MODULE: GENERAL PATHOLOGY II

UNIT: GENETIC DISEASES

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OUTLINE

	Topic	Duration (hours)
1.	Introduction to Genetics and Genetic Basis of Disease	2
2.	Single Gene Disorders – Autosomal Dominant	2
3.	Single Gene Disorders – Autosomal Recessive – SCD and Thalassaemia	2
4.	Single Gene Disorders – Autosomal Recessive – Cystic Fibrosis and Albinism	2
5.	Sex Linked Disorders	1
6.	Chromosomal Disorders	1
7.	Polygenic Disorders – Birth Defects	2
8.	Polygenic Disorders – CVS	2
9.	Polygenic Disorders – R/S and Immune system	2
10.	Polygenic Disorders – Neurological and MSS	2
11.	Polygenic Disorders – Endocrine system and Skin	2
	TOTAL	**20**

TOPIC 1: INTRODUCTION TO GENETICS AND GENETIC BASIS OF DISEASE

Learning Objectives

At the end of the lesson the learner will be able to: -
1) Describe the structure and function of chromosomes and genes
2) Describe the processes of cell division and protein synthesis
3) Describe the mechanisms of genetic disease inheritance patterns and development

1.0 INTRODUCTION

- Genetics is the scientific study of heredity (passing of characteristics from parents to their offspring) through particles called genes while molecular genetics is the study of chemical basis of heredity
- Genetic disorder – illness or disease caused by one or more abnormalities of the genome(gene)
- The human genome is the entire "treasury of human inheritance."
- The 46 human chromosomes (22 pairs of autosomal chromosomes and 2 sex chromosomes) between them house almost 3 billion base pairs of DNA that contains about 20,500 protein-coding genes
- Coding regions make up less than 5% of the genome (the function of all the remaining DNA is not clear) and some chromosomes have a higher density of genes than others
- Most genetic diseases are the direct result of a mutation in one gene
- Traditionally - **3 types of** diseases namely genetically determined, environmentally determined and the combination

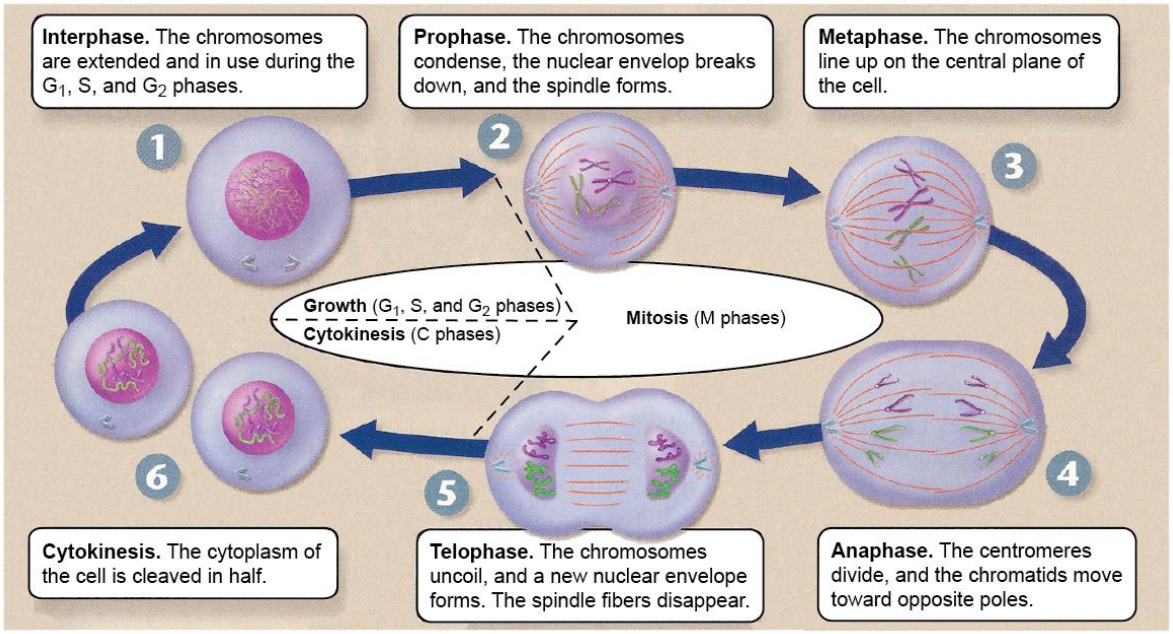
Terminology

	Term	Description/definition
1)	Gene	
2)	Genome	
3)	Chromosome	
4)	Genetic code	

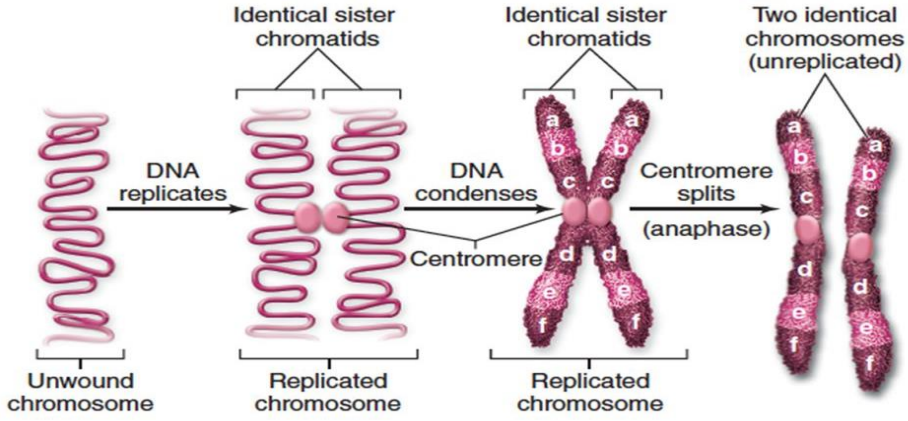
2.0 CELL CYCLE

- Cell growth and reproduction are fundamental processes responsible for continued survival (growth, repair and replacement) and creation of new organisms
- Cell growth depends on genetic information from the DNA (contains blueprints that specify construction of proteins such as hormones and structural proteins)
- Cell growth and reproduction processes constitute the **cell life cycle**
- The cell cycle has four sequential phases - G1, S, G2 and mitosis

Diagram 1.1: The Cell Cycle



Changes in a Chromosome During Cell Cycle



3.0 MITOSIS

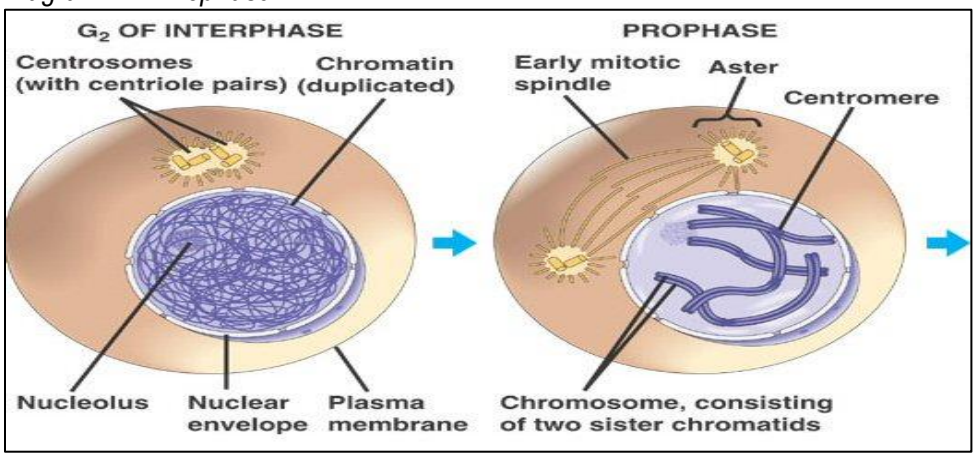
Introduction

- Mitosis is the division of the ***nucleus into 2 identical nuclei***, which occurs during cell division and involves organization and distribution nuclear DNA
- Takes place in four phases - prophase, metaphase, anaphase, and telophase

Phase 1- Prophase (“*before phase”)*

- Nucleus envelope falls apart and the paired (sister) chromatids coil up to form dense compact chromosomes (sister chromatids are joined together by the centromere)
- Nucleolus and nuclear membrane disappear and two structures called **centrosomes** appear next to the disappearing nucleus
- Centrosomes move toward opposite poles of the cell and as they separate
- Spindle fibers form (two types kinetochore and polar fibers)

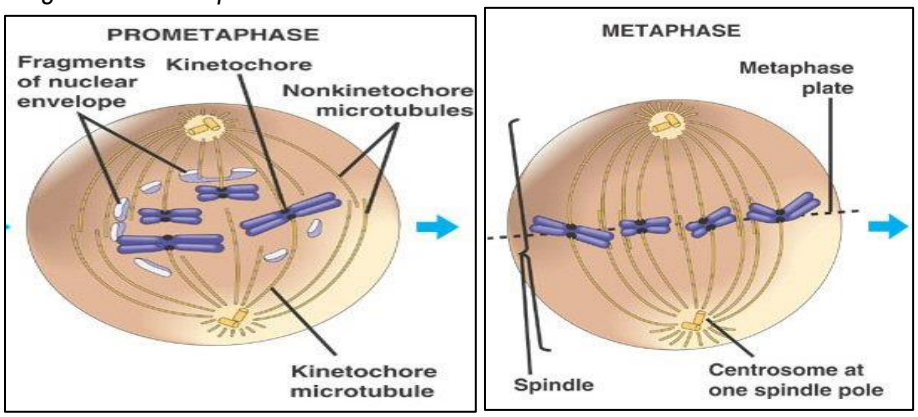
Diagram 1.2: Prophase



Phase 2 - Metaphase (“position-changing phase”)

- Chromosomes are moved and aligned along a plane at the equator of the cell midway between the centriole pairs at opposite poles of the cell (equatorial plane) by the kinetochore fibers attached to the centromeres
- One chromatid of each chromosome faces one pole of the cell with the identical sister chromatid facing the opposite pole and each chromatid then attaches to a spindle fibre

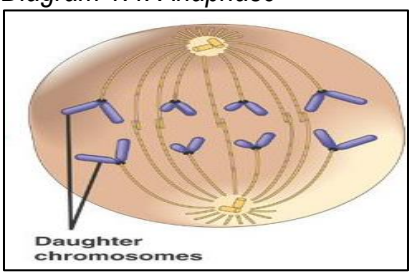
Diagram 1.3: Metaphase



Phase 3 - Anaphase ("apart phase")

- Centromere of each chromosome splits to form two chromosomes each consisting of a single DNA molecule and each chromosome is pulled toward the opposite poles (centromeres)
- Sister chromatids move apart and are thus separated from each other and are now considered to be individual chromosomes.

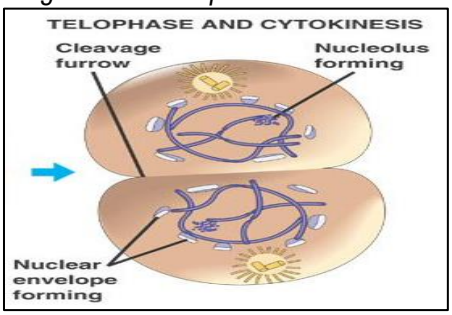
Diagram 1.4: Anaphase



Phase 4 - Telophase ("end phase" or "completion phase")

- Chromosomes reach opposite ends of the cell and spindle fibers disassemble
- Chromosome return to its original form and location within the cell
- A new nuclear envelope forms around the chromosomes at each end of the cell.

