space in the midclavicular line (or 4-6th intercostal space in the midaxillary line) and infiltrate with 1% ***lidocaine*** down to the pleura overlying the pneumothorax.

Insert a 16G cannula into the pleural space. Remove the needle and connect the cannula to a 3-way tap and a 50mL syringe. Aspirate up to 2.5L of air (50mL×50). Stop if resistance is felt, or if the patient coughs excessively. Request a CXR to confirm resolution of the pneumothorax. If successful, consider discharging the patient and repeating the CXR after 24h to exclude recurrence, and again after 7-10d. Advise to avoid air travel for 6 weeks after a normal CXR. Diving should be permanently avoided.

If aspiration is unsuccessful (in a significant, symptomatic pneumothorax), insert an intercostal drain (see OPPOSITE).

Lumbar puncture (LP)

Contraindications

• Bleeding diathesis; • Cardiorespiratory compromise; • Infection at site of needle insertion, and most importantly: • ↑Intracranial pressure (suspect if very severe headache, ↓level of consciousness with falling pulse, rising BP, vomiting, focal signs, or papilloedema). Give urgent treatment as needed and discuss urgently with a relevant clinician with a view to CT scanning. CT is not infallible, so be sure your indication for LP is strong.

Method

Explain to the patient **what** sampling CSF entails, **why** it is needed, that **co-operation** is vital, and that they can **communicate with you** at all stages.

- Place the patient on his or her left side, with the back on the edge of the bed, fully flexed (knees to chin). Avoid allowing the patient to slump.
- Landmarks: plane of iliac crests through the level of L3/4 (see BOX). In adults, the spinal cord ends at the L1/2 disc. Mark L3/4 intervertebral space

(or one space below, L4/5), eg by a gentle indentation of a thumb-nail on the overlying skin (better than a ballpoint pen mark, which might be erased by the sterilizing fluid).

- Wash hands. Don a mask and sterile gloves.
- Sterilize the back with tincture of iodine (unless allergic).
- Open the spinal pack. Check manometer fittings. Have 3 plain sterile tubes and 1 fluoride tube (for glucose) ready.
- Inject 0.25-0.5mL 1% ***lidocaine*** (p559) under skin at marked site.
- Wait 1min, then insert spinal needle (22G, stilette in place) through the mark aiming towards umbilicus. Feel resistance of spinal ligaments, and then the dura, then a 'give' as the needle enters the subarachnoid space. **NB:** Keep the needle's bevel facing **up**, parallel with dural fibres.
- Withdraw stilette. Wait for CSF.
- Measure CSF 'opening' pressure with a manometer.
- Catch fluid in three sequentially numbered bottles (<5-10mL total). Consider taking and privately reserving a labelled sample in case of an accident!
- Remove needle and apply dressing. Send CSF promptly for ***microscopy***, ***culture***, ***protein***, and ***glucose*** (do plasma glucose too)—call the lab to let them know. If applicable, also send for: cytology, fungal studies, TB culture, virology (including Herpes PCR), syphilis serology, oligoclonal bands (with serum sample for comparison) if multiple sclerosis suspected. Is there xanthochromia (p692)?
- Lying flat for >1h is traditionally advised (probably unnecessary), checking CNS observations and BP regularly. Post-LP headache is partly preventable by reducing CSF leakage by using finer needles shaped to part the dura rather than cut it: see BOX.

CSF composition

Normal values:

Lymphocytes <5/mm^3; no polymorphs; protein <0.4g/L; glucose >2.2mmol/L (or $\gtrsim$50% plasma level); pressure <200mmCSF.

In meningitis:

See p806.

In multiple sclerosis:

See p488.

Bloody tap:

This is an artefact due to piercing a blood vessel, which is indicated (unreliably) by fewer red cells in successive bottles, and no yellowing of CSF (xanthochromia). To estimate how many white cells (*W*) were in the CSF before the blood was added, use the following:

$$W = \text{CSF WCC} - [(\text{blood WCC} \times \text{CSF RBC}) \div \text{blood RBC}]$$

If the blood count is normal, the rule of thumb is to subtract from the total CSF WCC (per µL) one white cell for every 1000 RBCs. To estimate the true protein level, subtract 10mg/L for every 1000 RBCs/mm^3 (be sure to do the count and protein estimation on the same bottle). **NB:** High protein levels in CSF make it appear yellow.

Subarachnoid haemorrhage:

Xanthochromia (yellow supernatant on spun CSF). Red cells in equal numbers in all bottles (unreliable). RBCs will excite an inflammatory response (eg CSF WCC raised), most marked after 48h.

Raised protein:

Meningitis; MS; Guillain-Barré syndrome.

Very raised CSF protein:

Spinal block; TB; or severe bacterial meningitis.

Post-LP headache

Risk:

~30%, typically occurring within 24h of LP, with resolution over hours to 2wks (mean: 3-4d). Patients describe a constant, dull, ache bilaterally which is more frontal than occipital. The most characteristic symptom is of **positional (orthostatic) exacerbation**—worse when upright and usually pain-free when recumbent. There may be mild meningism or nausea. The pathology is thought to be continued leakage of CSF from the puncture site and intracranial **hypo**tension, though there may be other mechanisms involved.[15]

Prevention:

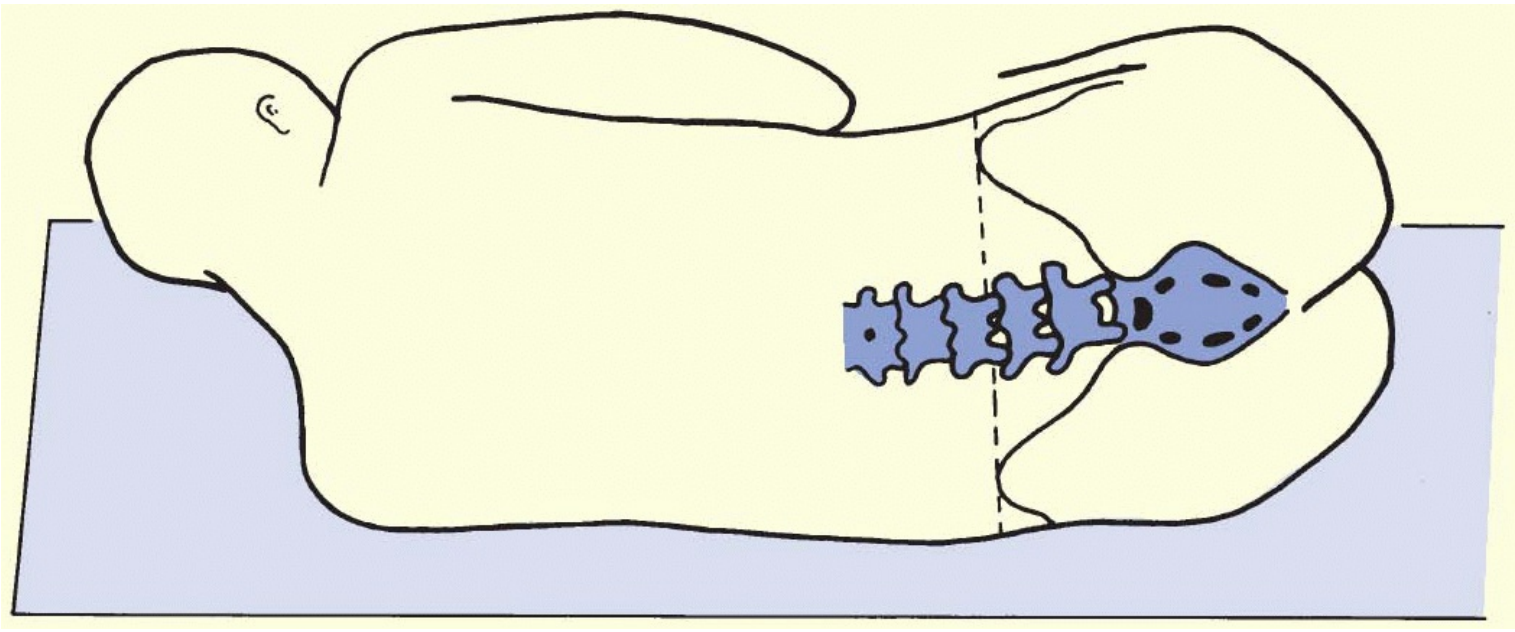
Use the smallest spinal needle that is practical (22G) and keep the bevel aligned as described OPPOSITE. **Blunt** needles (more expensive!) can reduce risk, perhaps from 30% to 5%—and are recommended (ask an anaesthetist about supply).[16] Collection of CSF takes too long (>6min) if needles smaller than 22G are used.[17]

Treatment:

Despite years of anecdotal advice to the contrary, none of the following have ever been shown to be a risk factor: position during or after the procedure; hydration status before, during, or after; amount of CSF removed; immediate activity or rest post-LP.[MET18] 18 Time is a consistent healer. For severe or prolonged headaches, ask an anaesthetist about a **blood patch**.[RCT19] This is a careful injection of 20mL of autologous venous blood into the adjacent epidural space (said to 'clog-up the hole'). Immediate relief occurs in 95%.

NB: Post-LP brain MRI scans often show diffuse meningeal enhancement with gadolinium. This is thought to be a reflection of increased blood flow secondary to intracranial hypotension. Interpret these scans with caution and in the context of the patient's clinical situation.

Defining the 3rd - 4th lumbar vertebral interspace



After Vakil Diagnosis & Management of Medical Emergencies, OUP

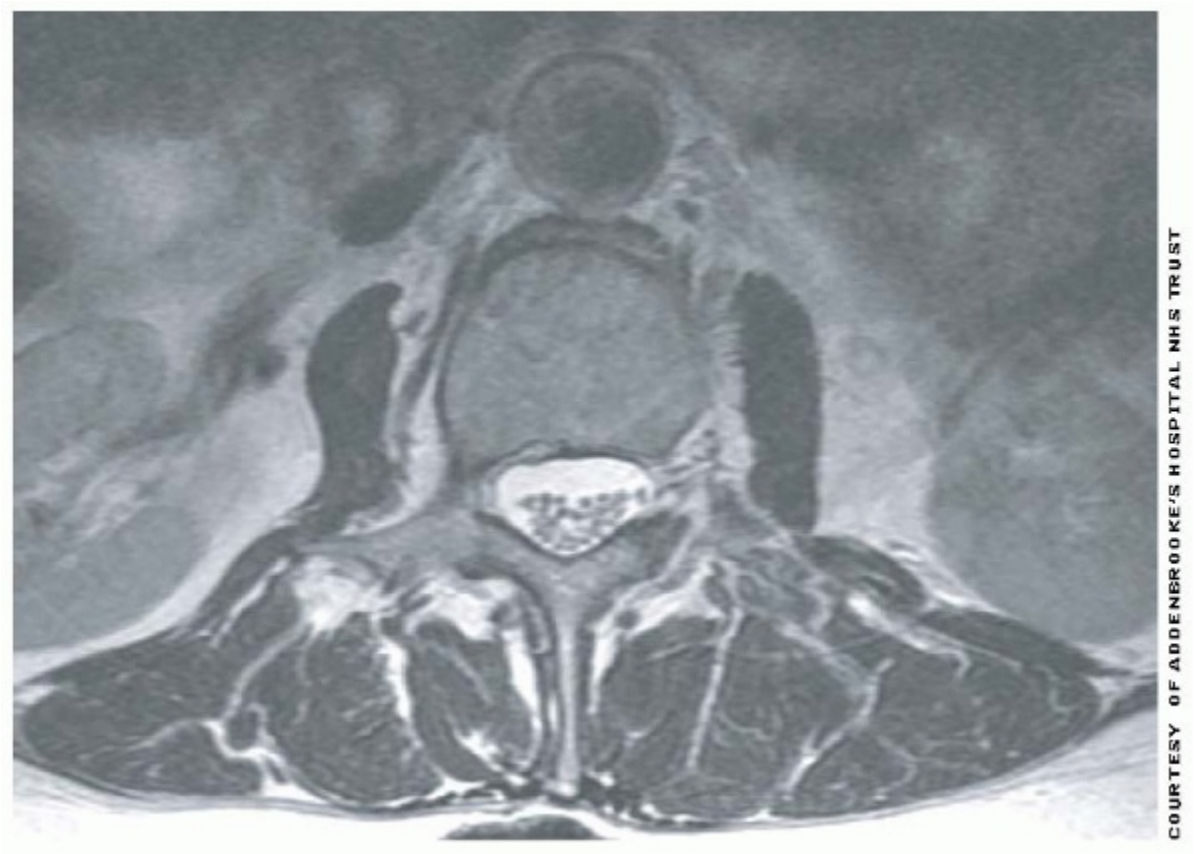


Fig 1. Axial T2 weighted MRI of the lumbar spine. The conus ends at the L1/L2 level with continuation of the cauda equina. Lumbar puncture below the L2 level will not damage the cauda equina as the nerve roots will part around an LP needle.

Cardioversion/defibrillation

▸Do not wait for a crisis before familiarizing yourself with the defibrillator, as there several types. Day 1 on a new ward should include a visit to the 'defib trolley'.

Indications:

VF/VT, fast AF (p116), supraventricular tachycardias if other treatments (p112) have failed or there is haemodynamic compromise.

Aim:

To completely depolarize the heart using a direct current.

Procedure:

- Unless critically unwell, conscious patients require a general anaesthetic.
- Almost all defibrillators are now paddle-free and use 'hands free' pads instead (less chance of skin arc than jelly). Place the pads (eg Littmann™ Defib Pads) on chest, 1 over apex (p29) and 1 below right clavicle. The positions are often given by a diagram on the reverse of the pad.
- ***Monophasic defibrillators*** **(fig 1)**: Set the energy level at 360J for VF/VT; 100J for AF; 50J for atrial flutter.
- ***Biphasic defibrillators*** **(fig 2)**: Impedence is less with a biphasic shock and 150J is used for shocks for VF/VT. They use less energy and are just as effective as monophasic defibrillators in cardioversion of AF, if not better.[RCT][20][RCT][21] One large retrospective study showed that biphasic cardioversion of atrial flutter was not as successful.[22]
- ***Automatic external defibrillators (AED):*** Can be used by anyone who can turn them on and apply the pads. Follow the instructions given by the AED.

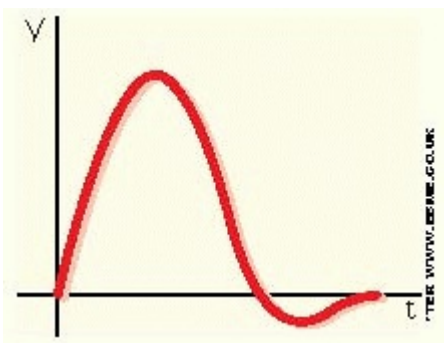


Fig 1. The dampened sine monophasic waveform.

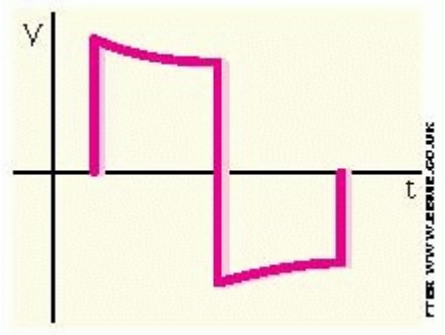


Fig 2. Rectilinear biphasic waveform with truncated exponential decay. Most new external defibrillators use this waveform.

Shocking:

Clearly state that you are charging the defibrillator.

Make sure no one else is touching the patient, the bed, or anything in turn touching these.

Remove oxygen from the patient as it is flammable and could be ignited by a flash arc.

Clearly state that you are about to shock the patient.

Press the button(s) on the electrode(s) to give the shock. If there is a change in rhythm before you shock and the shock is no longer required, turn the dial to 'discharge'. Do not allow anyone to approach until the reading has dropped to 0J.

After a shock: watch ECG; repeat the shock (at 200J once again, then 360J subsequently if monophasic).

Consider anticoagulation, as the risk of emboli is increased.

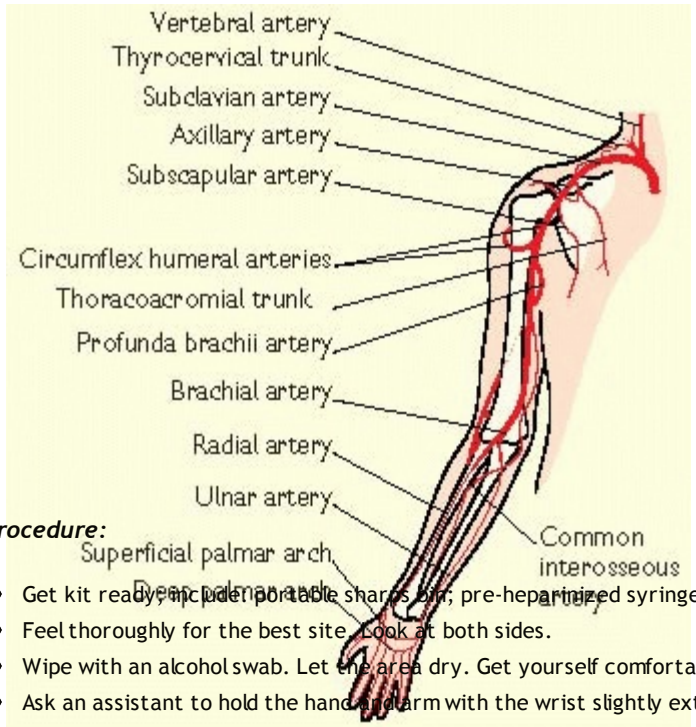
Get an up-to-date 12-lead ECG.

NB: For AF and SVT, it is necessary to synchronize the shock on the R-wave of the ECG (by pressing the 'SYNC' button on the machine). This ensures that the shock does not initiate a ventricular arrhythmia. **If the sync mode is engaged in VF, the defibrillator will not discharge!**

▸In children, use 2J/kg, then 4J/kg in VF/VT; if monophasic, and if >10kg, use **adult** paddles; OHCS p239.

Taking arterial blood gas (ABG) samples[1]

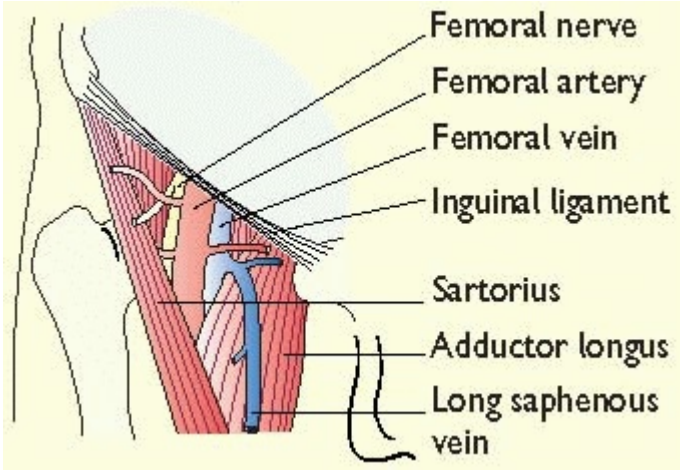
The reaction of a patient to ABG sampling is often very different to when they are subjected to venepuncture, so try to explain that the blood sample you are about to take is going to feel different and is for a different purpose (p148 for indications & analysis). The usual site is the radial artery at the wrist. ▸Don't use this site if there is an arteriovenous fistula for haemodialysis.



Procedure:

- Get kit ready; include portable sharps bin; pre-heparinized syringe; needle—blue size (23G) is good; gloves; alcohol swab; gauze swab; tape.
- Feel thoroughly for the best site. Look at both sides.
- Wipe with an alcohol swab. Let the area dry. Get yourself comfortable.
- Ask an assistant to hold the hand and arm with the wrist slightly extended.
- Before sampling, expel any excess heparin in the syringe. Infiltration over the artery with a small amount of 1% ***lidocaine*** (p559) through a 25G (orange) needle makes the procedure painless.
- Hold the syringe like a pen, with the needle bevel up. Let the patient know you are about to take the sample. Feel for the pulse with your other hand and enter at 45°, aiming **beneath** the finger you are feeling with.
- The syringe will fill up on it is own in a pulsatile manner if you are in the artery. Rarely, entry into a vein next to the artery will give a similar result. Colour of the blood is no guide its source!
- Remove the needle when enough blood has been taken (1-2mL to allow for spillage or a dud reading from the machine) and apply firm pressure until any leakage is stemmed to avoid a large lump followed by a massive bruise!
- Expel any air from the syringe as this will alter the oxygenation of the blood. Cap and label the sample, noting if the patient was on supplementary oxygen. Take the sample to the nearest analysis machine or send it by express delivery to the lab (which may be by your own feet). If it is going to stand for any foreseeable length of time then put the sample in a bag of ice.
- Syringes and analysis machines differ, so get familiar with the local nuances.

The other site that is amenable to ABG sampling is the femoral artery. Surprisingly this may be less uncomfortable as it is a relatively less sensitive area and because when supine, the patient cannot see the needle and thus may feel less apprehensive. The brachial artery can also be used, but be aware that median nerve sits closely on its medial side.



Cricothyroidotomy

Essence

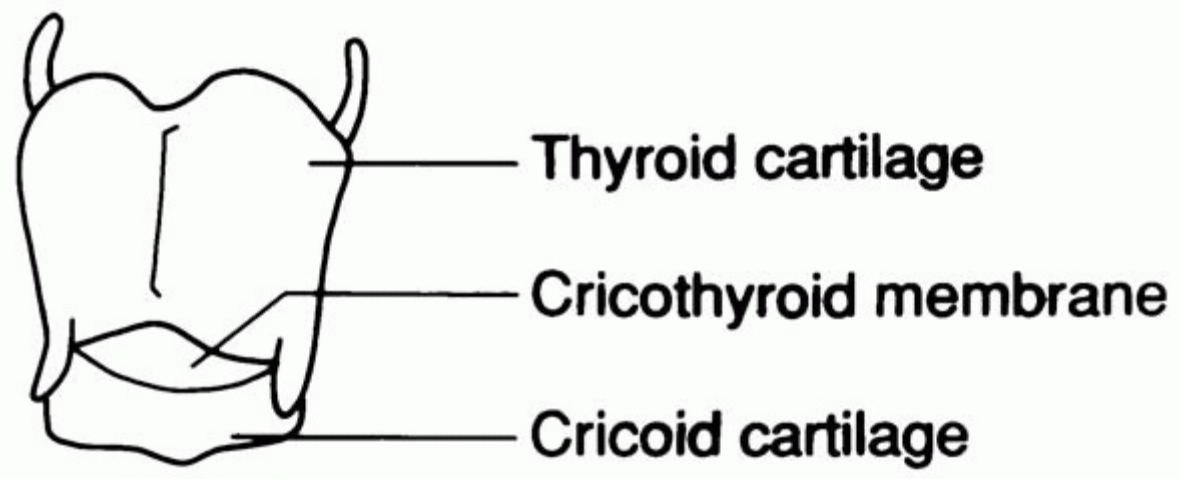
An emergency procedure to overcome airway obstruction above the level of the larynx.

Indications

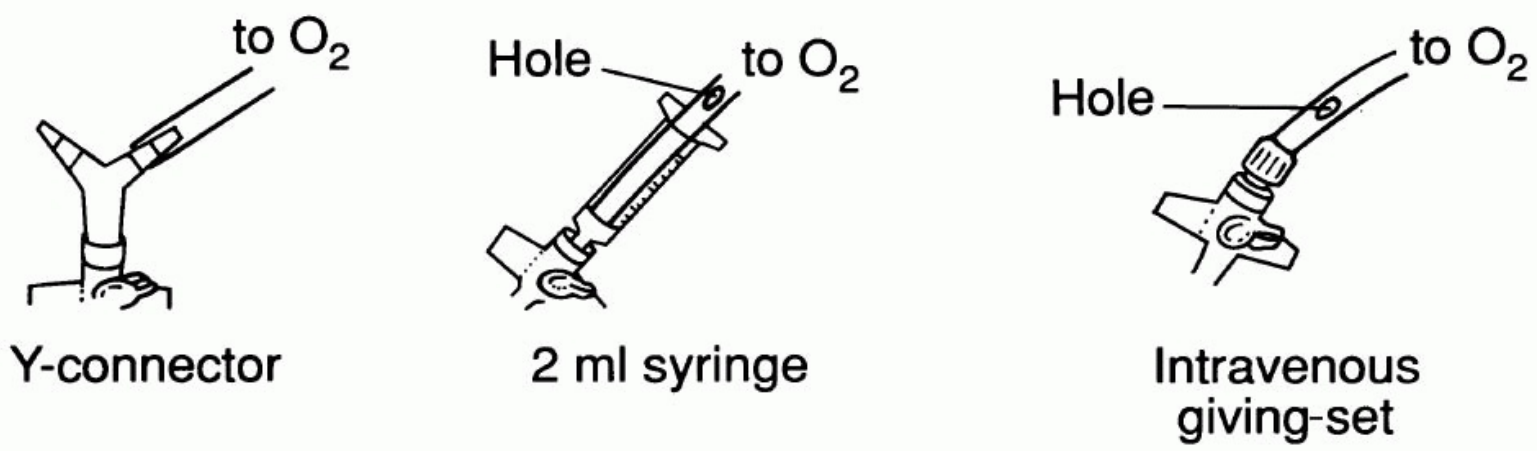
Upper airway obstruction when endotracheal intubation not possible, eg irretrievable foreign body; facial oedema (burns, angio-oedema); maxillofacial trauma; infection (epiglottitis).

Procedure

Lie the patient supine with neck extended (eg pillow under shoulders) unless there is suspected cervical-spine instability. Run your index finger down the neck anteriorly in the midline to find the notch in the upper border of the thyroid cartilage: just below this, between the thyroid and cricoid cartilages, is a depression—the cricothyroid membrane.



1 ***Needle cricothyroidotomy:*** Pierce the membrane with large-bore cannula (14G) attached to syringe: withdrawal of air confirms position; ***lidocaine*** may or may not be required). Slide cannula over needle at 45° to the skin superiorly in the sagittal plane. Use a Y-connector or improvise connection to O_2 supply at 15L/min: use thumb on Y-connector to allow O_2 in over 1s and CO_2 out over 4s ('transtracheal jet insufflation'). This is the preferred method in children <12yrs. This will only sustain life for 30-45min before CO_2 builds up.



2 ***Mini-Trach II®:*** This contains a guarded blade, introducer, 4mm uncuffed tube (slide over introducer) with ISO connection and binding tape. The patient will have to be ventilated via a bag, as the resistance is too high to breathe spontaneously. This will sustain for 30-45min.

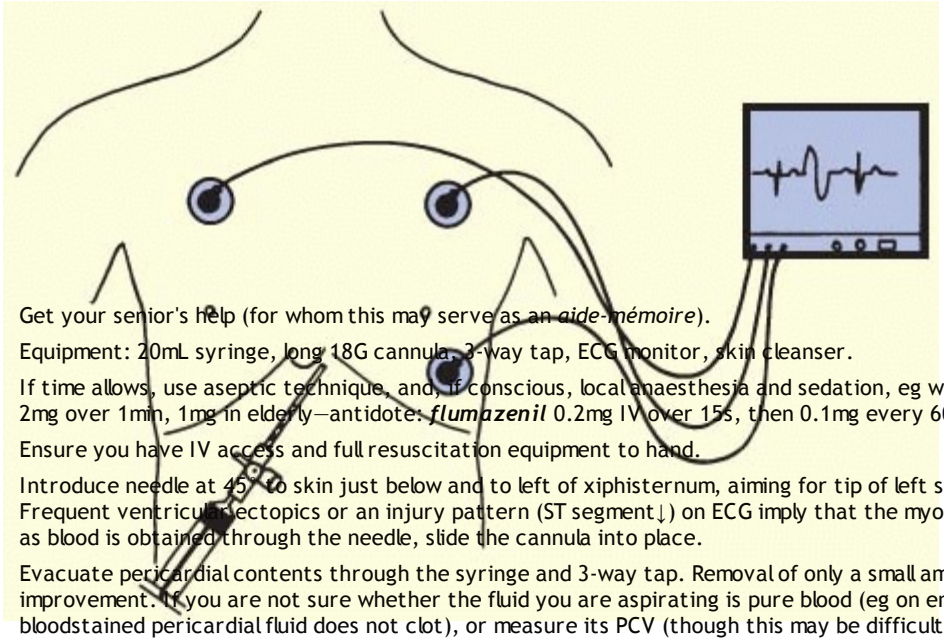
3 ***Surgical cricothyroidotomy:*** Smallest tube for prolonged ventilation is 6mm. Introduce high-volume low-pressure cuff tracheostomy tube through a horizontal incision in membrane. Take care not to cut the thyroid or cricoid cartilages.

Complications

Local haemorrhage ± aspiration; posterior perforation of trachea ± oesophagus; subglottic stenosis; laryngeal stenosis if membrane over-incised in childhood; tube blockage; subcutaneous tunnelling; vocal cord paralysis or hoarseness (the recurrent laryngeal nerve runs superiorly in the tracheooesophageal groove).

▸**NB:** Needle and Mini-Trach® are temporary measures pending formal tracheostomy.

Emergency needle pericardiocentesis[1]



- Get your senior's help (for whom this may serve as an *aide-mémoire*).
- Equipment: 20mL syringe, long 18G cannula, 3-way tap, ECG monitor, skin cleanser.
- If time allows, use aseptic technique, and, if conscious, local anaesthesia and sedation, eg with ***midazolam***: titrate up to 0.1mg/kg IV—start with 2mg over 1min, 1mg in elderly—antidote: ***flumazenil*** 0.2mg IV over 15s, then 0.1mg every 60s, up to 1mg in total.
- Ensure you have IV access and full resuscitation equipment to hand.
- Introduce needle at 45° to skin just below and to left of xiphisternum, aiming for tip of left scapula. Aspirate continuously and watch ECG. Frequent ventricular ectopics or an injury pattern (ST segment↓) on ECG imply that the myocardium has been breached—withdraw slightly. As soon as blood is obtained through the needle, slide the cannula into place.
- Evacuate pericardial contents through the syringe and 3-way tap. Removal of only a small amount of fluid (eg 20mL) can produce marked clinical improvement. If you are not sure whether the fluid you are aspirating is pure blood (eg on entering a ventricle), see if it clots (heavily bloodstained pericardial fluid does not clot), or measure its PCV (though this may be difficult in the acute setting).
- You can leave the cannula *in situ* temporarily, for repeated aspiration. If there is reaccumulation, pericardiectomy may be needed.
- Send fluid for microscopy and culture, as needed, including tests for TB.

Complications:

Laceration of ventricle or coronary artery (± subsequent haemopericardium); aspiration of ventricular blood; arrhythmias (ventricular fibrillation); pneumothorax; puncture of aorta, oesophagus (± mediastinitis), or peritoneum (± peritonitis).

Subclavian venous cannulation

Subclavian venous cannulae may be inserted to provide a measurement of the central venous pressure (CVP), to administer certain drugs (eg ***amiodarone***, chemotherapy), or for intravenous access (fluid therapy, TPN). They are not without hazards (see complications below), so decide whether the patient requires one first, and then ask for help if you are inexperienced. In an emergency the procedure can be done using the landmark method (described below), though NICE now recommends that all central venous catheterisation should now be performed using US guidance.[1][23] See TABLE for contraindications.

Procedure:

- If possible, get written consent for the procedure (p554). Check clotting + platelets.
- Position the patient flat, with 1 pillow. Head-down tilt may help if volume depleted.

▸ This can compromise cardiac function and precipitate catastrophic acute LVF.

- Wash hands, don a gown and sterile gloves. This is an aseptic procedure.
- Clean the area with chlorhexidine or iodine solution (unless allergic to these), and apply sterile drapes.
- Assemble the catheter, and flush all the lumina with saline.
- Identify the insertion point: 1cm below the junction of the medial third and lateral 2/3 of the clavicle. Nick the skin with a scalpel.
- Using a green needle inject 5-10mL of 1-2% ***lidocaine*** (p559) under the skin and into the subcutaneous tissues, down to the clavicle.
- Using the introducer needle, and an appropriate syringe partly filled with saline, puncture the skin and advance the needle to the clavicle. Once you hit the clavicle, move the needle under the clavicle and aim for the opposite sternoclavicular joint. This methods reduces the risk of puncturing the pleura. Aspirate as you advance the needle and you should be able to cannulate the subclavian vein. When in the vein you should be able to easily aspirate blood.
- Remove the syringe, keeping the needle still and insert the guide-wire. Remove the needle over the wire but **never** let go of the wire or it may all enter the vein, making removal very difficult. The wire should advance with ease, if it does not, you will have to restart the procedure as you should not remove the wire through the needle.
- Next, feed the dilator over the wire. Often twisting it slightly will facilitate its insertion. **NB:** Always have one hand on the wire.
- Remove the dilator and feed the catheter over the wire, remembering to have the end of the wire in your hand before the tip of the catheter enters the skin.
- Feed the catheter into the vein, remove the wire, and check that blood can be aspirated through each lumen.
- Flush each lumen, and then stitch the catheter in place.
- Order a CXR to check the position of the catheter and exclude a pneumothorax.
- If a cannula is found to be located in the internal jugular vein (**fig 2**, p574), it must be withdrawn and another reinserted.

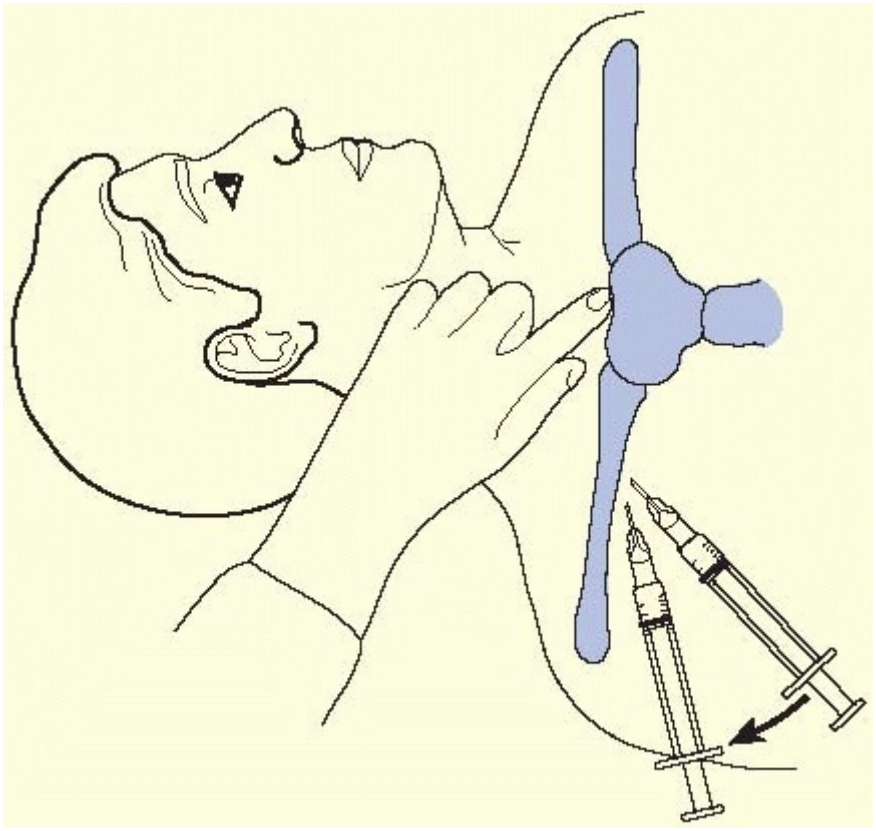
Complications (~20% in total):

- Haemorrhage; arterial puncture or cannulation; AV fistula formation.
- Internal jugular cannulation; air embolism.
- Pneumothorax; haemothorax; chylothorax (lymph).
- Phlebitis; thrombus formation on tip or in vein. In patients with a high risk of VTE (eg malignancy), a continuous infusion of unfractionated ***heparin*** may reduce the risk of thrombosis.[24]
- Bacterial colonisation; cellulitis; sepsis. ▸If taking blood cultures in a febrile patient with a central venous line, remember to take samples from the central line and from a new peripheral site (ie not a pre-existing cannula).

Other sites of insertion

include the femoral vein (see BOX, p759) and the internal jugular vein (see BOX, p31). There is evidence to suggest that the femoral approach is associated with a higher rate of line infection and thrombosis.[RCT][25]

Right subclavian vein puncture—infraclavicular approach



Contraindications to central venous cannulation

Absolute	Relative
Infection at insertion site	Coagulopathy
Significant tricuspid regurgitation	Ipsilateral carotid endarterectomy

Renal cell cancer involving the right atrium	Newly inserted cardiac pacemaker leads

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Inserting a temporary cardiac pacemaker

Often it is wiser to liaise with a specialist pacing centre to arrange prompt, definitive pacing than to try temporary transvenous pacing, which often has complications (see below) which may delay a definitive procedure.

Possible indications in the acute phase of myocardial infarction:

• *Complete AV block:*

- With inferior MI (right coronary artery occlusion) pacing may only be needed if symptomatic; spontaneous recovery may occur.
- With anterior MI (representing massive septal infarction).

• *Second degree block:*

- Wenckebach (p111 implies decremental AV node conduction; may respond to ***atropine*** in an inferior MI; pace if anterior MI.
- Type 2 block is usually associated with distal fascicular disease and carries high risk of complete heart block, so pace in both types of MI.

• *First degree block:*

Observe carefully: 40% develop higher degrees of block.

• *Bundle branch block:*

Pace prophylactically if evidence of trifascicular disease (p86) or non-adjacent bifascicular disease.

• *Sino-atrial disease + serious symptoms:*

Pace unless responds to ***atropine***.

Other indications where temporary pacing may be needed:

- Pre-op: if surgery is required in patients with type 2 or complete heart block (whether or not MI has occurred); do 24h ECG; liaise with the anaesthetist.
- Drug poisoning, eg with ß-blockers, digoxin, or verapamil.
- Symptomatic bradycardia, uncontrolled by ***atropine*** or ***isoprenaline***.
- Suppression of drug-resistant VT and SVT (overdrive pacing; do on ITU).
- Asystolic cardiac arrest with P-wave activity (ventricular standstill).
- During or after cardiac surgery—eg around the AV node or bundle of His.

Technique for temporary transvenous pacing

Learn from an expert.