Diagram 1.5: Telophase



4.0 MEIOSIS

Introduction

- Meiosis is a process of nuclear division that reduces the number of chromosomes in new cells to half the number in the original cell (produces four haploid cells)
- One parent cell divides twice to produce four haploid daughter cells
- Proceeds in two main stages namely **meiosis I** and **meiosis II** (the sister chromatids of each chromosome are separated)

Meiosis I

- Homologous pairs are separated

Prophase I

- Chromosomes become thick and visible and **each homologous pair is tangled together**
- Portions of chromatids may break off and attach to adjacent chromatids on the homologous chromosome in a process called **crossing-over**
- Crossing-over results in genetic recombination by producing a new mixture of genetic material
- Each pair consists of four chromatids, because each chromosome in the pair had replicated before meiosis began
- The nucleoli and the nuclear envelope disappear and the spindle fibers form

Metaphase I

- Homologous pairs (tetrads) are still together and arrange in the middle of the cell.

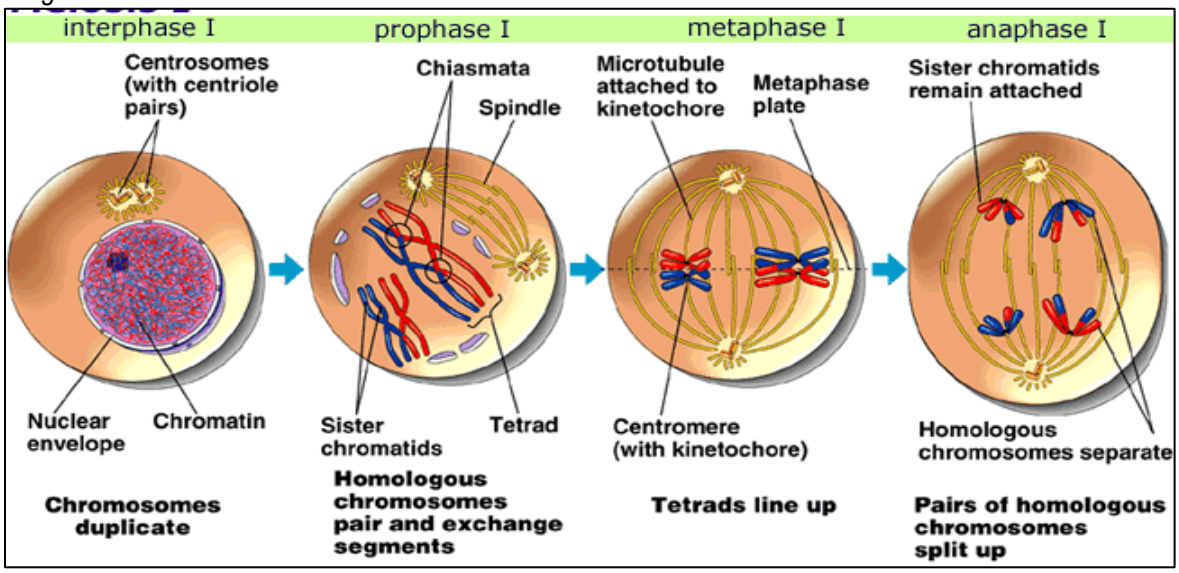
Anaphase I

- Homologous pairs of chromosomes separate from each other and the spindle fibers pull one member from each pair to opposite ends of the cell

Telophase I

- Cytokinesis takes place and each new cell is haploid, containing one chromosome from each pair

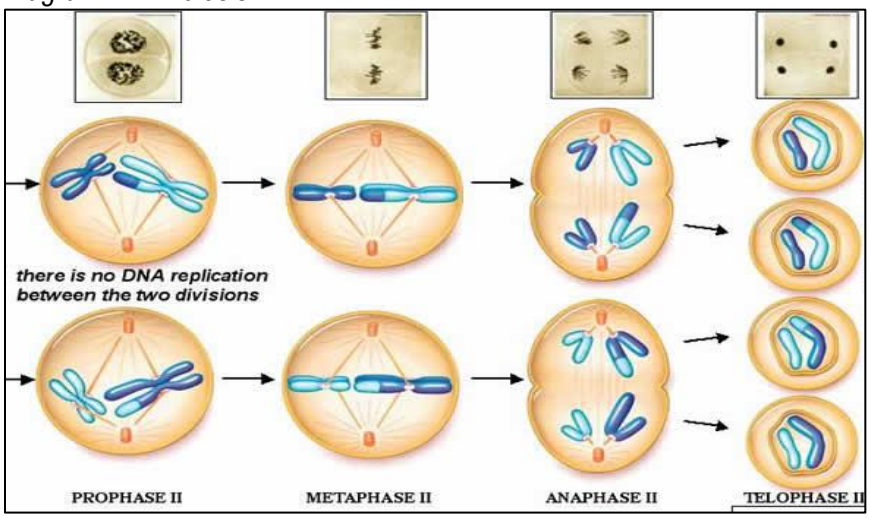
Diagram 1.6: Meiosis I



Meiosis II

- Resembles mitosis where chromosomal replication does not occur between meiosis I and meiosis II
- Meiosis I proceeds directly to meiosis II without going through interphase
- Begins with two haploid cells and ends with four haploid cells

Diagram 1.7: Meiosis II



Prophase II Metaphase II

- Chromosomes align on the metaphase plate during metaphase II in preparation for centromeres to divide in the next phase

Anaphase II

- Chromosomes divide at the centromeres and the resulting chromosomes each with one chromatid move towards the opposite plates of the cell

Telophase II and Cytokinesis

- Four haploid nuclei (containing chromosomes with single chromatids) are formed
- Division of the cytoplasm cytokinesis results in four haploids cells
- Spindle fibers reform and attach to centromeres in prophase II

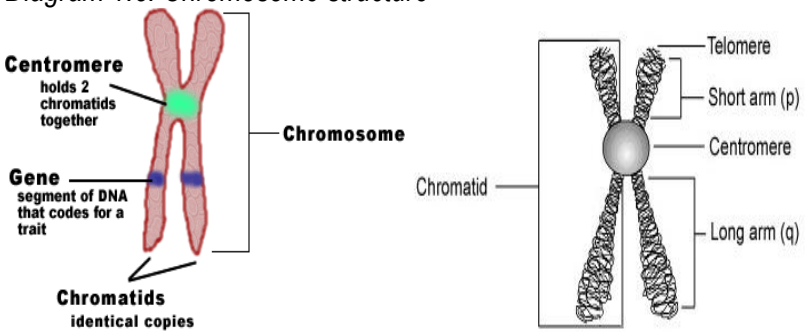
5.0 CHROMOSOMES

- Are structures that transmit hereditary traits and control synthesis of all proteins in the body
- Normal human cell nucleus contains a set of 23 pairs of chromosomes (Greek *chromos* = coloured; *soma* = body) of which 22 pairs are autosomal and a pair of sex chromosomes (called chromosomes because of their ability to take up colour stains)
- Each chromosome contains a DNA molecule, histones[1] and non-histone proteins
- Many **histones** are organized into bobbin like cores onto which the DNA helixes are coiled
- Histone cores regulate the DNA activity because tightly packed DNA cannot function as a template for formation of RNA or for replication of a new DNA
- Non-histone proteins form essential as structural proteins, activators, inhibitors and enzymes

Structure of the Chromosome

- Each chromosome has a narrow waist called **centromere**, which divides the chromosome into short and long arms labelled p and q respectively and it is also the region where the two chromatids cross each other
- Distal end (the tip) of each chromosome is called the **telomere**
- Chromosomes can be seen under the light microscope only when the cell is ready to divide
- It contains many **DNA units called genes**

Diagram 1.8: Chromosome structure



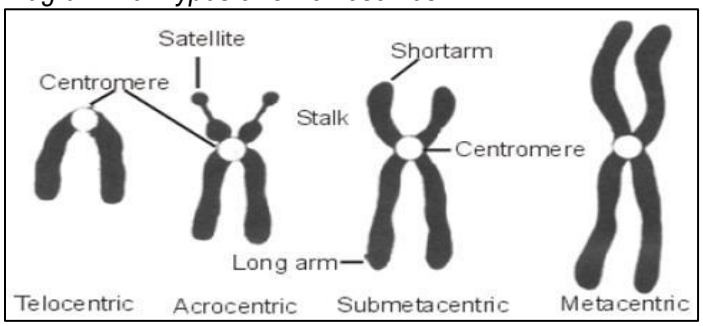
Classification

- Based on the location of the centromere
  i) Metacentric chromosomes –centromere is exactly in the middle e.g. chr. number 1, 3, 16, 19 and 20
  ii) Sub metacentric chromosomes – centromere divides the chromosome into a short arm (p) and a long arm (q)

[1] Histones are small electro-positively charged molecules that form a large protein mass in the chromosome

iii) Acrocentric chromosomes – have a very short arm with a centromere that is located off the centre in an unusual position (eccentric) e.g. chromosomes number 13, 14, 15, 21, 22 and the Y chromosome.
iv) Telocentric chromosomes

Diagram 1.9: Types of Chromosomes



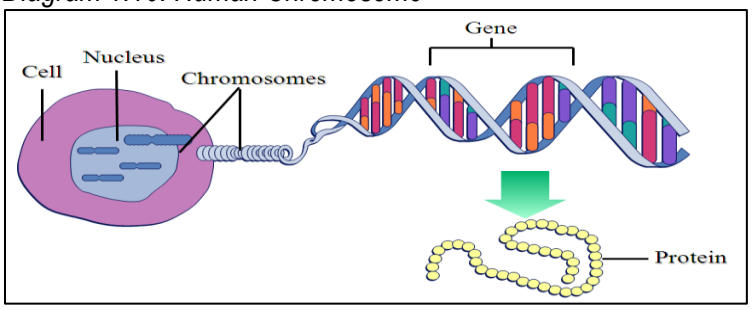
Chromosome numbers

- Each human body cell contains 46 (23 pairs of) chromosomes (2n) while the one with only one complete set of chromosomes is called a haploid cell (1n) e.g. gametes, eggs & sperm cells
- Human chromosomes are categorized as either sex chromosomes or autosomes i.e. 1 pair of sex chromosomes (XX– females and XY for males) and the 22 pairs of autosome

6.0 DNA

- Is contained on the chromosome
- Cells have powerful internal feedback control systems that maintain homeostatic operations (each gene has a feedback control mechanism) through activation or inactivation of genes or enzyme regulation
- DNA controls protein synthesis by means of the genetic code

Diagram 1.10: Human Chromosome



Functions of DNA

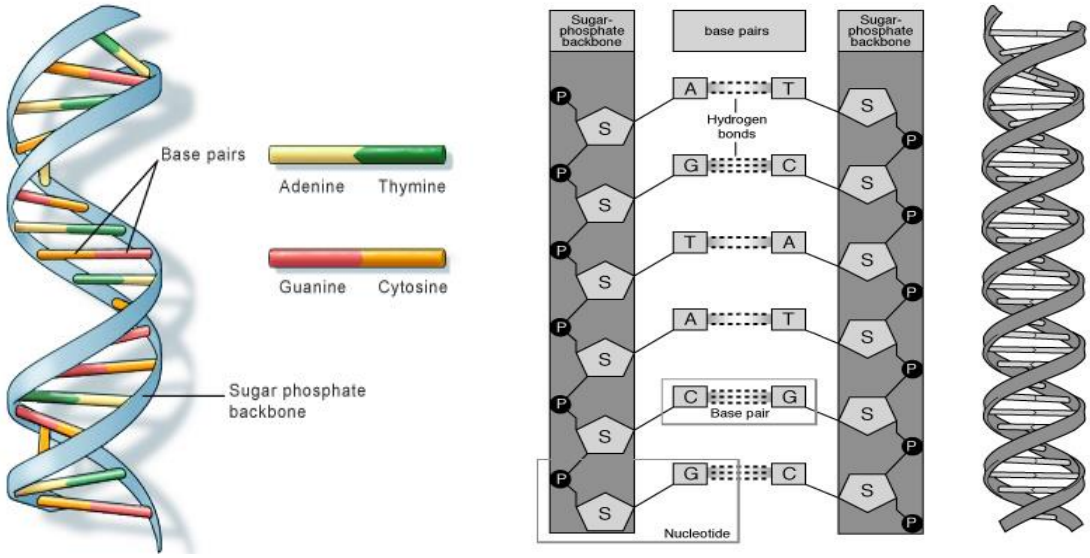
1. Carry information of inheritance
2. Protein synthesis
3. Control of biochemical processes in the cells

Structure

- Formed from phosphoric acid, deoxyribose sugar and four nitrogenous bases – two purines (adenine and cytosine) and two pyrimidines (thymine and cytosine)

- DNA molecule consists of two parallel chains twisted (double helix) connected at various points with rings made up of organic bases held together by hydrogen bonds in specific relationship - purines link up with pyrimidines; A–T and C–G.