- ***Preparation:*** Monitor ECG; have a defibrillator to hand; check that a radiographer with screening equipment is present.[1] Create a sterile field and ensure the pacing wire fits down the cannula easily. Insert a peripheral cannula.
- ***Insertion:*** Place the cannula into the subclavian or internal jugular vein (p762). If this is difficult, access to the right atrium can be achieved *via* the femoral vein. Pass the pacing wire through the cannula into the right atrium. It will either pass easily through the tricuspid valve or loop within the atrium. If the latter occurs, it is usually possible to flip the wire across the valve with a combined twisting and withdrawing movement. Advance the wire slightly. At this stage the wire may try to exit the ventricle through the pulmonary outflow tract. A further withdrawing and rotation of the wire will aim the tip at the apex of the right ventricle. Advance slightly again to place the wire in contact with the endocardium. Remove any slack to ↓risk of subsequent displacement.
- ***Checking the threshold:*** Connect the wire to the pacing box and set the 'demand' rate slightly higher than the patient's own heart rate and the output to 3V. A paced rhythm should be seen. Find the pacing threshold by slowly reducing the voltage until the pacemaker fails to stimulate the tissue (pacing spikes are no longer followed by paced beats). The threshold should be less than 1V, but a slightly higher value may be acceptable if it is stable—

eg after a large infarction.

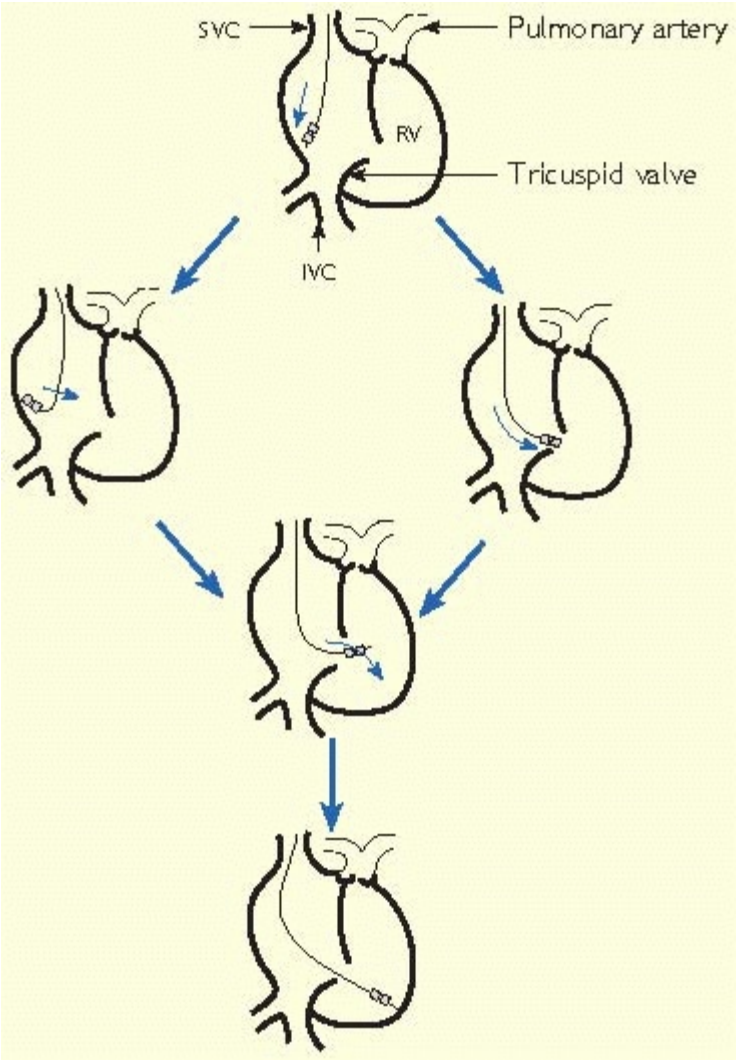
- ***Setting the pacemaker:*** Set the output to 3V or over 3 times the threshold value (whichever is higher) in 'demand' mode. Set the rate as required. Suture the wire to the skin, and fix with a sterile dressing.
- Check the position of the wire (and exclude pneumothorax) with a CXR.
- Recurrent checks of the pacing threshold are required over the next few days. The formation of endocardial oedema can raise the threshold by a factor of 2-3.

[1] Balloon-flotation techniques do not need radiographic guidance, have been shown to be quicker and easier to insert, with fewer complications compared to placement of semi-rigid electrode wires. RCT

Complications

Pneumothorax; sepsis; cardiac perforation; pacing failure: from loss of capture, loss of electrical continuity in pacing circuit, or electrode displacement.

Siting a temporary cardiac pacemaker



Non-invasive transcutaneous cardiac pacing

This method (performed through a defibrillator with external pacing facility) has the advantages of being quicker, less risky than the transvenous route, and easier to perform. Its main disadvantage is the pain caused by skeletal muscle contraction in the non-sedated patient. Indications for pacing via the transcutaneous route are as OPPOSITE, **plus** if transvenous pacing (or someone able to perform it) is unavailable or non-imminent in an emergency situation.

▸▸ Give sedation and analgesia, eg ***midazolam*** + ***morphine*** IV titrated to effect.

▸▸ Clipping chest hair may help improve electrical contact; ▸don't shave the skin, as nicks can predispose to electrical burns. Ensure the skin is dry.

▸▸ Almost all modern transcutaneous devices can function through defibrillation 'hands free' pads, and so these can be applied as for defibrillation (see p758). If necessary, the pads can be placed in an AP position: anteriorly over the V2-V3 electrode position and posteriorly at the same level, just below the scapula.

▸▸ Select 'demand' mode, (which synchronises the stimulus with the R wave, so avoiding pacing on the T wave—which can provoke VF or VT) and adjust the ECG gain so that QRS complexes can be seen.

▸▸ Select an appropriate pacing rate: eg 60-90bpm in an adult.

▸▸ Set the pacing current at the lowest setting and turn on the pacemaker.

▸▸ Increase the pacing current until electrical capture occurs (normally from 50- 100mA), which can be confirmed by seeing a wide QRS complex **and** a T wave on the trace (ventricular electrical capture). This does not necessarily mean that there has been mechanical capture—one clinical trial has described using emergency cardiac ultrasound to assess for this.[26]

▸▸ There will be some interference from skeletal muscle contraction on the ECG trace, as well as possible artefact, which could be mistaken for a QRS complex. The absence of a T wave is an important discriminator between the two.

▸▸ CPR can continue with the pads in place, though only when the pacing unit is **off**.

▸▸ Once adequate cardiac output has been maintained, seek expert help and arrange transvenous pacing.

Acknowledgements

We thank Dr Iain Wilson who is our Specialist Reader for this chapter.

Editors: Longmore, Murray; Wilkinson, Ian B; Turmezei, Tom; Cheung, Chee Kay
Title: *Oxford Handbook of Clinical Medicine, 7th Edition*

21

Emergencies

Don't go so fast: we're in a hurry! Talleyrand to his coachman

Introduction to emergencies

There is nothing more intoxicating than spending a day saving lives, but as night creeps on, and you start losing more patients than you should, despair can hit with the force of ice. It is no comfort to know that you are now wiser and older (by 100yrs). So when you find yourself washing your hands between one death and the next, for one second be honest with yourself, and write of your errors and sorrows on the surface of the water—a few temporary ambiguous squiggles framing your thoughts and the life that is lost. This is not about audit and accountability (this comes later: now you need to fortify yourself to survive this onslaught)—so, in case a manager is looking over your shoulder, pull the plug, and as the water flows away, know that it mingles with the rising tide of our own failings at the bedside, through which we have surfaced—no doubt a little faster than we should. At your next bedside you may do better if you can buy time: time to take a history, time to think, and time to ask. To buy this precious time, support vital functions, as follows.

Preliminary assessment (primary survey)

Airway	Protect cervical spine, if injury possible. Assessment: any signs of obstruction? Ascertain patency Management: establish a patent airway.
Breathing	Assessment: determine respiratory rate, check bilateral chest movement, percuss and auscultate. Management: if no respiratory effort, treat as arrest (see inside back cover), intubate and ventilate. If breathing compromised, give high concentration O_2, manage according to findings, eg relieve tension pneumothorax.
Circulation	Assessment: check pulse and BP; is he peripherally shut-down?; check capillary refill; look for evidence of haemorrhage. Management: • if no cardiac output, treat as arrest (inside back cover) • if shocked, treat as on p778.
Disability	Assess 'level of consciousness' with **AVPU** score (**a**lert? responds to **v**oice? to **p**ain? **u**nresponsive?); check pupils: size, equality, reactions. *Glasgow Coma scale*, if time allows.
Exposure	Undress patient, but cover to avoid hypothermia.

Quick history from relatives may assist with diagnosis: *Events* surrounding onset of illness, evidence of overdose/suicide attempt, any suggestion of trauma? *Past medical history:* Especially diabetes, asthma, COPD, alcohol, opiate or street drug abuse, epilepsy or recent head injury; recent travel. *Medication:* Current drugs. *Allergies*.

Once ventilation and circulation are adequate, you may have bought enough time to carry out history, examination, investigations, and appropriate management in the usual way.

Headache: differential diagnosis

No signs on examination

- Tension headache
- Migraine
- Cluster headache
- Post-traumatic
- Drugs (nitrates, calcium channel antagonists)
- Carbon monoxide poisoning or anoxia

Signs of meningism?

- Meningitis (may not have fever or rash)
- Subarachnoid haemorrhage (examination may be normal)

Decreased conscious level or localizing signs?

- Encephalitis/meningitis
- Stroke
- Cerebral abscess
- Subarachnoid haemorrhage
- Tumour
- Subdural haematoma
- TB meningitis

Papilloedema?

- Tumour
- Malignant hypertension
- Benign intracranial hypertension
- Any CNS infection, if prolonged (eg >2wks)—eg TB meningitis

Others

- Temporal arteritis (ESR↑)
- Glaucoma
- Paget's disease (Alk Phos ↑↑)
- Sinusitis
- Altitude sickness
- Cervical spondylosis
- Venous sinus occlusion (focal neurological deficits)
- Vertebral artery dissection (neck pain and cerebellar/medullary signs)

Worrying features or 'red flags'[1]

- First and worst headache—*subarachnoid haemorrhage*
- Thunderclap headache—*subarachnoid haemorrhage;* (p470 for other causes).
- Unilateral headache and eye pain—*cluster headache, acute glaucoma*
- Unilateral headache and ipsilateral symptoms—*migraine, tumour, vascular*
- Cough-initiated headache—*raised* ICP/*venous thrombosis*
- Persisting headache ± scalp tenderness in over 50s—*temporal arteritis*
- Headache with fever or neck stiffness—*meningitis*
- Change in the pattern of 'usual headaches'
- Decreased level of consciousness

Two other vital questions:

- Where have you been? (malaria)
- Might you be pregnant? (pre-eclampsia; especially if proteinuria and BP↑)

Breathlessness: emergency presentations

Wheezing?

- Asthma
- COPD
- Heart failure
- Anaphylaxis

Stridor?

(Upper airway obstruction)

- Foreign body or tumour
- Acute epiglottitis
- Anaphylaxis
- Trauma, eg laryngeal fracture

Crepitations?

- Heart failure
- Pneumonia
- Bronchiectasis
- Fibrosis

Chest clear?

- Pulmonary embolism
- Hyperventilation
- Metabolic acidosis, eg diabetic ketoacidosis (DKA)
- Anaemia

- Drugs, eg salicylates
- Shock (may cause air hunger, p778)
- Pneumocystis pneumonia
- Central causes

Others

- Pneumothorax—pain, increased resonance
- Pleural effusion—'stony dullness'

Chest pain: differential diagnosis

First exclude any potentially life-threatening causes, by virtue of history, brief examination, and limited investigations. Then consider other potential causes. For the full assessment of cardiac pain, see p80 & p104.

Life-threatening

- Acute myocardial infarction
- Angina/acute coronary syndrome
- Aortic dissection
- Tension pneumothorax
- Pulmonary embolism
- Oesophageal rupture

Others

- Pneumonia
- Chest wall pain
  - Muscular
  - Rib fractures
  - Bony metastases
  - Costochondritis
- Gastro-oesophageal reflux
- Pleurisy
- Empyema
- Pericarditis
- Oesophageal spasm
- Herpes zoster
- Cervical spondylosis
- Intra-abdominal
  - Cholecystitis
  - Peptic ulceration
  - Pancreatitis
- Sickle-cell crisis

Before discharging patients with undiagnosed chest pain, be sure in your own mind that the pain is not cardiac (this pain is usually dull, may radiate to jaw, arm, or epigastrium, and is usually associated with exertion). Do CXR, ECG, FBC, U&E, and 'cardiac' enzymes, including troponin T p104). Discuss options with a colleague, and the patient. Don't simply turn people out on to the street.

▸Just because the patient's chest wall is tender to palpation, this doesn't mean the cause of the chest pain is musculoskeletal. Even if palpation reproduces the same type of pain, ensure that you exclude all potential life-threatening causes. Although chest wall tenderness has discriminatory value against

cardiac pain, it may be a feature of a pulmonary embolism.

Coma

Definition

Unrousable unresponsiveness.

Causes of coma

Metabolic:

Drugs, poisoning, eg carbon monoxide, alcohol, tricyclics

Hypoglycaemia, hyperglycaemia (ketoacidotic, or HONK, p816)

Hypoxia, CO_2 narcosis (COPD)

Septicaemia

Hypothermia

Myxoedema, Addisonian crisis

Hepatic/uraemic encephalopathy

Neurological:

Trauma

Infection meningitis (p806); encephalitis, eg Herpes simplex give IV aciclovir if the slightest suspicion (p388), *tropical:* malaria (▸▸p385; do thick films), typhoid, rabies, trypanosomiasis

Tumour: cerebral/meningeal tumour

Vascular, subdural/subarachnoid haemorrhage, stroke, hypertensive encephalopathy

Epilepsy: non-convulsive status (p477) or post-ictal state

Immediate management

see OPPOSITE (and coma CNS exam, p776)

- Assess airway, breathing, and circulation. Consider intubation if GCS <8. Support the circulation if required (ie IV fluids). Give O_2 and treat any seizures. Protect the cervical spine.
- Check blood glucose in all patients. Give 50mL 50% dextrose IV immediately if presumed hypoglycaemia.
- IV thiamine if any suggestion of Wernicke's encephalopathy.
- IV naloxone for opiate intoxication (may also be given IM or via ET tube); IV flumazenil for benzodiazepine intoxication if airway compromised (may precipitate seizures especially if tricyclic intoxication)

Examination

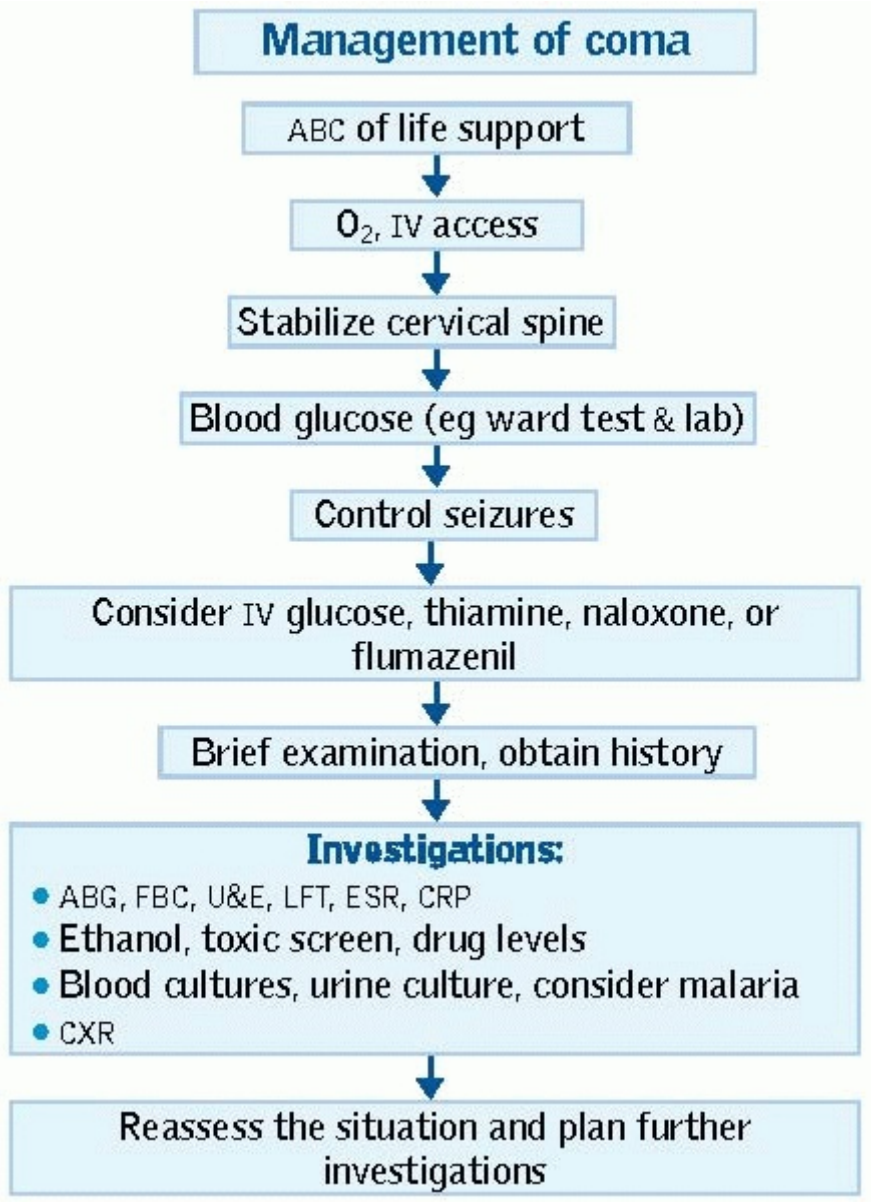
- Vital signs are vital—obtain full set, including temperature.
- Signs of trauma—haematoma, laceration, bruising, CSF/blood in nose or ears, fracture ‘step’ deformity of skull, subcutaneous emphysema, ‘panda eyes’.
- Stigmata of other illnesses: liver disease, alcoholism, diabetes, myxoedema.
- Skin for needle marks, cyanosis, pallor, rashes, poor turgor.
- Smell the breath (alcohol, hepatic fetor, ketosis, uraemia).
- Meningism (p806) ▸but do *not* move neck unless cervical spine is cleared.
- Pupils (p777) size, reactivity, gaze.
- Heart/lung exam for murmurs, rubs, wheeze, consolidation, collapse.
- Abdomen/rectal for organomegaly, ascites, bruising, peritonism, melaena.
- Are there any foci of infection (abscesses, bites, middle ear infection?)
- Any features of meningitis: neck stiffness, rash, focal neurology?
- Note the *absence* of signs, eg *no* pin-point pupils in a known heroin addict.

Quick history

from family, ambulance staff, bystanders: Abrupt or gradual onset? How found—suicide note, seizure? If injured, suspect cervical spinal injury and do not move spine (OHCS p768). Recent complaints—headache, fever, vertigo, depression? Recent medical history—sinusitis, otitis, neurosurgery, ENT procedure? Past medical history—diabetes, asthma, ↑BP, cancer, epilepsy, psychiatric illness? Drug or toxin exposure (especially alcohol or other recreational drugs)? Any travel?

Taking stock

The diagnosis may be clear, eg hyperglycaemia, alcohol excess, drug poisoning, uraemia, pneumonia, hypertensive, or hepatic encephalopathy (p251). If there are localizing CNS signs and no history of trauma, and there is no fever, the diagnosis is only probably stroke. In all undiagnosed coma patients or in those with focal neurological signs, a CT scan is very helpful. A lumbar puncture may be needed for meningitis (p806) or subarachnoid haemorrhage (p470).



NB: check pupils every few minutes during the early stages, particularly if trauma is the likely cause. Doing so is the quickest way to find a localizing sign (so helpful in diagnosis, but remember that false localizing signs do occur)—and observing changes in pupil behaviour (eg becoming fixed and dilated) is the quickest way of finding out just how bad things are.

The Glasgow coma scale (GCS)

This gives a reliable, objective way of recording the conscious state of a person. It can be used by medical and nursing staff for initial and continuing assessment. It has value in predicting ultimate outcome. 3 types of response are assessed:

Best motor response

This has 6 grades:

6 *Carrying out request ('obeying command'):* The patient does simple things you ask (beware of accepting a grasp reflex in this category).

5 *Localizing response to pain:* Put pressure on the patient's fingernail bed with a pencil then try supraorbital and sternal pressure: purposeful movements towards changing painful stimuli is a 'localizing' response.

4 *Withdraws to pain:* Pulls limb away from painful stimulus.

3 *Flexor response to pain:* Pressure on the nail bed causes abnormal flexion of limbs—decorticate posture.

2 *Extensor posturing to pain:* The stimulus causes limb extension (adduction, internal rotation of shoulder, pronation of forearm)—decerebrate posture.

1 *No response to pain.*

Note that it is the best response of any limb which should be recorded.

Best verbal response

This has 5 grades:

5 *Oriented:* The patient knows who he is, where he is and why, the year, season, and month.

4 *Confused conversation:* The patient responds to questions in a conversational manner but there is some disorientation and confusion.

3 *Inappropriate speech:* Random or exclamatory articulated speech, but no conversational exchange.

2 *Incomprehensible speech:* Moaning but no words.

1 *None.*

Record level of best speech.

Eye opening

This has 4 grades:

4 *Spontaneous eye opening.*

3 *Eye opening in response to speech:* Any speech, or shout, not necessarily request to open eyes.

2 *Eye opening in response to pain:* Pain to limbs as above.

1 *No eye opening.*

An overall score is made by summing the score in the 3 areas assessed. Eg: no response to pain + no verbalization + no eye opening = 3. Severe injury, GCS ≤8; moderate injury, GCS 9-12; minor injury, GCS 13-15.

NB: An abbreviated coma scale, **AVPU**, is sometimes used in the initial assessment ('primary survey') of the critically ill:

- **A** = **a**lert
- **V** = responds to **v**ocal stimuli
- **P** = responds to **p**ain
- **U** = **u**nresponsive

Some centres score GCS out of 14, not 15, omitting 'withdrawal to pain'.

NB: The GCS scoring is different in young children; see OHCS p201.

The neurological examination in coma

This is aimed at locating the pathology in 1 of 2 places. Altered level of consciousness implies either **(1)** a diffuse, bilateral, cortical dysfunction (usually producing loss of awareness with normal arousal) or **(2)** damage to the ascending reticular activating system (ARAS) located throughout the brainstem from the medulla to the thalami (usually producing loss of arousal with unassessable awareness). The brainstem can be affected directly (eg pontine haemorrhage) or indirectly (eg compression from trans-tentorial or cerebellar herniation secondary to a mass or oedema).

- Level of consciousness; describe using *objective* words.
- Respiratory pattern—Cheyne-Stokes (p54), hyperventilation (acidosis, hypoxia, or rarely, neurogenic), ataxic or apneustic (breath-holding) breathing (brainstem damage with grave prognosis).
- Eyes—almost all patients with ARAS pathology will have eye findings.

Visual fields

In light coma, test fields with visual threat. No blink in 1 field suggests hemianopsia and contralateral hemisphere lesion.

Pupils

Normal direct & consensual = intact midbrain. *Midposition (3-5mm) non-reactive ± irregular* = midbrain lesion. *Unilateral dilated & unreactive* ('fixed') = 3rd nerve compression. *Small, reactive* = pontine lesion ('pinpoint pontine pupils') or drugs. *Horner's syndrome* (p694) = ipsilateral lateral medulla or hypothalamus lesion, may precede uncal herniation. Beware patients with false eyes or who use eye drops for glaucoma.

Extraocular movements (EOMs)—

observe resting position and spontaneous movement; then test the vestibulo-ocular reflex (VOR) with either the *Doll's-head manoeuvre* (normal if the eyes keep looking at the same point in space when the head is quickly moved laterally or vertically) or *ice water calorics* (normal if eyes deviate towards the cold ear with nystagmus to the other side). If present, the VOR exonerates *most* of the brainstem from the VII nerve nucleus (medulla) to the III (midbrain). *Don't move the head unless the cervical spine is cleared.*

Fundi—

papilloedema, subhyaloid haemorrhage, hypertensive retinopathy, signs of other disease (eg diabetic retinopathy).

- Examine for CNS asymmetry (tone, spontaneous movements, reflexes).

▸▸Shock

Essence

Circulatory failure resulting in inadequate organ perfusion. *Generally* systolic BP is <90mmHg. Signs: pallor, pulse↑, capillary return↓ (press a nailbed), air hunger, oliguria. Causes are either *pump failure* or *peripheral circulation failure*.

Pump failure

- ***Cardiogenic shock***
- ***Secondary:*** *pulmonary embolism, tension pneumothorax, cardiac tamponade.*

Peripheral circulation failure

- ***Hypovolaemia***

  Bleeding: trauma, ruptured aortic aneurysm, ruptured ectopic pregnancy. *Fluid loss:* Vomiting (eg GI obstruction), diarrhoea (eg cholera), burns, pools of sequestered (unavailable) fluids ('third spacing', eg in pancreatitis). *Heat exhaustion* may cause hypovolaemic shock (also hyperpyrexia, oliguria, rhabdomyolysis, consciousness↓, hyperventilation, hallucination, incontinence, collapse, coma, pin-point pupils, LFT↑, and DIC, p336).

- ***Anaphylaxis***
- ***Sepsis:*** Gram -ve (or +ve) septicaemic shock from endotoxin-induced vasodilatation may be sudden and severe, with shock and coma but no signs of infection (fever, WCC↑).
- ***Neurogenic:*** eg post-spinal surgery.
- ***Endocrine failure:*** Addison's disease or hypothyroidism; see p818.
- ***Iatrogenic:*** Drugs, eg anaesthetics, antihypertensives.

Assessment

▸ABC.

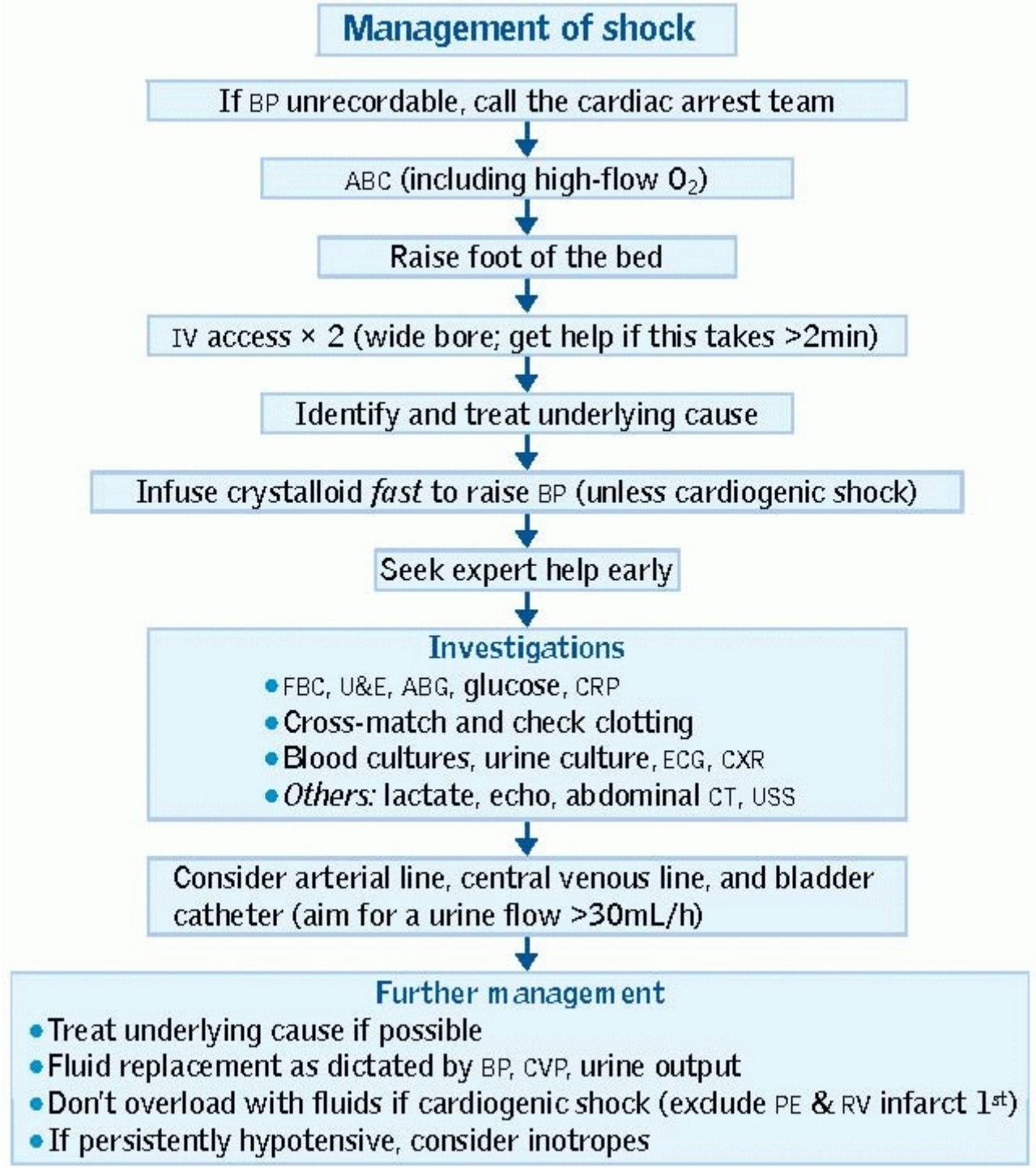
- ECG: rate, rhythm, ischaemia?
- *General:* cold and clammy—cardiogenic shock or fluid loss. Look for signs of anaemia or dehydration—skin turgor, postural hypotension? Warm and well perfused, with bounding pulse—septic shock. Any features suggestive of anaphylaxis—history, urticaria, angio-oedema, wheeze?
- CVS: usually tachycardic (unless on ß-blocker, or in spinal shock—OHCS p772) and hypotension. But in the young and fit, or pregnant women, the systolic BP may remain normal, although the *pulse pressure* will narrow, with up to 30% blood volume depletion. Difference between arms—aortic dissection?
- JVP *or central venous pressure:* If raised, cardiogenic shock likely.
- *Check abdomen:* any signs of trauma, or aneurysm? Any evidence of GI bleed?— check for melaena.

Management

▸If BP unrecordable, call the cardiac arrest team.

See opposite for general management. Specific measures:

- ***Anaphylaxis:*** p780.
- ***Cardiogenic shock:*** p788.
- ***Septic shock:*** (if no clue to source, p372): IV cefuroxime 1.5g/6-8h (after blood culture) or gentamicin (p738; do levels; reduce in renal failure) + antipseudomonal penicillin, eg ticarcillin (as Timentin®, p368, max dose 3.2g/4h IVI). Give colloid, or crystalloid, by IVI. Refer to ITU if possible for monitoring ± inotropes; aim for CVP 8-12mmHg, MAP >65mmHg. Urine >35ml/h. Low dose steroids may help as may recombinant human activated Protein C.
- ***Hypovolaemic shock:*** Fluid replacement: saline or colloid initially; if bleeding use blood; risks and benefits: see p570. Titrate against BP, CVP, urine output. Treat the underlying cause. If severe haemorrhage, exsanguinating, or more than 1L of fluid required to maintain BP, consider using group-specific blood, or O Rh-ve blood (p570). Correct electrolyte abnormalities. Acidosis often responds to fluid replacement.
- ***Heat exposure (heat exhaustion):*** tepid sponging + fanning; avoid ice and immersion. Resuscitate with high-sodium IVI, such as 0.9% saline ± hydrocortisone 100mg IV. Dantrolene seems ineffective. Chlorpromazine 25mg IM may be used to stop shivering. Stop cooling when core temperature <39°C.



NB: Remember that higher flow rates can be achieved through peripheral lines than through 'standard' gauge central lines.

If cause unclear: [prescription take] as hypovolaemia—most common cause, and reversible. Ruptured abdominal aortic aneurysm: aim for a systolic BP of ~90mmHg.

SIRS, sepsis, and related symptoms

The pathogenesis of sepsis and septic shock is becoming increasingly understood. The 'systemic inflammatory response syndrome' (SIRS) is thought to be a central component, involving cytokine cascades, free radical production, and the release of vasoactive mediators. SIRS is defined as the presence of 2 or more of the following features:[4]

- Temperature >38°C or <36°C
- Tachycardia >90 bpm
- Respiratory rate >20 breaths/min or P_aCO_2 <4.3 kPa

- WBC >12×10^9/L or <4×10^9 /L, or >10% immature (band) forms

Related syndromes include:

Sepsis:

SIRS occurring in the presence of infection.

Severe sepsis:

Sepsis with evidence of organ hypoperfusion eg hypoxaemia, oliguria, lactic acidosis, or altered cerebral function.

Septic shock:

Severe sepsis with hypotension (systolic BP <90mmHg) despite adequate fluid resuscitation, or the requirement for vasopressors/inotropes to maintain blood pressure.

Septicaemia was used to denote the presence of multiplying bacteria in the circulation, but has been replaced with the definitions above.[5]

▸▸Anaphylactic shock

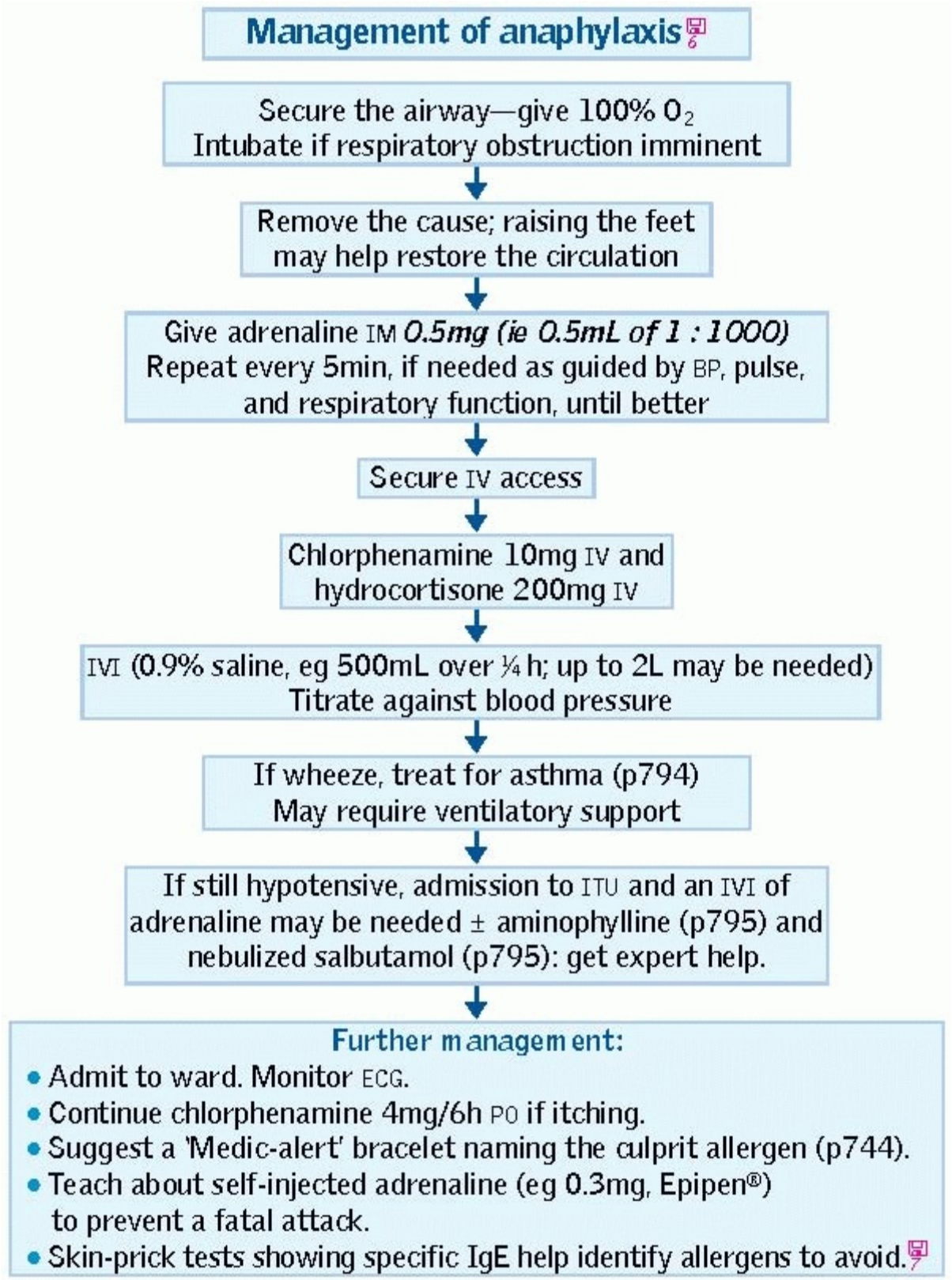
Type I IgE-mediated hypersensitivity reaction. Release of histamine and other agents causes: capillary leak; wheeze; cyanosis; oedema (larynx, lids, tongue, lips); urticaria. More common in atopic individuals. An *anaphylactoid reaction* results from direct release of mediators from inflammatory cells, without involving antibodies, usually in response to a drug, eg acetylcysteine.

Common precipitants

- Drugs, eg penicillin, and contrast media in radiology
- Latex
- Stings, eggs, fish, peanuts, strawberries, semen

Signs and symptoms

- Itching, erythema, urticaria, oedema
- Wheeze, laryngeal obstruction, cyanosis
- Tachycardia, hypotension



NB: ▸▸*adrenaline (=epinephrine) is given* IM *and NOT IV unless the patient is severely ill, or has no pulse. The IV dose is* ***different:*** *100*µg *per min—titrating with the response. This is 1*mL *of* ***1 : 10,000 solution*** *per minute. Stop as soon as a response has been obtained.*

If on a B-blocker, consider salbutamol IV in place of adrenaline.

Acute myocardial infarction*

A common medical emergency, and prompt appropriate treatment saves lives and myocardium. If in doubt, seek immediate help. Diagnosis: p104.

Pre-hospital management

Arrange an emergency ambulance. Aspirin 300mg PO (unless clear contraindication). Analgesia, eg morphine 5-10mg IV + metoclopramide 10mg IV (avoid IM injections, as risk of bleeding with thrombolysis). Sublingual GTN unless hypotensive.

Management

See OPPOSITE for acute measures.

Thrombolysis

effective in reducing mortality if given early. Greatest benefit is seen if given <12h of the onset of chest pain, but some benefit up to 24h. The British Heart Foundation advises that the time from onset of pain to thrombolysis should be <90min (<60min if possible).

Indications for thrombolysis:

Presentation within *12*h of chest pain with:

- ST elevation >2mm in 2 or more chest leads or
- ST elevation >1mm in 2 or more limb leads or
- Posterior infarction (dominant R waves and ST depression in V_1-V_3)
- New onset left bundle branch block.

Presentation within *12-24*h if continuing chest pain and/or ST elevation.