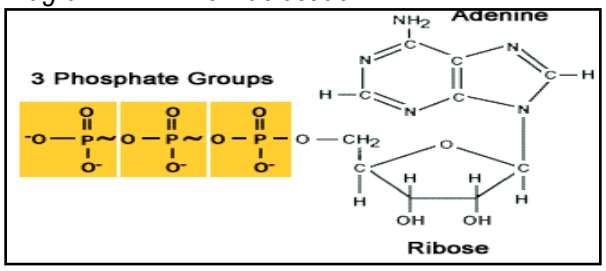
Diagram 1.11: Structure of DNA



Nucleic Acids

- Contain Information carried by genes (compare to application packages in the computer)
- There are two principal types of nucleic acids– deoxyribonucleic acid (DNA) mainly confined to the nucleus and the ribonucleic acid (RNA) found mainly in the cytoplasm
- Made up of blocks of complex molecules called nucleotides.
- A nucleotide is made up of three molecules – a 5-carbon sugar (pentose), an organic base and phosphoric acid linked together.

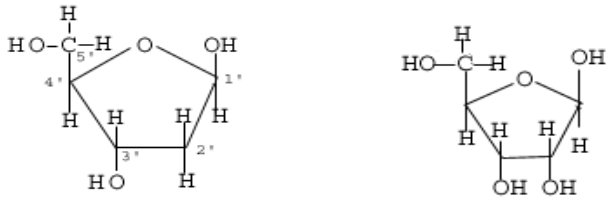
Diagram 1.12: The Nucleotide



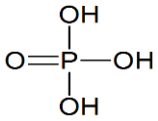
The Sugar

- The pentose sugar, either a **ribose sugar** ($C_5H_{10}O_5$) or **deoxyribose sugar** ($C_5H_{10}O_4$) which has lost one molecule of oxygen from a ribose sugar

Diagram 1.13: Ribose and Deoxyribose Sugar



Phosphate or Phosphoric acid (H_3PO_4) group



Organic Bases

- Are complex compounds made up of intricate rings of carbon and nitrogen atoms
- Five organic bases– adenine (A), guanine (G), thymine (T), cytosine (C) and uracil (U)
- Adenine and guanine are purines (double rings) and the rest are pyrimidines (single rings)

Diagram 1.14: Purines

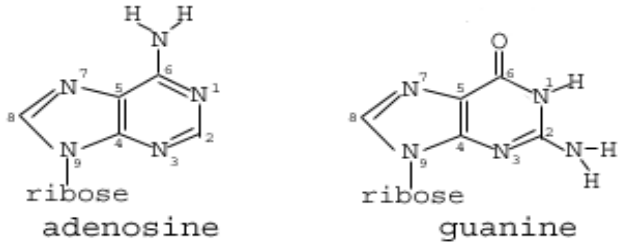
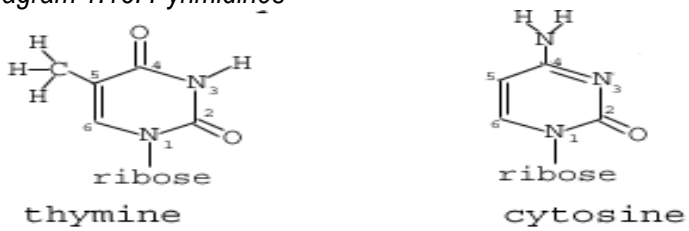


Diagram 1.15: Pyrimidines

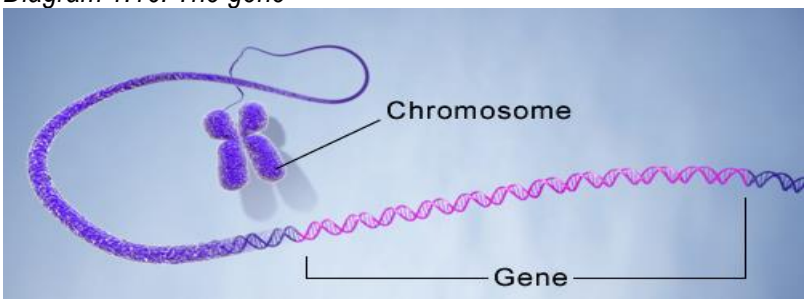


7.0 GENES

Introduction

- A gene is the basic physical and functional unit of heredity
- Contain information needed to synthesize a particular protein molecule
- They are segments of a DNA molecule of a chromosome
- They are an arrangement of different **codons** along the DNA. A codon is a section of 3 successive base pairs (triplet)
- Each codon codes or forms code word (message) for one amino acid
- Determine characteristics living things inherit from their parents e.g. sex, height, hair colour, etc.

Diagram 1.16: The gene



Genetic Code

- A set of instructions by which information encoded in genetic material (DNA or RNA sequence) is translated into proteins by cells
- Set of corresponding codons in RNA and amino acids in proteins
- The code defines a mapping between tri-nucleotide sequences [condons] and amino acids)
- A codon defines a single amino acid e.g. AUG (methionine) and UGG (tryptophan)
- There are 64 codons and 20 essential amino acids

8.0 PROTEIN SYNTHESIS

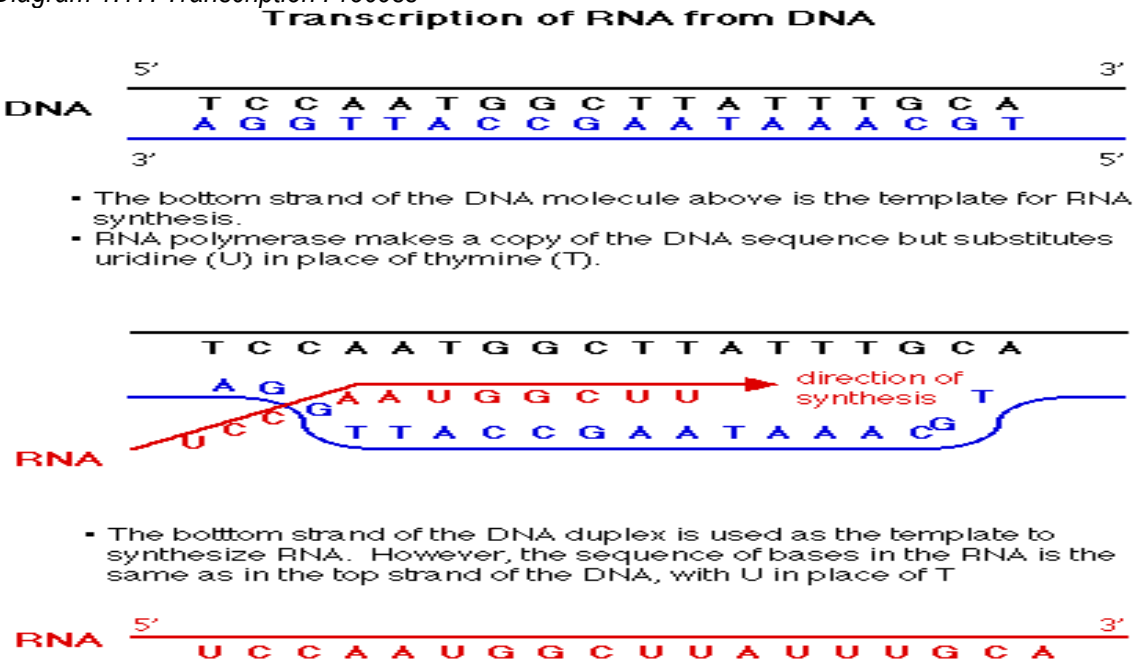
Introduction

- Takes place in **two steps – transcription** and **translation**
- Transcription occurs in the nucleus and involves DNA and mRNA and translation takes place in the cytoplasm and involves the tRNA, rRNA and ribosomes

Transcription

- Is the process of making an RNA copy of a gene sequence from a DNA strand in the cell nucleus - the messenger RNA(mRNA)
- Involves assembly of the RNA chain from activated nucleotides using the DNA strand as a template by adding RNA nucleotides until it encounters a new sequence of DNA nucleotides (**chain terminating sequence**)

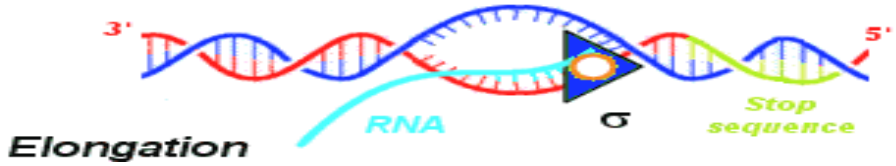
Diagram 1.17: Transcription Process



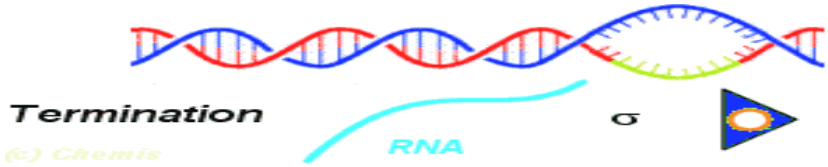
- The chain breaks away from the DNA strands and the DNA chain rebinds with the complementary bases joining up
- The RNA is forced away from the DNA and is released into nucleoplasm
- Takes place in three main steps
  i) RNA Polymerase Binds to DNA
    - DNA is unzipped and partially unwinds into two separate strands

- One strand acts as a template for mRNA synthesis and the other acts as a cover
- RNA polymerase attaches to the DNA at a specific area called the **promoter region**
- RNA nucleotides present in the nucleoplasm attach themselves to the exposed based on the DNA molecule

ii) Elongation
- RNA nucleotides align themselves along the DNA bind to each to each other forming a chainlike strand called ***messenger RNA (mRNA)*** under the influence of *RNA polymerase*
- mRNA strand peels away from the DNA (**a transcript of a gene**)



iii) Termination
- RNA polymerase moves along the DNA until it reaches a terminator sequence.
- When the single helix mRNA is complete it will separate from the DNA and the DNA will re-zip into the double helix
- mRNA is proofread and edited by the **spliceosome** removing non-coding portions (**introns**) and putting together the remaining pieces (**exons – coding regions**)
- Edited mRNA is transported out of the nucleus through the pores in the nuclear envelope.

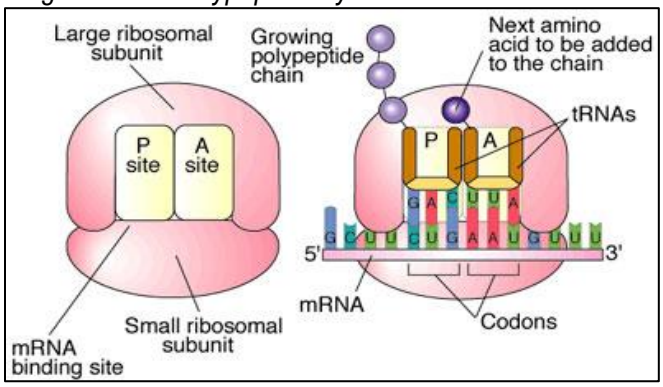


Translation

- Is the process of translating the sequence of a messenger RNA(mRNA) molecule to a sequence of amino acids during protein synthesis in the cytoplasm?
- The mRNA, rRNA and tRNA all come together
- The rRNA consists of two parts – the **large ribosomal unit** (with the A and P sites) and the **small ribosomal** unit for polypeptide synthesis and elongation
- The tRNA molecules have an amino acid attachment site and it also carries an anticodon (complementary nucleotide sequence to a given codon)
- Steps
  i. mRNA attaches to two subunits of ribosomes which sandwich it
  ii. As the mRNA moves through the rRNA from the 5' 9(with AUG) to the terminating codon at the 3' end, the tRNA picks up the appropriate amino acid in the cytoplasm that is coded for by the mRNA that its anticodon matches
  iii. The first codon AUG will start in the A site and the tRNA with the appropriate anticodon (UAC) will meet up to start codon bringing

iv. Once completed the complex moves to the site P site
v. The next codon will move in and a new amino acid brought in
vi. The two amino acids in the rRNA will then form a peptide bond
vii. The first tRNA will disconnect from its UAC amino acid and go back to the cytoplasm while the 2nd tRNA will move to the P site with third tRNA getting to A site
viii. As the ribosomes move along the mRNA strand more amino acids are added until the end of the mRNA.
ix. mRNA is degraded in the cytoplasm by a combination of endonucleases and exonucleases

Diagram 1.18: Polypeptide Synthesis Process



9.0 PATHOGENESIS OF GENETIC DISEASES

- Occur as a result of **inheritance** or **acquisition** of altered genetic material

Talking Point
1. Explain how genetic composition determines causation of disease
2. What determines the magnitude of the clinical features of genetic disorders

9.1. Inheritance of Genetic Diseases

- Mode of inheritance is the manner in which a particular genetic trait or disorder is passed from one generation to the next
- Inheritance patterns trace the transmission of genetically encoded traits, conditions or diseases to offspring
- Genetic conditions caused by a mutation in a single gene follow predictable patterns of inheritance within families
- Modes of inheritance include single gene (Mendelian), multifactorial and mitochondrial

Single gene (Mendelian) Inheritance
- Also referred to as Mendelian inheritance as they follow transmission patterns
- Four types of Mendelian inheritance patterns - autosomal dominant, autosomal recessive, X-linked dominant and x-linked recessive
- Several laws guide Mendelian inheritance
  1. Mendel's First law - The law of segregation
     - States that during the formation of reproductive cells (gametes), pairs of hereditary factors (genes) for a specific trait separate so that offspring receive one factor from each parent
  2. Mendel's Second law - The law of independent Assortment
     - States that chance determines which factor for a particular trait is inherited.

- Each of the two alleles of one gene may combine with either of the alleles of another gene.
- This brings in the concept of probability in that transmission of genes occurs as independent events with different chance of fusion.

3. Mendel's Third law - The law of Dominance
   - States that one of the factors for a pair of inherited traits will be dominant and the other recessive, unless both factors are recessive

Multifactorial Inheritance (Complex, Polygenic)

- Caused by a combination of environmental factors and mutations in multiple genes
- For example, different genes that influence breast cancer susceptibility have been found on chromosomes 6, 11, 13, 14, 15, 17, and 22
- Some common chronic diseases are multifactorial disorders e.g. heart disease, arthritis, Alzheimer's disease, obesity
- Multifactorial inheritance also is associated with heritable traits such as fingerprint patterns, height, eye colour, and skin colour.

Mitochondrial Inheritance

- Is caused by mutations in the non-nuclear DNA of mitochondria
- Mitochondria are unique organelles with multiple copies of a circular chromosome found in the cytoplasm of cells
- Mitochondria are only inherited from the mother's egg, thus only females can transmit the trait to offspring, however they pass it on to all of their offspring
- The primary function of mitochondria is conversion of molecule into usable energy
- Many diseases transmitted by mitochondrial inheritance affect organs with high-energy use such as the heart, skeletal muscle, liver, and kidneys

9.2. Acquisition of Genetic Diseases

- Caused by acquired mutations or changes in parts of the DNA
- Mutation due to exposure to environmental factors – drugs, radiations, metals, infections
- Only become heritable if the mutation occurs in the germ line (germline cells include the gametes and the cells that produce the gametes)
- A person suffers from a genetic condition may be determined to some degree by environmental factors

10.0 PATHOPHYSIOLOGY OF GENETIC DISEASES

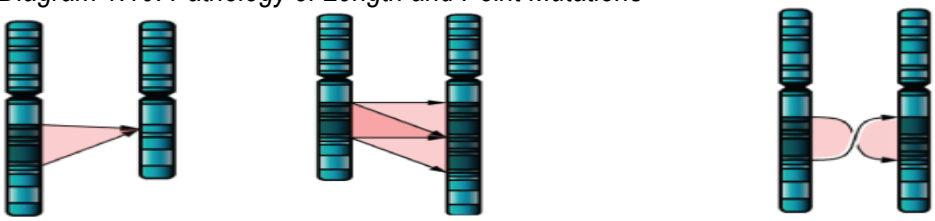
1) Mutation

- Mutation is a permanent alteration in the DNA sequence that makes up the gene
- May be spontaneous or induced
- Classification
  i) Hereditary mutations
     - Inherited from a parent and are present throughout a person's life
     - Also called germ-line mutations because they are present in the parent's egg/sperm
  ii) Acquired (somatic) mutations
     - Happen in a single cell early in embryogenic development

- Genetic changes are not present in a parent's egg or sperm cells

- Broadly there are two types of mutations namely length and point mutations
  i) Length mutations involve gain or loss of genetic material through deletions, duplications and insertions
  ii) Point mutations result in alteration of the genetic code with no gain or loss of genetic material where a single nucleotide base is replaced by a different nucleotide base
- Mistake results in an incorrect polypeptide chain and eventually protein thus affecting the structure and/or function of the protein in question and process the protein is/are involved in
- There are four categories of mutation
  i) DNA base substitution, insertion and deletion
  ii) Unequal crossing-over and related structural modifications of chromosomes
  iii) Partial or complete gene inversion and duplication
  iv) Irregular number of chromosomes

Diagram 1.19: Pathology of Length and Point Mutations



Deletion Duplication/insertion Inversion

2) Protein synthesis defects

- Defects in protein synthesis results in enzyme defects/deficiencies, receptor and structural protein defects

11.0 CLASSIFICATION OF GENETIC DISORDERS

1) Monogenic (mendelian) disorders
   a) Autosomal Disorders - autosomal dominant disorders and autosomal recessive disorders
   b) Sex (X-linked) disorders - X-linked dominant disorders and X-linked recessive disorders
2) Chromosomal aberrations
   a) Numerical abnormalities – aneuploidy and polyploidy
   b) Structural abnormalities - translocations, deletions and inversions
3) Polygenic disorders (multifactorial inheritance)
   a) Diabetes mellitus (Endocrine pathology)
   b) Hypertension (Circulation)
   c) Gout (discussed here + see Crystals)
   d) Schizophrenia (Psychiatry)
   e) Congenital heart disease - certain forms (Heart)
   f) Some types of cancer (ovarian, breast, colon)
4) Mitochondrial Disorders

Study Questions

1) **Explain the difference and relationship between congenital disease and genetic disease**
2) **Explain the following terms - Alleles, chromosome, gene, dominant and recessive**

TOPIC 2: AUTOSOMAL SINGLE GENE DISORDERS

Learning Objectives

- At the end of the lesson the learner will be able to explain the pathology of single gene autosomal dominant disorders

1.0 INTRODUCTION

- Result from mutation of a single gene that has a large effect
- Mutations may occur in one or both members of a pair of genes causing a permanent change in the DNA of the cell
- Autosomal disorders are usually carried on the somatic cells and they are usually transmitted to the next generation

2.0 CLASSIFICATION OF SINGLE GENE DISORDERS

- Single gene disorders are classified according to whether the
    i. Location of the mutation
        a. On an autosome – Autosomal disorders
        b. On the sex chromosome – Sex linked disorders (X and Y Linked disorders)
    ii. Number of mutant genes
        a. Heterozygous - one mutant and one normal gene in a pair
        b. Homozygous - both members of the pair are affected
    iii. Genotype expression
        a. Recessive disorders
        b. Dominant disorders

3.0 AUTOSOMAL DISORDERS

- The mutation occurs on the autosomes
- Can be classified as autosomal dominant disorders and autosomal recessive disorders

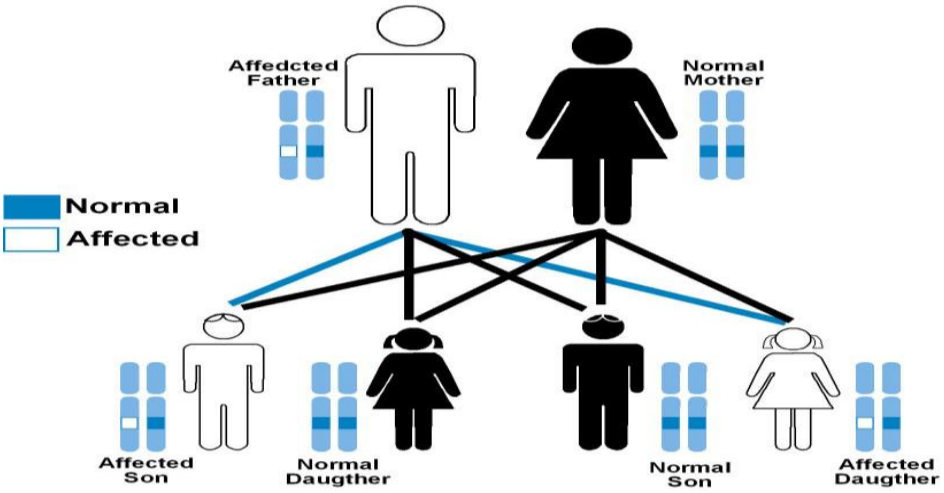
4.0 AUTOSOMAL DOMINANT DISORDERS

4.1. Introduction

- Requires that only one mutant gene be passed onto the child from the mother or father and only occurs if one or both parents have the resulting genetic disease
- Mutated gene determining the abnormal phenotype **is dominant to that coding for normal development**
- Presence of the abnormal gene leads to disease that occur in every generation of an affected family or may not be transmitted to the next generation
- Mutations affect structural proteins e.g. collagen or regulatory proteins such as receptors
- Onset of clinical features is later than in autosomal recessive disorders

4.2. Transmission (Mode of Inheritance) of Autosomal Dominant

Diagram 2.1: Mode of Inheritance



4.3. Pathology

- Main effects of autosomal dominant disorders result from abnormalities arising in **proteins** responsible for cell membrane, enzymes, enzyme inhibitor receptors, transport of oxygen, ions, extra cellular structures of cells, homeostasis and growth regulation

4.4. Examples

- **Achondroplasia**; Adult polycystic kidney; Familial hypercholesterolaemia; Familial polyposis coli; **Hereditary spherocytosis**; Huntington disease; **Marfan's syndrome;** **Neurofibromatosis** (von Recklinghausen's disease); **Osteogenesis imperfect**; Von Willibrand disease

5.0 INDIVIDUAL AUTOSOMAL DOMINANT DISORDERS

1. ACHONDROPLASIA

- Achondroplasia means without cartilage formation
- There is **failure of ossification of bones** at the epiphyseal plates of long bone resulting in severe short-limb dwarfism
- Long bones are abnormally short but the skull grows normally leading to a relatively large skull