Thrombolysis contraindications: (consider urgent angioplasty instead)

- Internal bleeding
- Prolonged or traumatic CPR
- Heavy vaginal bleeding
- Acute pancreatitis
- Active lung disease with cavitation
- Recent trauma or surgery (<2wks)
- Cerebral neoplasm
- Severe hypertension (>200/120mmHg)
- Suspected aortic dissection
- Previous allergic reaction
- Pregnancy or <18wks postnatal
- Severe liver disease
- Oesophageal varices
- Recent head trauma
- Recent haemorrhagic stroke

Relative CI:

History of severe hypertension; peptic ulcer; history of CVA; bleeding diathesis; pregnancy; ≤18 weeks post-partum; anticoagulants.

Streptokinase

(SK) is the usual thrombolytic agent. Dose: 1.5 million units in 100mL 0.9% saline IVI over 1h. SE: nausea; vomiting; haemorrhage; stroke (1%); dysrhythmias. Any hypotension usually responds to slowing down or stopping the infusion. Also watch for allergic reactions and anaphylaxis (rare). Do not repeat unless it is within 4d of the first administration.

Alteplase

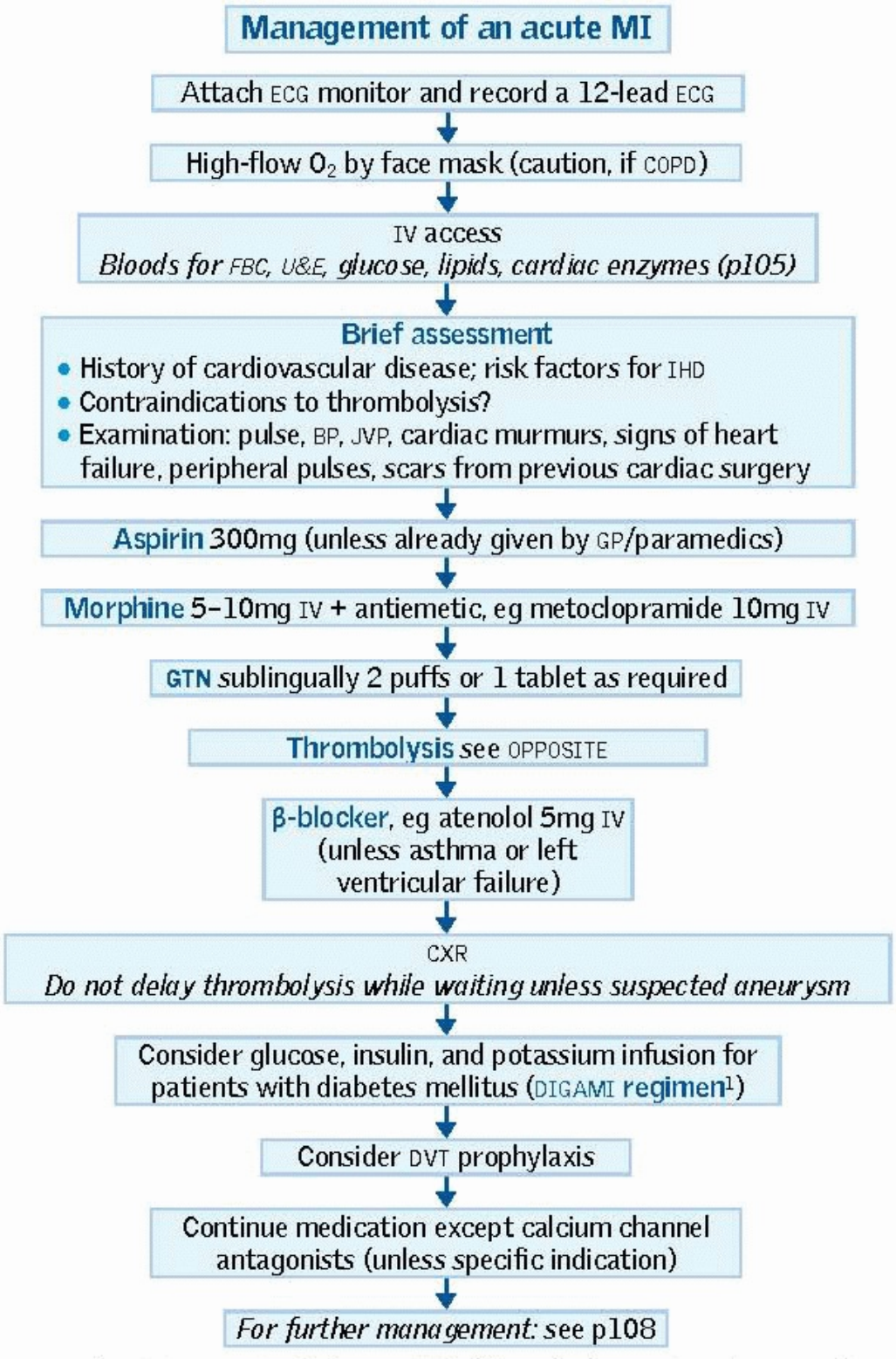
(rt-PA), followed by heparin, may be indicated if the patient has previously received SK (>4d ago) or reacted to SK. Accelerated rt-PA has benefit if given within 6h, especially in younger patients with anterior MI. *Reteplase* is given as 2 IV boluses 2h apart, and *tenecteplase* is given by bolus injection (over 10sec), which in some cases may be an advantage.

Complications

- Recurrent ischaemia or failure to reperfuse (usually detected as persisting pain and ST-segment elevation in the immediate aftermath of thrombolysis): analgesia, GTN, ß-blocker, consider re-thrombolysis or angioplasty.
- Stroke.
- Pericarditis: analgesics, try to avoid NSAIDs.
- Cardiogenic shock: see p788 and heart failure: see p786.

Right ventricular infarction

- Confirm by demonstrating ST elevation in RV3/4, and/or echo. NB: RV4 means that V_4 is placed in the right 5^{th} intercostal space in the midclavicular line.
- Treat hypotension and oliguria with fluids.
- Avoid nitrates and diuretics.
- Intensive monitoring and inotropes may be useful in some patients.



1 ***Note on the role of glucose, potassium, and insulin infusion (GKI) in acute MI.*** *GKI* in acute MI has gone in and out of vogue. Evidence for insulin infusion in whatever form in diabetic patients is more clear, and this should probably be part of our 'best care' management. More recently, interest has focused on the role of such infusions in non-diabetic patients. Some, but not all, studies/meta-analyses suggest benefit: R Diaz 1998 *Circulation* **98** 2227 G Krljanac Am J Cardiol 2005 **96** 053

NB: ▸*If pain is uncontrolled, especially if continuing ST elevation, consider re-thrombolysis with rt-PA (no bolus), tenecteplase, or rescue angioplasty.*

Acute coronary syndrome—without ST-elevation

Acute coronary syndrome (ACS) includes *unstable angina*, evolving *myocardial infarction* (MI), and non-Q wave or subendocardial MI. Although the underlying pathology is similar, management differs and, therefore, ACS is usually divided into 2 classes:

- *ACS with ST segment elevation* or new LBBB (acute MI see p782).
- *ACS without ST segment elevation* (unstable angina or non-Q wave MI).

ACS is associated with a greatly increased risk of MI (up to 30% in the 1st month). Patients should be managed medically until symptoms settle. They are then investigated by angiography with a view to possible angioplasty or surgery (CABG).

Assessment

Brief history:

previous angina, relief with rest/nitrates, history of cardiovascular disease, risk factors for IHD.

Examination:

pulse, BP, JVP, cardiac murmurs, signs of heart failure, peripheral pulses, scars from previous cardiac surgery.

Investigations

ECG: ST depression; flat or inverted T waves; or normal. FBC, U&E, glucose, lipids, cardiac enzymes. CXR.

Measurement of cardiac troponins helps to predict which patients are at risk of a cardiac event, and who can be safely discharged early.[8] Note that 2 different forms of troponin are measured: troponin T and troponin I: they have different reference intervals (consult your lab).

Management

▸See OPPOSITE for acute management

▸For management of ACS with ST-elevation, see p782.

The aim of drug therapy is twofold:

1. Anti-ischaemic, eg ß-blocker, nitrate, calcium channel antagonist.
2. Antithrombotic, eg aspirin, low molecular weight heparin, abciximab, which interfere with platelet activation, and so reduce thrombus formation.

Further measures:

- Wean off *glyceryl trinitrate* (GTN) infusion when stabilized on oral drugs.
- Stop heparin when pain-free for 24h, but give at least 3-5 days of therapy.
- Check serial ECGs and cardiac enzymes for 2-3d.
- Address modifiable risk factors: smoking, hypertension, hyperlipidaemia, diabetes.
- Gentle mobilization.

▸*If symptoms recur, refer to a cardiologist for urgent angiography and angioplasty or* CABG.

Prognosis

Overall risk of death ~1-2%, but ~15% for refractory angina despite medical therapy. Risk stratification can help predict those most at risk and allow intervention to be targeted at those individuals. The following are associated with an increased risk:

- Haemodynamic instability: hypotension, pulmonary oedema.
- T-wave inversion or ST segment depression on resting ECG.
- Previous MI.
- Prolonged rest pain.
- Older age.
- Diabetes mellitus.

Indications for consideration of invasive intervention:

- Poor prognosis, eg pulmonary oedema.
- Refractory symptoms.
- Positive exercise tolerance tests (ETT) at low workload.
- Non-Q wave MI.

Acute management of ACS without ST-segment elevation

Admit to CCU and monitor closely

↓

High-flow O_2 by face mask

↓

Analgesia: eg morphine 5–10mg IV + metoclopramide 10mg IV

↓

Nitrates: GTN spray or sublingual tablets as required

↓

Aspirin: 300mg PO (unless contraindicated) *reduces risk of* MI *and death*

↓

Oral β-blocker: eg metoprolol 50–100mg/8h or atenolol 50–100mg/24h

If β-blocker contraindicated (asthma, COPD, LVF, bradycardia, coronary artery spasm), give rate-limiting calcium antagonist (eg verapamil[1] 80–120mg/8h PO, or diltiazem 60–120mg/8h PO)

↓

Low molecular weight heparin: (eg enoxaparin 1mg/kg/12h or dalteparin 120U/kg/12h SC)

Alternatively: unfractionated heparin 5000U IV bolus then IVI

Check APTT 6-hourly. Alter IVI rate to maintain APTT at 1.5–2.5 times control

↓

IV nitrate if pain continues

(eg GTN 50mg in 50mL 0.9% saline at 2–10mL/h)

titrate to pain, and maintain systolic BP >100mmHg

↓

Record ECG while in pain

↓

High-risk patients

(persistent or recurrent ischaemia, ST-depression, diabetes, ↑troponin)

- Infusion of a GPIIb/IIIa antagonist (eg tirofiban) and, ideally, urgent angiography.
- Addition of clopidogrel may also be useful

↓

Optimize drugs:

- β-blocker; Ca^{2+} channel antagonist; ACE-i; nitrate.
- Intensive statin regimens, *starting at top dosages*, may decrease long- *and* short-term mortality/adverse events, eg by stabilizing plaques.[2,3]

↓

►*If symptoms fail to improve, refer to a cardiologist for urgent angiography ± angioplasty or CABG*

Low-risk patients

(no further pain, flat or inverted T-waves, or normal ECG, and negative troponin)

- May be discharged if a repeat troponin (>12h) is negative.
- Treat medically and arrange further investigation eg stress test, angiogram.

1 Do not use verapamil and a β-blocker together (can cause asystole).

2 Comparing intensive & moderate lipid lowering with statins after ACS. N=4162. Cannon C *NEJM* 2004

3 Intensive statin therapy—a sea change in cardiovascular prevention. Topol E *NEJM* 2004.

▸▸Severe pulmonary oedema

Causes

- Cardiovascular—usually left ventricular failure—post-MI, or ischaemic heart disease. Also mitral stenosis, arrhythmias, and malignant hypertension.
- ARDS (p170, any cause, eg trauma, malaria, drugs), look for predisposing factors, eg trauma, post-op, sepsis. *Is aspirin overdose or glue-sniffing/drug abuse likely*? Ask friends/relatives.
- Fluid overload.
- Neurogenic, eg head injury.

Differential diagnosis

Asthma/COPD, pneumonia, and pulmonary oedema are often hard to distinguish, especially in the elderly, where that may co-exist. Do not hesitate to treat all 3 simultaneously (eg with salbutamol nebulizer, furosemide IV, diamorphine, amoxicillin—p368).

Symptoms

Dyspnoea, orthopnoea (eg paroxysmal), pink frothy sputum. NB: drugs; other illnesses (recent MI/COPD or pneumonia).

Signs

Distressed, pale, sweaty, pulse↑, tachypnoea, pink frothy sputum, pulsus alternans, JVP↑, fine lung crackles, triple/gallop rhythm (p32), wheeze (cardiac asthma). Usually sitting up and leaning forward. Quickly examine for possible causes.

Investigations

- CXR (p121)—cardiomegaly, signs of pulmonary oedema: look for shadowing (usually bilateral), small effusions at costophrenic angles, fluid in the lung fissures, and Kerley B lines (linear opacities).
- ECG—signs of MI.
- U&E; 'cardiac' enzymes, ABG.
- Consider echo.
- Plasma BNP may be helpful if diagnosis in question.

Management

Begin treatment before investigations. See OPPOSITE.

Monitoring progress:

BP; heart rate; cyanosis; respiratory rate; JVP; urine output, ABG.

Once stable and improving:

- Daily weights; BP and pulse/6h. Repeat CXR.
- Change to oral furosemide or bumetanide.
- If on large doses of loop diuretic, consider the addition of a thiazide (eg bendroflumethiazide or metolazone 2.5-5mg daily PO).
- ACE-i if left ventricular failure. If ACE-i contraindicated, consider hydralazine and nitrate (may also be more effective in (Afrocaribbeans)[10].
- Also consider ß-blocker and spironolactone.
- Is the patient suitable for cardiac transplantation?
- Consider digoxin ± warfarin, especially if AF.

Nesiritide, recombinant human brain natriuretic peptide, may have a role in the short-term management of decompensate cardiac failure as it improves haemodymanics in such patients.[11] However, it is expensive and further data on safety and outcome are required before it is more widely adopted.

Management of heart failure

Sit the patient upright

↓

Oxygen
100% if no pre-existing lung disease

↓

IV access and monitor ECG
Treat any arrhythmias, eg AF (p110–p116)

↓

Investigations whilst continuing treatment
see OPPOSITE

↓

Diamorphine 2.5–5mg IV slowly
Caution in liver failure and COPD

↓

Furosemide 40–80mg IV slowly
Larger doses required in renal failure

↓

GTN spray 2 puffs SL or 2 × 0.3mg tablets SL
Don't give if systolic BP <90mmHg

↓

Necessary investigations, examination, and history

↓

If systolic BP ≥100mmHg, start a nitrate infusion
eg isosorbide dinitrate 2–10mg/h IVI; keep systolic BP ≥90mmHg

↓

If the patient is worsening: further dose of furosemide 40–80mg
Consider ventilation (invasive or non-invasive eg CPAP; get help)
or increasing nitrate infusion
Alternatively venesect 500mL blood (rarely done)

↓

If systolic BP <100mmHg, treat as cardiogenic shock (p788),
ie consider a Swan–Ganz catheter and inotropic support

Notes

- If failure to improve, reassess and consider alternative diagnoses, eg hypertensive heart failure, aortic dissection, pulmonary embolism, pneumonia.
- There are logical reasons for considering using nitrates first-line rather than loop diuretics: nitrates reduce pre- and after-load and are coronary vasodilators. In contrast most of the acute beneficial effects of loop diuretics stem from venodilatation rather than diuresis. Only small randomized trials have compared the two therapies but nitrates seem as, if not more effective that loop diuretics.[12]

▸▸Cardiogenic shock

This has a high mortality. ▸Ask a senior physician's help both in formulating an *exact* diagnosis and in guiding treatment.

Cardiogenic shock is shock caused primarily by the failure of the heart to maintain the circulation. It may occur suddenly, or after progressively worsening heart failure.

Causes

- Myocardial infarction
- Arrhythmias
- Pulmonary embolus
- Tension pneumothorax
- Cardiac tamponade
- Myocarditis; myocardial depression (drugs, hypoxia, acidosis, sepsis)
- Valve destruction (endocarditis)
- Aortic dissection

Management

If the cause is myocardial infarction prompt revascularization (thrombolysis or acute angioplasty) is vital; ▸▸see p782[1] for indications and contraindications.

- Manage in Coronary Care Unit, if possible.
- Investigation and treatment may need to be done concurrently.
- See OPPOSITE for details of management.
- *Investigations* ECG, U&E, CK, ABG, CXR, echo. If indicated, CT thorax (aortic dissection/PE) or [V with dot above]/[Q with dot above] scan.
- *Monitor* CVP, BP, ABG, ECG; urine output. Do a 12-lead ECG every hour until the diagnosis is made. Consider a Swan-Ganz catheter to assess pulmonary wedge pressure and cardiac output, and an arterial line to monitor pressure. Catheterize for accurate urine output.

Cardiac tamponade

Essence:

Pericardial fluid collects → intra-pericardial pressure rises → heart cannot fill → pumping stops.

Causes:

Trauma, lung/breast cancer, pericarditis, myocardial infarct, bacteria, eg TB. *Rarely:* Urea↑, radiation, myxoedema, dissecting aorta, SLE.

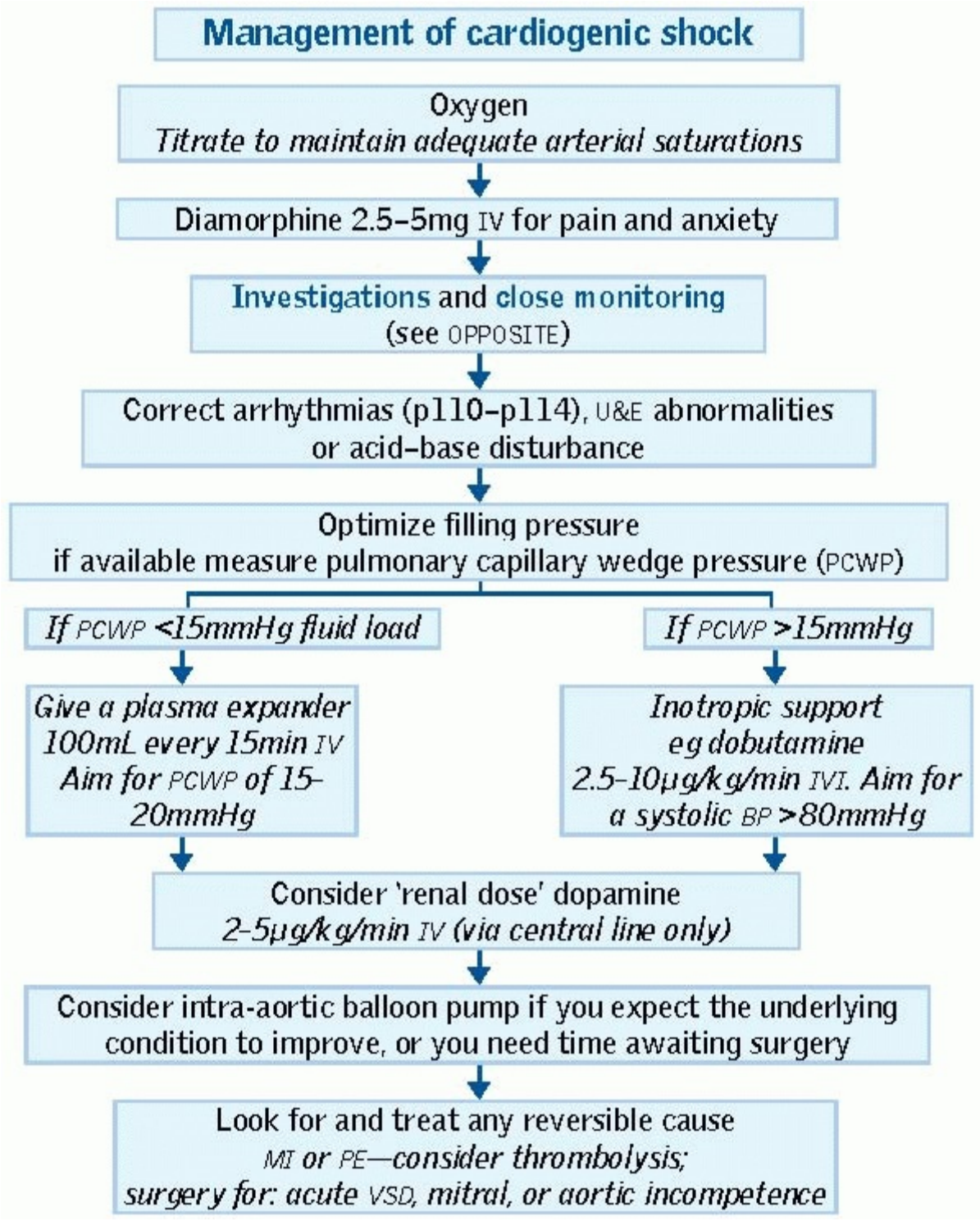
Signs:

Falling BP, a rising JVP, and muffled heart sounds (Beck's triad); JVP↑ on inspiration (Kussmaul's sign); pulsus paradoxus (pulse fades on inspiration). Echocardiography may be diagnostic. CXR: globular heart; left heart border convex or straight; right cardiophrenic angle <90°. ECG: electrical alternans (p140).

Management:

This can be very difficult. Everything is against you: time, physiology, and your own confidence, as the patient may be too ill to give a history, and signs may be equivocal—but bitter experience has taught us not to equivocate for long.

▸▸Request the presence of your senior at the bedside (do not make do with telephone advice). With luck, prompt pericardiocentesis (p761) brings swift relief. While awaiting this, give O_2, monitor ECG, and set up IVI. Take blood for group and save.



▸▸Broad complex tachycardia

ECG shows rate of >100bpm and QRS complexes >120ms (>3 small squares on ECGs done at the standard UK rate of 25mm/s).

Principles of management

If in doubt, treat as ventricular tachycardia (the commonest cause). Identify the underlying rhythm and treat accordingly.

Differential

- Ventricular tachycardia (VT) including torsade de pointes
- SVT with aberrant conduction, eg AF, atrial flutter
- Pre-excited tachycardias, eg AF, atrial flutter, or AV re-entry tachycardia with underlying WPW (p112).

(NB: Ventricular ectopics should not cause confusion when occurring singly; but if >3 together at a rate of >120, this constitutes VT.)

Identification of the underlying rhythm

may be difficult, seek expert help. Diagnosis is based on the history: if IHD/MI the likelihood of a ventricular arrhythmia is >95%, a 12-lead ECG, and the lack of response to IV adenosine (p112).

ECG findings in favour of VT:

- Fusion beats or capture beats (ECG p115).
- Positive QRS concordance in chest leads.
- Marked left axis deviation or rightwards axis.
- AV dissociation (occurs in 25%) or 2 : 1 or 3 : 1 AV block.
- QRS complex >160ms.
- Any atypical bundle-branch-block pattern.

Management

Give high-flow O_2 by mask and monitor O_2 saturations.

- Connect patient to a cardiac monitor and have a defibrillator to hand.
- Correct electrolyte abnormalities.
- Check for adverse signs. Low cardiac output (clammy, consciousness↓, BP <90); oliguria; angina; pulmonary oedema.
- Obtain 12-lead ECG (request CXR) and obtain IV access.

If haemodynamically unstable

- Synchronized DC shock (see Resuscitation Guidelines inside back cover).
- Correct any hypokalaemia and hypomagnesaemia: 60mmol KCl at 30mmol/h, and 5mL 50% magnesium sulphate over 30min).
- Follow with amiodarone 300mg IV over 20-60min.
- For refractory cases procainamide or sotalol may be considered.

If haemodynamically stable

- Correct hypokalaemia and hypomagnesaemia: as above.
- Amiodarone 300mg IV over 20-60 min. Alternatively lidocaine 50mg (2.5mL of 2% solution) IV over 2min, repeated every 5min up to 200mg.
- If this fails, use synchronized DC shock.

After correction of VT

- Establish the cause (via the history and tests above)
- Maintenance anti-arrhythmic therapy may be required. If VT occurs after MI, give IV amiodarone or lidocaine infusion for 12-24h; if 24h after MI, also start oral anti-arrhythmic: sotalol (if good LV function) or amiodarone (if poor LV function).
- Prevention of recurrent VT: surgical isolation of the arrhythmogenic area or implantation of tiny automatic defibrillators may help.

Ventricular fibrillation

(ECG p115 Use non-synchronized DC shock (there is no R wave to trigger defibrillation, p758): see inside back cover.

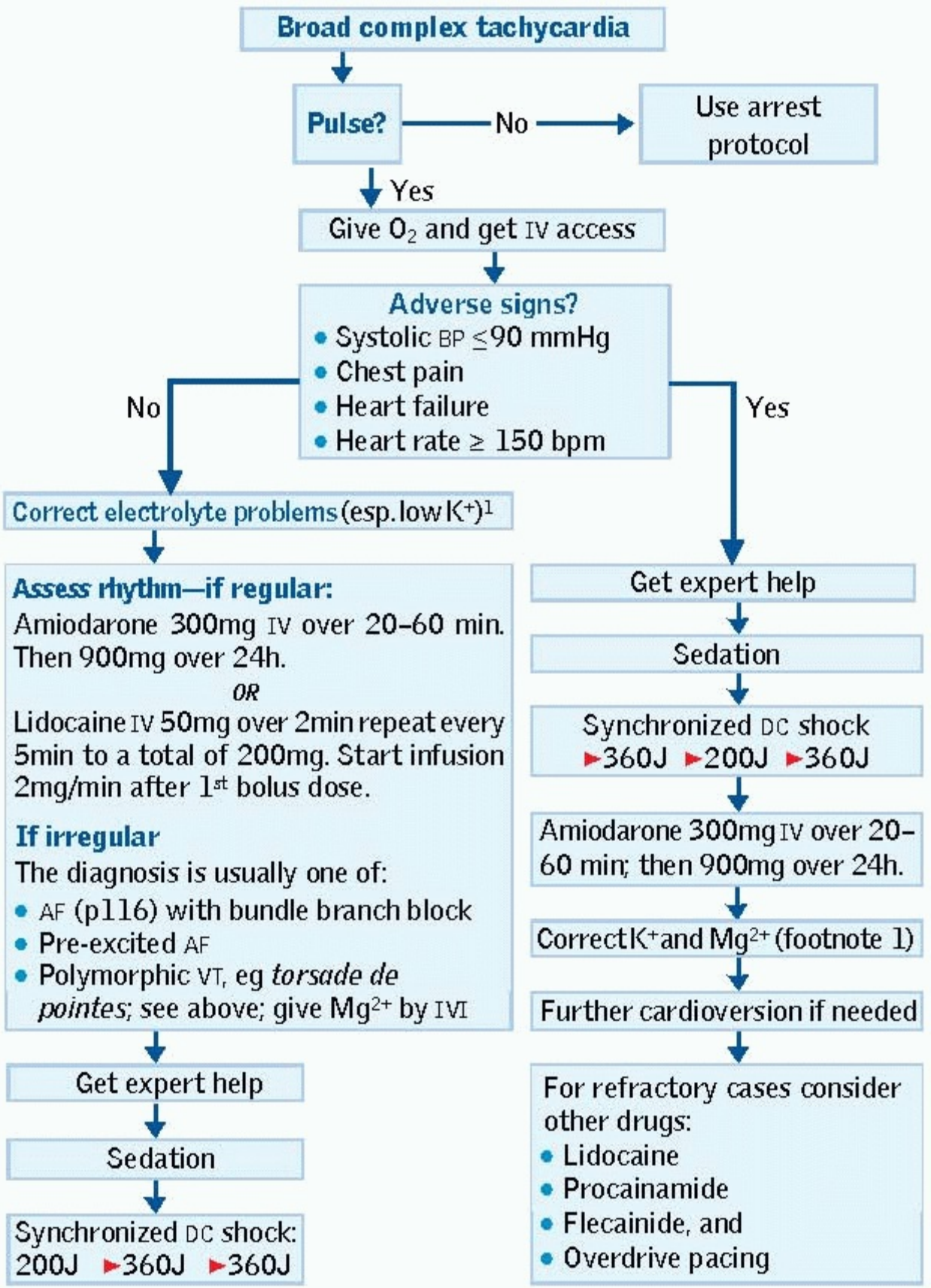
Ventricular extrasystoles (ectopics)

are the commonest post-MI arrhythmia but they are also seen in healthy people (often >10/h). Patients with frequent ectopics post-MI have a worse prognosis, but there is no evidence that antidysrhythmic drugs improve outcome, indeed they may increase mortality.

Torsade de pointes:

A form of VT, with a constantly varying axis, often in the setting of long-QT syndromes (ECG p115); causes, p702. This can be congenital or acquired, eg from drugs (eg some anti-dysrhythmics, tricyclics, antimalarials, and newer antipsychotics). Torsade in the setting of congenital long-QT syndromes can be treated with high doses of ß-blockers.

In acquired long-QT syndromes, stop all predisposing drugs, correct hypokalaemia, and give $MgSO_4^{2+}$ (2g IV over 10 min). Alternatives include: overdrive pacing or isoprenaline IVI to increase heart rate.



1 If potassium low: give **potassium chloride** by IVI, up to 60mmol, max. rate 30mmol/h. Give **magnesium sulfate** IVI 5mL 50% in 30min.

▸▸Narrow complex tachycardia

ECG shows rate of >100bpm and QRS complex duration of <120ms (<3 small squares on ECGs done at the standard UK rate of 25mm/s).

Differential diagnosis

- *Sinus tachycardia:* normal P-wave followed by normal QRS.
- *Atrial tachyarrhythmias:* Rhythm arises in atria, AV node is a bystander.
  - Atrial fibrillation (AF): absent P-wave, irregular QRS complexes.
  - Atrial flutter: atrial rate ~260-340bpm. Saw-tooth baseline, due to continuous atrial electrical activity. Ventricular rate often 150bpm (2 : 1 block).
  - Atrial tachycardia: abnormally shaped P-waves, may outnumber QRS.
  - Multifocal atrial tachycardia: 3 or more P-wave morphologies, irregular QRS complexes.
- *Junctional tachycardia:* AV-node is part of the pathway. P-wave either buried in QRS complex or occurring after QRS complex.
  - AV nodal re-entry tachycardia.
  - AV re-entry tachycardia, includes an accessory pathway, eg WPW (p112).

Principles of management

See algorithm OPPOSITE.

- If the patient is compromized, use DC cardioversion.
- Otherwise, identify the underlying rhythm and treat accordingly. The chief thing is to decide whether the rhythm is regular or not (likely AF).
- Vagal manoeuvres (carotid sinus massage, Valsalva manoeuvre) transiently increase AV block, and may unmask an underlying atrial rhythm.
- If unsuccessful, give adenosine which causes transient AV block. It has a short half-life (10-15s) and works in 2 ways:
  - by transiently slowing ventricles to show the underlying atrial rhythm,
  - by cardioverting a junctional tachycardia to sinus rhythm.

Give 6mg IV bolus into a large vein, followed by saline flush, while recording a rhythm strip. If unsuccessful, give 12mg, then one further 12mg bolus. Warn about SE: transient chest tightness, dyspnoea, headache, flushing. ***Relative* CI***:* asthma, 2nd/3rd-degree AV block or sinoatrial disease (unless pacemaker). ***Interactions:*** potentiated by dipyridamole, antagonized by theophylline.

Specifics

Sinus tachycardia:

Identify and treat underlying cause.

Supraventricular tachycardia:

If adenosine fails, use verapamil 2.5-5mg IV over 2-3min. **NB:** NOT if on a ß-blocker. If no response, a further 5mg IV over 3min (if age <60yrs). Alternatives: atenolol 5mg IV or sotalol 20-120mg IV (over 10min); or amiodarone. If unsuccessful, use DC cardioversion.

Atrial fibrillation/flutter:

Manage along standard lines (p116).

Atrial tachycardia:

Rare; may be due to digoxin toxicity: withdraw digoxin, consider digoxin-specific antibody fragments. Maintain K+ at 4-5mmol/L.

Multifocal atrial tachycardia:

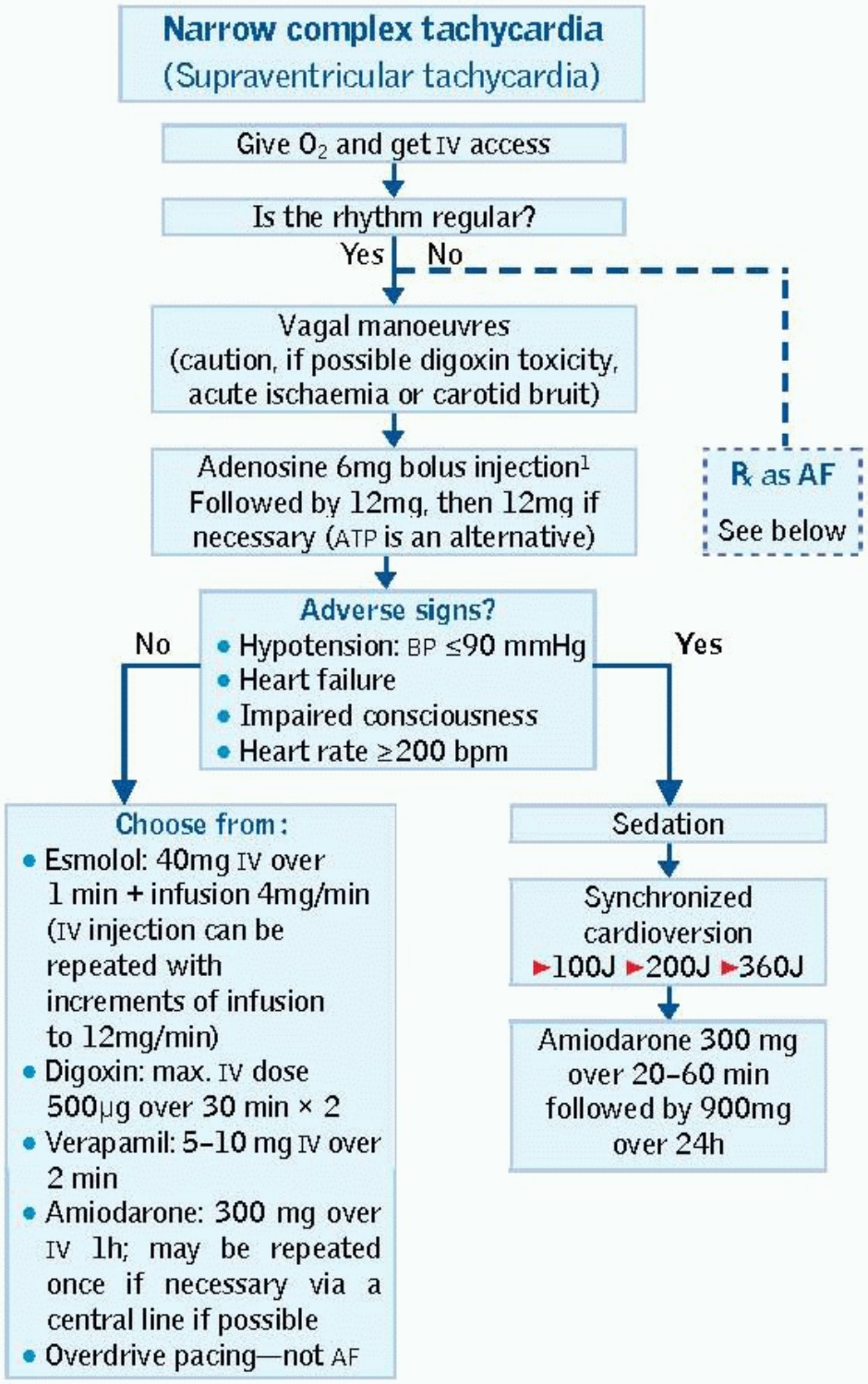
Most commonly occurs in COPD. Correct hypoxia and hypercapnia. Consider verapamil if rate remains >110bpm.

Junctional tachycardia:

Where anterograde conduction through the AV node occurs, vagal manoeuvres are worth trying. Adenosine will usually cardiovert a junctional rhythm to sinus rhythm. If it fails or recurs, ß-blockers (or verapamil— ***not*** with ß-blockers, digoxin, or class I agents such as quinidine). If this does not control symptoms, consider radiofrequency ablation.

Wolff-Parkinson-White (WPW) syndrome

(ECG p117) Caused by congenital accessory conduction pathway between atria and ventricles. Resting ECG shows short P-R interval and widened QRS complex due to slurred upstroke or 'delta wave'. 2 types: WPW type A (+ve δ wave in V1), WPW type B (-ve δ wave in V_1). Patients present with SVT which may be due to an AVRT, (p112) pre-excited AF, or pre-excited atrial flutter. Risk of degeneration to VF and sudden death. [prescription take] flecainide, propafenone, sotalol, or amiodarone. Refer to cardiologist for electrophysiology and ablation of the accessory pathway.



1 Consult *BNF* if on dipyridamole or has had a heart transplant

See Resuscitation Council (UK) guidance for more details (www.resus.org.uk)

Irregular narrow complex tachycardia

- Treat as AF —by far the most likely diagnosis.
- Control rate with either ß blocker or digoxin.
- If onset <48h consider cardioversion with either amiodarone, 300mg in over 20-60 min, then 900mg over 24h; or DC shock, see p758.
- Consider anticoagulation with heparin and/or warfarin to reduce the risk of stroke.

▸▸Acute severe asthma[13]

▸The severity of an attack is easily underestimated.

▸An atmosphere of calm helps.

Presentation

Acute breathlessness and wheeze.

History

Ask about usual and recent treatment; previous acute episodes and their severity and best peak expiratory flow rate (PEF). Have they been admitted to ITU?

Differential diagnosis

Acute infective exacerbation of COPD, pulmonary oedema, upper respiratory tract obstruction, pulmonary embolus, anaphylaxis.

Investigations

PEF—but may be too ill; arterial blood gases; CXR (to exclude pneumothorax, infection); FBC; U&E.

Assessing the severity of an acute asthmatic attack

Severe attack:

- Unable to complete sentences
- Respiratory rate >25/min
- Pulse rate >110 beats/min
- Peak expiratory flow <50% of predicted or best

Life-threatening attack:

- Peak expiratory flow <33% of predicted or best
- Silent chest, cyanosis, feeble respiratory effort
- Bradycardia or hypotension
- Exhaustion, confusion, or coma
- Arterial blood gases: normal/high P_aCO_2 >5kPa (36mmHg) P_aO_2 <8kPa (60mmHg) low pH, eg <7.35

Treatment

▸Life-threatening or severe asthma, see OPPOSITE.

- Salbutamol 5mg **nebulized with oxygen**.
- If PEF remains <75%, repeat salbutamol and give prednisolone 30mg PO.
- Monitor oxygen saturation, heart rate, and respiratory rate.