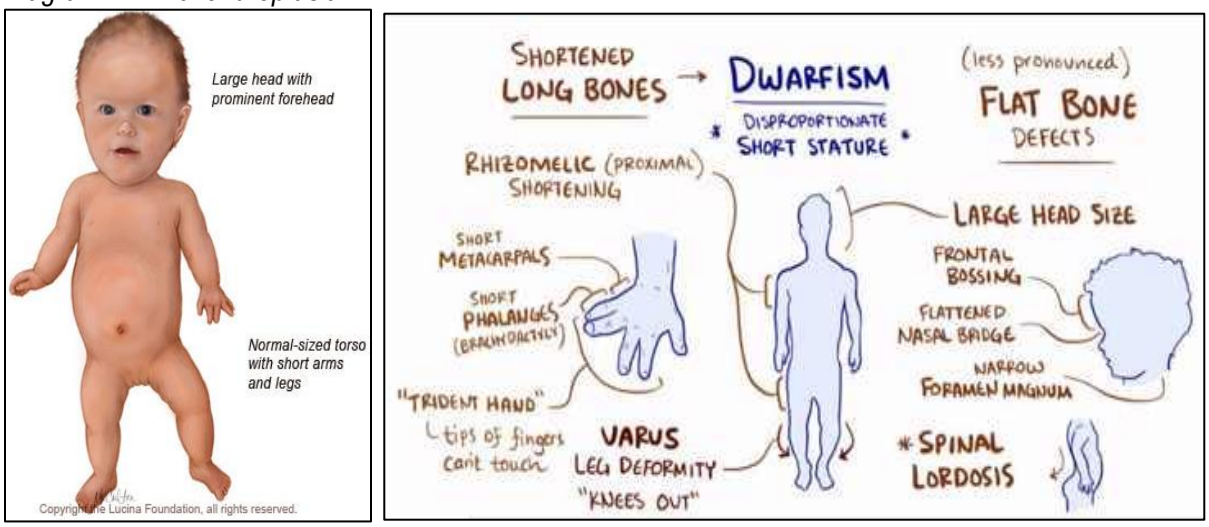
Pathophysiology

- Caused by mutations in the FGFR3 gene (located on chromosome 4 and 14) which encodes a protein called **Fibroblast Growth Factor Receptor 3**(receptor site of action of a major growth factor responsible for lengthening bones)
- Retards growth of long bones resulting in abnormally shaped shorter bones and thus a shorter stature

Risk Factors

- A parent with achondroplasia
- Advanced paternal age causing spontaneous mutations

Diagram 2.2: Achondroplasia



Clinical Features

- Short stature, a long trunk, and shortened limbs, which are noticeable at birth
- Large head with a prominent forehead and underdeveloped portions of the face
- Knock-knee or bowed-leg deformity, hands and the feet appear large, but the fingers and toes are short and stubby; excessive curve of the lower back and a waddling walking pattern
- Dental problems and weight control problems
- Dental problems from overcrowding of teeth
- Neurologic and respiratory problems
- Fatigue, pain, and numbness in the lower back and the spine

2. HEREDITARY SPHEROCYTOSIS

- Caused by intrinsic defects in the red cell membrane that render the red cells spheroid, less deformable and vulnerable to spleenic sequestration

Cause

- Mutation of the gene **SPTBN1** on chromosome 1 which results in deficiency of the structural protein of the red cell membrane called **spectrin** resulting in spheroidal contour and smaller size of red cells that are not flexible

Pathology

- Defective cell membrane of the red blood cells

Pathogenesis

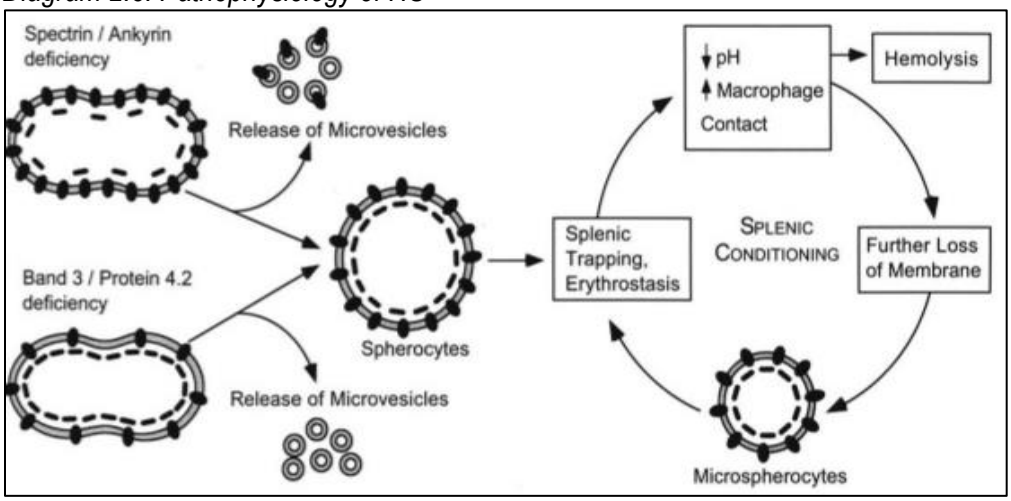
- Inheritance of mutant **SPTBN1** gene that codes for structural protein spectrin

Pathophysiology

- Defects in **membrane structural proteins** result in the weakening of vertical linkages between membrane surface proteins and the phospholipid layer
- Reduced phospholipid and cholesterol content favours excessive permeability to Na^+ resulting in loss of surface membrane area relative to volume

- This alters the shape of the red cells to become spherical with reduced flexibility (**increased rigidity**) and increased permeability (causes osmotic fragility)
- This process is countered by increased glycolytic process producing ATP needed by Na pump in order to pump Na ions from the cell resulting in an increase cell turnover and loss of membrane lipid producing micro-spherocytes
- In the spleen there is less glucose available hence the destruction of cells due to lack of deformability characteristic to enhance their passage in the red pulp of the spleen
- Red cells with decreased deformability are retained in the spleenic pulp for unduly long time or the cells find the environment of acidic pH and low glucose concentration in the spleenic pulp unfavourable.

Diagram 2.3: Pathophysiology of HS



Clinical Features

- Features of haemolytic anaemia – pallor, jaundice, hyper-bilirubinaemia, increased reticulocyte count, splenomegaly, gall stones

3. OSTEOGENESIS IMPERFECTA (OI)

- OI means imperfectly formed bone (also called Brittle bone disease - disorder of bone fragility)
- Inheritance can be autosomal-dominant, autosomal-dominant with new mutations, or autosomal-recessive

Pathogenesis

- Inheritance of a mutant gene
- Results from mutations on genes COL1A1 (on chromosome 17) and COL1A2 (on chromosome 7) which carry instructions for making type 1 collagen
-

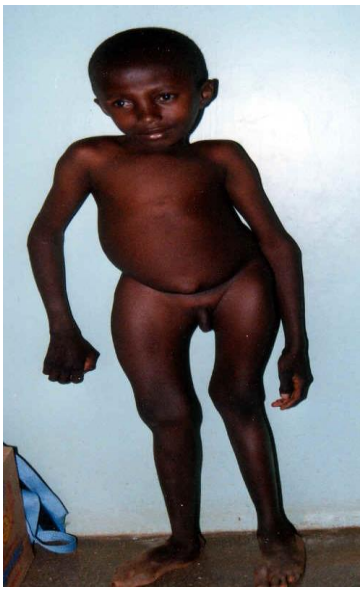
Pathophysiology

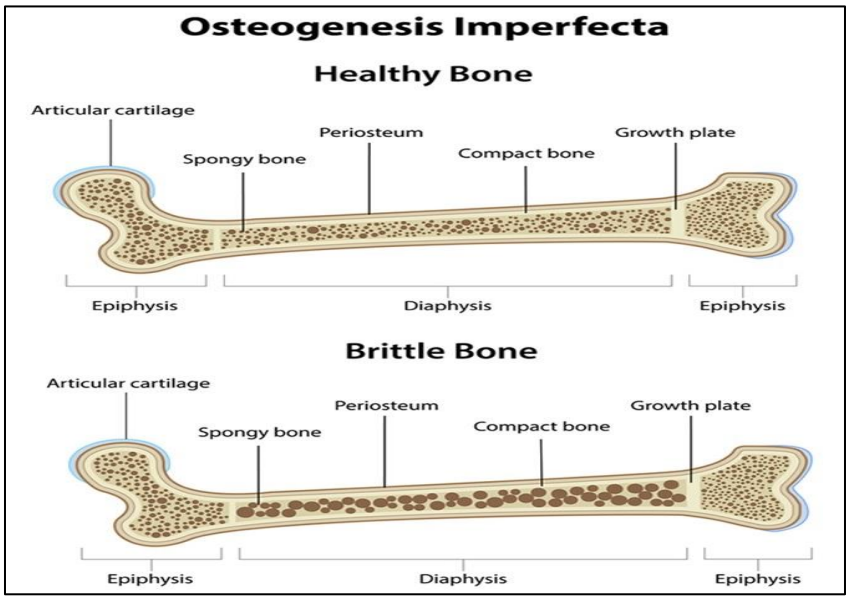
- Mutations result in **failure of synthesis of collagen** leading to formation of **brittle bone** due to failure of osteoblasts to synthesize bone tissues

Pathology

- Defective bone formation – brittle bone

Diagram 2.3: Osteogenesis Imperfecta





Types

Type	Description and Pathology
1	• Mildest and most common form of brittle bone disease • Body produces quality collagen but not enough resulting in mildly fragile bones • Typically have bone fractures due to mild traumas (much less common in adults) • Teeth may also be affected, resulting in dental cracks and cavities
2	• Most severe form of brittle bone disease (can be life-threatening) • Body either doesn't produce enough collagen or produces collagen that's poor quality • Cause bone deformities (a narrowed chest, broken or misshapen ribs), or underdeveloped lungs
3	• A severe form of brittle bone disease that causes bones to break easily • Body produces enough collagen but its poor quality • Bone deformities are common and may get worse as your child gets older
4	• Most variable form of brittle bone disease with symptoms range from mild to severe • Body produces enough collagen but the quality is poor • Children with type 4 OI are typically born with bowed legs (bowing tends to lessen with age)

Clinical Features

- Four major clinical features
  i) Osteoporosis with abnormal bone fragility – weak bones, pathological fractures, bone deformities, bow legs (genu vara) and arms, kyphosis, scoliosis
  ii) Blue sclera
  iii) Dentinogenesis imperfect
  iv) Hearing impairment – deafness
- Other features include ligamentous laxity and hypermobility of joints, short stature, and easy bruising, flat feet
- Heart defects and respiratory defects

Complications

1) Multiple pathological fractures
2) Hearing loss
3) Heart Failure
4) Recurrent Chest infections
5) Deformities – chest, spinal cord

4. MARFAN'S SYNDROME

- A genetic disorder that causes connective tissues—which provide substance, shape and support to many parts of the body—to be weaker than they should be
- Often weakens the aorta creating the risk of an aortic tear, leak or aneurysm
- Results from abnormality of the structural protein - collagen an essential connective tissue in the body affecting the skeleton, eyes and the cardiovascular system
- A serious condition that can affect many parts of the body - including the heart and blood vessels, lungs, bones, joints, eyes and skin.

Pathology

- Inheritance of mutant FBN1 which codes for **glycoprotein fibrilin-1**

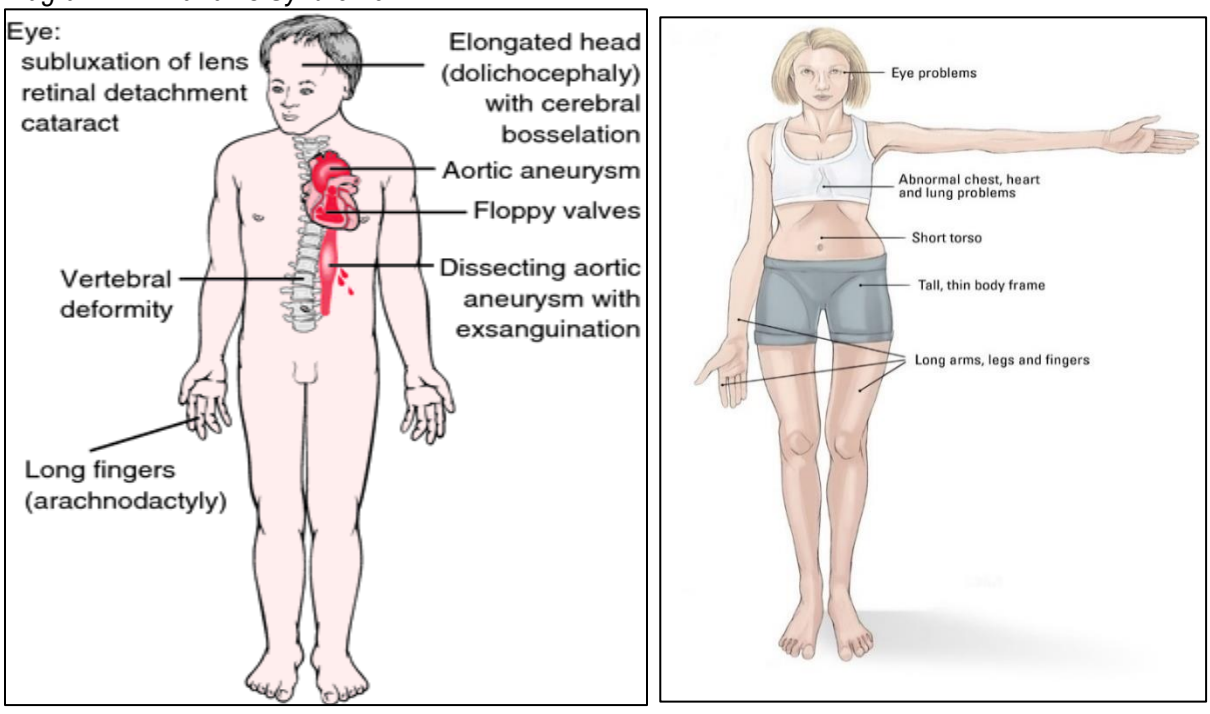
Pathophysiology

- Glycoprotein fibrilin-1 is the main constituent of the microfibrils of the extracellular matrix glycoprotein
- Reduced or abnormal fibrilin-1 leads to tissue weakness, increased transforming factor signalling and loss of cell-matrix interactions

Pathology

- Poor formation of the extracellular matrix

Diagram 2.4: Marfan's Syndrome



Clinical Features

- Tall and slender build with disproportionate long arms, legs, fingers and toes
- Exceptionally long extremities (lower and upper limbs), long tapering fingers and toes (arachnodactly)
- Heart murmurs (weakness of heart valves – AV valves and aortic)
- Extreme near-sightedness - ectopia lentis (dislocation or subluxation of the lens)
- Flat feet and an abnormally curved spine (laxity of joints resulting in hyper extensibility of the joints and spinal deformities such as kyphosis (forward bending) and scoliosis (lateral bending)
- A high arched palate and crowded teeth
- Pectus excavatum or cavinatum

5. NEUROFIBROMATOSIS

- NF is a genetic disorder causing lesions in the skin, nervous system and skeleton
- Characterized by changes in skin colouring (pigmentation) and growth of tumours affecting the brain, spinal cord, nerves and skin

Pathophysiology

- Result from a mutation in or deletion of the **NF1** gene located on chromosome 17q (von Recklinghausen disease) or NF2 (merlin protein) located on chromosome 22p
- NF1 codes for neurofibromin protein which serves as a tumour suppressor thus decreased production results failure to regulate growth of cells leading to formation of tumours on the nerves
- There are three types –
  i) Type 1 - von Recklinghausen's disease
     - More common form Neurofibromin
  ii) Type 2 - presents with multiple neural tumours involving nerve trunks in the skin and internal organs

Diagram 2.6: Neurofibromatosis Type 1

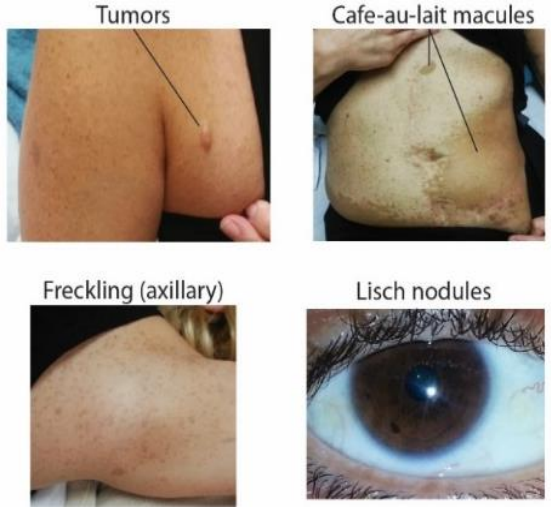
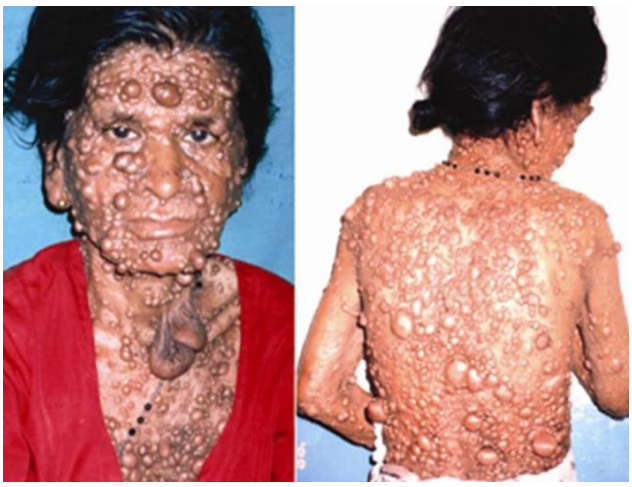


Diagram 3.7: Neurofibromatosis Type 2



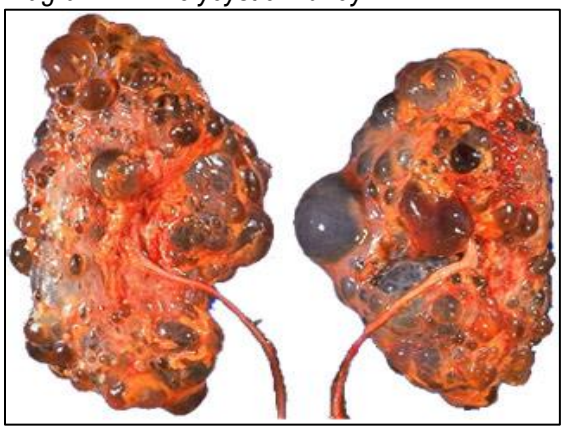
Clinical Features

1) Dermal features - Café-au-lait spots (light brown skin spots), axillary or inguinal freckles, skin-fold freckling, hypopigmented macules, urticaria pigmentosa, naevus anaemicus and benign cherry angiomas, juvenile xanthogranulomas (benign orange papules)
2) Neurofibromas - may be in the skin or subcutaneous tissues; cutaneous neurofibromas
3) Ocular problems
   - Tumours of the optic nerve (gliomas) occur
   - Most common presentation is asymmetrical visual field defects.
   - In NF2, posterior subcapsular or juvenile cataracts can precede CNS symptoms.
4) Skeletal problems
   - Congenital pseudoarthrosis, bowing of the tibia is the most common presentation, thinning and angulation of long bones with prominence of the anterior tibia and progressive deformity can occur throughout early childhood, bowing of the forearm (less common), fractures (spontaneously or after trivial injury), asymmetrical thoracic cage with flaring or prominence of the inferior ribs, scoliosis (with or without kyphosis), osteoporosis
5) Neurological problems
   - Develop from tumours and malformations, including aqueduct stenosis
   - Skull deformity can lead to pulsating exophthalmos.
   - Severe scoliosis can deform the spine, causing cord compression and respiratory compromise
   - Pressure on peripheral and spinal nerves and the spinal cord will also have neurological sequel
   - Epilepsy (mild)
   - Acute or progressive sensory disturbance, motor deficit and inco-ordination or sphincter disturbance, which may indicate an intracranial lesion or spinal cord compression.
6) Cardiovascular problems
   - Congenital heart disease (pulmonary stenosis and hypertension)
   - Carotid artery stenosis/occlusion and cerebral aneurysm may occur with NF1.
7) Gastrointestinal (GI) –
   - Abdominal bloating, pain, dyspepsia, haemorrhage and constipation may suggest a GI neurofibroma, anaemia and GI bleeding.
8) Psychological - disfigurement and the unpredictable course of NF may cause anxiety & depression
9) Endocrine - precocious puberty occurs and is associated with tumours of the optic chiasma
10) Obstetric
   - Increased risk of perinatal complications in NF1, higher stillbirth rate, IUGR
   - During pregnancy, neurofibromas may grow in size and number and there is the risk of cord compression if spinal plexiform neurofibromas expand
   - Pelvic neurofibromas may impede delivery of the baby

6. POLYCYSTIC KIDNEY (PKD)

- A large portion of the renal parenchyma is changed into cysts of variable size
- There are 2 forms namely adult PKD (autosomal dominant disease) and infantile PKD (autosomal recessive disease)
- Occurs due to mutations of genes PDK1 and PDK2 located on chromosome 16

Diagram 2.7: Polycystic Kidney



Clinical Features

- Dull ache in the lumbar regions, haematuria, passage of blood clots in urine, renal colic, hypertension, urinary tract infection and progressive chronic renal failure with polyuria and proteinuria

7. VON WILLIBRAND DISEASE

- Is an inherited bleeding disorder that affects both sexes equally

Pathophysiology

- Results from mutation of ***vWF*** gene is located on the short arm of chromosome 12
- Found on the megakaryocytes and endothelial cell
- The mutation causes quantitative or qualitative abnormality of Von Willebrand (vWB) VIIIR factor which is a plasma glucoprotein
- vWB factor is synthesized by vascular endothelium and megakaryocytes and its abnormalities include reduced synthesis of all oligomers associated with amino acid defects, which prevents formation of complexes.
- Functions of the glycoproteins include
    - Platelet adhesion to vascular sub endothelium hence its deficiency results in prolonged bleeding time, low platelet adhesion (this differentiates it from Haemophilia)
    - Carrier protein for Factor VIII that is a coagulation protein and protects it from premature destruction.

Clinical Features

- Anaemia resulting from excessive bleeding from cuts, injuries, epistaxis, gastro-intestinal tract, gums, menorrhagia and haemoarthrosis

SUMMARY (TAKE AWAY)

Disorder	Gene affected	Pathology	Main Features
Achondroplasia			
Adult polycystic kidney			
Hereditary spherocytosis			
Marfan's syndrome			
Neurofibromatosis			
Osteogenesis imperfecta			

TOPIC 3: AUTOSOMAL RECESSIVE DISORDERS (SICKLE CELL & THALASSAEMIA)

Objectives

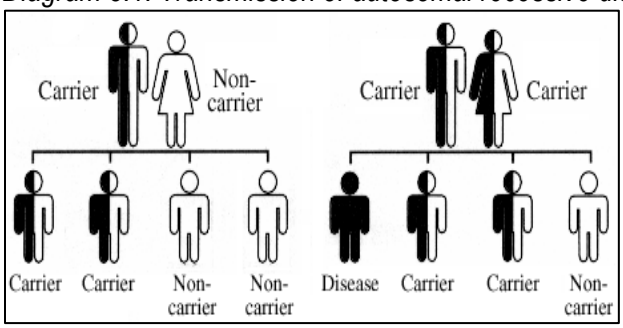
At the end of the lesson the learner will be able to explain the pathology of single gene autosomal recessive disorders (sickle cell and thalassemia)

1.0 INTRODUCTION

- Require that both copies of the inherited gene carry mutations
- Mutations may be passed on by carriers
- Typically, not seen in every generation of an affected family
- **Examples** include - **Albinism**; Congenital deafness; **Cystic Fibrosis**; Haemoglobinopathies – **Thalassemia and Sickle cell disease**; Storage disorders e.g. Gaucher's disease; Wilson's disease