Discharge

Patients, before discharge, must have:

- Been on discharge medication for 24h.
- Had inhaler technique checked.
- Peak flow rate >75% predicted or best with diurnal variability <25%.
- Steroid and bronchodilator therapy.
- Own a PEF meter and have management plan.
- GP appointment within 1wk.
- Respiratory clinic appointment within 4wks.

Drugs used in acute asthma

Salbutamol

($ß_2$-agonist)

SE:

Tachycardia, arrhythmias, tremor, K^+↓.

Hydrocortisone

(steroid)

Aminophylline

(Inhibits phosphodiesterase; ↑[cAMP]).

SE:

pulse↑; arrhythmias, nausea, seizures. The amount of IVI aminophylline may need altering according to the individual patient: always check the BNF. Monitor ECG.

- *Factors which may necessitate reduction of dose:* Cardiac or liver failure, drugs which increase the half-life of aminophylline, eg cimetidine, ciprofloxacin, erythromycin, contraceptive steroids.
- *Factors which may require ↑dose:* Smoking, drugs which shorten the half-life, eg phenytoin, carbamazepine, barbiturates, rifampicin.
- ▸Aim for plasma concentration of 10-20µg/mL (55-110µmol/L). Serious toxicity (BP↓, arrhythmias, cardiac arrest) can occur at concentrations ≥25µg/mL. Measure plasma K^+: theophyllines may cause K^+↓. Don't load patients already on oral preparations. Stick with one brand (bioavailability varies).

Immediate management of acute severe asthma[14]

Assess severity of attack (see above). Warn ITU if attack severe.

Start treatment immediately (prior to investigations).

- Sit patient up and give high-dose O_2 in: 100% via non-rebreathing bag.
- Salbutamol 5mg (or terbutaline 10mg) plus ipratropium bromide 0.5mg **nebulized with O_2**.
- Hydrocortisone 100mg IV or prednisolone 40-50mg PO or both if very ill.
- CXR to exclude pneumothorax.

If life-threatening features (above) present:

- Inform ITU, and seniors.
- Add magnesium sulphate ($MgSO_4$) 1.2-2g IV over 20min.
- Give salbutamol nebulizers every 15min, or 10mg continuously per hour.

Further management

If improving

- 40-60% O_2.
- Prednisolone 40-50mg/24h PO.
- Nebulized salbutamol every 4h.

- Monitor peak flow and oxygen saturations.

▸▸If patient not improving after 15-30min

- Continue 100% O_2 and steroids.
- Hydrocortisone 100mg IV or prednisolone 30mg PO if not already given.
- Give salbutamol nebulizers every 15min, or 10mg continuously per hour.
- Continue ipratropium 0.5mg every 4-6h.

▸▸If patient still not improving

- Discuss with seniors and ITU.
- Repeat salbutamol nebulizer every 15min.
- $MgSO_4$ 1.2-2g IV over 20min, unless already given.
- Consider aminophylline; if not already on a theophylline, load with eg 5mg/kg IVI over 20min,[1] then 500µg/kg/h where kg is ideal body weight, p434—eg in a small adult: 750mg/24h; large adult 1200mg/24h. Adjust dose according to plasma theophylline, if available. Do levels if infusion lasts >24h. Alternatively, give salbutamol IVI, eg 3-20µg/min. IPPV may be required.

- If no improvement, or life-threatening features are present, consider transfer to ITU, accompanied by a doctor prepared to intubate.

Monitoring the effects of treatment

- Repeat PEF 15-30min after initiating treatment.
- Pulse oximeter monitoring: maintain S_aO_2 >92%.
- Check blood gases within 2h if: initial P_aCO_2 was normal/raised or initial P_aO_2 <8kPa (60mmHg) or patient deteriorating.
- Record PEF pre- and post-ß-agonist in hospital at least 4 times.

Once patient is improving

- Wean down and stop aminophylline over 12-24h.
- Reduce nebulized salbutamol and switch to inhaled ß-agonist.
- Initiate inhaled steroids and stop oral steroids if possible.
- Continue to monitor PEF. Look for deterioration on reduced treatment and beware early morning dips in PEF.
- Look for the cause of the acute exacerbation and admission.

Acute exacerbations of COPD

Common medical emergency especially in winter. May be triggered by viral or bacterial infections.

Presentation

Increasing cough, breathlessness, or wheeze. Decreased exercise capacity.

History

Ask about usual/recent treatments (especially home oxygen), smoking status, and exercise capacity (may influence a decision to ventilate the patient).

Differential diagnosis

Asthma, pulmonary oedema, upper respiratory tract obstruction, pulmonary embolus, anaphylaxis.

Investigations

- Peak expiratory flow (PEF)—but may be too ill.
- Arterial blood gases.
- CXR to exclude pneumothorax and infection.
- FBC; U&E; CRP.
- ECG.
- Blood cultures (if pyrexial).
- Send sputum for culture.

Management

- Look for a cause, eg infection, pneumothorax.
- See OPPOSITE for acute management.
- Prior to discharge, liaise with GP regarding steroid reduction, domiciliary oxygen (p168), smoking, pneumococcal & 'flu vaccinations (p152).

Treatment of stable COPD:

See p168 for further information.

Non-pharmacological:	Stop smoking, encourage exercise, treat poor nutrition or obesity, influenza, vaccination.
Pharmacological:	
• Mild	Short-acting β_2-agonist or ipratropium PRN.
• Moderate	Regular short-acting β_2-agonist and/or ipratropium. Consider corticosteroid trial.
• Severe	Combination therapy with regular short-acting β_2-agonist and ipratropium. Consider corticosteroid trial (p169). Assess for home nebulizers.

More advanced disease:

- Consider pulmonary rehabilitation in moderate/severe disease.
- Consider long-term oxygen therapy if P_aO_2 <7.3kPa (p168).
- Indications for surgery: recurrent pneumothoraces; isolated bullous disease; lung volume reduction surgery (selected patients).
- Assess social circumstances and support required. Identify and treat depression.
- Air travel may be hazardous if P_aO_2 <6.7kPa; check availability of O_2.

Management of acute COPD

Controlled oxygen therapy
Start at 24–28%; vary according to ABG.
Aim for a P_aO_2 >8.0kPa with a rise in P_aCO_2 <1.5kPa

↓

Nebulized bronchodilators
Salbutamol 5mg/4h and ipratropium 500µg/6h

↓

Steroids
IV hydrocortisone 200mg and oral prednisolone 30–40mg

↓

Antibiotics
Use if evidence of infection, eg amoxicillin 500mg/8h PO, p153

↓

Physiotherapy to aid sputum expectoration

↓

If no response
Repeat nebulizers and consider IV aminophylline[1]

↓

If no response
1. Consider nasal intermittent positive pressure ventilation (*NIPPV*) *if respiratory rate >30 or pH <7.35.*
It is delivered by nasal mask and a flow generator

↓

2. Consider intubation[2] & ventilation if pH <7.26 and P_aCO_2 is rising

↓

3. Consider a respiratory stimulant drug, eg doxapram 1.5–4mg/min IV *SE: agitation, confusion, tachycardia, nausea*
Only for patients who are not suitable for mechanical ventilation
A short-term measure only, and rarely used now NIPPV available

1 Aminophylline: Do not give a loading dose to patients on maintenance methylxanthines (theophyllines/aminophylline). Load with 250mg over 20min, then infuse at a rate of ~500µg/kg/h. Check plasma levels if given for >24h. ECG monitoring is required.

2 A decision to ventilate will depend on the patient's premorbid state—exercise capacity, home oxygen, and comorbidity. Ask about this information before you need to make this decision.

Oxygen therapy

- The greatest danger is hypoxia, which probably accounts for more deaths than hypercapnia. *Don't leave patients severely hypoxic.*
- However, in some patients, who rely on their hypoxic drive to breathe, too much oxygen may lead to a reduced respiratory rate, and hypercapnia, with a consequent fall in conscious level.
- Therefore, care is required with O_2, especially if there is evidence of CO_2 retention. Start with 24-28% O_2 in such patients. Reassess after 30min.
- Monitor the patient carefully. Aim to raise the P_aO_2 above 8.0kPa with a rise in P_aCO_2 <1.5kPa.
- In patients without evidence of retention at baseline use 28-40% O_2, but still monitor and repeat ABG.

▸▸Pneumothorax (see image p735)

▸▸*Tension pneumothorax*

requires immediate relief (see below). Do not delay management by obtaining a CXR.

Causes

Often spontaneous (especially in young thin men) due to rupture of a subpleural bulla. Other causes: asthma; COPD; TB; pneumonia; lung abscess; carcinoma; cystic fibrosis; lung fibrosis; sarcoidosis; connective tissue disorders (Marfan's syndrome, Ehlers-Danlos syndrome); trauma; iatrogenic (subclavian CVP line insertion, pleural aspiration or biopsy, percutaneous liver biopsy, positive pressure ventilation).

Clinical features

Symptoms:

There may be no symptoms (especially in fit young people with small pneumothoraces) or there may be sudden onset of dyspnoea and/or pleuritic chest pain. Patients with asthma or COPD may present with a sudden deterioration. Mechanically ventilated patients may present with hypoxia or an increase in ventilation pressures.

Signs:

reduced expansion, hyper-resonance to percussion and diminished breath sounds on the affected side. *With a tension pneumothorax, the trachea will be deviated away from the affected side and the patient will be very unwell.*

Investigations

▸*A* **CXR** *should not be performed if a tension pneumothorax is suspected, as it will delay immediate necessary treatment.* Otherwise, request an expiratory film, and look for an area devoid of lung markings, peripheral to the edge of the collapsed lung (see p735). *Ensure the suspected pneumothorax is not a large emphysematous bulla.* Check ABG in dyspnoeic patients and those with chronic lung disease.

Management

Depends on whether it is a primary or secondary (underlying lung disease) pneumothorax, size and symptoms—see OPPOSITE.

- Pneumothorax due to trauma or mechanical ventilation requires a chest drain.
- Aspiration of a pneumothorax, see p755
- Insertion and management of a chest drain, see p754.

Surgical advice:

Arrange if: bilateral pneumothoraces; lung fails to expand after intercostal drain insertion; 2 or more previous pneumothoraces on the same side; or history of pneumothorax on the opposite side.

▸▸Tension pneumothorax (see p735)

This is a medical emergency.

Essence:

Air drawn into the pleural space with each inspiration has no route of escape during expiration. The mediastinum is pushed over into the contralateral hemithorax, kinking and compressing the great veins. Unless the air is rapidly removed, cardiorespiratory arrest will occur.

Signs:

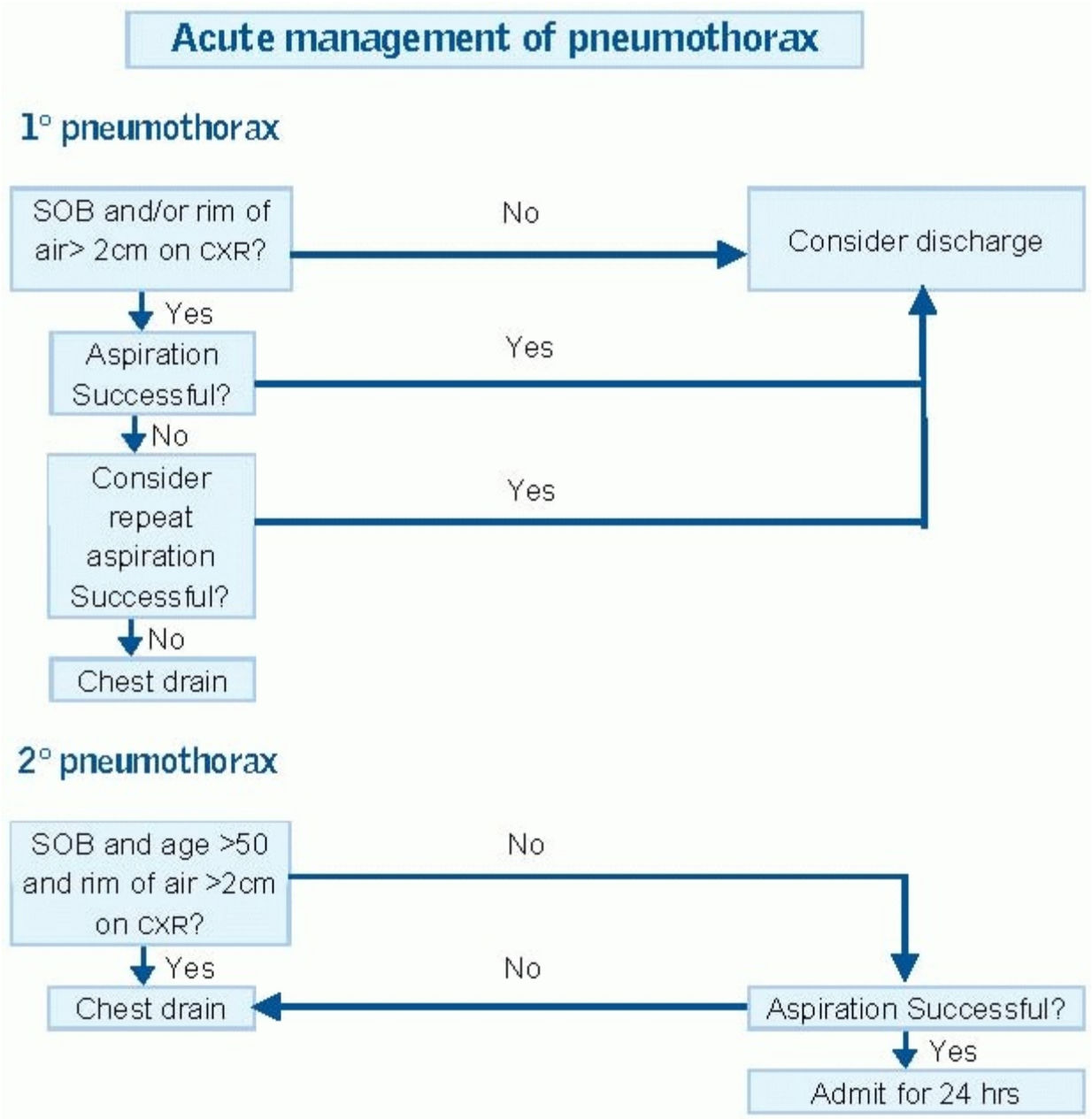
Respiratory distress, tachycardia, hypotension, distended neck veins, trachea deviated away from side of pneumothorax. Increased percussion note, reduced air entry/breath sounds on the affected side.

Treatment:

To remove the air, insert a large-bore (14-16G) needle with a syringe, partially filled with 0.9% saline, into the 2nd intercostal interspace in the midclavicular line on the side of the suspected pneumothorax. Remove plunger to allow the trapped air to bubble through the syringe (with saline as a water seal) until a chest tube can be placed. Alternatively, insert a large-bore Venflon in the same location.

Do this *before* requesting a CXR.

Then insert a chest drain. See p754.



Aspiration of a pneumothorax:

▸▸see p755.

Intercostal tube drainage:

For insertion, see p754.

- Use a small tube (10-14F) unless blood/pus is also present.
- Never clamp a bubbling tube.
- Tubes may be removed 24h after the lung has re-expanded and air leak has stopped (ie the tube stops bubbling). This is done during expiration or a Valsalva manoeuvre.
- If the lung fails to re-expand within 48h, or if there is a persistent air leak, specialist advice should be obtained, as suction or surgical intervention may be required.
- If suction is required, high volume, low pressure (-10 to -20cm H_2O) systems are required.

Pneumonia[15]

An infection of the lung parenchyma. Incidence of community-acquired pneumonia is 12 per 1000 adults. Of these, 1 will require hospitalization, and mortality in these patients is still 10%.

Common organisms

- *Streptococcus pneumoniae* is the commonest cause (60-75%).
- *Mycoplasma pneumoniae* (5-18%).
- *Staphylococcus aureus*.
- *Haemophilus influenzae*.
- *Legionella* species and *Chlamydia psittaci*.
- Gram-negative bacilli, often hospital-acquired or immunocompromised, eg *Pseudomonas* especially in those with COPD.
- Viruses including influenza account for up to 15%.

Symptoms

- Fever, rigors, malaise, anorexia, dyspnoea, cough, purulent sputum (classically 'rusty' with pneumococcus), haemoptysis, and pleuritic chest pain.

Signs

- Fever, cyanosis, herpes labialis (pneumococcus), confusion, tachypnoea, tachycardia, hypotension, signs of consolidation (diminished expansion, dull percussion note, increased tactile vocal fremitus/vocal resonance, bronchial breathing), and a pleural rub.

Investigations

- CXR (X-ray images, fig 1 on p714).
- Oxygen saturation arterial blood gases if S_aO_2 <92% or severe pneumonia.
- FBC, U&E, LFT, CRP, atypical serology.
- Blood and sputum cultures.
- Pleural fluid may be aspirated for culture.
- Bronchoscopy and bronchoalveolar lavage if the patient is immunocompromised or on ITU.

Severity

Calculate the core adverse features 'CURB-65' score:

- **C**onfusion (abbreviated mental test ≤8);
- **U**rea >7mmol/L;
- **R**espiratory rate ≥30/min;
- **BP** <90/60mmHg).
- **A**ge≥65

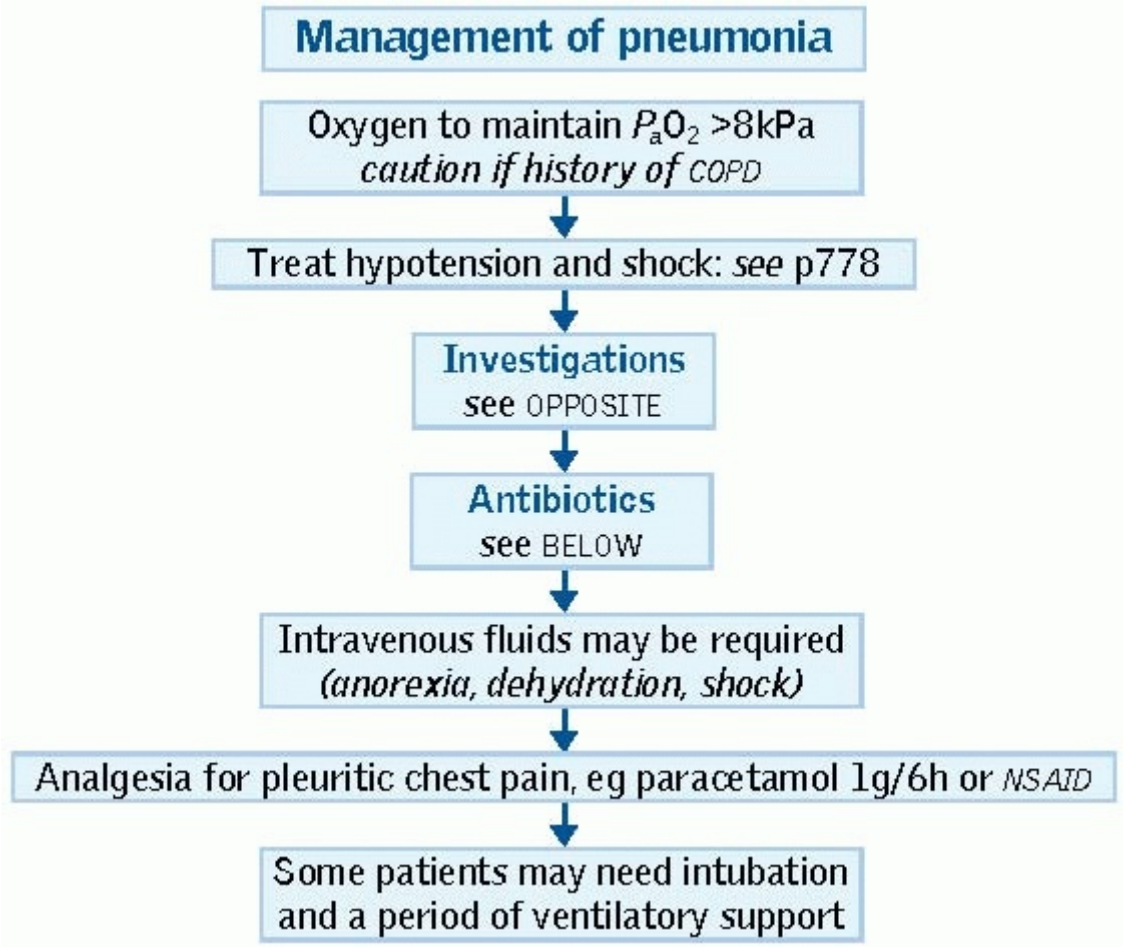
Score: 0-1 home treatment possible; 2 hospital therapy; ≥3 indicates severe pneumonia. Other features increasing the risk of death are: co-existing disease; bilateral/ multilobar involvement; P_aO_2 <8kPa/S_aO_2 <92%.

Management

See OPPOSITE.

Complications

Pleural effusion, empyema, lung abscess, respiratory failure, septicaemia, pericarditis, myocarditis, cholestatic jaundice, renal failure.



Antibiotic treatment of pneumonia

Clinical setting	Organisms	Antibiotic (further dosage details: p368 & p369)
Community acquired		
Mild, no previous [prescription take]	*Streptococcus pneumoniae Haemophilus influenzae*	Amoxicillin 500mg-1.0g/8h or erythromycin[1] 500mg/6h PO
Mild	*Streptococcus pneumoniae Haemophilus influenzae Mycoplasma pneumoniae*	Amoxicillin 500mg-1.0g/8h PO + erythromycin[1] 500mg/6h PO or fluoroquinolone if IV required: ampicillin 500mg/6h + erythromycin[1] 500mg/6h IVI
Severe	As above	Co-amoxiclav IV or cephalosporin IV (eg Cefuroxime 1.5g/8h IV) AND erythromycin[1] 1g/6h IVI
Atypical	*Legionella pneumophilia*	Clarithromycin 500mg/12h PO/IVI ± rifampicin
	Chlamydia species	Tetracycline
	Pneumocystis jiroveci	High-dose co-trimoxazole (see p398, p399)
Hospital acquired		
	Gram negative bacilli Pseudomonas Anaerobes	Aminoglycoside IV + antipseudomonal penicillin IV eg

		ticarcillin, p368 or 3rd gen. cephalosporin IV (p369)
Aspiration		
	Streptococcus pneumoniae Anaerobes	Cefuroxime 1.5g/8h IV + metronidazole 500mg/8h IV
Neutropenic patients		
	Gram positive cocci Gram negative bacilli Fungi (p160)	Aminoglycoside IV + antipseudomonal penicillin IV or 3rd gen. cephalosporin IV Consider antifungals after 48h
3rd gen=3rd generation, eg cefotaxime, p369; gentamicin is an example of an aminoglycoside (p371).		

[1] Clarithromycin 500mg/12h PO/IVI may be used in place of erythromycin throughout the above.

▸▸Massive pulmonary embolism (PE)

▸Always suspect pulmonary embolism (PE) in sudden collapse 1-2wks after surgery. Death rate in England and Wales: 30,000-40,000/yr.

Mechanism

Venous thrombi, usually from DVT, pass into the pulmonary circulation and block blood flow to lungs. The source is often occult.

Risk factors

- Malignancy.
- Surgery—especially pelvic.
- Immobility.
- The Pill (there is also a slight risk attached to HRT).
- Previous thromboembolism and inherited thrombophilia, see p358.

Prevention

Early post-op mobilization is the simplest method; consider:

- Antithromboembolic (TED) stockings.
- Low molecular weight heparin prophylaxis SC.

- Avoid contraceptive pill if at risk, eg major or orthopaedic surgery.
- Recurrent PEs may be prevented by anticoagulation, vena caval filters are of limited use, and should be combined with anticoagulation.

Signs and symptoms

- Acute dyspnoea, pleuritic chest pain, haemoptysis, and syncope.
- Hypotension, tachycardia, gallop rhythm, JVP↑, loud P_2, right ventricular heave, pleural rub, tachypnoea, and cyanosis, AF.

Classically, PE presents 10d post-op, with collapse and sudden breathlessness while straining at stool—but PE may occur after any period of immobility, or with no predisposing factors. Breathlessness may be the only sign. Multiple small emboli may present less dramatically with pleuritic pain, haemoptysis, and gradually increasing breathlessness.

▸Look for a source of emboli—especially DVT (is a leg swollen?).

Investigations

- U&E, FBC, baseline clotting.
- ECG (commonly normal or sinus tachycardia); right ventricular strain pattern V1-3 (p84), right axis deviation, RBBB, AF, may be deep S-waves in I, Q-waves in III, inverted T-waves in III ('$S_I\ Q_{III}\ T_{III}$').
- CXR—often normal; decreased vascular markings, small pleural effusion. Wedge-shaped area of infarction. Atelectasis.
- ABG: hyperventilation + gas exchange↓: P_aO_2↓, P_aCO_2↓, pH often↑, p148.
- CT pulmonary angiography is sensitive and specific in determining if emboli are in pulmonary arteries. If helical CT is unavailable, a *ventilation-perfusion ([V with dot above]/[Q with dot above]) scan* can aid diagnosis. If [V with dot above]/[Q with dot above] scan is equivocal, pulmonary angiography or bilateral venograms may help (MRI venography or plethysmography are alternatives).
- D-dimer blood test, ↑ if thrombosis present. May help in excluding a PE.

Management

See OPPOSITE for immediate management.

- Try to prevent further thrombosis with compression stockings.
- Heparin concurrently with warfarin for ≥5d, and until INR >2. Then stop.
- If obvious remedial cause, 6wks' treatment with warfarin may be sufficient. Otherwise, continue for at least 3-6 months (long-term if recurrent emboli, or underlying malignancy).
- Is there an underlying cause, eg thrombophilic tendency (p358), malignancy (especially prostate, breast, or pelvic cancer), SLE, or polycythaemia?

▸If good story and signs, make the diagnosis. Start treatment (OPPOSITE) before definitive investigations: most PE deaths occur within 1h.

Management of massive pulmonary embolism

Oxygen, 100%

↓

Morphine 10mg IV with antiemetic
if the patient is in pain or very distressed

↓

►If critically ill, consider immediate surgery

↓

IV access and start heparin
either unfractionated heparin ~10,000U IV bolus
then ~18U/kg/h IVI as guided by APTT (p334)
or low molecular weight heparin, eg tinzaparin 175U/kg/24h SC

↓

What is the systolic BP?

<90 mmHg
Start rapid
colloid infusion[1]

↓

If BP still↓ after 500mL
colloid, dobutamine 2.5–
10µg/kg/min IV; aim for
systolic BP >90mmHg

↓

If BP still low, consider
noradrenaline

↓

If the systolic BP
<90mmHg after 30–
60min of standard
treatment, clinically
definite PE and no CI
(p782), consider
thrombolysis.[2]

>90 mmHg
Start warfarin
10mg/24h PO (p334)

↓

Confirm diagnosis

1 Controversial, but some authorities say it is best to infuse plasma-expanding fluids even if CVP↑, to maintain BP & organ perfusion, see *Concise OTM* (*OUP*, 2000) page 151—but see Task Force on PE, European Society Cardiology *Eur Heart J* 2000 **21** 1301.

2 A standard regimen is: ***Loading dose:*** streptokinase 250,000U IVI over 30min.
Maintenance dose: streptokinase 100,000U/h IVI for 12–72h, according to response. **Or** rt-PA (alteplase) 10mg IV over 1–2min followed by 90mg IV over 2h; max 1.5mg/kg if patient <65kg.

▸▸Acute upper gastrointestinal bleeding[16]

Causes

- Peptic ulcer ~40%.
- Mallory Weiss tear 15%.
- Gastroduodenal erosions ~10%.
- Oesophagitis ~10%.
- Varices ~7%.
- Other: malignancy, vascular malformations, haemoptysis (swallowed blood).

Signs & symptoms

Haematemesis, or melaena, dizziness (especially postural), fainting, abdominal pain, dysphagia? Postural hypotension, hypotension, tachycardia (not if on ß-blocker), ↓JVP, ↓urine output, cool and clammy, signs of chronic liver disease (p252); telangiectasia or purpura; jaundice (biliary colic + jaundice + melaena suggests haemobilia). **NB:** ask about previous GI problems, drug use, and alcohol intake.

Management[17]:

Is the patient shocked?

- Cool & clammy to touch (especially nose, toes, fingers) ↓capillary refill.
- Pulse >100bpm.
- JVP <1cm H_2O.
- Systolic BP <100mmHg.
- Postural drop (>20mmHg on standing).
- Urine output <30mL/h.

If not shocked:

Insert 2 big cannulae; start slow saline IVI to keep lines patent; check bloods and monitor vital signs + urine output. Aim to keep Hb >8g/dL. **NB:** Hb may not fall until circulating volume is restored.

If shocked:

See OPPOSITE for management

CVP line:

Consider for high risk patients eg ↑age, CV disease, on ß-blockers.

Acute drug therapy:

Following successful endoscopic therapy in patients with **major** ulcer bleeding, IV omeprazole (80mg stat followed by 8mg/h for 72h) is recommended. There is no firm evidence to support the use of somatostatin or antifibrinolytic therapy in the majority of patients.

Variceal bleeding:

Resuscitate then proceed to urgent endoscopy for banding or sclerotherapy. Give octreotide 50µg/h IVI for 2-5d. Terlipressin may also be used. If massive bleed or bleeding continues, pass a Sengstaken-Blakemore tube p231. A bleed is the equivalent of a large protein meal so start treatment to avoid hepatic encephalopathy (p250). Esomeprazole 40mg PO may also be helpful in preventing stress ulceration.

Endoscopy:

Within 4h if you suspect variceal bleeding; within 12-24h if shocked on admission or significant comorbidity. Endoscopy can identify the site of bleeding, estimate the risk of rebleeding (see opposite) and can be used to administer treatment.

No site of bleeding identified:

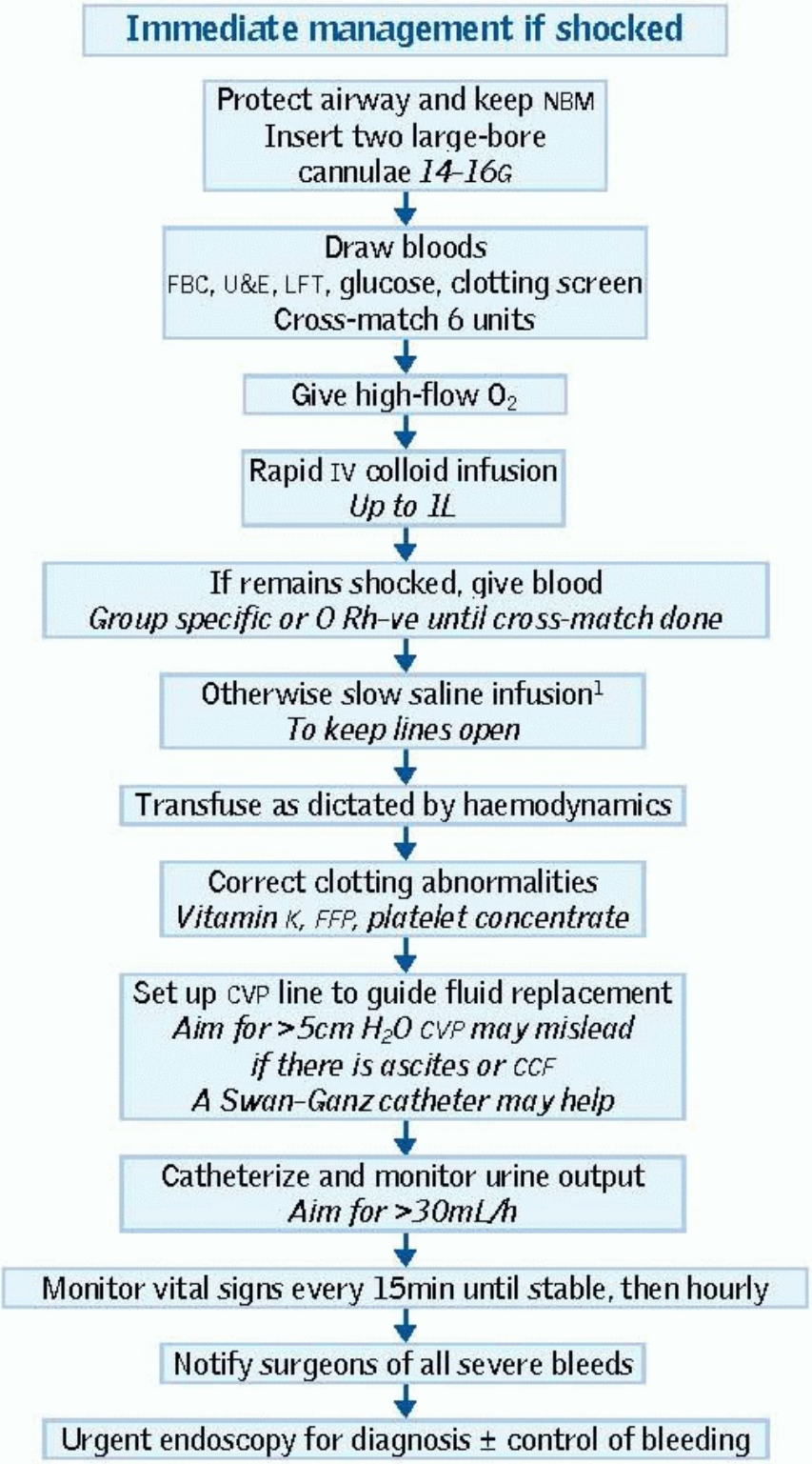
Bleeding site missed on endoscopy; bleeding site has healed (Mallory-Weiss tear or Dieulafoy's lesion); nose bleed (swallowed blood); site distal to 3rd part of the duodenum (Meckel's diverticulum, colonic site).

Rebleeds

Serious event: 40% of patients who rebleed will die. If ‘at risk’ maintain a high index of suspicion. If a rebleed occurs, check vital signs every 15min and call senior cover. To prevent rebleeding in endoscopically-proven high risk cases, IVI omeprazole has been tried, eg 80mg followed by an infusion of 8mg/h for 72h, then 20mg/24h PO for 8wks.[18]

Signs of a rebleed:

- Rising pulse rate.
- Falling JVP ± decreasing hourly urine output.
- Haematemesis or melaena.
- Fall in BP (a late and sinister finding) and decreased conscious level.



1 Avoid saline in patients with decompensated liver disease (ascites, peripheral oedema) as it worsens ascites, and despite a low serum sodium, patients have a high body sodium. Use whole blood, or salt-poor albumin for resuscitation, and 5% dextrose for maintenance.

Rockall scoring system for prognosis in acute GI bleeding[19]

	Score			
Variable	**0**	**1**	**2**	**3**
Age	<60	60-80	>80	
Shocked?	No	SBP >100 pulse >100	SBP <100, pulse >100	
Co-morbidity?	None		Any major	Renal/liver failure, or malignancy
Diagnosis	Mallory-Weiss or normal	All other diagnoses	Malignancy	
Bleeding visible?	None/spot		Visible blood/clot spurting vessel	
Score <3 means an excellent prognosis; >8 means a high risk of death				

▸▸Meningitis[ND]

▸***Do not*** delay treatment, it may save a life.

▸Make sure the referring GP gives a dose of antibiotic (benzylpenicillin, eg 1.2g IM/IV) before sending the patient to you if possible.

Early features

Headache, leg pains, cold hands and feet, abnormal skin colour.[21]

Later signs

- Meningism: neck stiffness, photophobia, Kernig's sign (pain + resistance on passive knee extension with hip fully flexed).
- Conscious level ↓, coma.
- Seizures (~20%) ± focal CNS signs (~20%).

- Petechial rash (non-blanching—see **fig 1**; may only be 1 or 2 spots, or none).
- Signs of galloping sepsis: slow capillary refill; DIC; BP↓. T° and pulse: ↑ or normal.

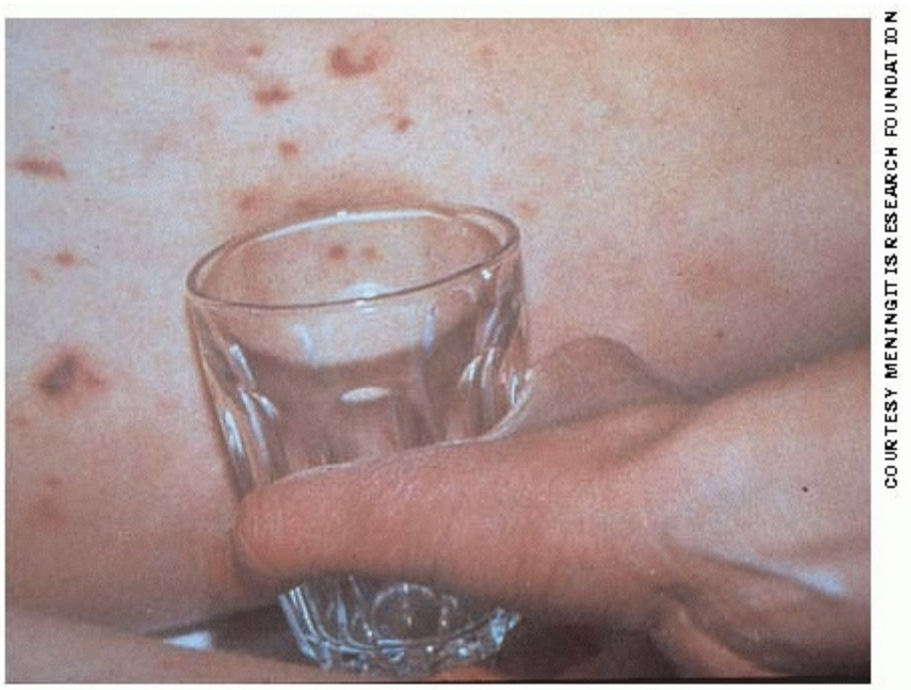


Fig 1. Glass test for purpura[20]

Common organisms

- Meningococcus
- Pneumococcus
- *Haemophilus influenzae*
- *Listeria monocytogenes*

Differential

Malaria, encephalitis, septicaemia, subarachnoid bleed, dengue, tetanus.

Management

- Careful examination: pay attention to neurology; look for rashes; assess GCS.
- If shocked, resuscitate with fluids and oxygen.
- If ICP raised, summon help immediately and inform neurosurgeons.
- Start antibiotics (below) immediately.

Investigations

- U&E, FBC, LFT, glucose, coagulation screen.
- Blood culture, throat swabs (1 for bacteria, 1 for virology), stool sample for viruses.
- Lumbar puncture (p756) if safe.[1] Don't forget to measure the opening pressure! (7-18cm CSF is normal; in meningitis it may be >40; typically 14-30). **Contraindications** are: suspected intracranial mass lesion, focal signs, papilloedema, trauma, middle ear pathology or major coagulopathy. Send samples for MC&S, gram stain, protein estimation, glucose, and to virology.