2.0 TRANSMISSION (MODE OF INHERITANCE)

Diagram 3.1: Transmission of autosomal recessive disorders

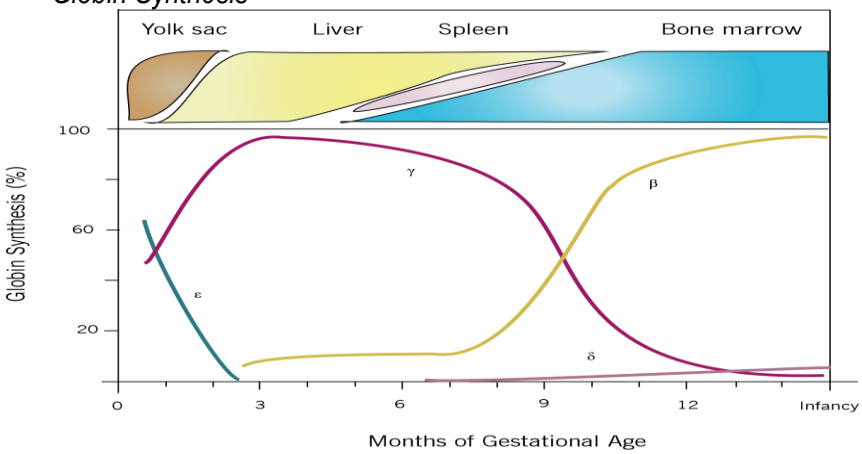


3.0 HAEMOGLOBINOPATHIES

3.1. Haemoglobin

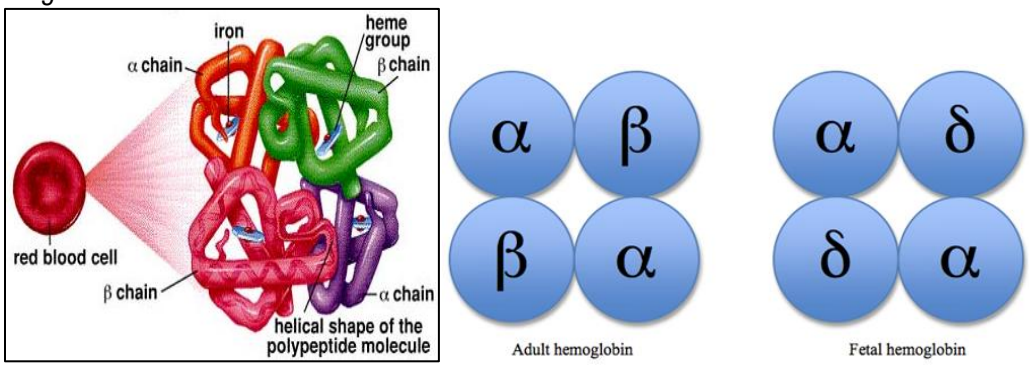
- Haemoglobin comprises of the haem component (made up of pyrrole rings and contains Fe) that transports oxygen and globin (made up of chains of amino acids and facilitates oxygen transportation by the haem by providing a suitable environment)

Globin Synthesis



- Four polypeptide chairs exist viz□□□□□γ, □□determined by sequences of amino acids).
- Normal Hb[2] consists of a pair of alpha□□□□□chains and another pair of either beta □□□chains or gamma □□□chains or delta (□) chains
- Distribution of Hb types in a normal red blood cell - HbA (adult) which accounts for, 96-98%, HbF (foetal) - 0-10% and HbA_2 that is 1.5 – 3%
- Haemoglobin molecule undergoes structural changes during oxygen uptake & release
- In a deoxygenated state the beta chains rotate apart facilitating the functional properties of haemoglobin
- Important features of the **oxygen transport system** are:
  1) Hb has a high affinity for oxygen in the lungs and a low affinity for oxygen in tissues.
  2) Myoglobin has a higher affinity for oxygen than Hb at low oxygen concentrations
  3) Haemoglobin transports carbon dioxide back to the lungs where it is expelled.
  4) Haemoglobin releases its oxygen preferentially to exercising muscle rather than to resting muscle

Diagram 3.2: Structures of Haem



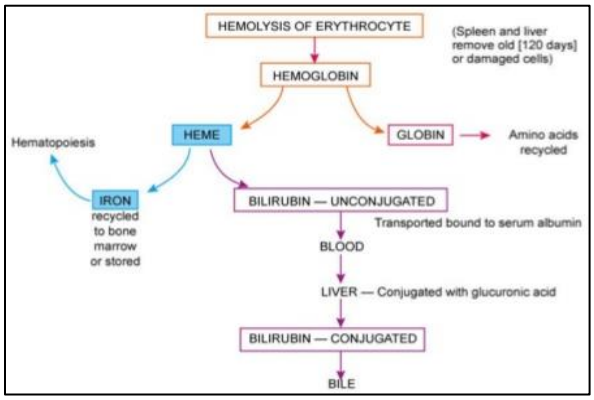
HbA (2□□and 2□); HbA_2 (2□ and 2□□ and HbF (2□ and 2□)

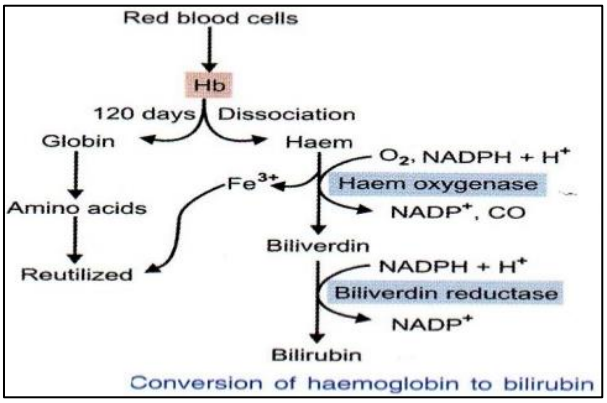
Table: Differences Between Adult and Foetal Haemoglobin

	Adult Hb	**Foetal Hb**
1.	Contains 2□ and 2□□chains	Contains 2□ and 2□ chains
2.	□ chain contains 146 amino acids	□ chain contains 146 amino acids but 37 of which differ from chain of HbA
3.	Normally 98% in adults	Normally absent in adults but present in the foetus
4.	Saturates at a relatively high oxygen tension	Saturates at low oxygen tension
5.	Binds with 2-3 DPG	Binds less avidly with 2-3 DPG
6.	Not resistant to the action of alkali	Resistant to action of alkali

[2] Haemoglobin

Breakdown of Hb





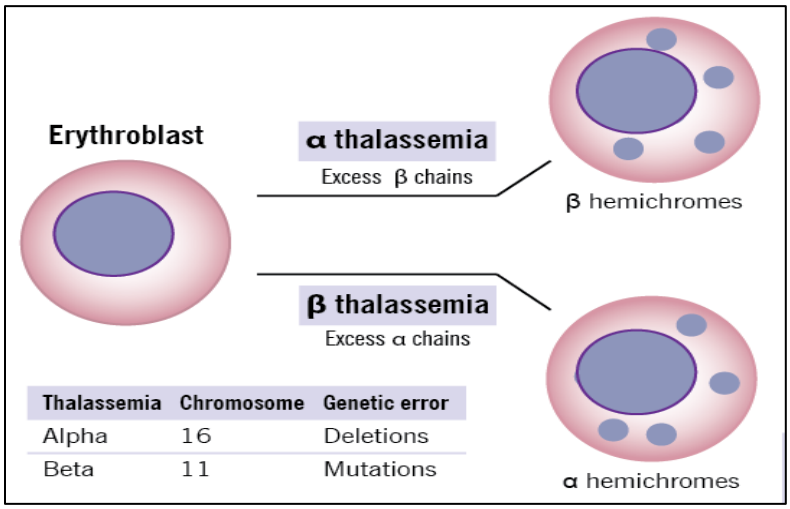
4.0 THALASSEMIA

Introduction

- An inherited disorder associated with abnormal haemoglobin and anaemia
- Normal adults have a major component of HbA (90%), minor HbA_2 (2–3%) and HbF
- Main haemoglobin in foetal life is HbF and traces of which are found in normal adults

Pathogenesis

- Thalassemia results when mutations affecting the genes involved in Hb biosynthesis lead to decreased Hb production. The changes could be from mutations or deletions
- Clinical phenotype results from both the diminished amount of the particular globin chain as well as from the resultant chain imbalance that occurs because of normal production of the other globin chain.

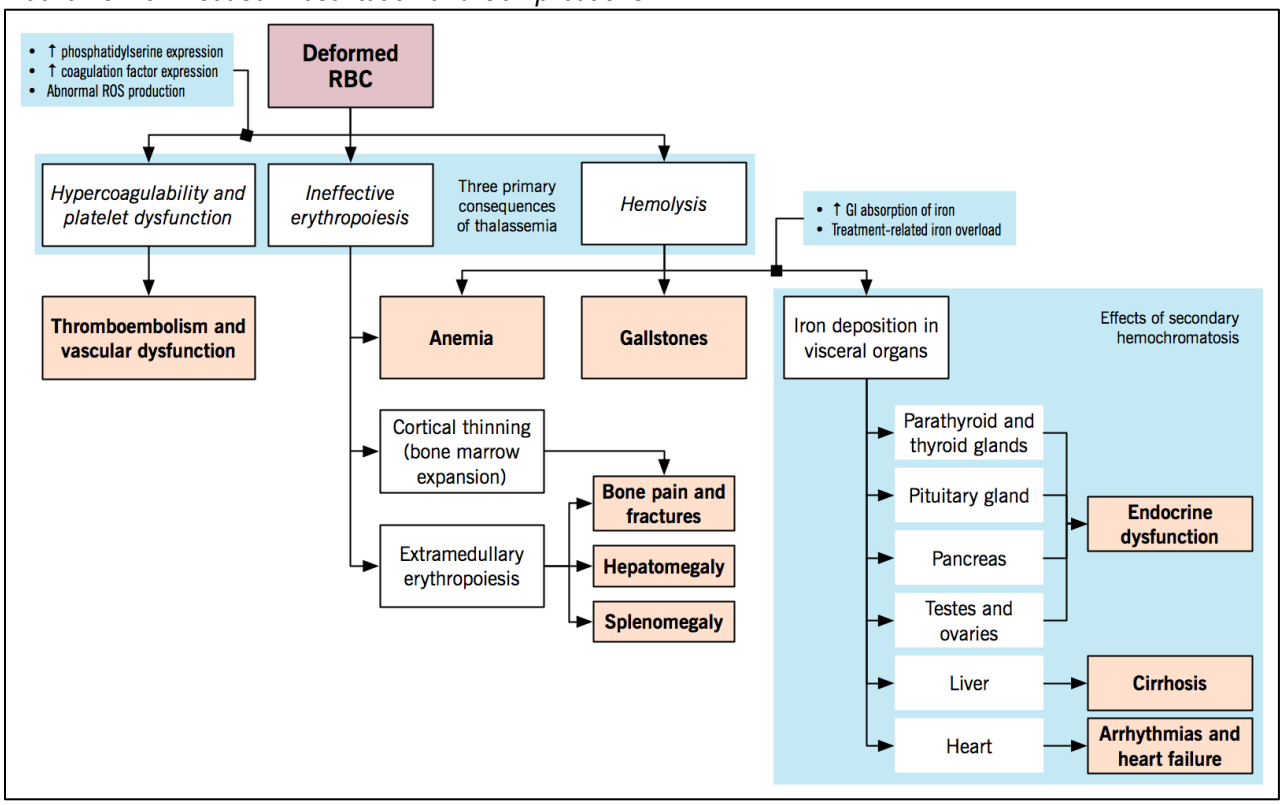


Thalassemia	Chromosome	Genetic error
Alpha	16	Deletions
Beta	11	Mutations

Pathophysiology

- Result from mutations that involve either the □or □ globin genes
- In □□thalassemia there is reduced synthesis of □globin chains resulting in diminished synthesis of HbA
- There are three varieties of□□thalassemia namely – □□*thalassemia major, intermedia and minor*.
- □□Thalassemia is characterized by reduced or absent □-globin chains

Mechanism of Disease Presentation and Complications



Clinical Features

- Pallor, irritability, growth retardation, abdominal swelling – splenomegaly and hepatomegaly, jaundice and facial and skeletal changes

Alpha Thalassemia

- Results from inheritance of two genes namely HBA1 and HBA2 as a result of deletions
- **Results in reduced production of** haemoglobin.
- There are two types of alpha-thalassemia namely Hb Bart and HbH
- Hb Bart is the more severe form characterized by hydrops fetalis; severe anaemia; hepatosplenomegaly; heart defects; and abnormalities of the urinary system or genitalia. Most babies with this condition are stillborn or die soon after birth.
- HbH causes a mild disease associated with mild to moderate anaemia; hepatosplenomegaly; jaundice; or bone changes.