CSF in meningitis	*Pyogenic*	*Tuberculous* (p387)	*Viral ('aseptic')*
Appearance	Often turbid	Often fibrin web	Usually clear
Predominant cell[1]	Polymorphs	Mononuclear	Mononuclear
Cell count/mm^3	Eg 90-1000+	10-1000	50-1000
Glucose[†]	<½ plasma	<½ plasma	>½ plasma
Protein (g/L)	>1.5	1-5	<1
Bacteria	In smear & culture	Often none in smear	None seen or cultured

There are no certain rules

- CT head before LP if mass lesion or raised ICP suspected (eg conscious ↓).
- CXR.

Antibiotics

Local policies vary. If in doubt ask. The following are suggestions only, where the organism is unknown:

- <55yrs: cefotaxime 2mg/6h slow IV.
- >55yrs: cefotaxime as above + ampicillin 2g IV/4h (for *Listeria*).
- Aciclovir if viral encephalitis suspected.
- Once organism isolated, seek urgent microbiological advice.

▸▸Meningitis Rx: If outside hospital, let ***nothing*** delay IV/IM benzylpenicillin 1.2g while awaiting transport. In hospital: **ABC**s; high-flow O_2. IVI + fluid resus. Ask a nurse to draw up cefotaxime 2g. **Do septicaemic or meningitic features predominate?**

See British Infection Society guideline 2005

Septicaemic signs to fore: eg ↓capillary refill time; cold hands + feet (occurs before BP falls); rash. 2006 data

- Do not attempt LP
- **Cefotaxime** 2g IV
- Get help from critical care team
- Signs of shock?

Yes

Take to ITU for:
- Fluid resuscitation
- Pre-emptive intubation
- Inotropes/vasopressors
- Activated protein C[2]
- Aim for systolic BP of >80mmHg and urine flow >30mL/h

No

Careful monitoring

Repeat review

Meningitic signs predominate, ie neck stiffness; photophobia [22]

Dexamethasone 4–10mg/6h IV[1]

If no shock, or ICP↑ signs, **Do LP.** If not sure, get senior help

2g **cefotaxime** IV post-LP at once (pre-LP, if to be delayed by >½h)

If signs of ↑ICP, take to ITU; and do **not** do LP

Nurse at 30°; have low threshold for intubation. NB: don't rely on CT to rule out ↑ICP. Also, papilloedema is a late sign.

If immunocompromized, get help; add **ampicillin** 2g/6h IV for *Listeria*, also if >55yrs old

Subsequent therapy: Cefotaxime 2–4g/8h IVI (eg for 10d); ↓dose in renal failure; see p369 and ***data sheet*** (SPC). **Maintenance fluids:** avoid overhydration and underhydration (despite ICP↑). [23] **Isolate** for 1st 24h. If response to the above is poor consider pre-emptive **intubation & ventilation** ± **inotropic/vasopressor** support (p778).

Offer prophylaxis to: • Household contacts (in droplet range). • Those who have kissed the patient's mouth. • Yourself (rarely needed [24]). Give **rifampicin** (600mg/12h PO for 2 days; children >1yr 10mg/kg/12h; <1yr 5mg/kg/12h) or **ciprofloxacin** (500mg PO, 1 dose child 5–12yrs: 250mg stat). Neither is guaranteed in pregnancy, but are recommended (harm is unlikely).

1 Dexamethasone 0.15mg/kg/6h IV eg from just *before* 1st antibiotic dose[●]; evidence is now good-ish, esp. for pneumococcal meningitis and in children. Avoid dexamethasone in septic shock, known meningococcal disease, immunocompromized states, and in post-op meningitis. **2** *Drotrecogin alfa (activated)* is approved by NICE.

Emergency management of encephalitis[ND]

Suspect encephalitis whenever odd behaviour, ↓consciousness, cranial nerve lesions, or paralysis is preceded by a prodrome (T°↑, rash, lymphadenopathy, cold sores, conjunctivitis, meningeal signs, seizures). It is often necessary to treat before the exact cause is known—often viral with no *specific* treatment (arboviruses; CMV, EBV; p389; measles; Japanese B or West Nile encephalitis) but as specific treatment *is* available for herpes simplex encephalitis, aim to start **aciclovir** within 30min$_{25}$ of the patient arriving (▸▸10mg/kg/8h IVI over 1h) for 14-21 days. Specific therapies also exist for CMV & toxoplasmosis (p392).

Tests:

Blood & viral culture (throat; CSF; MSU)/PCR; enhanced CT (MRI if contrast-allergic) pre-LP; toxoplasma tests (p392). △△: Malaria, rabies, TB, SLE, hypoglycaemia, beri-beri (give vit B1 if in doubt, p707).

Supportive therapy:

See ICP↑, p812; **dexamethasone** 10mg/6h IV has a role.

▸▸Status epilepticus

This means seizures lasting for >30min, or repeated seizures without intervening consciousness. Mortality and the risk of permanent brain damage increase with the length of attack. Aim to terminate seizures lasting more than a few minutes as soon as possible (<20min).

Status usually occurs in known epileptics. If it is the 1st presentation of epilepsy, the chance of a structural brain lesion is high (>50%). Diagnosis of tonic-clonic status is usually clear. Non-convulsive status (eg absence status or continuous partial seizures with preservation of consciousness) may be more difficult: look for subtle eye or lid movement. For other signs, see p477. An EEG can be very helpful. ▸*Could the patient be pregnant* (any pelvic mass)? If so, eclampsia (OHCS p48) is the likely diagnosis, check the urine and BP: call a senior obstetrician—immediate delivery may be needed.

Investigations

- Bedside glucose, the following tests can be done once [prescription take] has started: Glucose, blood gases, U&E, Ca^{2+}, FBC, ECG.
- Consider anticonvulsant levels, toxicology screen, LP, culture blood and urine, EEG, CT, carbon monoxide level.
- Pulse oximetry, cardiac monitor.

Treatment

See OPPOSITE. Basic life support—and these agents:

1. ***Lorazepam*** ~4mg as a slow bolus (≤2min) into a large vein. Beware respiratory arrest during the last part of the injection. Have full resuscitation facilities to hand for all IV benzodiazepine use. (Alternative: ***diazepam*** as ***Diazemuls®*** but it is less long-lasting—give 10mg IV over 2min; if needed, repeat at 5mg/min, until seizures stop or 20mg given—or significant respiratory depression occurs.) The rectal route is an alternative for diazepam if IV access is difficult.[1] ***Buccal midazolam*** (Epistatus®) is an easier to use oral alternative; dose for those 10yrs old and older: 10mg (1mL); if 1-4yrs old, 0.5mL; if 6-12 months old, 0.25mL; squirt half the volume between the lower gum and the cheek on each side. While waiting for this to work, prepare other drugs. If fits continue …
2. **Phenytoin infusion:** 15mg/kg IVI, at a rate of ≤50mg/min. (Don't put diazepam in same line: they don't mix.) Beware BP↓ and do not use if bradycardic or heart block. Requires BP and ECG monitoring. 100mg/6-8h is a maintenance dose (check levels). If fits continue …
3. **Diazepam infusion:** 100mg in 500mL of 5% dextrose; infuse at about 40mL/h (3mg/kg/24h). Close monitoring, especially respiratory function, is vital. It is most unusual for seizures to remain unresponsive following this. If they do, allow the idea to pass through your mind that they could be pseudoseizures (p698), particularly if there are odd features (pelvic thrusts; resisting attempts to open lids and your attempts to do passive movements; arms and legs flailing around).
4. **Dexamethasone** 10mg IV if vasculitis/cerebral oedema (tumour) possible.
5. **General anaesthesia** This requires expert guidance on ITU.

As soon as seizures are controlled, start oral drugs (p484). Ask what the cause was, eg hypoglycaemia, pregnancy, alcohol, drugs, CNS lesion or infection, hypertensive encephalopathy, inadequate anticonvulsant dose (p482).

Management of status epilepticus

Open and maintain the airway, lay in recovery position
Remove false teeth if poorly fitting, insert oral/nasal airway, intubate if necessary

↓

Oxygen, 100% + suction (as required)

↓

IV access and take blood:
- U&E, LFT, FBC, glucose (eg BM test®), calcium
- Toxicology screen if indicated, anticonvulsant levels

↓

Thiamine 250mg IV over 10min if alcoholism or malnourishment suspected.
Unless glucose known to be normal, IV glucose 50mL 50%

↓

Correct hypotension with fluids

↓

Slow IV bolus phase—to stop seizures: eg lorazepam 4mg

↓

IV infusion phase: If seizures continue, start phenytoin, 15mg/kg IVI, at a rate of ≤50mg/min. Monitor ECG and BP. 100mg/6–8h is a maintenance dose (check levels).
Alternative: diazepam infusion:100mg in 500mL of 5% dextrose; infuse at ~40mL/h as opposite

↓

General anaesthesia phase: Continuing seizures require expert help with paralysis and ventilation with continuous EEG monitoring in ITU

NB: ▸**Never** spend longer than 20min on someone with status epilepticus without having help at the bedside from an anaesthetist.

Cerebral abscess

Suspect this in any patient with ICP↑, especially if there is fever or ↑WCC. It may follow ear, sinus, dental, or periodontal infection; skull fracture; congenital heart disease; endocarditis; bronchiectasis. It may also occur in the absence of systemic signs of inflammation.

Signs:

Seizures, fever, localizing signs, or signs of ↑ICP. Coma. Signs of sepsis elsewhere (eg teeth, ears, lungs, endocarditis).

Investigations:

CT/MRI (eg 'ring-enhancing' lesion); ↑WBC, ↑ESR; biopsy.

Treatment:

Urgent neurosurgical referral; treat ↑ICP (p812). If frontal sinuses or teeth are the source, the likely organism will be *Strep. milleri* (microaerophilic), or oropharyngeal anaerobes. In ear abscesses, *B. fragilis* or other anaerobes are most common. Bacterial abscesses are often peripheral; toxoplasma lesions (p392) are deeper (eg basal ganglia). NB: ask yourself: is there underlying immunosuppression?

▸▸Head injury

▸If the pupils are unequal, diagnose rising intracranial pressure (ICP), eg from extradural haemorrhage, and summon urgent neurosurgical help (p474). Retinal vein pulsation at fundoscopy helps exclude ICP↑.

Initial management

(See OPPOSITE) Write full notes. Record times.

- Involve neurosurgeons at an early stage, especially with comatosed patients, or if raised ICP suspected.
- Examine the CNS. Chart pulse, BP, T°, respirations + pupils every 15min.
- Assess anterograde amnesia (loss from the time of injury, ie post-traumatic) and retrograde amnesia—its extent correlates with the severity of the injury, and it never occurs without anterograde amnesia.
- Nurse semi-prone if no spinal injury; meticulous care to bladder & airway.

Who needs a CT head?

- If any of the following are present, a CT is required immediately:
- GCS <13 at any time, or GCS 13 or 14 at 2h following injury
- Focal neurological deficit
- Suspected open or depressed skull fracture, or signs of basal skull fracture
- Post-traumatic seizure
- Vomiting >once
- Loss of consciousness AND any of the following
  - Age ≥65
  - Coagulopathy
  - 'Dangerous mechanism of injury' eg RTA, fall from great height
  - Antegrade amnesia of >30min.

When to ventilate immediately:

- Coma ≤8 on Glasgow coma scale (GCS; p776)
- P_aO_2 <9kPa in air (<13kPa in O_2) or P_aCO_2 >6kPa
- Spontaneous hyperventilation (P_aCO_2 <3.5kPa)
- Respiratory irregularity.

Ventilate before neurosurgical transfer if:

- Deteriorating level of consciousness
- Bilateral fractured mandible
- Bleeding into mouth, eg skull base fracture
- Seizures.

Risk of intracranial haematoma in adults

Fully conscious, no skull fracture = <1:1000

Confused, no skull fracture = 1:100

Fully conscious, skull fracture = 1:30

Confused, skull fracture = 1:4

Criteria for admission

- Difficult to assess (child; post-ictal; alcohol intoxication).
- CNS signs; severe headache or vomiting; fracture.
- Loss of consciousness does **not** require admission if well, and a responsible adult is in attendance.

Drowsy trauma patients (GCS <15 to >8) smelling of alcohol:

Alcohol is an unlikely cause of coma if plasma alcohol <44mmol/L. If unavailable, estimate blood alcohol level from the osmolar gap, p664. If blood alcohol ≈ 40mmol/L, osmolar gap " 40mmol/L. Never assume signs are just alcohol.

Complications

Early:

Extradural/subdural haemorrhage, seizures.

Late:

Subdural, p474; seizures; diabetes insipidus; parkinsonism; dementia.

Indicators of a bad prognosis

Old age, decerebrate rigidity, extensor spasms, prolonged coma, ↑BP, P_aO_2↓ (on blood gases), T° >39°C. 60% of those with loss of consciousness of >1 month will survive 3-25yrs, but may need daily nursing care.

For *Spinal cord injury & Persistent vegetative states*, see OHCS (p768-p776 & p778).

Immediate management plan

ABC

↓

Oxygen, 100%
Intubate and hyperventilate if necessary
NB: beware of a cervical spine injury

↓

Stop blood loss and support circulation
Treat for shock if required (p778)

↓

Treat seizures with diazepam

↓

Assess level of consciousness (GCS)
Antegrade and retrograde amnesia

↓

Rapid examination survey

↓

Investigations:
U&Es, glucose, FBC, blood alcohol, toxicology screen, ABG & clotting

↓

Neurological examination

↓

Brief history
When? Where? How? Had a fit? Lucid interval? Alcohol?

↓

Evaluate lacerations of face or scalp
Palpate deep wounds with sterile glove to check for step deformity. Note obvious skull/facial fractures[1]

↓

Check for CSF leak, from nose (rhinorrhoea) or ear
Any blood behind the ear drum?
If either is present, suspect basilar skull fracture: do CT
Give tetanus toxoid, and refer at once to neurosurgeons

↓

Palpate the neck posteriorly for tenderness and deformity
If detected, or if the patient has obvious head injury, or injury above the clavicle with loss of consciousness, immobilize the neck and get cervical spine radiographs

↓

Radiology
As indicated: cervical spine, chest X-rays; CT of head

1 Periorbital (raccoon sign), or postauricular (Battle sign) ecchymoses.

▸▸Raised intracranial pressure (ICP↑)

There are 3 types of cerebral oedema:

- Vasogenic: ↑ capillary permeability—tumour, trauma, ischaemia, infection.
- Cytotoxic: cell death, eg from hypoxia.
- Interstitial: eg obstructive hydrocephalus.

Because the cranium defines a fixed volume, brain swelling quickly results in ↑ICP which may produce a sudden clinical deterioration. Normal ICP is 0-10mmHg. The oedema from severe brain injury is probably both cytotoxic and vasogenic.

Causes

- Primary or metastatic tumours.
- Head injury.
- Haemorrhage (subdural, extradural, subarachnoid; intracerebral, intraventricular).
- Meningoencephalitis; brain abscess.
- Hydrocephalus; cerebral oedema; status epilepticus.

Signs & symptoms

- Headache; drowsiness; vomiting; seizures. History of trauma.
- Listlessness; irritability; drowsiness; falling pulse and rising BP (Cushing's response); coma; Cheyne-Stokes respiration; pupil changes (constriction at first, later dilatation—do not mask these signs by using agents, such as tropicamide, to dilate the pupil to aid fundoscopy).
- Papilloedema is an unreliable sign, but venous pulsation at the disc may be absent (absent in ~50% of normal people, but *loss* of it is a useful sign).

Investigations

- U&E, FBC, LFT, glucose, serum osmolality, clotting, blood culture, CXR.
- CT head.
- Then consider lumbar puncture if safe. Measure the opening pressure!

Treatment

The goal is to ↓ICP and avert secondary injury. Urgent neurosurgery is required for the definitive treatment of ↑ICP from focal causes (eg haematomas). This is achieved via a craniotomy or burr hole. Also, an ICP monitor (or bolt) may be placed to monitor pressure. Surgery is generally *not* helpful following ischaemic or anoxic injury.

Holding measures

are listed OPPOSITE.

Herniation syndromes

Uncal herniation

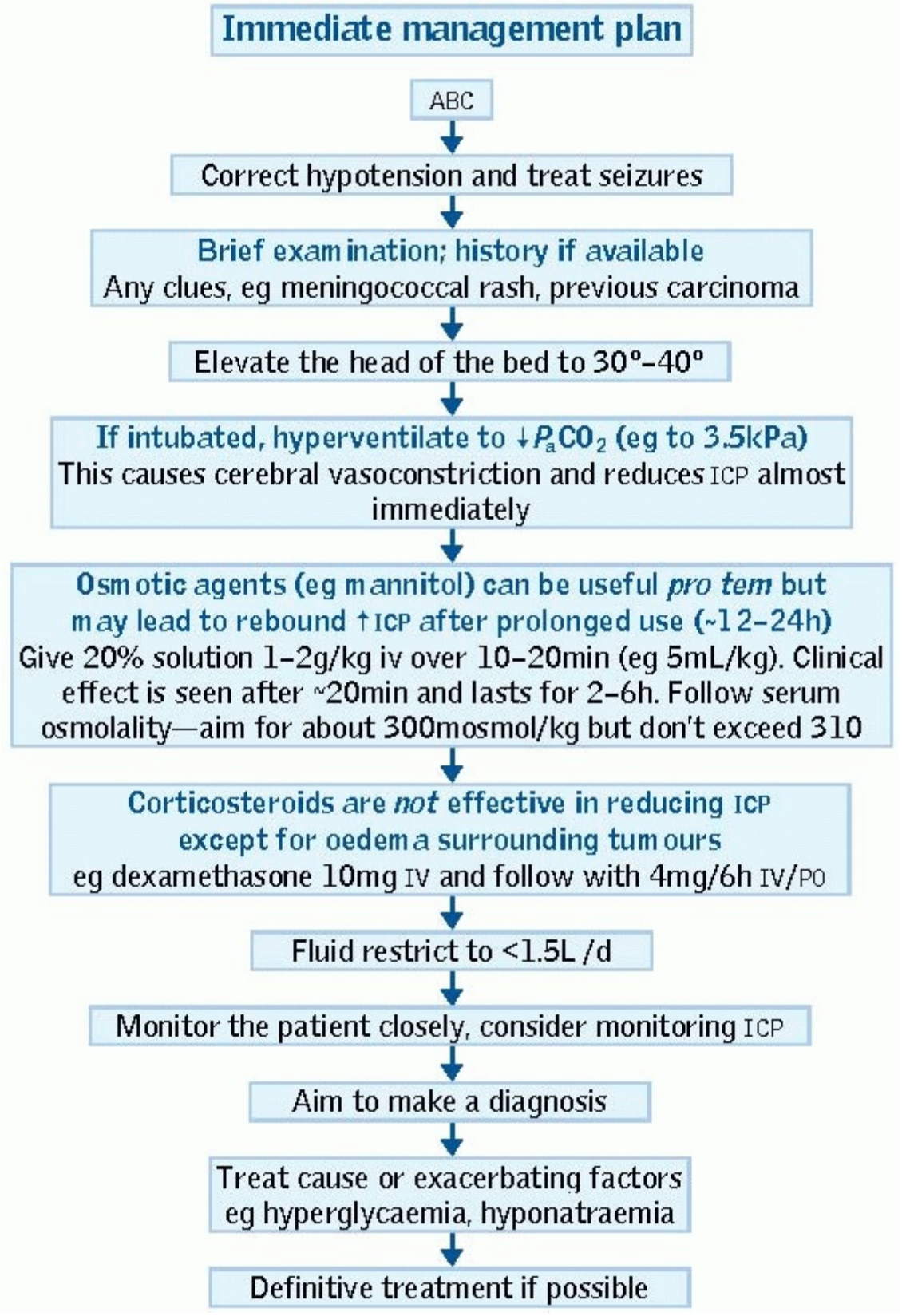
is caused by a lateral supratentorial mass which pushes the ipsilateral inferomedial temporal lobe (uncus) through the temporal incisura and against the midbrain. The 3rd nerve, travelling in this space, gets compressed causing a dilated ipsilateral pupil, then ophthalmoplegia (a fixed pupil localizes a lesion poorly but is 'ipsi-lateralizing'). This may be followed (quickly) by contralateral hemiparesis (pressure on the cerebral peduncle) and coma from pressure on the ascending reticular activating system (ARAS) in the midbrain.

Cerebellar tonsil herniation

is caused by ↑pressure in the posterior fossa forcing the cerebellar tonsils through the foramen magnum. Ataxia, VI nerve palsies, and +ve Babinskis (upgoing plantars) occur first, then loss of consciousness, irregular breathing, and apnoea. This syndrome may proceed very rapidly given the small size of, and poor compliance in, the posterior fossa.

Subfalcian (cingulate) herniation

is caused by a frontal mass. The cingulate gyrus (medial frontal lobe) is forced under the rigid falx cerebri. It may be silent unless the anterior cerebral artery is compressed and causes a stroke—eg contralateral leg weakness ± abulia (lack of decision-making).



▸▸Diabetic ketoacidosis (DKA)

Hyperglycaemic ketoacidotic coma only occurs in type I diabetes: it may be the mode of presentation, eg a 1-3-day history of gradual decline into dehydration, acidosis, and coma. Precipitants include: infection, surgery, MI, non-compliance, or wrong insulin dose. The diagnosis requires ketosis and acidosis (pH <7.3).

Signs & symptoms

- Polyuria, polydipsia, lethargy, anorexia, hyperventilation, ketotic breath, dehydration, vomiting, abdominal pain, coma.

Investigations

- Lab glucose, U&E, HCO^-_3, amylase, osmolality, ABG, FBC, blood cultures.
- Urine tests: ketones, MSU; CXR.
- To estimate plasma osmolarity: $2[Na^+]$ + [urea] + [glucose] mmol/L.

Pitfalls in diabetic ketoacidosis

- ***Plasma glucose*** is usually high, but not always, especially if insulin continued.
- ***High* WCC** may be seen in the absence of infection.
- ***Infection:*** often there is no fever. Do MSU, blood cultures, and CXR. Start broad-spectrum antibiotics early if infection is suspected.
- ***Creatinine:*** some assays for creatinine cross-react with ketone bodies, so plasma creatinine may not reflect true renal function.
- ***Hyponatraemia*** is common, due to osmolar compensation for the hyperglycaemia. ↑ or ↔ $[Na^+]$ indicates severe water loss. As treatment commences Na^+ rises as water enters cells. Na^+ is also low due to an artefact; corrected plasma $[Na^+] = Na^+ + 2.4[(\text{glucose} - 5.5)/5.5]$.
- ***Ketonuria*** does not equate with ketoacidosis. Normal individuals may have up to ++ketonuria after an overnight fast. Not all ketones are due to diabetes— consider alcohol if glucose normal. Test plasma with Ketostix® or Acetest® to demonstrate ketonaemia.
- ***Recurrent ketoacidosis:*** blood glucose may return to normal long before ketones are removed from the blood, and a rapid reduction in the amount of insulin administered may lead to lack of clearance and return to DKA. This may be avoided by maintaining a constant rate of insulin, eg 4-5U/h IVI, and co-infusing dextrose 10-20% to keep plasma glucose at 6-10mmol/L—the extended insulin regimen.
- ***Acidosis*** but without gross elevation of glucose may occur, but consider overdose (eg aspirin) and lactic acidosis (in elderly diabetics).
- ***Serum amylase*** is often raised (up to ×10) and non-specific abdominal pain is common, even in the absence of pancreatitis.

Management

See OPPOSITE. Dehydration is more life-threatening than hyperglycaemia —so its correction takes precedence.

- Monitor potassium, glucose, creatinine, HCO^-_3, hourly initially. Aim for a fall in glucose of 5mmol/h, and correction of the acidosis. The use of venous HCO^-_3 as a guide to progress, may prevent the need for repeated arterial blood gas sampling.
- Flow chart of vital signs, conscious level, urine output, and ketones; insert catheter if no urine passed for >4h. Monitoring CVP may sometimes be helpful in guiding fluid replacement.
- Find and treat infection (lung, skin, perineum, urine after cultures).
- Give heparin 5000U/8h (or low molecular weight version) SC until mobile.

- Change to SC insulin when ketones are ≤1+ and eating (p193).

NB: if acidosis is severe (pH <7), some give IV bicarbonate (eg 1mL/kg of 8.4% over 1h, and recheck arterial pH); others never give it because of effects on the Hbdissociation curve and cerebral circulation—discuss with senior.

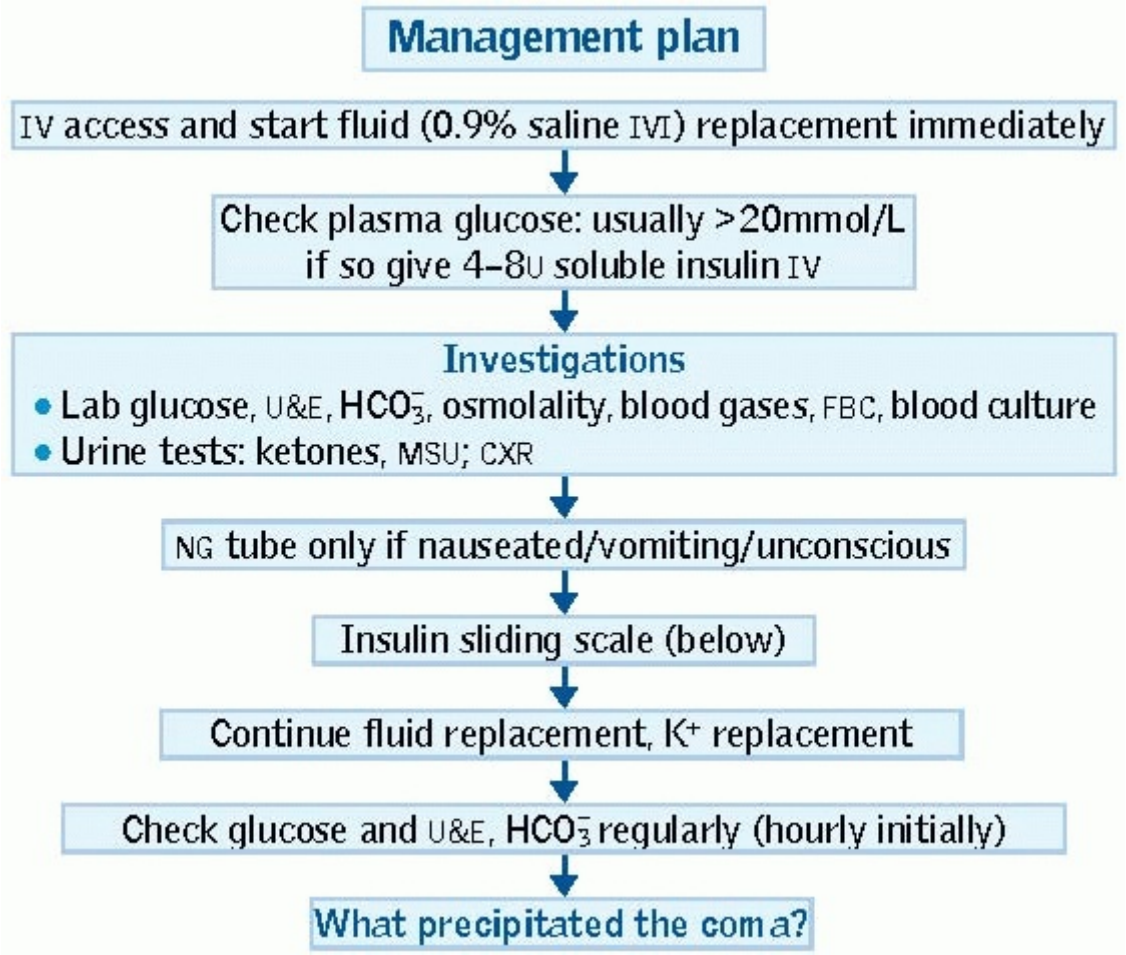
Complications

Cerebral oedema, aspiration pneumonia, hypokalaemia, hypomagnesaemia, hypophosphataemia, thromboembolism.

▸Talk with the patient: ensure there are no further preventable episodes.

Other emergencies:

Hyperosmolar non-ketotic coma & hypoglycaemia: p816.



Fluid replacement

- Give 1 litre (L) of 0.9% saline stat. Then, typically, 1L over the next hour, 1L over 2h, 1L over 4h, then 1L over 6h
- Use dextrose saline or 5% dextrose when blood glucose is <15mmol/L
- Those >65yrs or with CCF need less saline more cautiously

Potassium replacement

- Total body potassium is invariably low, and plasma K^+ falls as K^+ enters cells with treatment
- Don't add K^+ to the first bag, less will be required in renal failure or oliguria. Check U&E hourly initially, and replace as required:

Serum K^+ (mmol/L)	Amount of KCl to add per litre of IV fluid:
<3.0	40mmol
3-4	30mmol
4-5	20mmol

Sliding scale of insulin via IVI pump in diabetic ketoacidosis

Add 50U soluble insulin (Actrapid/Humulin-S) to 50mL saline in a syringe (1U/mL)

Hourly glucose result (mmol/L)	Soluble insulin	If infection or insulin resistance (p191)
0-3.9	0.5U/h	1U/h
4-7.9	1	2
8-11.9	2	4
12-16.0	3	6
>16	4	8

If no pump, load with 10U IM, then give 4-6U/h IM while glucose is >14mmol/L.

▸▸Other diabetic emergencies

Hypoglycaemic coma

Usually *rapid* onset; may be preceded by odd behaviour (eg aggression), sweating, pulse↑, seizures.

Management:

Give 20-30g dextrose IV eg 200-300ml of 10% dextrose. This is preferable to 50-100mL 50% dextrose which harms veins. Expect prompt recovery. Glucagon 1mg IV/IM is nearly as rapid as dextrose but will not work in drunk patients. Dextrose IVI may be needed for severe prolonged hypoglycaemia. Once conscious, give sugary drinks and a meal.

Hyperglycaemic hyperosmolar non-ketotic (HONK) coma

Only those with type-2 diabetes are at risk of this. The history is longer (eg 1wk), with marked dehydration and glucose >35mmol/L. Acidosis is absent as there has been no switch to ketone metabolism—the patient is often old, and presenting for the first time. The osmolality is >340mosmol/kg. Focal CNS signs may occur. The risk of DVT is high, so give *full* heparin anticoagulation (p334).[26]

Rehydrate over 48h with 0.9% saline IVI, eg at ½ the rate used in ketoacidosis. Wait an hour before giving any insulin (it may not be needed, and you want to avoid rapid changes). If it is needed, 1U/h might be a typical initial dose. Look for the cause, eg MI, or bowel infarct.

Hyperlactaemia

is a rare but serious complication of DM (eg after septicaemia or biguanide use). Blood lactate: >5mmol/L. Seek expert help. Give O_2. Treat any sepsis vigorously.

▸▸Thyroid emergencies

Myxoedema coma

Signs & symptoms:

Looks hypothyroid (p204); >65yrs; hypothermia; hyporeflexia; glucose↓; bradycardia; coma; seizures.

History:

Prior surgery or radioiodine for hyperthyroidism.

Precipitants:

Infection; myocardial infarction; stroke; trauma.

Examination:

Goitre; cyanosis; heart failure; precipitants.

Treatment:

Preferably in intensive care.

- Take venous blood for: T3, T4, TSH, FBC, U&E, cultures, cortisol.
- Take arterial blood for P_aO_2.
- Give high-flow O_2 if cyanosed. Correct any hypoglycaemia.
- Give T3 (triiodothyronine) 5-20µg IV slowly. Be cautious: this may precipitate manifestations of undiagnosed ischaemic heart disease.
- Give hydrocortisone 100mg/8h IV—vital if pituitary hypothyroidism is suspected (ie no goitre, no previous radioiodine, no thyroid surgery).
- IVI 0.9% saline. Be sure to avoid precipitating LVF.
- If infection suspected, give antibiotic, eg cefuroxime 1.5g/8h IVI.

- Treat *heart failure* as appropriate (p122).
- Treat *hypothermia* with warm blankets in warm room. Beware complications (hypoglycaemia, pancreatitis, arrhythmias). See p832.

Further therapy:

T3 5-20µg/4-12h IV until sustained improvement (eg ~2-3d) then thyroxine (T4=levothyroxine) 50µg/24h PO. Continue hydrocortisone. Give IV fluids as appropriate (hyponatraemia is dilutional).

Hyperthyroid crisis (thyrotoxic storm)

Sign & symptoms:

Severe hyperthyroidism: fever, agitation, confusion, coma, tachycardia, AF, D&V, goitre, thyroid bruit, 'acute abdomen' picture.

Precipitants:

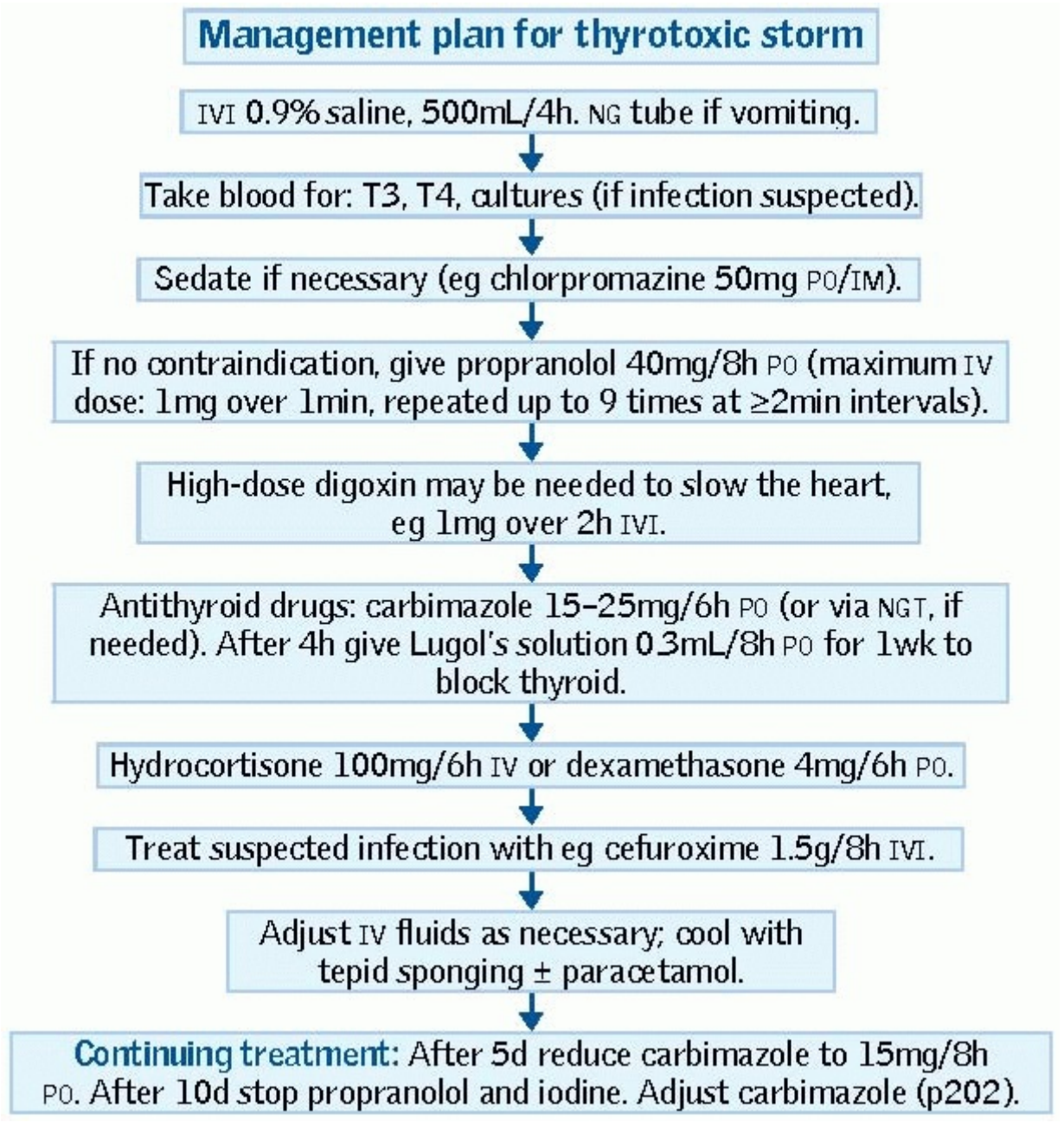
Recent thyroid surgery or radioiodine; infection; MI; trauma.

Diagnosis:

Confirm with technetium uptake if possible, but do not wait for this if urgent treatment is needed.

Treatment:

Enlist expert help from an endocrinologist. See OPPOSITE.



▸▸Addisonian crisis

Signs & symptoms:

Patients may present in shock (tachycardia; peripheral vasoconstriction; postural hypotension; oliguria; weak; confused; comatose)— typically (but not always!) in a patient with known Addison's disease, or someone on long-term steroids who has forgotten to take tablets. An alternative presentation is with hypoglycaemia.

Precipitating factors:

Infection, trauma, surgery.

Management:

If suspected, treat before biochemical results.

- Take blood for cortisol (10mL heparin or clotted) and ACTH if possible (10mL heparin, to go straight to laboratory).
- Hydrocortisone sodium succinate 100mg IV stat.
- IVI: use a plasma expander first, for resuscitation, then 0.9% saline.
- Monitor blood glucose: the danger is hypoglycaemia.
- Blood, urine, sputum for culture.
- Give antibiotics (eg cefuroxime 1.5g/8h IVI).

Continuing treatment

- Glucose IV may be needed if hypoglycaemic.
- Continue IV fluids, more slowly. Be guided by clinical state.
- Continue hydrocortisone sodium succinate 100mg IV/IM every 6h.
- Change to oral steroids after 72h if patient's condition good. The tetracosactrin (=tetracosactide) test is impossible while on hydrocortisone.
- Fludrocortisone is needed only if hydrocortisone dose <50mg/d and the condition is due to adrenal disease.
- Search for the cause, once the crisis is over.

▸▸Hypopituitary coma

Usually develops gradually in a person with known hypopituitarism. Rarely, the onset is rapid due to infarction of a pituitary tumour (pituitary apoplexy)—as symptoms include headache and meningism, subarachnoid haemorrhage is often misdiagnosed.

Presentation:

Headache; ophthalmoplegia; consciousness↓; hypotension; hypothermia; hypoglycaemia; signs of hypopituitarism (p216).

Tests:

T4; cortisol; TSH; ACTH; glucose. Pituitary fossa CT/MRI.

Treatment:

- Hydrocortisone sodium succinate 100mg IV/6h.
- Only after hydrocortisone begun: T3 10µg/12h PO.
- Prompt surgery is needed if the cause is pituitary apoplexy.

▸▸Phaeochromocytoma emergencies

Stress, abdominal palpation, parturition, general anaesthetic, or contrast media used in radiography may produce dangerous *hypertensive crises* (pallor, pulsating headache, hypertension, feels ‘about to die’).

Treatment

▸Get help.

- Phentolamine 2-5mg IV. Repeat to maintain safe BP.
- Labetalol is an alternative agent.
- When BP controlled, give phenoxybenzamine 10mg/24h PO (increase by 10mg/d as needed, up to 0.5-1mg/kg/12h PO); SE: postural hypotension; dizziness; tachycardia; nasal congestion; miosis; idiosyncratic marked BP drop soon after exposure. The idea is to increase the dose until the blood pressure is controlled and there is no significant postural hypotension. A β_1-blocker may also be given at this stage, usually to control any tachycardia (p100).

Surgery is usually done electively after a period of 4-6wks to allow full alpha blockade and volume expansion. When admitted for surgery the phenoxybenzamine dose is increased until significant postural hypotension.

Acute renal failure (ARF)—management

▸Seek expert help promptly: BP, urinary sediment, serum K^+, creatinine, and ultrasound ***must*** be rapidly known. Have them to hand. See p292.

Definition

Acute (over hours or days) deterioration in renal function, characterized by a rise in serum creatinine and urea, often with oliguric or anuria.

Causes[27]

- Hypovolaemia.
- Low cardiac output.
- Sepsis.
- Drugs.
- Obstruction (p286).
- Other eg hepatorenal syndrome (p231), vasculitis (p542).

Investigations

- U&E, Ca^{2+}, PO^{3-}_4, FBC, ESR, CRP, INR, LFT, CK, LDH, protein electrophoresis, hepatitis serology, auto-antibodies (p539), blood cultures.
- Urgent urine microscopy and cultures. White cell casts suggest infection, but are seen in interstitial nephritis, and red cell casts an inflammatory glomerular condition (p288).
- USS of the renal tract.
- ECG, CXR.

Management

See OPPOSITE for acute measures. Underlying principles are:

1. **1 Treat precipitating cause** Treat acute blood loss with blood transfusion, and sepsis with antibiotics (p372). ARF is often associated with other diseases that need more urgent treatment. For example, someone in respiratory failure *and* renal failure may need to be managed on ITU, not a renal unit, to ensure optimal management of the respiratory failure.
2. **2 Treat life-threatening hyperkalaemia** See OPPOSITE.
3. **3 Treat pulmonary oedema, pericarditis, and tamponade** (p788) Urgent dialysis may be needed. If in pulmonary oedema, and no diuresis, consider removing a unit of blood, before dialysis commences.
4. **4 Treat volume depletion** if necessary. Resuscitate quickly; then match input to output. Use a large-bore line in a large vein (central vein access can be risky in obvious volume depletion).
5. **5 Treat sepsis.**
6. **6 Further care.**
   - Has obstruction been excluded? ▸Examine for masses PR and *per vaginam*; arrange urgent ultrasound; is the bladder palpable? Bilateral nephrostomies relieve obstruction, provide urine for culture, and allow anterograde pyelography to determine the site of obstruction.
   - If worsening renal function but dialysis independent, consider renal biopsy.

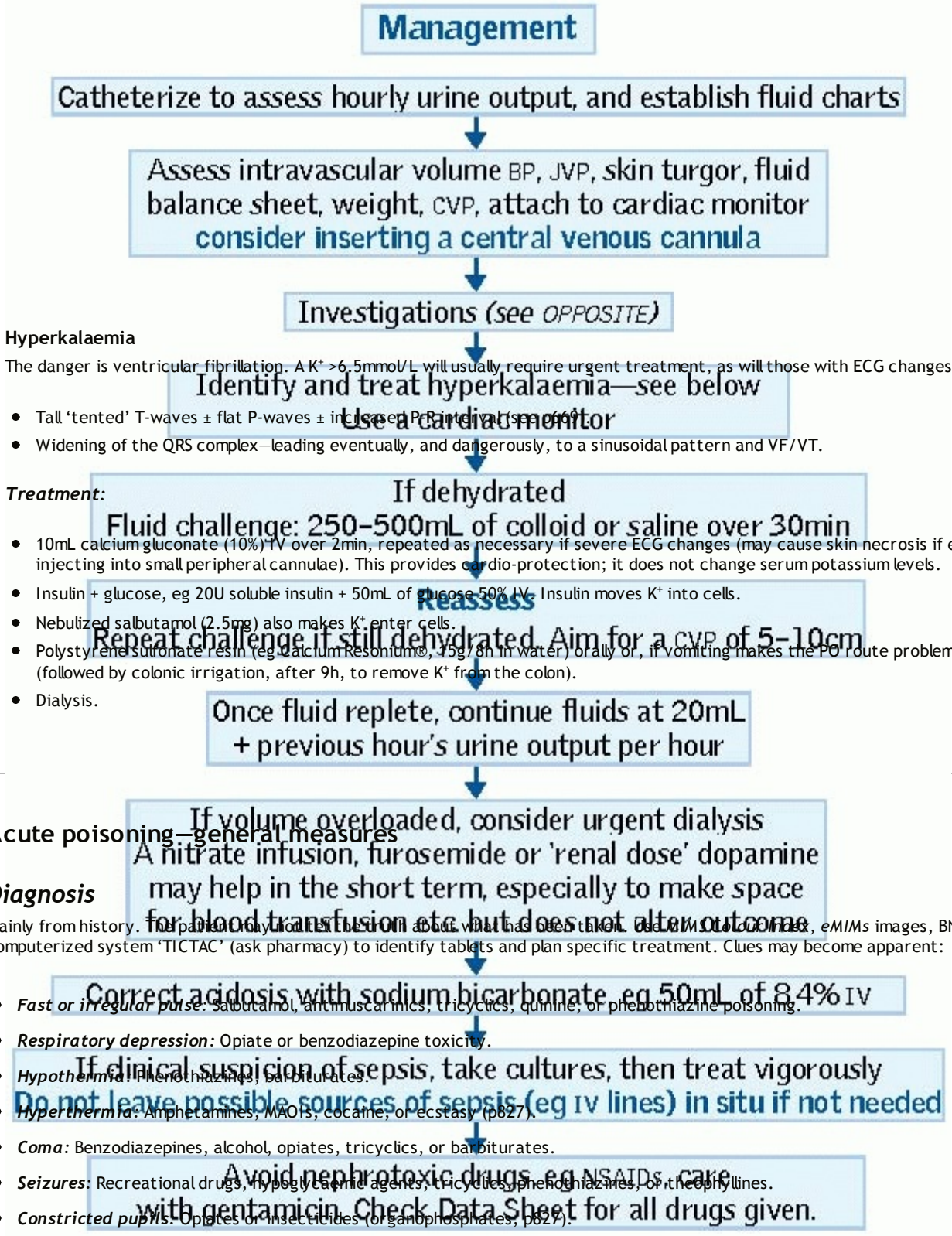
- Diet: high in calories (2000-4000kcal/d) with adequate high-quality protein. Consider nasogastric feeding or parenteral route if too ill.

Prognosis

Depends on cause (ATN mortality: surgery or trauma—60%, medical illness—30%, pregnancy—10%). Oliguric ARF is worse than non-oliguric—more GI bleeds, sepsis, acidosis, and higher mortality.

Urgent dialysis if:

- K^+ persistently high (>6.0mmol/L).
- Acidosis (pH <7.2).
- Pulmonary oedema and no substantial diuresis.
- Pericarditis. (In tamponade (p788), only dialyse *after* pressure on the heart is relieved.)
- High catabolic state with rapidly progressive renal failure.



Hyperkalaemia

The danger is ventricular fibrillation. A K^+ >6.5mmol/L will usually require urgent treatment, as will those with ECG changes:

- Tall 'tented' T-waves ± flat P-waves ± increased PR interval (see p669).
- Widening of the QRS complex—leading eventually, and dangerously, to a sinusoidal pattern and VF/VT.

Treatment:

- 10mL calcium gluconate (10%) IV over 2min, repeated as necessary if severe ECG changes (may cause skin necrosis if extravasation: avoid injecting into small peripheral cannulae). This provides cardio-protection; it does not change serum potassium levels.
- Insulin + glucose, eg 20U soluble insulin + 50mL of glucose 50% IV. Insulin moves K^+ into cells.
- Nebulized salbutamol (2.5mg) also makes K^+ enter cells.
- Polystyrene sulfonate resin (eg Calcium Resonium®, 15g/8h in water) orally or, if vomiting makes the PO route problematic, as a 30g enema (followed by colonic irrigation, after 9h, to remove K^+ from the colon).
- Dialysis.

Acute poisoning—general measures

Diagnosis

mainly from history. The patient may not tell the truth about what has been taken. Use *MIMS Toxicology Index*, *eMIMs* images, BNF descriptions, or the computerized system 'TICTAC' (ask pharmacy) to identify tablets and plan specific treatment. Clues may become apparent:

- ***Fast or irregular pulse:*** Salbutamol, antimuscarinics, tricyclics, quinine, or phenothiazine poisoning.
- ***Respiratory depression:*** Opiate or benzodiazepine toxicity.
- ***Hypothermia:*** Phenothiazines, barbiturates.
- ***Hyperthermia:*** Amphetamines, MAOIs, cocaine, or ecstasy (p827).
- ***Coma:*** Benzodiazepines, alcohol, opiates, tricyclics, or barbiturates.
- ***Seizures:*** Recreational drugs, hypoglycaemic agents, tricyclics, phenothiazines, or theophyllines.
- ***Constricted pupils:*** Opiates or insecticides (organophosphates, p827).
- ***Dilated pupils:*** Amphetamines, cocaine, quinine, or tricyclics.
- ***Hyperglycaemia:*** Organophosphates, theophyllines, or MAOIs.
- ***Hypoglycaemia:*** Insulin, oral hypoglycaemics, alcohol, or salicylates.
- ***Renal failure:*** Salicylate, paracetamol, or ethylene glycol.
- ***Metabolic acidosis:*** Alcohol, ethylene glycol, methanol, paracetamol, or carbon monoxide poisoning—p826.
- ***↑Osmolality:*** Alcohols (ethyl or methyl); ethylene glycol. See p658.

Management

See OPPOSITE for a general guide to management.

- ***Take blood*** as appropriate (p824). Always check paracetamol and salicylate levels.
- ***Empty stomach*** if appropriate (p824).
- ***Consider specific antidote*** (p826) or oral activated charcoal (p824).

- ***If you are not familiar with the poison*** get more information. The *Data Sheet Compendium* SPC is useful. If in doubt how to act, phone the Poisons Information Service: in the UK phone 0870 600 6266.

Continuing care

Measure temperature, pulse, BP, and blood glucose regularly. Use a continuous ECG monitor. If unconscious, nurse semi-prone, turn regularly, keep eyelids closed. A urinary catheter will be needed if the bladder is distended, or renal failure is suspected, or forced diuresis undertaken. Take to ITU, eg if respiration↓.

Psychiatric assessment

Be sympathetic despite the hour! Interview relatives and friends if possible. Aim to establish:

- ***Intentions at time:*** Was the act planned? What precautions against being found? Did the patient seek help afterwards? Does the patient think the method was dangerous? Was there a final act (eg suicide note)?
- ***Present intentions.***
- ***What problems*** led to the act: do they still exist?
- ***Was the act*** aimed at someone?
- Is there a ***psychiatric disorder*** (depression, alcoholism, personality disorder, schizophrenia, dementia)?
- What are his ***resources*** (friends, family, work, personality)?

The assessment of suicide risk:

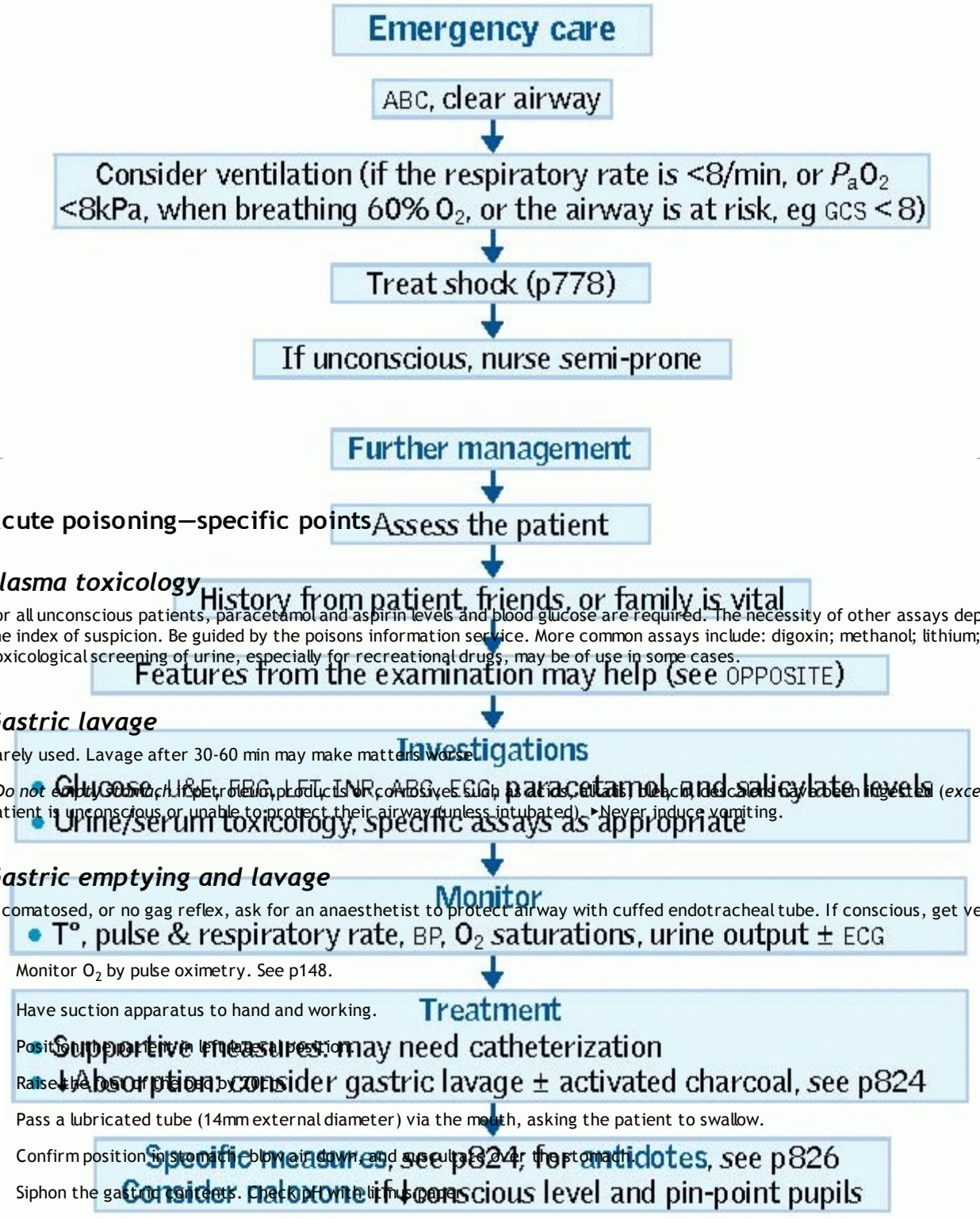
The following increase the chance of future suicide: original intention was to die; present intention is to die; presence of psychiatric disorder; poor resources; previous suicide attempts; socially isolated; unemployed; male; >50yrs old. See OHCS p338. There is an increased risk of death in the first year following initial presentation.

Referral to psychiatrist:

This depends partly on local resources. Ask advice if presence of psychiatric disorder or high suicide risk.

Common law or the Mental Health Act:

(in England and Wales) may provide for the detention of the patient against his or her will: see OHCS p400.



Acute poisoning—specific points

Plasma toxicology

For all unconscious patients, paracetamol and aspirin levels and blood glucose are required. The necessity of other assays depends on the drug taken and the index of suspicion. Be guided by the poisons information service. More common assays include: digoxin; methanol; lithium; iron; theophylline. Toxicological screening of urine, especially for recreational drugs, may be of use in some cases.

Gastric lavage

Rarely used. Lavage after 30-60 min may make matters worse.

▸*Do not empty stomach* if petroleum products or corrosives such as acids, alkalis, bleach, or cleaners have been ingested (*exception:* paraquat), or if the patient is unconscious or unable to protect their airway (unless intubated). ▸Never induce vomiting.

Gastric emptying and lavage

If comatosed, or no gag reflex, ask for an anaesthetist to protect airway with cuffed endotracheal tube. If conscious, get verbal consent.

- Monitor O_2 by pulse oximetry. See p148.
- Have suction apparatus to hand and working.
- Position the patient in left lateral position.
- Raise the foot of the bed by 20cm.
- Pass a lubricated tube (14mm external diameter) via the mouth, asking the patient to swallow.
- Confirm position in stomach—blow air down and auscultate over the stomach.
- Siphon the gastric contents. Check pH with litmus paper.
- Perform gastric lavage using 300-600mL tepid water at a time. Massage the left hypochondrium.
- Repeat until no tablets in siphoned fluid.
- Leave activated charcoal (50g in 200mL water) in the stomach unless alcohol, iron, Li^+, or ethylene glycol ingested.
- When pulling out tube, occlude its end (prevents aspiration of fluid remaining in the tube).

Activated charcoal

reduces the absorption of many drugs from the gut when given as a single dose of 50g with water, eg salicylates, paracetamol. It is given in repeated doses (50g/4h) to increase elimination of some drugs from the blood, eg carbamazepine, dapsone, theophyllines, quinine, digoxin, phenytoin, phenobarbital, and paraquat. Lower doses are used in children.

Help on the web: UK GPs and other NHS workers and departments may register with ***toxbase*** at www.spib.axl.co.uk for free up-to-date toxicological advice.

Some specific poisons and their antidotes

Benzodiazepines

Flumazenil (for respiratory arrest) 200µg over 15s; then 100µg at 60s intervals if needed. Usual dose range: 300-600µg IV over 3-6min (up to 1mg; 2mg if on ITU). May provoke fits.

B-blockers

Severe bradycardia or hypotension. Try atropine up to 3mg IV. Give glucagon 2-10mg IV bolus + 5% dextrose if atropine fails (± an atropine infusion of 50µg/kg/h). If unresponsive, consider pacing or an aortic balloon pump.

Cyanide

This fast-killing poison has affinity for Fe^{3+}, and inhibits the cytochrome system, ↓aerobic respiration.

3 phases:

- Anxiety ± confusion
- Pulse↑ or ↓
- Fits ± shock ± coma.

Treatment:

▸▸100% O_2, GI decontamination; if consciousness↓ either sodium nitrite + sodium thiosulfate, or dicobalt edetate 300mg IV over 1-5min, then 50mL 50% dextrose IV. (repeat up to twice); or hydroxocobalamin 5g over 30 min (70mg/kg), repeated once is required. *Get expert help*. See p831.

Carbon monoxide

Despite hypoxaemia skin is pink (or pale), not blue as carboxyhaemoglobin (COHb) displaces O_2 from Hb binding sites.

Symptoms:

Headache, vomiting, pulse↑, tachypnoea, and, if COHb >50%, fits, coma, & cardiac arrest. ▸▸Remove the source. Give 100% O_2. Metabolic acidosis usually responds to correction of hypoxia. If severe, anticipate cerebral oedema. Give mannitol IVI (p813). Confirm diagnosis with a heparinized blood sample (COHb >10%) quickly as levels may soon return to normal. Monitor ECG. *Hyperbaric O_2 may help: discuss with the poisons service if is or has been unconscious, pregnant, COHb >20%, or failing to respond.*

Digoxin

Symptoms:

Cognition↓, yellow-green visual halos, arrhythmias, nausea, & anorexia. If serious arrhythmias are present, correct hypokalaemia, and inactivate with digoxin-specific antibody fragments (Digibind®). If load or level is unknown, give 20 vials (800mg)—adult or child >20kg. Consult Data Sheet/SPC. Dilute in water for injections (4mL/38mg vial) and 0.9% saline (to make a convenient volume); give IVI over ½h, via a 0.22µm-pore filter. If the amount of digoxin ingested is known, the data-sheet/SPC will tell you how many vials of Digibind® to give, eg if 25 tabs of 0.25mg ingested, give 10 vials; if 50 tabs, give 20 vials; if 100 tabs, give 40 vials.

Heavy metals

Enlist expert help.

Iron

Deferoxamine 15mg/kg/h IVI; max 80mg/kg/d. **NB:** gastric lavage if iron ingestion in last hour; consider whole bowel irrigation.

Oral anticoagulants

If major bleed, treat with vitamin K, 5mg slow IV; give prothrombin complex concentrate 50U/kg IV (or if unavailable, fresh frozen plasma 15mL/kg IVI). For abnormal INR with no (or minimal) bleeding, see BNF. If it is vital that anticoagulation continues, enlist expert help. Warfarin can normally be restarted within 2-3d.

NB: coagulation defects may be delayed for 2-3d following ingestion.

Opiates

(Many analgesics contain opiates.) Give naloxone eg 0.4-2mg IV; repeat every 2min until breathing adequate (it has a short $t_{½}$, so it may need to be given often or IM; max. 10mg). Naloxone may precipitate features of opiate withdrawal— diarrhoea and cramps which will normally respond to diphenoxylate and atropine (Lomotil®—eg 2 tablets/6h PO). Sedate as needed (see p13). High-dose opiate misusers may need methadone (eg 10-30mg/12h PO) to combat withdrawal. Register opiate addiction (OHCS p362), and refer for help.

Phenothiazine poisoning

(eg chlorpromazine) No specific antidote. *Dystonia (torticollis, retrocollis, glossopharyngeal dystonia, opisthotonus):* try benzatropine 1-2mg IV/IM. Treat *shock* by raising the legs (± plasma expander IVI, or dopamine IVI if desperate). Restore body temperature. *Monitor* ECG. Avoid lidocaine in dysrhythmias. Use diazepam IV for prolonged fits in the usual way (p808). *Neuroleptic malignant syndrome* consists of: hyperthermia, rigidity, extrapyramidal signs, autonomic dysfunction (labile BP, pulse↑, sweating, urinary incontinence), mutism, confusion, coma, WCC↑, CPK↑; it may be treated with cooling. Dantrolene has been tried (p558).

Carbon tetrachloride poisoning

this solvent, used in many industrial processes, causes vomiting, abdominal pain, diarrhoea, seizures, coma, renal failure, and tender hepatomegaly with jaundice and liver failure. IV acetylcysteine may improve prognosis. Seek expert help.

Organophosphate insecticides

inactivate cholinesterase—the resulting increase in acetylcholine causes the **SLUD** response: salivation, lacrimation, urination, and diarrhoea. Also look for sweating, small pupils, muscle fasciculation, coma, respiratory distress, and bradycardia.

Treatment:

Wear gloves; remove soiled clothes. Wash skin. Take blood (FBC & serum cholinesterase activity). Give atropine IV 2mg every 10min till full atropinization (skin dry, pulse >70, pupils dilated). Up to 3 days' treatment may be needed. Also give pralidoxime 30mg/kg slowly IV (in the UK, the poisons information service will tell you how to get it; it is diluted with ≥10mL water for Injections). Repeat as needed every 30min; max 12g in 24h. Even if fits are not occurring, diazepam 5-10mg IV seems to help.

Paraquat poisoning

(Found in weed-killers.) This causes D&V, painful oral ulcers, alveolitis, and renal failure. Diagnose by urine test. Give activated charcoal *at once* (100g followed by a laxative, then 50g/3-4h, ± antiemetic). ▸*Get expert help*. Avoid O_2 early on (promotes lung damage).

Ecstasy poisoning

Ecstasy is a semi-synthetic, hallucinogenic substance (MDMA, 3,4-methylenedioxymethamphetamine). Its effects range from nausea, muscle pain, blurred vision, amnesia, fever, confusion, and ataxia to tachyarrhythmias, hyperthermia, hyper/hypotension, water intoxication, DIC, K^+↑, acute renal failure, hepatocellular and muscle necrosis, cardiovascular collapse, and ARDS. There is no antidote and treatment is supportive. Management depends on clinical and lab findings, but may include:

- Administration of activated charcoal and monitoring of BP, ECG, and temperature for at least 12h (rapid cooling may be needed).
- Monitor urine output and U&E (renal failure p293), LFT, CK, FBC, and coagulation (DIC p336). Metabolic acidosis may benefit from treatment with bicarbonate.
- Anxiety: diazepam 0.1-0.3mg/kg PO. Max IV does over 2min.
- Narrow complex tachycardias in adults: consider metoprolol 5-10mg IV.
- Hypertension can be treated with nifedipine 5-10mg PO or phentolamine 2-5mg IV. Treat hypotension conventionally (p778).
- Hyperthermia: attempt to cool, if rectal T° > 39°C. Consider dantrolene 1mg/kg IV (may need repeating: discuss with your senior and a poisons unit, p822). Hyperthermia with ecstasy is akin to serotonin syndrome, and propranolol, muscle relaxation and ventilation may be needed.[28]

Snakes (adders)

Anaphylaxis

p780.

Signs of envenoming:

BP↓ (vasodilatation, viper cardiotoxicity) D&V; swelling spreading proximally within 4h of bite; bleeding gums or venepuncture sites; anaphylaxis; ptosis; trismus; rhabdomyolysis; pulmonary oedema.

Tests:

WCC↑; clotting↓; platelets↓; U&E; urine RBC↑; CK↑; P_aO_2↓, ECG.

Management:

Avoid active movement of affected limb (so use splints/slings). *Avoid incisions and tourniquets*. ▸Get help.[29] Is antivenom indicated (IgG from venom-immunized sheep)?—eg 10mL IV over 15min (adults ***and*** children) of *European Viper Antiserum* (from Farillon) for adder bites; have adrenaline to hand —p780. Monitor ECG. For foreign snakes, see BNF.

Salicylate poisoning Children: *OHCS* p192

Aspirin is a weak acid with poor water solubility. It is present in many over-the-counter preparations. Anaerobic metabolism and the production of lactate

and heat are stimulated by the uncoupling of oxidative phosphorylation. Effects are dose-related, and potentially fatal:

- 150mg/kg: mild toxicity
- 250mg/kg: moderate
- >500mg/kg: severe toxicity.

Signs & symptoms

Unlike paracetamol, many early features. Vomiting, dehydration, hyperventilation, tinnitus, vertigo, sweating. Rarely; lethargy or coma, seizures, vomiting, ↓BP and heart block, pulmonary oedema, hyperthermia. Patients present initially with respiratory alkalosis due to a direct stimulation of the central respiratory centres and then develop a metabolic acidosis. Hyper- or hypoglycaemia may occur.

Management

General:

p822. Correct dehydration. Gastric lavage if within 1h, activated charcoal (may be repeated, but is of unproven value).

- Paracetamol and salicylate level, glucose, U&E, LFT, INR, ABG, HCO^-_3, FBC. Salicylate level may need to be repeated after 2h, due to continuing absorption if a potentially toxic dose has been taken.
- Levels over 700mg/L are potentially fatal.
- Monitor urine output, and blood glucose. If severe poisoning: salicylate levels, blood pH, and U&E. Consider urinary catheter and monitoring urine pH. Beware hypoglycaemia.
- Correct any metabolic acidosis with 1.26% HCO^-_3 (sodium bicarbonate).
- If plasma level >500mg/L (3.6mmol/L), consider alkalinization of the urine, eg 1.5L 1.26% HCO^-_3 with 40mmol KCl IV over 3h. Aim to make the **urine** pH 7.5-8.5. **NB:** monitor serum K^+ as hypokalaemia may occur.
- Consider dialysis if plasma level >700mg/L, and if renal or heart failure, seizures, severe acidosis, or persistently ↑plasma salicylate. ECG monitor.
- Discuss any serious cases with the local toxicological service or national poisons information service.

Paracetamol poisoning

150mg/kg, or 12g in adults may be fatal. However, prompt treatment can prevent liver failure and death. ▸1 tablet of paracetamol = 500mg.

Signs & symptoms

None initially, or vomiting ± RUQ pain. Later: jaundice and encephalopathy from liver damage (the main danger) ± renal failure.

Management

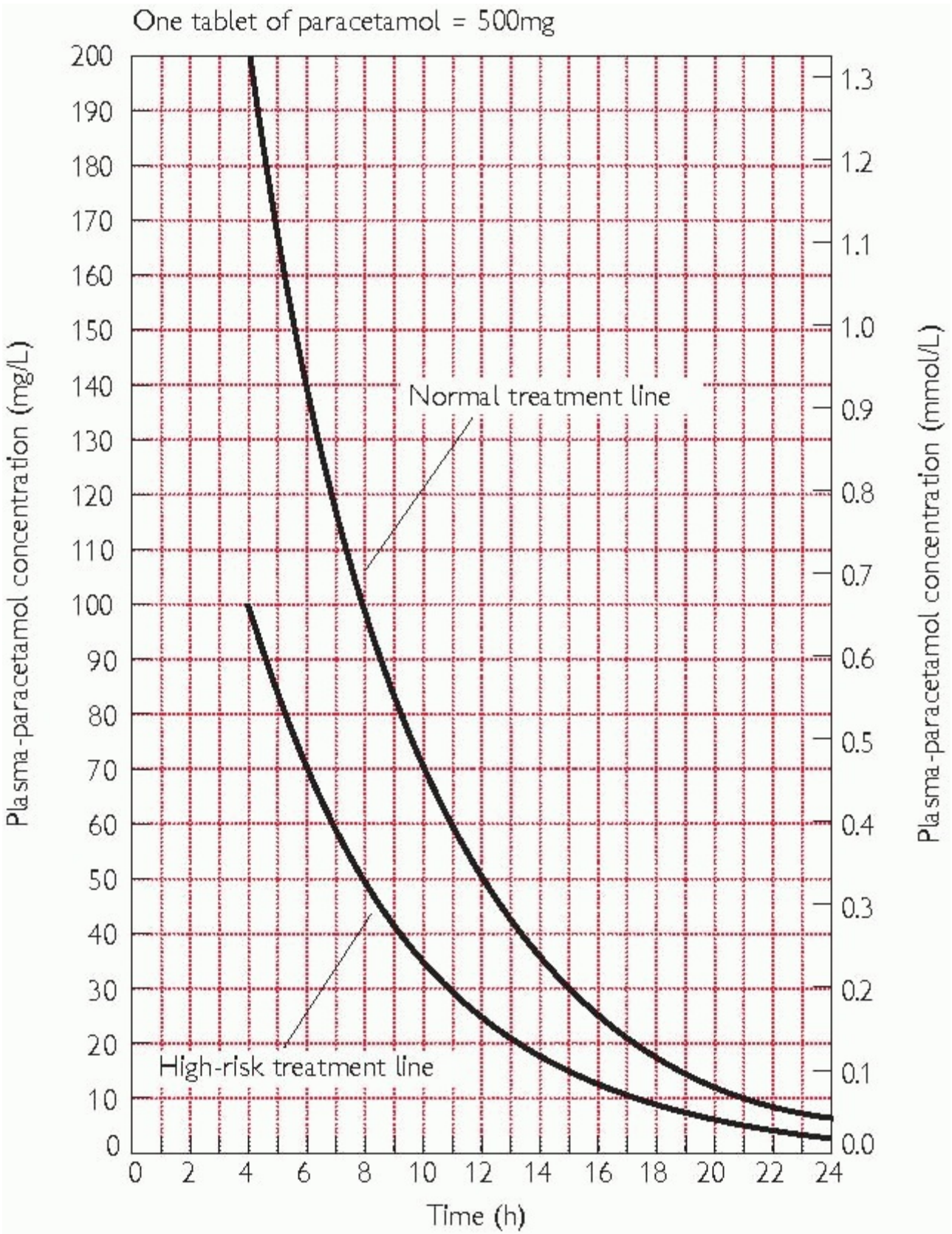
General measures

p822, lavage if >12g (or >150mg/kg) taken within 1h. Give activated charcoal if <8h since ingestion. Specific measures:

- Glucose, U&E, LFT, INR, ABG, FBC, HCO^-_3; blood paracetamol level at 4h post-ingestion.
- If <8h since overdose and plasma paracetamol is above the line on the graph OPPOSITE, start acetylcysteine.
- If >8h and suspicion of large overdose (>7.5g) err on the side of caution and start acetylcysteine, stopping it if level below treatment line and INR/ALT normal.
- Acetylcysteine is given by IVI: 150mg/kg in 200mL of 5% dextrose over 15min. Then 50mg/kg in 500mL of 5% dextrose over 4h. Then 100mg per kg/16h in 1L of 5% dextrose. Rash is a common SE: treat with chlorphenamine, and observe; do not stop unless anaphylatoid reaction with shock, vomiting, and wheeze (≤10%). An alternative is methionine 2.5g/4h PO for 16h (total: 10g), but absorption is unreliable if vomiting. Benefit is lessened by concurrent charcoal.
- If ingestion time is unknown, or it is staggered, or presentation is >15h from ingestion, treatment *may* help. ▸Get advice.
- The graph may mislead if HIV+ve (hepatic glutathione↓), or if long-acting paracetamol has been taken, or if pre-existing liver disease or induction of liver enzymes has occurred. ▸Beware glucose↓; ward-test hourly; INR/12h.
- Next day do INR, U&E, LFT. If INR rising, continue acetylcysteine until <1.4.
- If continued deterioration, discuss with the liver team. Don't hesitate to get help.

Criteria for transfer to a specialist unit:

- *Encephalopathy* or ICP↑. Signs of CNS oedema: BP >160/90 (sustained) or brief rises (systolic >200mmHg), bradycardia, decerebrate posture, extensor spasms, poor pupil responses. ICP monitoring can help, p812.
- INR >2.0 at <48h—or >3.5 at <72h (so measure INR every 12h). Peak elevation: 72-96h. LFTs are *not* good markers of hepatocyte death. If INR is *normal* at 48h, the patient may go home.
- *Renal impairment* (creatinine >200μmol/L). Monitor urine flow. Daily U&E and serum creatinine (use haemodialysis if >400μmol/L).
- *Blood pH <7.3* (lactic acidosis → tissue hypoxia). • *Systolic* BP <80mmHg.



Patients whose plasma-paracetamol concentrations are above the **normal treatment line** should be treated with acetylcysteine by intravenous infusion (or, provided the overdose has been taken **within 10-12h**, with methionine by mouth). Patients on enyzme-including drugs (eg carbamazepine, phenobarbital, phenytoin, rifampicin, and alcohol) or who are malnourished (eg in anorexia, in alcoholism, or those who are HIV-positive) should be treated if their plasma-paracetamol concentrations are above the **high-risk treatment line**. (We thank Dr Alun Hutchings for permission to reproduce this graph.)

▸▸Burns

Resuscitate and arrange transfer for all major burns. (>25% partial thickness in adult and >20% in children). Assess site, size, and depth of the burn. Referral is still warranted in cases of full thickness burns >5%, partial thickness burns >10% in adults or >5% in children or the elderly, burns of special sites, chemical and electrical burns and burns with inhalational injury.

Assessment

Burn size

is important to assess (see BOX) as it influences the size of the inflammatory response (vasodilatation, increased vascular permeability) and thus fluid shift from the intravascular volume. The size must be estimated to calculate fluid requirements. Ignore erythema.

Burn depth

determines healing time/scarring; assessing this may be hard, even when experienced. The big distinction is whether the burn is partial thickness (painful, red, and blistered) or full thickness (insensate/painless; grey-white). **NB:** burns can evolve, particularly over the 1st 48h.

Resuscitation

Airway:

Beware of upper airway obstruction developing if hot gases inhaled. Suspect if history of fire in enclosed space, soot in oral/nasal cavity, singed nasal hairs of hoarse voice. A flexible laryngo/bronchoscopy is useful. Involve anaesthetists early and consider early intubation.

Breathing:

Exclude life-threatening chest injuries (eg tension pneumothorax) and constricting burns. Give 100% O_2 if carbon monoxide poisoning is suspected (mostly from history, may have cherry-red skin, measure carboxyhaemoglobin (COHb) and compare to nomograms). With 100% O_2 $t_{½}$ of COHb falls from 250min to 40min (consider hyperbaric O_2 if: pregnant; CNS signs; >20% COHb). S_pO_2 (oximetry) is unreliable. Decompress if chest burns impair thorax excursion (OHCS p731).

Circulation:

Partial thickness burns >10% in a child and >15% in adults require IV fluid resuscitation. Put up 2 large-bore (14G or 16G) IV lines. Do not worry if you have to put these through burned skin, intraosseous access is valuable in infants (see OHCS). Secure them well: they are literally lifelines.

Use a *burns calculator* flow chart or a formula, eg: *Parkland formula* (popular): 4 × weight (kg) × % burn=mL Hartmann's solution in 24h, half given in 1st 8h.

Muir and Barclay formula:

[weight (kg) × %burn]/2=mL colloid (eg Haemaccel®) per unit time. Time periods are 4h, 4h, 4h, 6h, 6h, and 12h. Either formula is acceptable but must use appropriate fluid ie crystalloid for Parkland not colloid. **NB:** A meta-analysis (somewhat flawed) suggests the use of colloid (albumin) can cause ↑ mortality (slightly); it is also expensive. Replace fluid from the time of burn, not from the time first seen in hospital.

Formulae are only guides:

adjust IVI according to clinical response and urine output; aim for >0.5mL/kg/h (>1mL/kg/h in children), ~50% more in electrical burns and inhalation injury. Monitor T° (core & surface); catheterize the bladder.

Treatment

Do *not* apply cold water to extensive burns for long periods: this may intensify shock. Take care with circumferential full thickness burns of the limbs as compartment syndrome may develop rapidly particularly after fluid resuscitation. Decompress the limbs (escharotomy and fasciotomy) as necessary. If transferring to a burns unit, do not burst blisters or apply any special creams as this can hinder assessment. Simple saline gauze or Vaseline® gauze is suitable; cling film is useful as a temporary measure and relieves pain. Use morphine in IV aliquots and titrate for good analgesia. Ensure tetanus immunity. Antibiotic prophylaxis is not routine.

Definitive dressings

There are many dressings for partial thickness burns, eg biological (pigskin, cadaveric skin), synthetic (Mepitel®, Duoderm®) and silver sulfadiazine cream alone (Flamazine®) or with cerium nitrate as Flammacerium® (on a named-patient basis[UK]); it forms a leathery eschar which resists infection.[30] Major full thickness burns benefit from early tangential excision and split-skin grafts as the burn is a major source of inflammatory cytokines causing SIRS (systemic inflammatory response syndrome) and forms a rich medium for bacterial growth.

Smoke inhalation

Initially there is laryngospasm that leads to hypoxia and straining (leading to petechiae), then hypoxic cord relaxation leads to true inhalation injury. Free radicals, cyanide compounds, and carbon monoxide accompany thermal injury. Cyanide compounds (generated eg from burning plastics) bind reversibly with ferric ions in enzymes, so stopping oxidative phosphorylation, causing dizziness, headaches, and seizures. Tachycardia and dyspnoea soon give way to bradycardia and apnoea. Carbon monoxide is generated later in the fire as oxygen is depleted. NB: COHb levels do not correlate well with the severity of poisoning and partly reflect smoking status and urban living conditions. 100% O_2 is given to elute both cyanide and CO.

Involve ICU/anaesthetists early: early ventilation may be useful, consider repeated bronchoscopic lavage.

Enlist expert help in cyanide poisoning: there is no one regimen suitable for all situations. Clinically mild poisoning may be treated by rest, O_2, and amyl nitrite 0.2-0.4mL via an Ambu® bag. IV antidotes may be used for moderate poisoning: sodium thiosulfate is a common first choice. More severe poisoning may require eg hydroxocobalamin, sodium nitrite, and dimethylaminophenol.

Lund & Browder charts[1]

Hypothermia

▸*Have a high index of suspicion and a low-reading thermometer*. Most patients are elderly and do not complain, or feel, cold—so they have not tried to warm themselves up. In the young, hypothermia is usually either from cold exposure (eg near-drowning), or it is secondary to impaired level of consciousness (eg following excess alcohol or drug overdose).

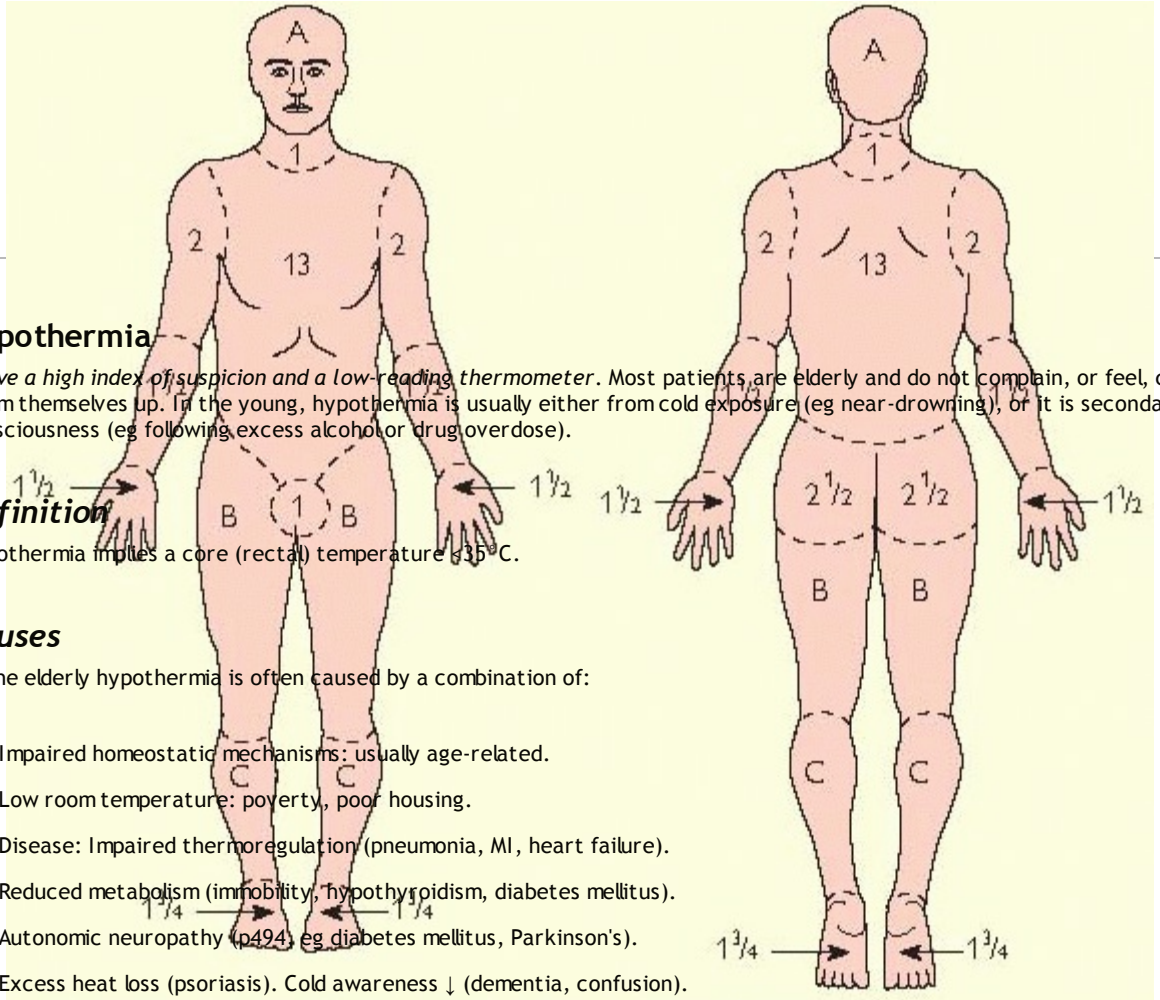
Definition

Hypothermia implies a core (rectal) temperature <35°C.

Causes

In the elderly hypothermia is often caused by a combination of:

- Impaired homeostatic mechanisms: usually age-related.
- Low room temperature: poverty, poor housing.
- Disease: Impaired thermoregulation (pneumonia, MI, heart failure).
- Reduced metabolism (immobility, hypothyroidism, diabetes mellitus).
- Autonomic neuropathy (p494; eg diabetes mellitus, Parkinson's).
- Excess heat loss (psoriasis). Cold awareness ↓ (dementia, confusion).
- Increased exposure to cold (falls, especially at night when cold).
- Drugs (major tranquillizers, antidepressants, diuretics). Alcohol.



The patient

How frozen I then became: I did not die, yet nothing of life remained.

So don't assume that if vital signs seem to be absent, the patient must be dead: rewarm (see below) and re-examine. If T° <32°C, this sequence may occur: ↓BP → coma → bradycardia → AF → VT → VF. The abdomen can feel 'colder than clay'. If >32°C, there may simply be pallor ± apathy.

Diagnosis

Check oral or axillary T°. If ordinary thermometer shows <36.5°C, use a low-reading one PR. Is the rectal temperature <35°C? Infra-red ear thermometers can accurately reflect core temperature.

Tests

Urgent U&E, plasma glucose, and amylase. Thyroid function tests; FBC; blood cultures. Consider blood gases. The ECG may show J-waves.

Treatment

- Ventilate if comatose or respiratory insufficiency.
- Warm IVI (for access or to correct electrolyte disturbance).
- Cardiac monitor (both VF and AF can occur during warming).
- Consider antibiotics for the prevention of pneumonia (p153). Give these routinely in patients over 65yrs with a temperature <32°C.
- Consider urinary catheter (to assess renal function).
- *Slowly rewarm*. Do not reheat too quickly, causing peripheral vasodilatation, shock, and death. Aim for a rise of ½°C/h. Old, conscious patients should sit in a warm room taking hot drinks. Thermal blankets may cause too rapid warming in old patients. The first sign of too rapid warming is falling BP. Treat by allowing patient to cool down slightly.
- Rectal temperature, BP, pulse, and respiratory rate every ½ hour.

NB: Advice is different for victims of sudden hypothermia from immersion. Here, eg if there has been a cardiac arrest, and T° <30°C, mediastinal warm lavage, peritoneal or haemodialysis, and cardiopulmonary bypass (no heparin if trauma) may be needed (OHCS p724).

Complications

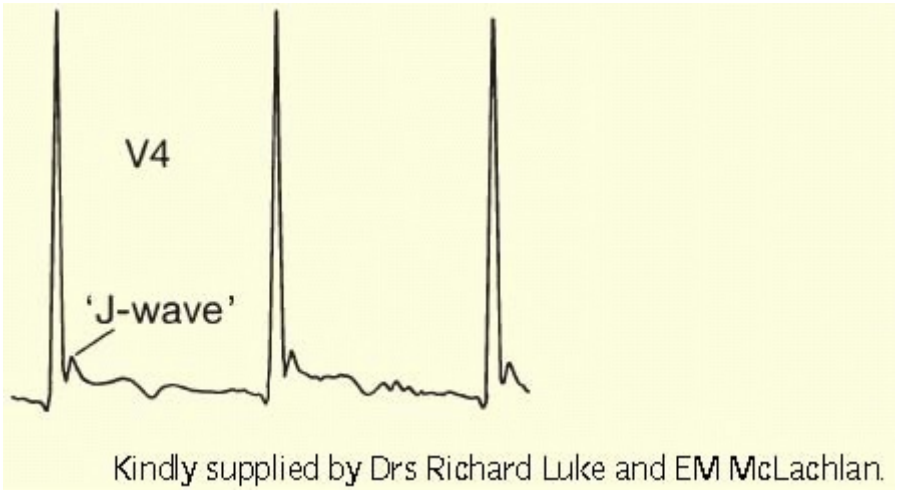
Arrhythmias (if there is a cardiac arrest continue resuscitating until T° >33°C, as cold brains are less damaged by hypoxia); pneumonia; pancreatitis; acute renal failure; intravascular coagulation.

Prognosis

Depends on age and degree of hypothermia. If age >70yrs and T° <32°C then mortality >50%.

Before hospital discharge

Anticipate problems. Will it happen again? What is her network of support? Review medication (could you stop tranquillizers)? How is progress to be monitored? Liaise with GP/social worker.



Major disasters

Planning

All hospitals have a detailed *Major Accident Plan*, but additionally the tasks of key personnel can be distributed on individual *Action Cards*.

At the scene

Call the police; tell them to take command.

Safety:

Is paramount—your own and others. Be visible (luminous monogrammed jacket) and wear protective clothing where appropriate (safety helmet; waterproofs; boots; respirator in chemical environment).

Triage:

See OHCS p797. Label **RED** if will die in a few mins if no treatment. **YELLOW** = will die in ~2h if no treatment; **GREEN** = can wait. (**BLUE** = dead).

Communications:

Are essential. Each emergency service will dispatch a control vehicle and will have a designated incident officer for liaison. Support medical staff from hospital report to the medical incident officer—he is usually the first doctor on the scene: his job is to assess then communicate to the receiving hospital the number and severity of casualties, to organize resupply of equipment and to replace fatigued staff. He must resist temptation to treat casualties as this compromises his role.

Equipment:

Must be portable and include: intubation and cricothyrotomy set; intravenous fluids (colloid); bandages and dressings; chest drain (+flutter valve); amputation kit (when used, ideally 2 doctors should concur); drugs—*analgesic:* morphine; *anaesthetic:* ketamine 2mg/kg IV over >60s (0.5mg/kg is a powerful analgesic without respiratory depression); limb splints (may be inflatable); defibrillator/monitor; ± pulse oximeter.

Evacuation:

Remember: with immediate treatment on scene, the priority for evacuation may be reduced (eg a tension pneumothorax—**RED**—relieved can wait for evacuation—becomes **YELLOW**), but those who may suffer by delay at the scene must go first. Send any severed limbs to the same hospital as the patient, ideally chilled—but not frozen.

At the hospital

a ‘major incident’ is declared. The *first receiving* hospital will take most of the casualties; the *support* hospital(s) will cope with overflow and may provide mobile teams so that staff are not depleted from the first hospital. A control room is established and the medical coordinator ensures staff have been summoned, nominates a triage officer, and supervises the best use of inpatient beds and ITU/theatre resources.

Blast injury

may be caused by domestic (eg gas explosion) or industrial (eg mining) accidents or by terrorist bombs. Death may occur without any obvious external injury (air emboli). Injury occurs in 6 ways:

1. **Blast wave** A transient (milliseconds) wave of overpressure expands rapidly producing cellular disruption, shearing forces along tissue planes (submucosal/subserosal haemorrhage) and re-expansion of compressed trapped gas—bowel perforation, fatal air embolism.
2. **Blast wind** This can totally disrupt a body or cause avulsive amputations. Bodies can be thrown and sustain injuries on landing.
3. **Missiles** Penetration or laceration from missiles are by far the commonest injuries. Missiles arise from the bomb or are secondary, eg glass.
4. **Flash burns** These are usually superficial and occur on exposed skin.
5. **Crush** Injuries: beware sudden death or renal failure after release.
6. **Psychological injury** Eg post-traumatic stress disorder (OHCS p347).

Treatment

Approach the same as any major trauma OHCS p726. Rest and observe any suspected of exposure to significant blast but without other injury. Gun-shot injury: see OHCS p720.

Source: I Greaves 1999 *Pre-hospital Medicine*, Arnold; S Mellor *Recent Advances in Surgery* 14, Churchill Livingstone, London 1991 p53-p68

Acknowledgements

1 *We thank Dr S Haydock (Specialist Reader) & Specialist Readers from other chapters.*

Many diseases may present as emergencies, but if you know about the following, you will be very unlucky to lose a patient from a disease not listed here, on a general medical take, provided you remember to ask for help.

Editors: **Longmore, Murray; Wilkinson, Ian B; Turmezei, Tom; Cheung, Chee Kay**
Title: ***Oxford Handbook of Clinical Medicine, 7th Edition***

▸▸Cardiorespiratory arrest

Ensure safety of patient and yourself. Confirm diagnosis (unconscious, apnoeic, absent carotid pulse).

Causes MI; PE; trauma; tension pneumothorax, electrocution; shock; hypoxia; hypercapnia; hypothermia; U&E imbalance; drugs, eg digoxin.

Basic life support Shout for help. Ask someone to call the arrest team and bring the defibrillator. Note the time. Begin CPR as follows (ABC):

Airway: Head tilt (if no spine injury) + chin lift/jaw thrust. Clear the mouth.

Breathing: Check breathing then give 2 breaths after 1st set of compressions, each inflation ~1s long. Use specialized bag and mask system (eg Ambu® system) if available and 2 resuscitators present. Otherwise, mouth-to-mouth breathing.

Chest compressions: Give 30 compressions to 2 breaths (30 : 2). CPR should not be interrupted except to give shocks or to intubate. Use the heel of hand with straight elbows. Centre over the lower 1/3 of the sternum; aim for 4cm compression at 100/min.

Advanced life support For algorithm and details, see over. Notes: Place defibrillator paddles on chest as soon as possible and set monitor to read through the paddles if delay in attaching leads. Assess rhythm: is this VF/pulseless VT? The following assumes monophasic defibrillator.

- In **VF/VT**, defibrillation must occur without delay: 360J (150-360J biphasic).
- **Asystole and electromechanical dissociation** (synonymous with pulseless electrical activity) are rhythms with a poorer prognosis than VF/VT, but potentially remediable (see box next page). Treatment may be life-saving.
- Obtain IV access and intubation if possible.
- Look for reversible causes of cardiac arrest, and treat accordingly.
- Check for pulse if ECG rhythm compatible with a cardiac output.
- **Reassess ECG rhythm.** Repeat defibrillation if still VF/VT. All shocks are 360J.
- Send someone to find the patient's notes and the patient's usual doctor. These may give clues as to the cause of the arrest.
- If IV access fails, adrenaline, atropine, and lidocaine may be given down the tracheal tube but absorption is unpredictable. Give 2-3 times the IV dose diluted in ≥10mL 0.9% saline followed by 5 ventilations to assist absorption. Intracardiac injection is not recommended.

When to stop resuscitation No general rule, as survival is influenced by the rhythm and the cause of the arrest. In patients without myocardial disease, do not stop until core temperature is >33°C and pH and potassium are normal. Consider stopping resuscitation after 20min if there is refractory asystole or electromechanical dissociation.

After successful resuscitation:

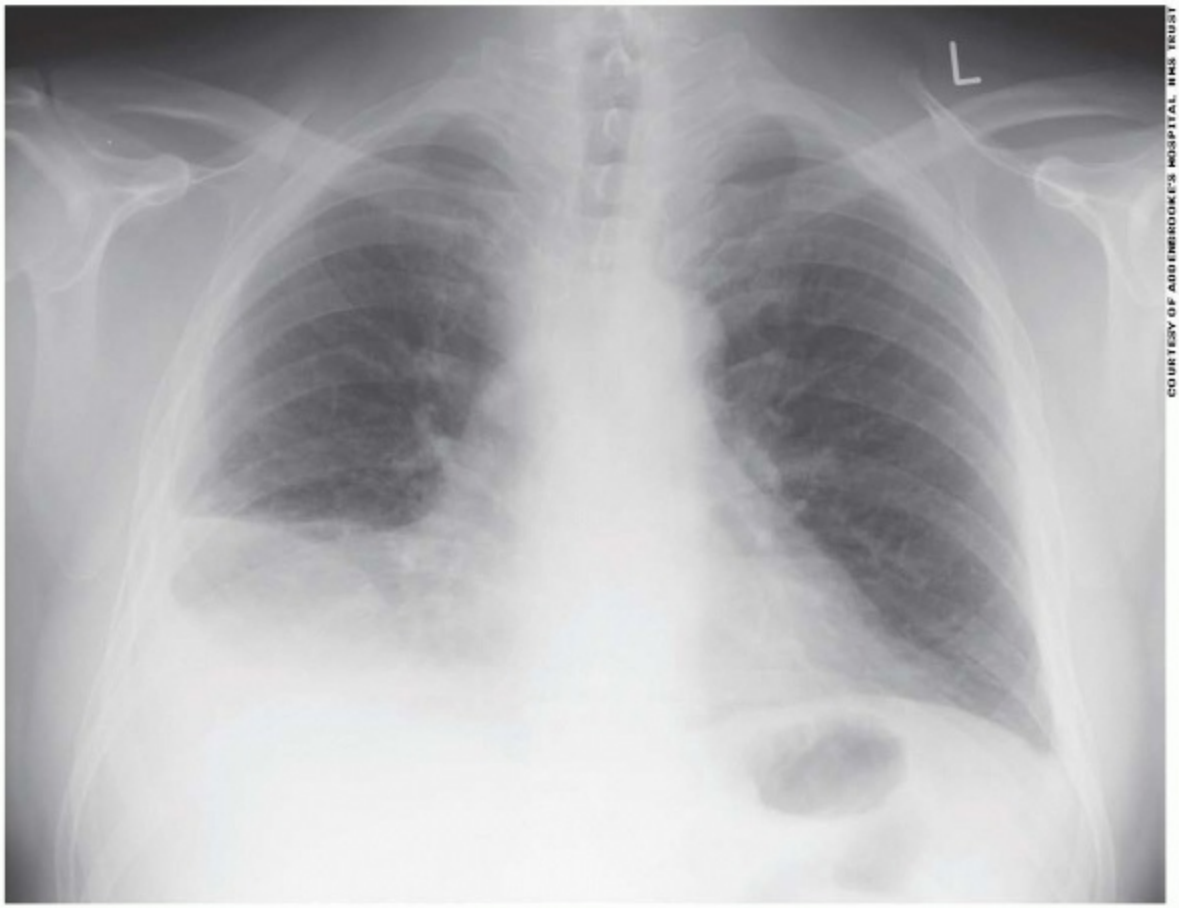
- 12-lead ECG; CXR, U&Es, glucose, blood gases, FBC, CK/troponin.
- Transfer to coronary care unit/ITU.
- Monitor vital signs.
- Whatever the outcome, explain to relatives what has happened.

When '*do not resuscitate*' may be a valid decision (UK DoH guidelines)

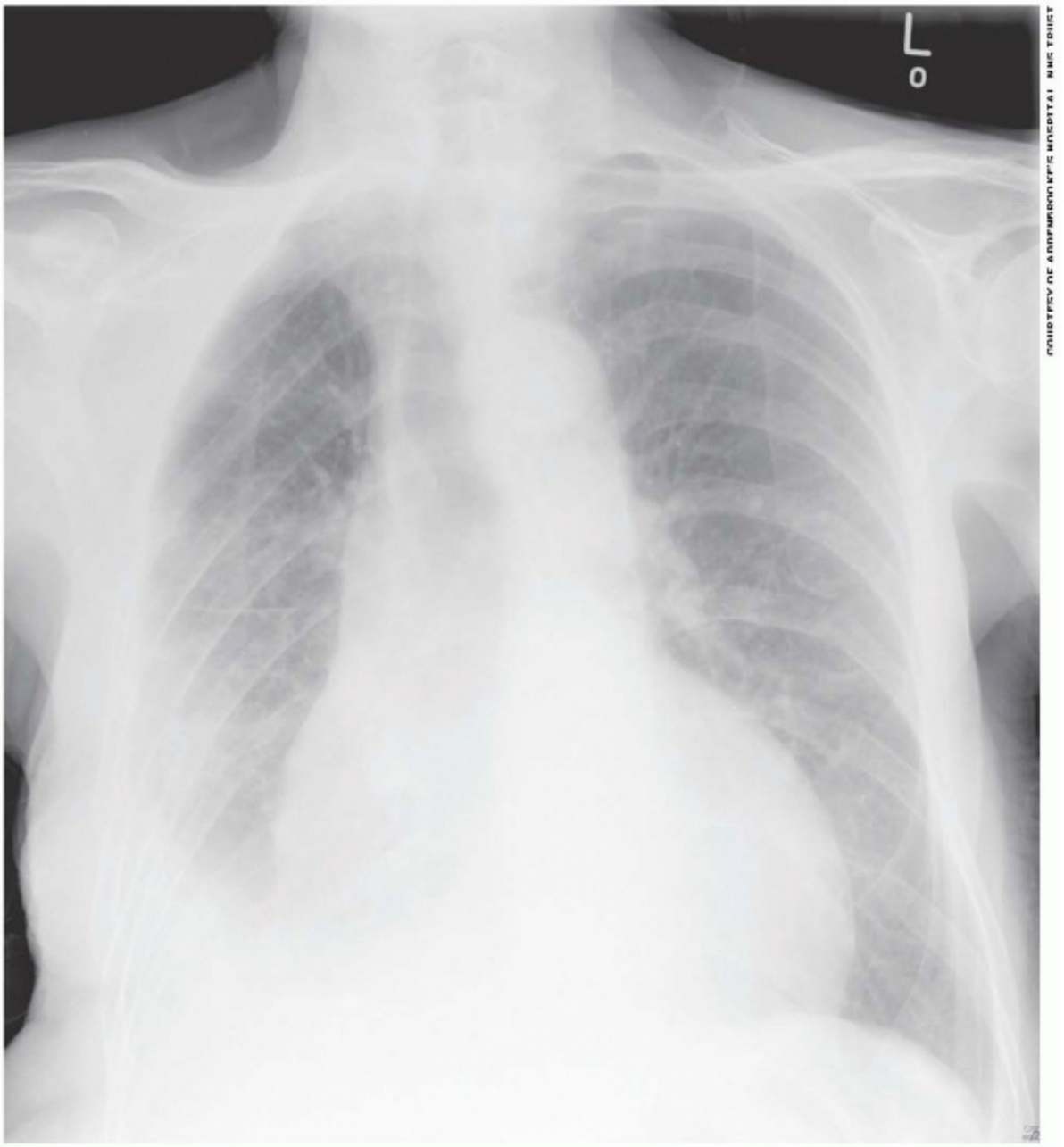
- If a patient's condition is such that resuscitation is unlikely to succeed.
- If a mentally competent patient has consistently stated or recorded the fact that he or she does not want to be resuscitated.
- If the patient has signed an advanced directive forbidding resuscitation.
- If resuscitation is not in a patient's interest as it would lead to a poor quality of life (often a great imponderable!). ▸*Ideally, involve patients and relatives in the decision **before** the emergency.* When in doubt, resuscitate.

Editors: Longmore, Murray; Wilkinson, Ian B; Turmezei, Tom; Cheung, Chee Kay
Title: *Oxford Handbook of Clinical Medicine, 7th Edition*

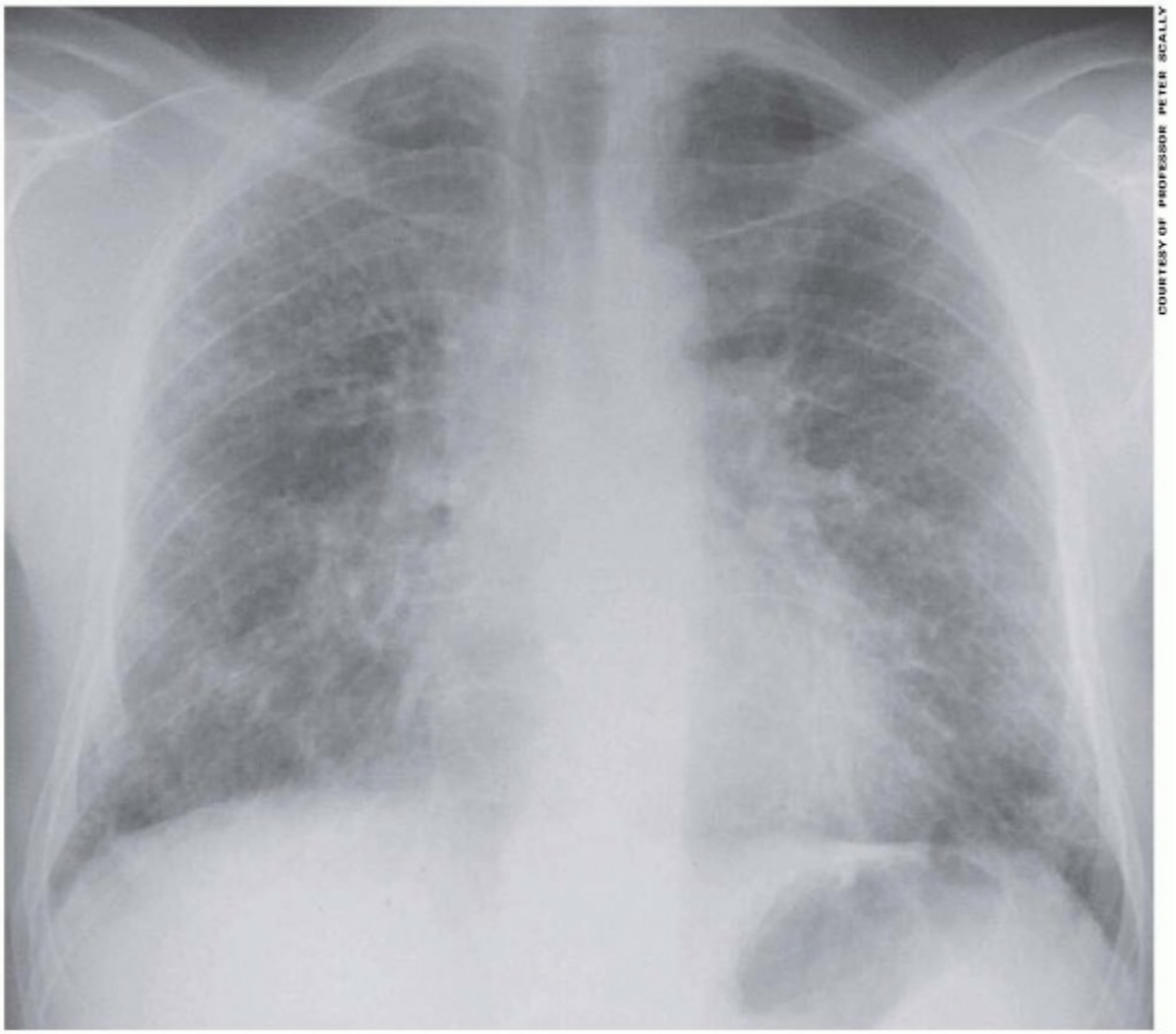
Enlarged Radiology Images



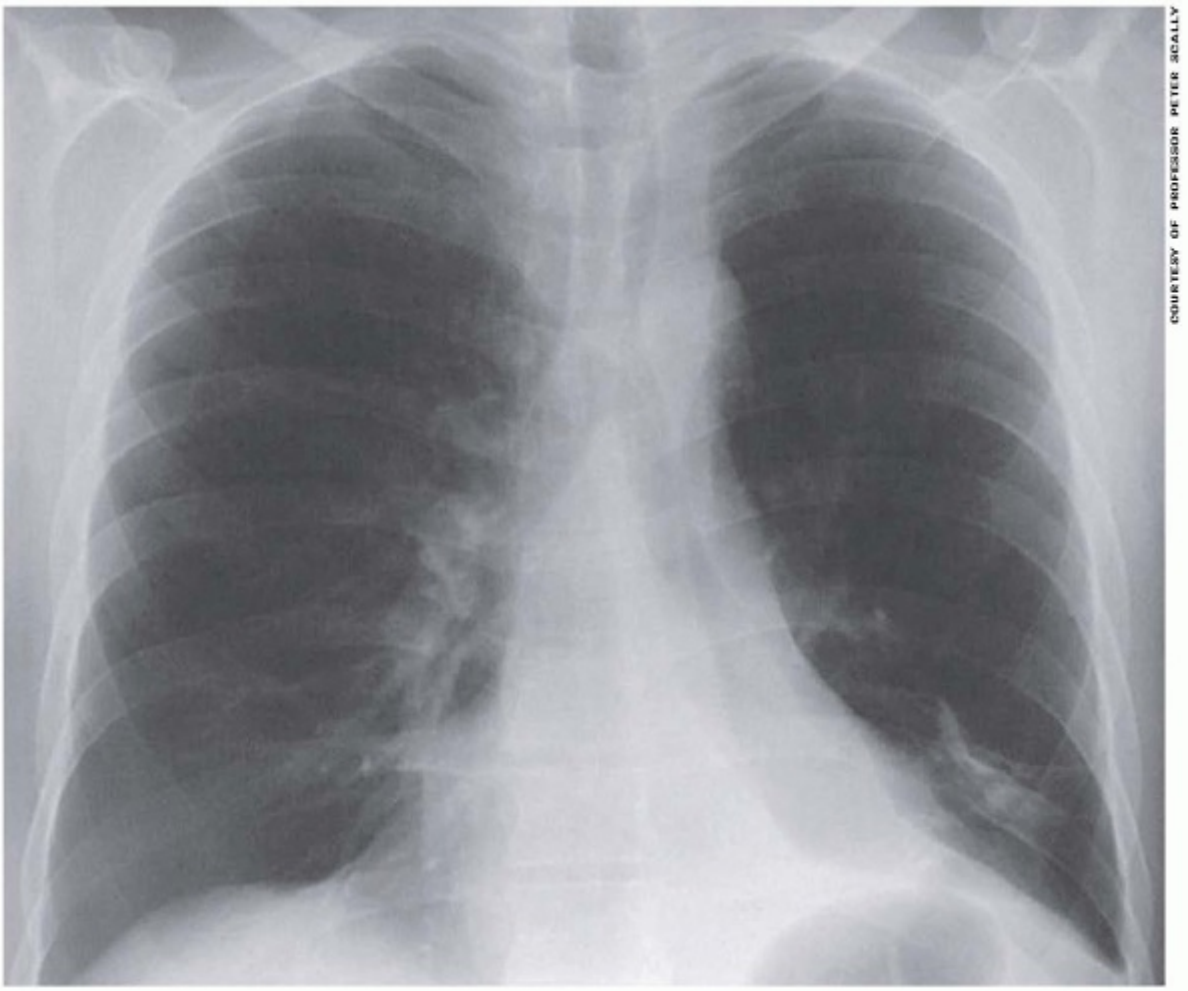
Middle lobe consolidation and a right pleural effusion. (see black and white image)



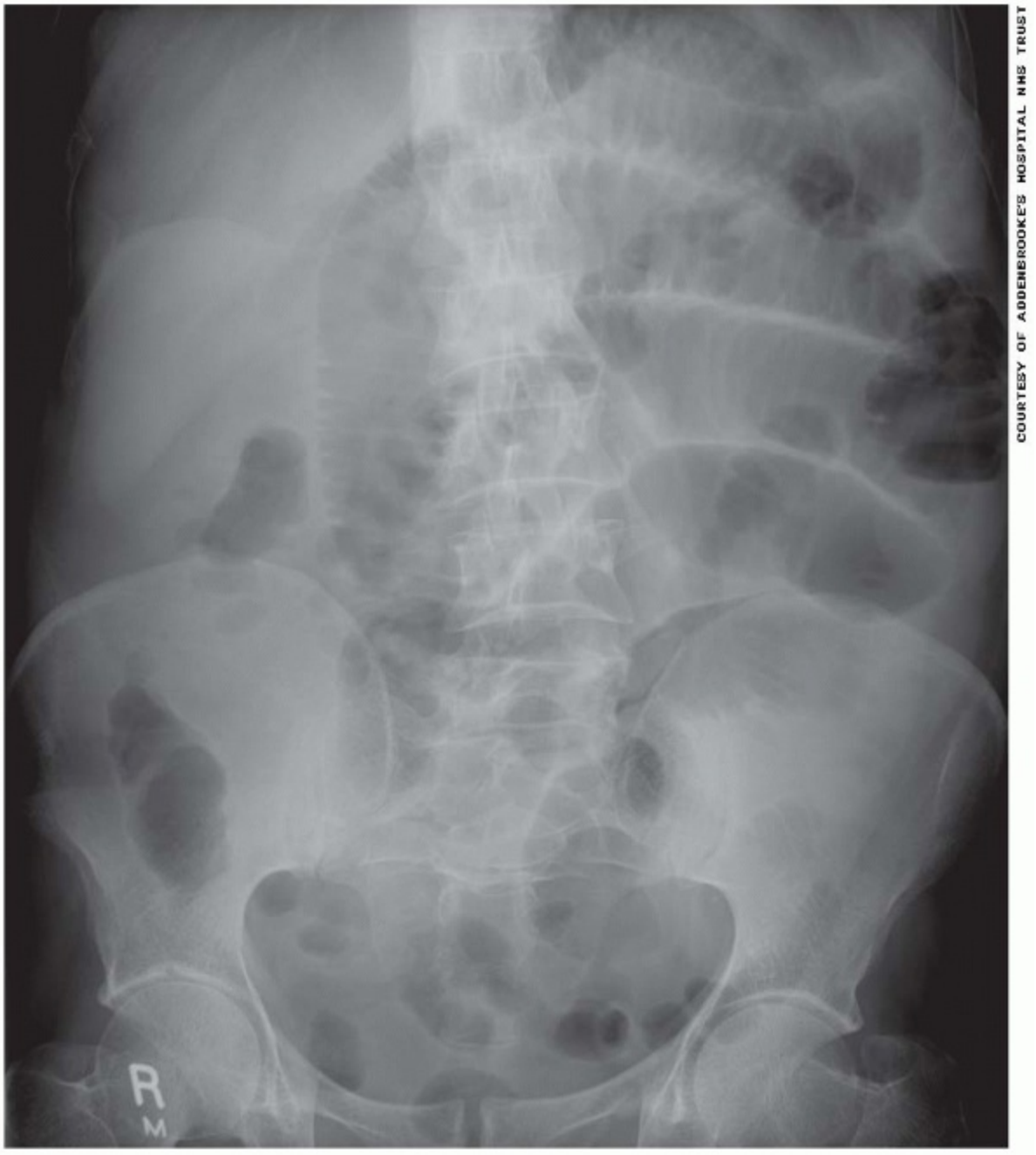
There is cardiomegaly and loss of the right costophrenic angle from a pleural effusion: consistent with heart failure. (see black and white image)



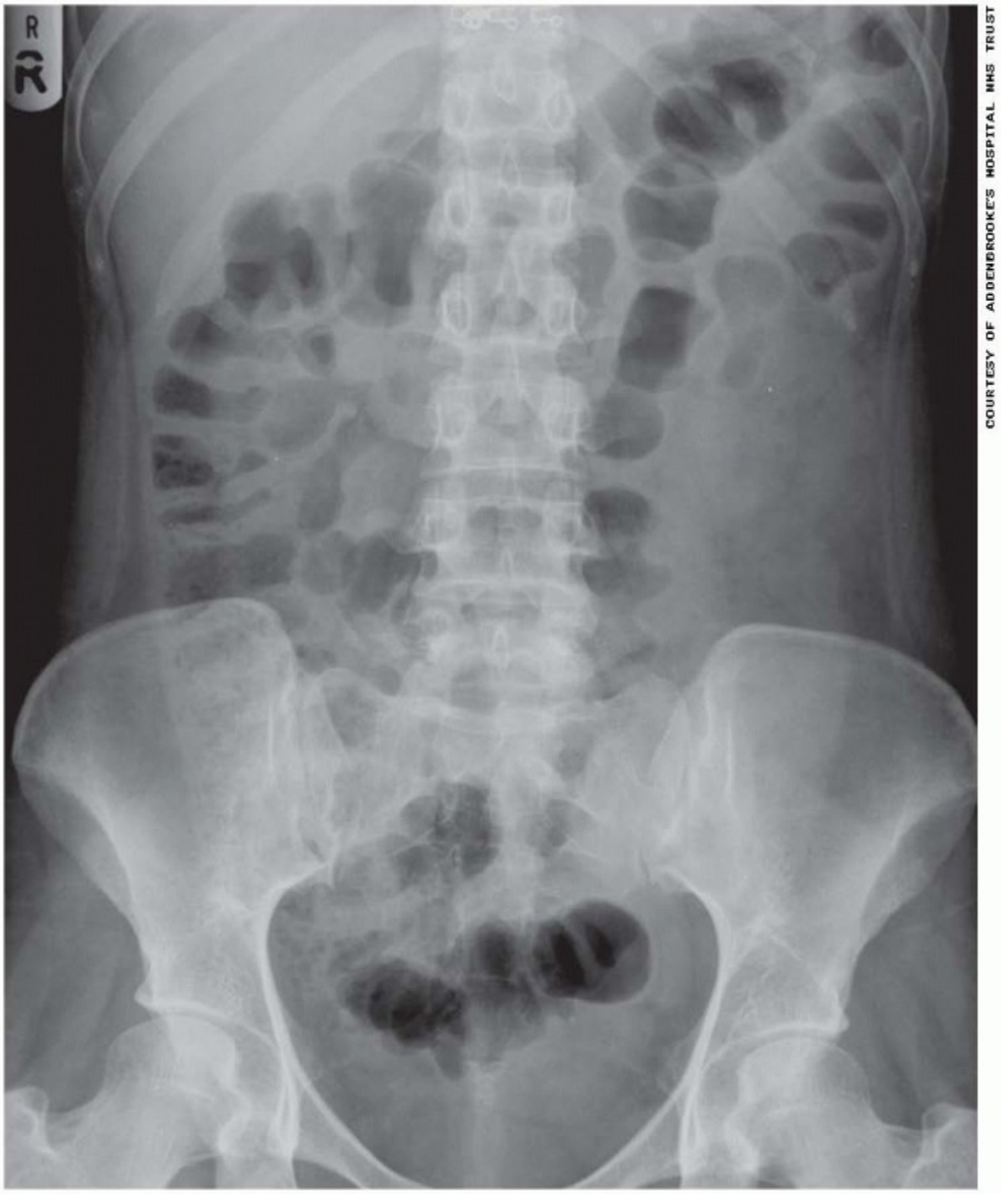
Diffuse reticular shadowing secondary to interstitial lung disease. The diagnosis was fibrosing alveolitis (UIP). (see black and white image)



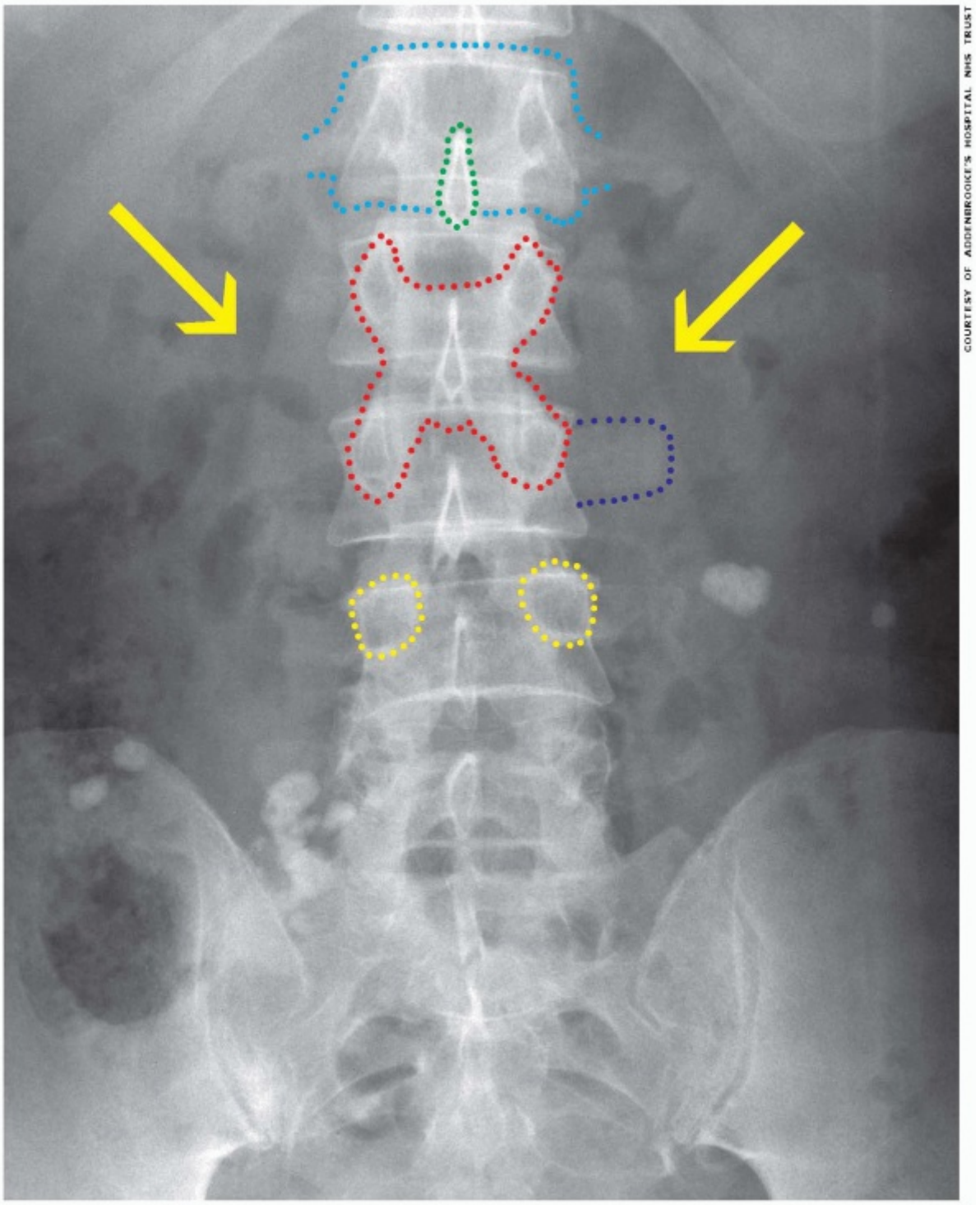
Collapse of the left lower lobeâthe triangular opacity behind the heart. Also, the left main bronchus has been pulled down. (see black and white image)



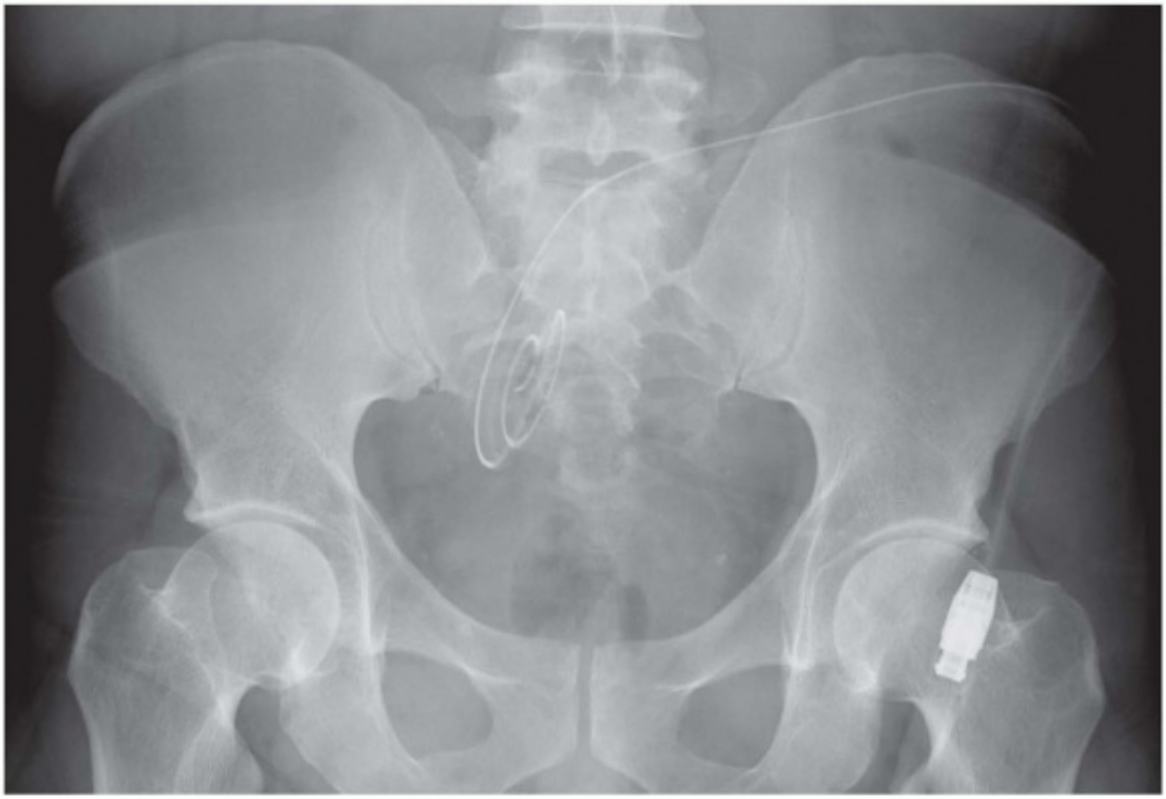
The gas pattern seen in small bowel obstruction. (see black and white image)



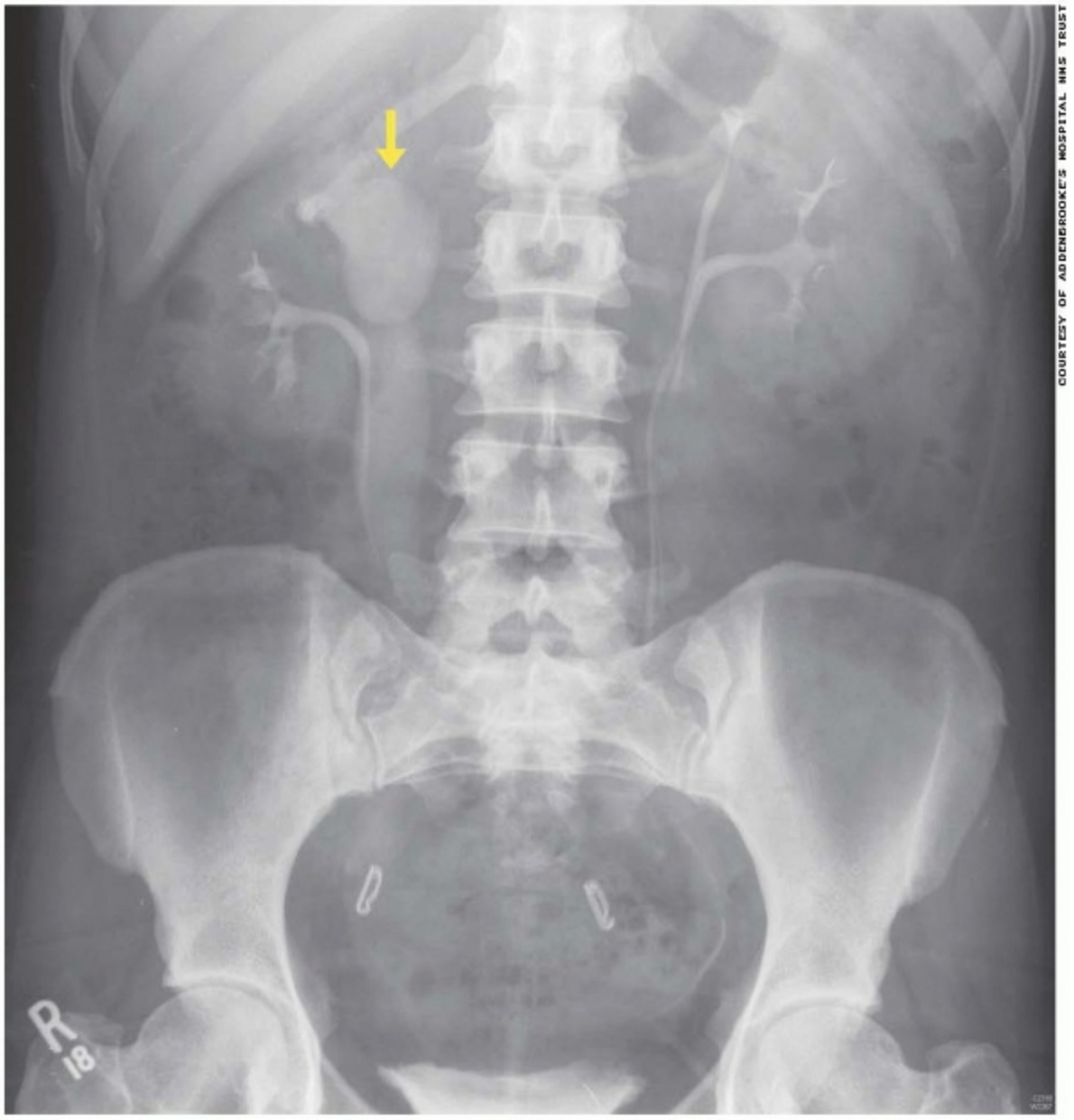
Normal large bowel gas pattern. (see black and white image)



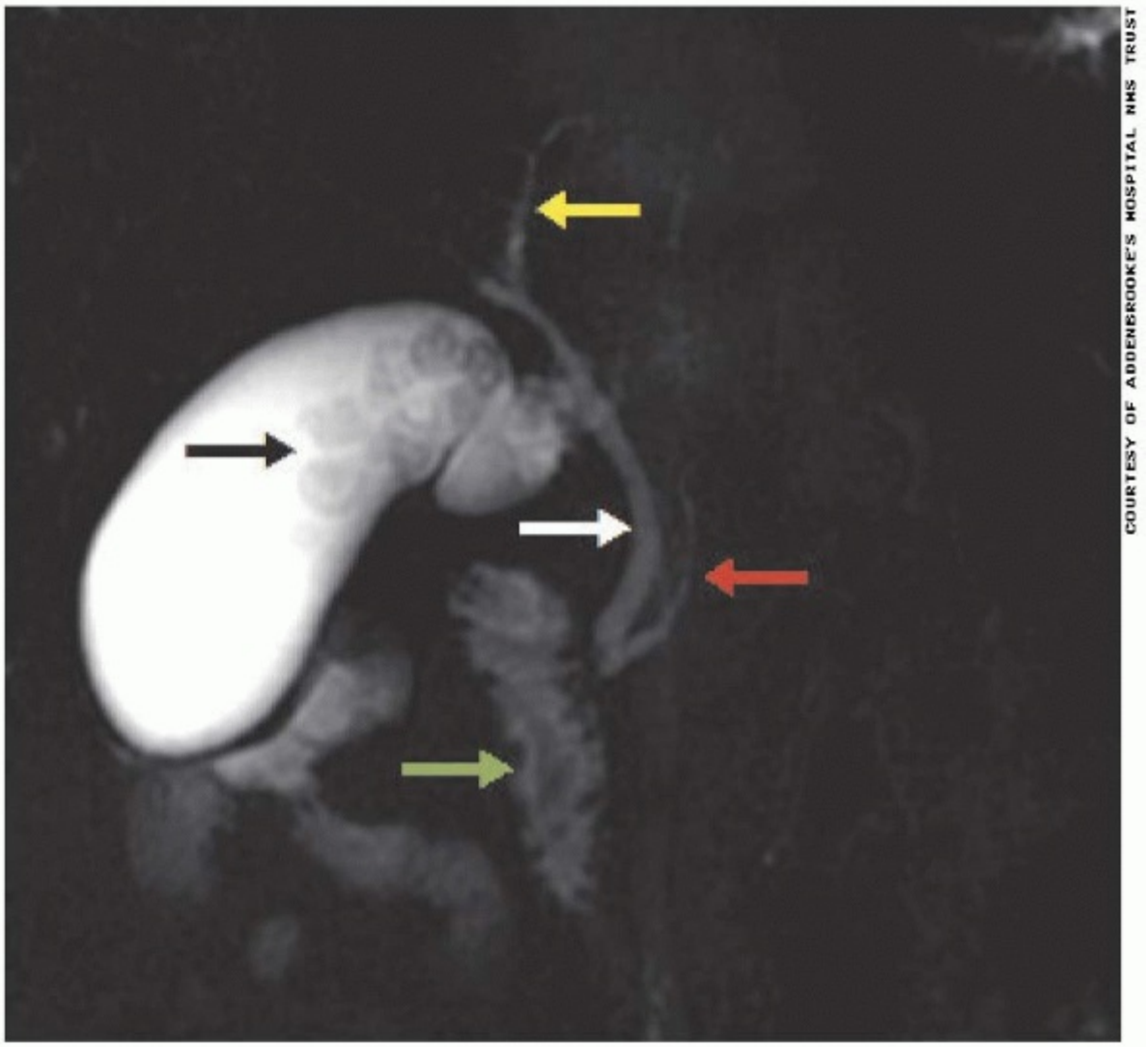
AXR showing calcified mesenteric lymph nodes. Also note; psoas lines (arrows); spinous process (green); transverse process (blue); pedicles (orange): facet joint processes (outline in red); vertebral body (cyan). (see black and white image)



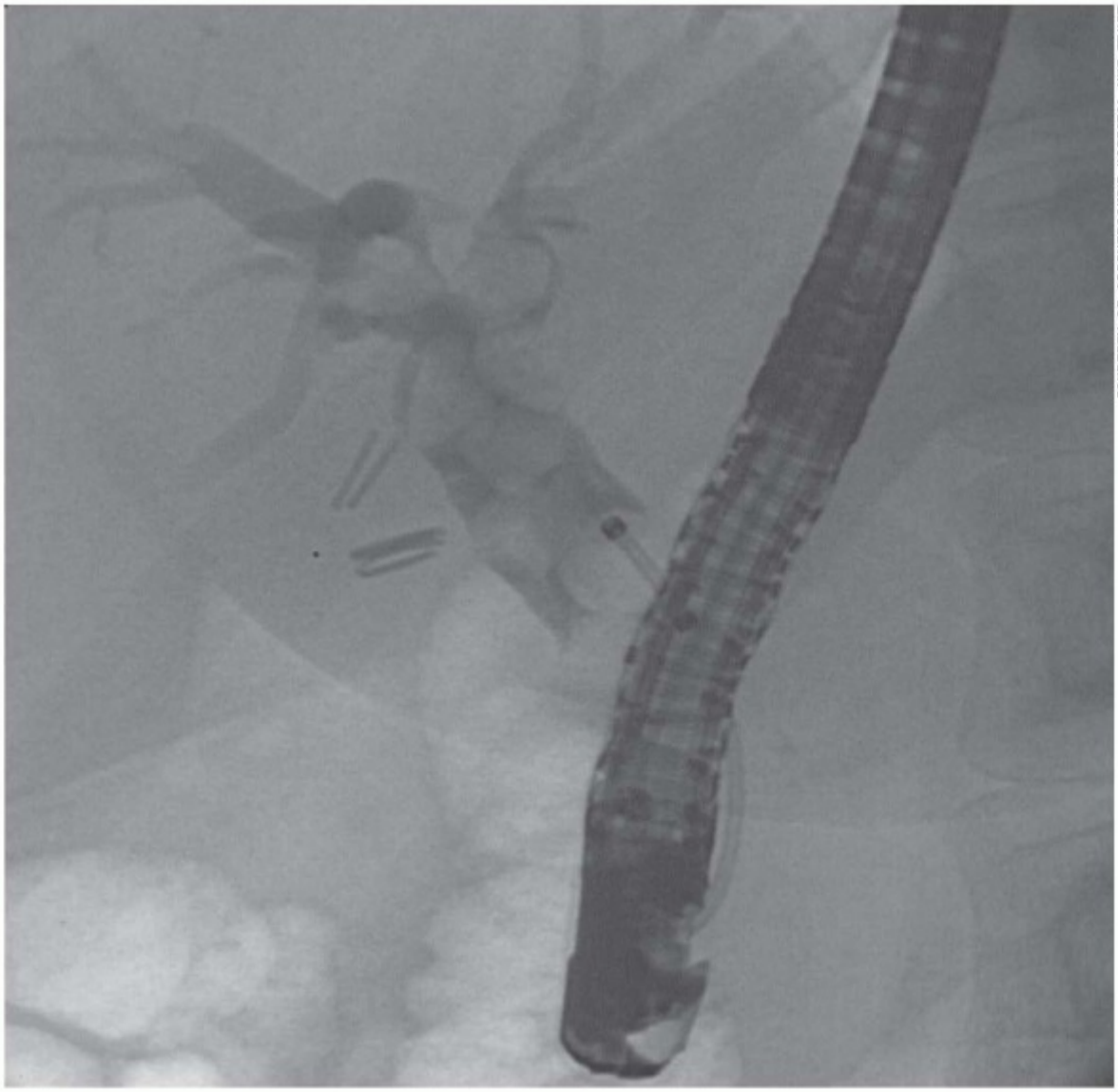
A CAPD catheter (for continuous ambulatory peritoneal dialysis). (see black and white image)



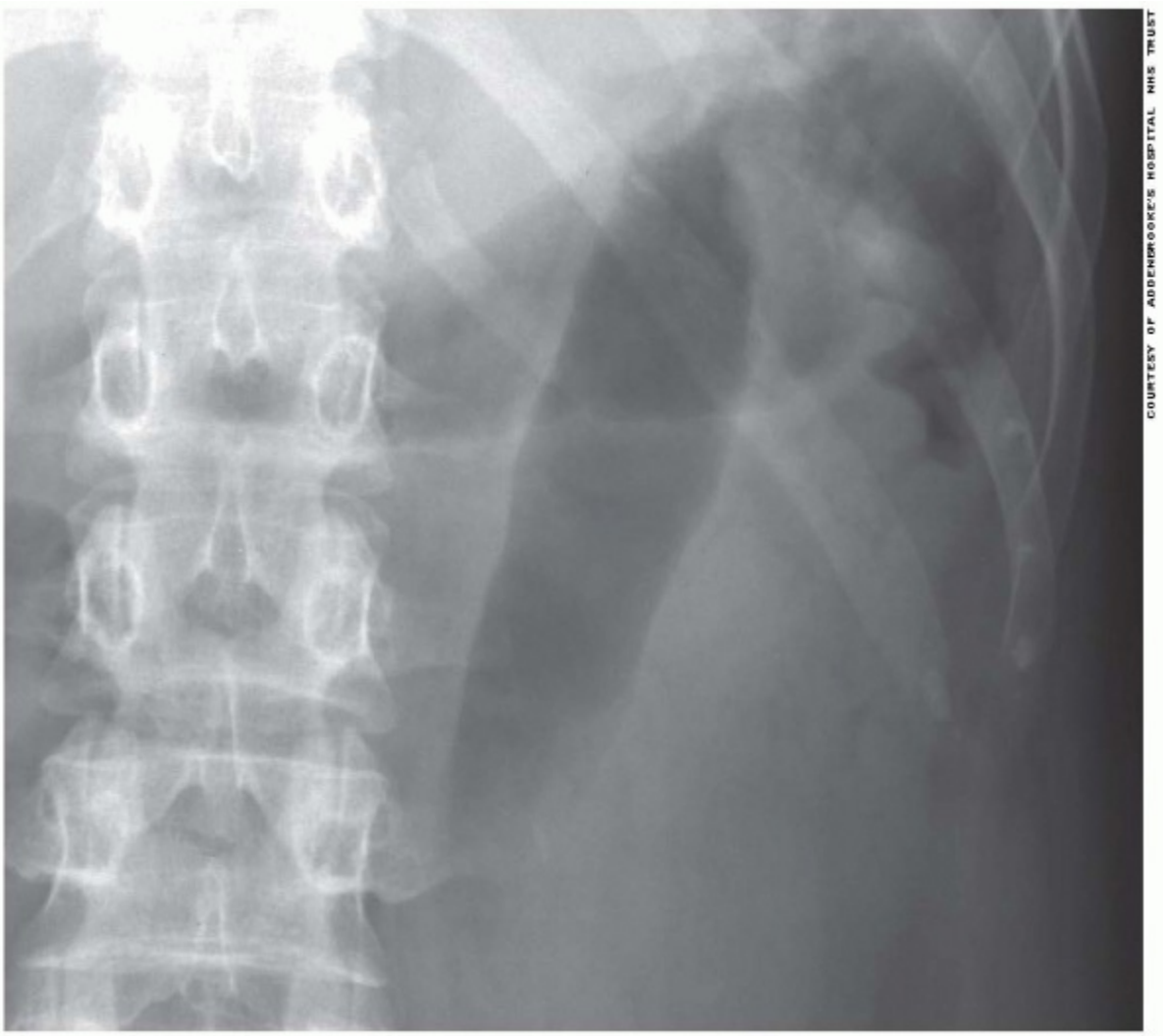
IVU: bilateral duplex ureters. The superior ureter moiety (arrowed) is ectopic and enters the bladder, urethra or vagina more inferiorly than the normally placed inferior ureter moiety. The superior ureter may be associated with a ureterocele and is more likely to obstruct. The inferior ureter may be associated with reflux nephropathy and scarring. (see black and white image)



Normal MRCP of the biliary system showing: left hepatic duct (yellow arrow); multiple gallstones in the gallbladder (black arrow); common bile duct (white arrow); pancreatic duct (red arrow); duodenum (green arrow). (see black and white image)



The ERCP shows dilated intra- and extrahepatic ducts. The multiple fill-ing defects relate to calculi within and obstructing the ducts. Note cholecystectomy clips. (see black and white image)



Part of the descending colon with mucosal thickening and loss of normal haustral pattern; seen in colitis. (see black and white image)

Editors: Longmore, Murray; Wilkinson, Ian B; Turmezei, Tom; Cheung, Chee Kay
Title: *Oxford Handbook of Clinical Medicine, 7th Edition*

Useful Doses for the New House Officer

▸These pages outline typical adult doses, and the commoner side-effects, of medications that a new house officer will be called upon to prescribe. If in any doubt, consult a drug formulary (eg British National Formulary, BNF, www.bnf.org).

Drug	Dose and frequency	Notes
Analgesics	(see p454 for more details on analgesia)	
Aspirin	300-900mg/4-6h PO, max. 4g/24h	SE of NSAIDs: gastritis; bronchospasm; hypersensitivity. CI: GI ulcer/bleeding; NSAID-induced asthma; coagulopathy. Avoid aspirin in children (risks Reye's syndrome).
Diclofenac	50mg/8h PO/PR	
Ibuprofen	400mg/6h PO, max. 2.4g/24h	
Paracetamol	0.5-1g/4-6h PO, max 4g/24h	Avoid if hepatic impairment.
Codeine phosphate	30-60mg/4h PO/IM max. 240mg/24h	
Dihydrocodeine tartrate	30mg/4-6h PO, OR 50mg/4-6h IM/SC	
Meptazinol	200mg/3-6h PO, OR 50-100mg/2-4h IM/IV	Patients with chronic pain (eg malignancy) may require higher doses. SE of opioids: nausea and vomiting; constipation; drowsiness; hypotension; respiratory depression, dependence. CI: Acute respiratory depression, acute alcoholism. Use carefully in head injury, as may hinder neurological assessment.
Oxycodone	5mg/6h PO	

Pethidine	50-100mg/4h PO/IM/SC	
Tramadol	50-100mg/4h PO/IM/IV	
Morphine	5-10mg/4h PO/IM/SC	
Antibiotics	(see p366-374)	
Antiemetics		
Cyclizine	50mg/8h PO/IM/IV	
Metaclopramide	10mg/8h PO/IM/IV	May cause extrapyramidal SE, especially in young adults.
Ondansetron	8mg/8h PO, or 4mg IM/IV	
Antihistamines		

Chlorphenamine	10-20mg IM/IV, maximum 40mg/24h OR 4mg/6h PO		
Cetirizine	5-10mg/24h PO		
Levocetirizine	5mg/24h PO		SE of antihistamines: Drowsiness; urinary retention; dry mouth; blurred vision; GI disturbance; arrhythmias. Drowsiness is less commoner with newer drugs, eg cetirizine, fexofenadine.
Fexofenadine	120-180mg/24h PO		
Loratadine	10mg/24h PO		
Desloratadine	5mg/24h PO		
Gastric acid reducing drugs			
Cimetidine	400mg/6-12h PO		
Ranitidine	150mg/12h PO		SE of H_2-blockers: GI disturbance; ↑LFT.
Omeprazole	20-40mg/24h PO		
Esomperazole	20-40mg/24h PO		SE of PPIs: GI disturbance; hypersensitivity. ▸ Acid-reducing drugs may mask symptoms of gastric cancer; use with care in middle-aged patients.
Lansoprazole	15-30mg/24h PO		

Pantoprazole	20-40mg/24h PO	
Heparins	(see p334 for more details on anticoagulation)	
Unfractionated heparin	*DVT* prophylaxis: 5000u/12h sc	SE of heparins: bleeding; thrombocytopenia; hypersensitivity; hyperkalaemia; osteoporosis after prolonged use. CI: coagulopathy; peptic ulcer; recent cerebral bleed; recent trauma or surgery; active bleeding.
Enoxaparin	*DVT* prophylaxis: 20-40mg/24h SC. DVT/PE treatment: 1.5mg/kg/24h SC until warfarinized. Unstable angina: 1mg/kg/12h sc for 2-8d	
Tinzaparin	*DVT prophylaxis:* 3500U/24h SC (eg starting 2h pre-op). *DVT/PE treatment:* 175U/kg per 24h SC till warfarinized.	
Dalteparin	*DVT prophylaxis:* 2500-5000U/24h SC. *DVT/PE treatment:* 200U/kg/d SC (18,000U/24h maximum). *Unstable angina:* 120U/kg/12h SC (up to 10,000U/12h maximum) for 5-8d.	
Hypnotics		
Temazepam	10-20mg PO at night	SE: Drowsiness; dependence. Zopicolone also causes bitter taste and GI disturbances. CI: Respiratory depression; myasthenia.
Zopiclone	3.75-7.5mg PO at night	

Tranquilizers		
Haloperidol	2-5mg IM/IV initially, then every 4-8h till response, maximum 18mg in total.	SE: Extrapyramidal effects, sedation, hypotension, antimuscarinic effects, neuroleptic malignant syndrome.
Others		
Naloxone	*In opiate overdose:* 0.8-2mg IV repeated every 2-3min to a maximum of 10mg if respiratory function does not improve. *To reverse opiate-induced respiratory depression:* 100-200µg IV every 2min.	SE: tachycardia; fibrillation. Can precipitate opiate withdrawl.
Flumazenil	*To reverse benzodiazepines:* 200µg IV over 15s, then 100µg every 60s if required, up to 1mg maximum.	SE: convulsions (esp. in epileptics); nausea and vomiting; flushing. Avoid if patient has a life-threatening illness controlled by benzodiazepines (eg status epilepticus).

Editors: Longmore, Murray; Wilkinson, Ian B; Turmezei, Tom; Cheung, Chee Kay
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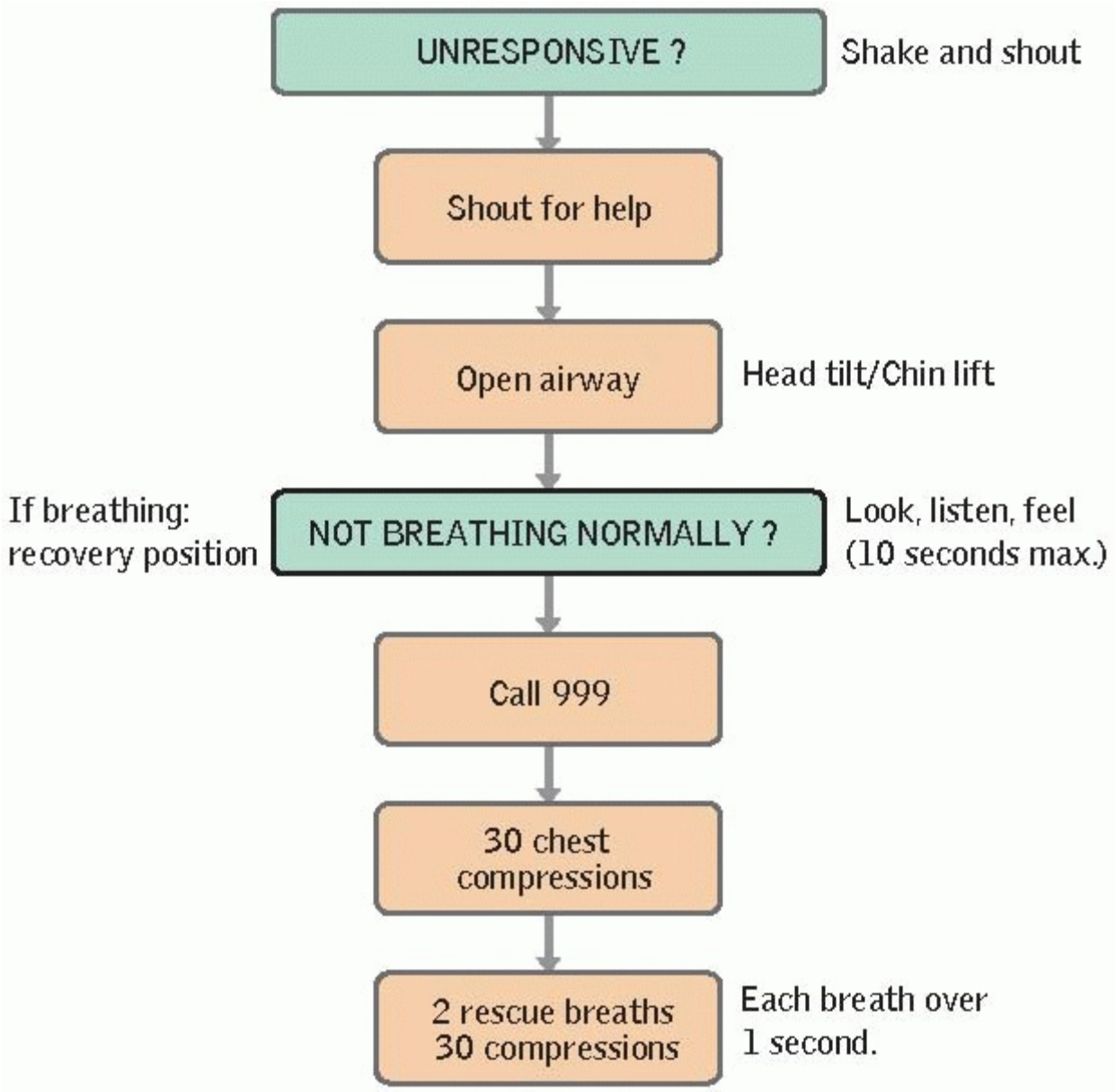
UK Adult Basic Life-Support Algorithm 2005[1]

The algorithm assumes that only one rescuer is present, with no equipment. (If a defibrillator is to hand, get a rhythm readout, and defibrillate, as opposite, as soon as possible.)



Send or go for help as soon as possible according to guidelines

Managing the airway

You open the airway by tilting the head and lifting the there is no question of spinal trauma.

Use a close-fitting mask if available, held in place by thumbs pressing downwards either side of the mouth-piece; palms against cheeks.

Chest compressions

Cardiopulmonary resuscitation (CPR) involves compressive force over the lower sternum with the heal of the hands placed one on top of the other, directing the weight of your body through your vertical, straight, arms. Depth of compression: 4cm. Rate of compressions: 100/min.

Remember that these are guidelines only, and that the exact circumstances of the cardiorespiratory arrest will partly determine best practice. The guidelines are also more consensus-based than evidence based (p644), and are likely to be adapted from time to time, for example, as consensus develops about the best recovery positionâeg semi-lateral position, with under-most arm either straight at the side, in dorsal position, or in the ventral position cradling the head with the upper-most arm crossing it (more stable, but possible risk to arm blood flow).[2]

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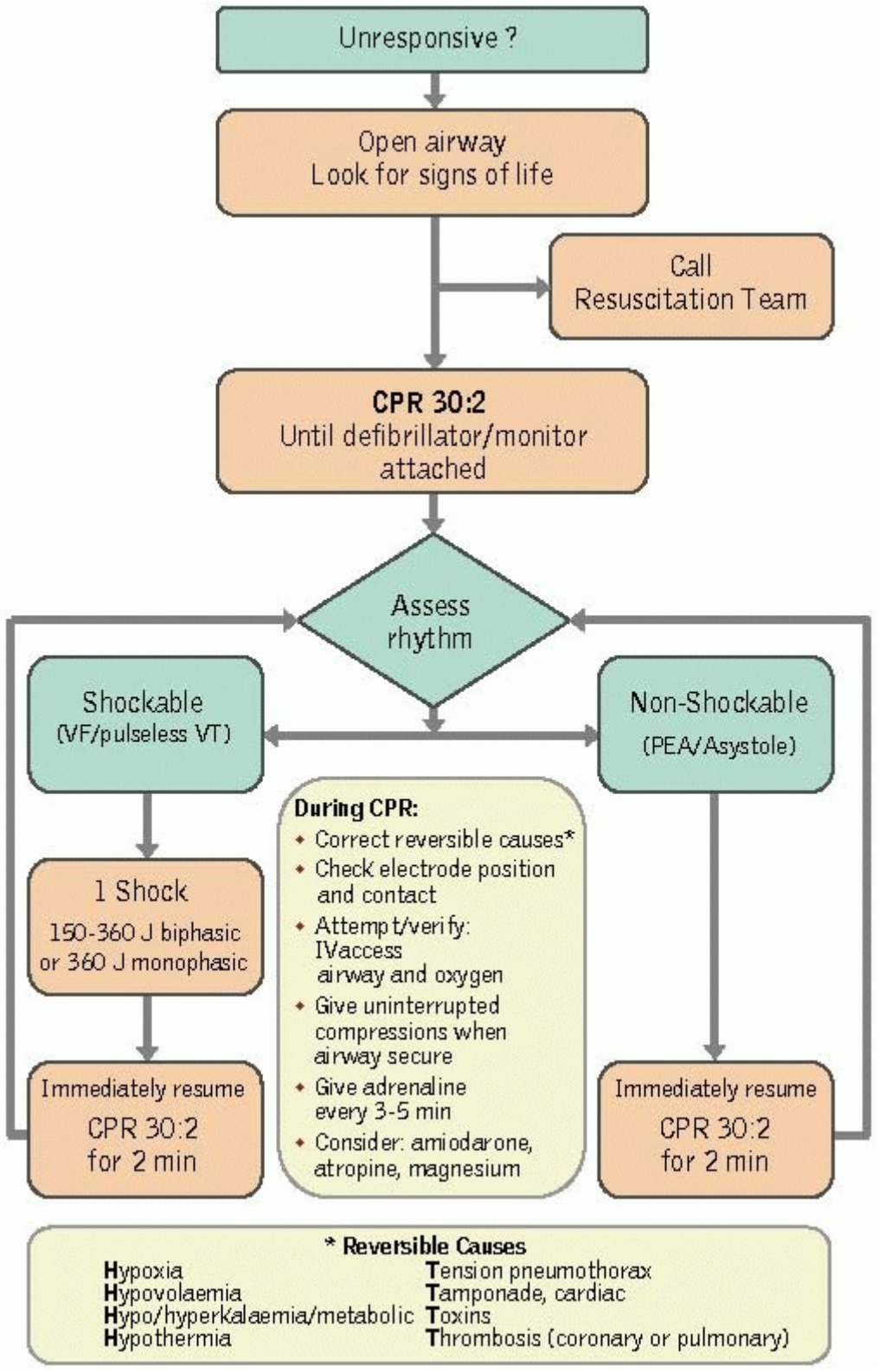
Cardiac arrest: 2005 Adult Advanced Life-Support Algorithm[1]

Each step assumes the previous one has been unsuccessful



***Do not interrupt* CPR** for >10s, except to defibrillate.

Resistant* VF/VT *consider:

- Amiodarone 300mg IV (peripherally if no central access). A further 150mg may be given, followed by an infusion of 1mg/min for 6h, then 0.5mg/min for 6h.
- Alterative to amiodarone are:

- Lidocaine 100mg IV; can repeat once; then give 2-4mg/min IVI.

- Procainamide 30mg/min IV to a total dose of 17mg/kg.

- Seek expert advice from a cardiologist.

Asystole/PEA: Give adrenaline 1mg immediately IV access is achieved. Give atropine 3mg IV once if asystole or PEA + rate < 60/min. If P waves the patient may respond to pacing.

Treat acidosis with good ventilation. Sodium bicarbonate may worsen intracellular acidosis and precipitate arrhythmias, so use only in severe acidosis after prolonged resuscitation (eg 50mL of 8.4% solution by IVI).