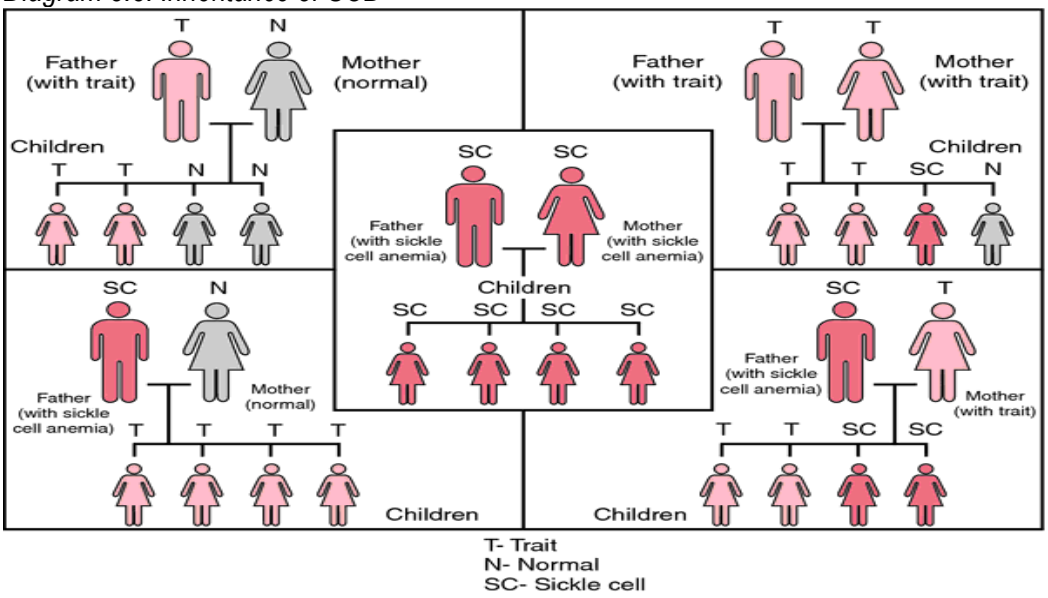
5.0 SICKLE CELL DISEASE (SCD)

Introduction

- ***Sickle Cell Disease (SCD)*** is a hereditary disorder of hemoglobin synthesis caused by a mutation in the globin gene that changes the sixth amino acid from glutamic acid to valine resulting in abnormal sickling (rigid, inflexibled and sickle-shaped) of Red Blood Cells (RBCs) under low oxygen conditions
- Sickle cell anemia is the homozygous state for Hb-S gene, while the heterozygous state is known as Sickle cell trait

- The orthopaedic manifestations of SCD are mainly attributable to the impairment of local circulation due to the clumping of sickle cells.
- Sickle cell disease describes a group of inherited blood disorders associated with an abnormal haemoglobin characterized by chronic anaemia, painful events (crises), and various complications due to associated tissue and organ damage
- Characterized by red blood cells that assume an abnormal, rigid, sickle shape (normal red blood cells with normal haemoglobin are smooth, disk-shaped, and flexible)
- Normal red blood cells typically live 90-120 days, but sickle cells only survive 10-20 days

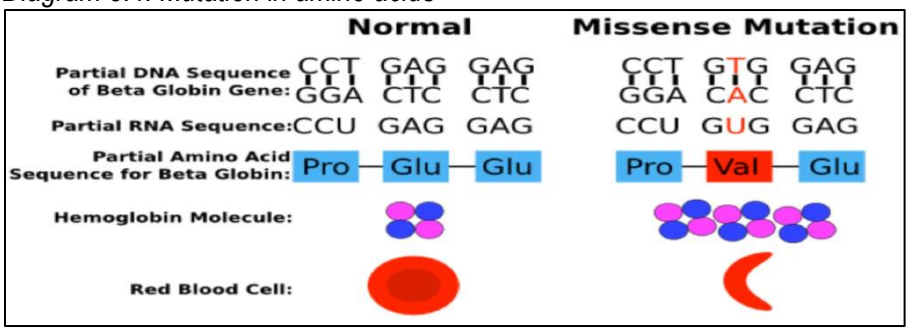
Diagram 3.3: Inheritance of SCD



Pathogenesis

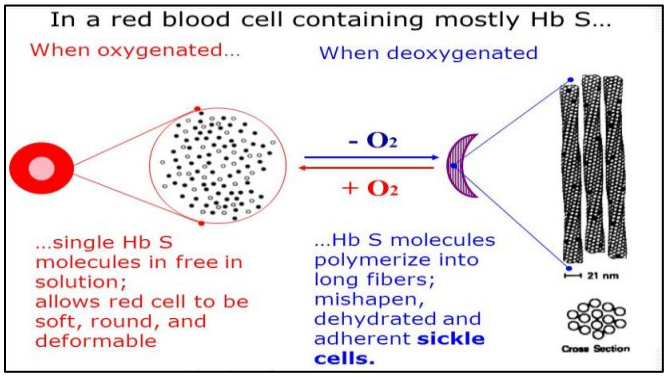
- SCD is an inherited, autosomal recessive, condition caused by point mutation in the β-globin gene on chromosome 11 (single nucleotide change (GAT to GTT)
- Mutation causes the sixth amino acid to be changed from glutamic acid to valine
- Symptoms usually do not develop until the age of 6-12 months because of high levels of circulating foetal haemoglobin
- After infancy, erythrocytes of patients with sickle cell anaemia contain approximately 90% haemoglobin S (HbS), 2-10% hemoglobin F (HbF), and a normal amount of minor fraction of adult hemoglobin (HbA2). Adult hemoglobin (HbA), which usually gains prominence at the age of 3 months, is absent

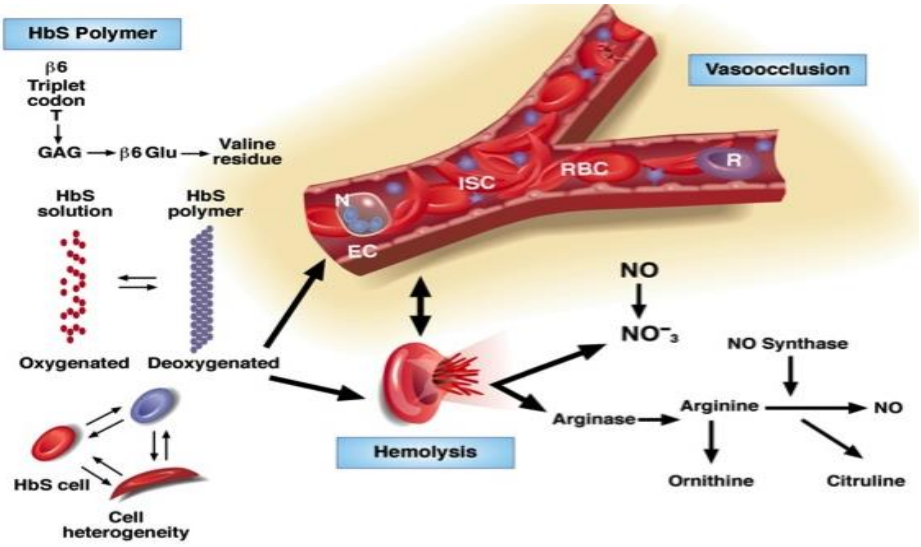
Diagram 3.4: Mutation in amino acids



Pathophysiology

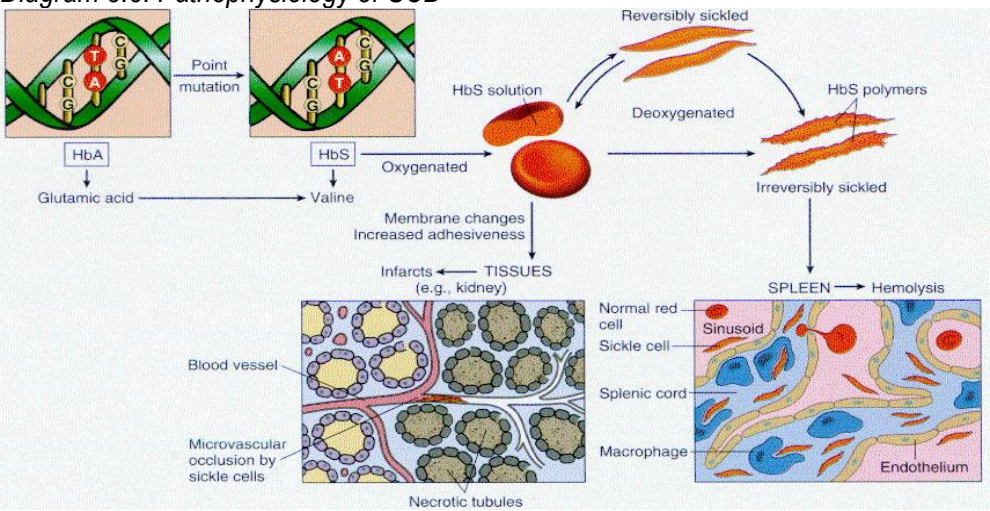
- Normal RBCs are quite elastic, which allows the cells to deform to pass through capillaries
- Loss of red blood cell elasticity is central to the pathophysiology of sickle-cell disease
- Resultant haemoglobin (called HbS) has abnormal physiochemical properties, and is prone to polymerization with other haemoglobin molecules under conditions of low oxygen tension
- The normally freely flowing cytosol of red cells become viscous making the red cell much less deformable and impairing its ability to traverse tight capillary beds
- As HbS continues to **polymerize the entire RBC is deformed giving the characteristic sickle shape**





- Under deoxy conditions, HbS undergoes marked decrease in solubility, increased viscosity, and polymer formation which distorts red blood cells into a sickle shape and decreases their elasticity
- Low-oxygen tension promotes red blood cell sickling and repeated episodes of sickling damage the cell membrane and decreases the cell's elasticity
- The cells fail to return to normal shape when normal oxygen tension is restored and these rigid blood cells are unable to deform as they pass through narrow capillaries, leading to vessel occlusion and ischaemia
- Low oxygen tension in the spleen accelerates sickling & destruction of red blood cells
- The bone marrow attempts to compensate by creating new red cells, it does not match the rate of destruction resulting in haemolysis and subsequently anaemia

Diagram 3.5: Pathophysiology of SCD



Pathology

- Changes in RBCs result in a disease with cardinal signs such as hemolytic anemia, painful vaso-occlusive crisis and multiple organ damage from micro infarcts, including heart, skeleton, spleen, and central nervous system
- When the alpha chains move apart to give up oxygen the amino acid substitution leads to locking of the adjacent ends of alpha chains with the abnormal beta chains
- Hb molecules become stuck in rows distorting the red cells forming sickle shapes in deoxygenated blood which facilitates destruction of red blood cells (haemolysis)
- Hbs gives up oxygen more readily than HbA hence provides good tolerance to exercise at low Hb levels
- Intravascular sickling of red blood cells leads to multi-organ dysfunction

Mechanisms of Haemolysis

1) Extravascular haemolysis accounts for 2/3 of the destruction of red cells and mediated by IgG antibodies and carried out by the macrophages (phagocytosis)
2) Intravascular haemolysis accounts for 1/3 of cases of red cell destruction and usually fuelled by increased mechanical fragmentation and changes in proteins in the cell membranes

Diagram 3.6: Consequences of Sickling

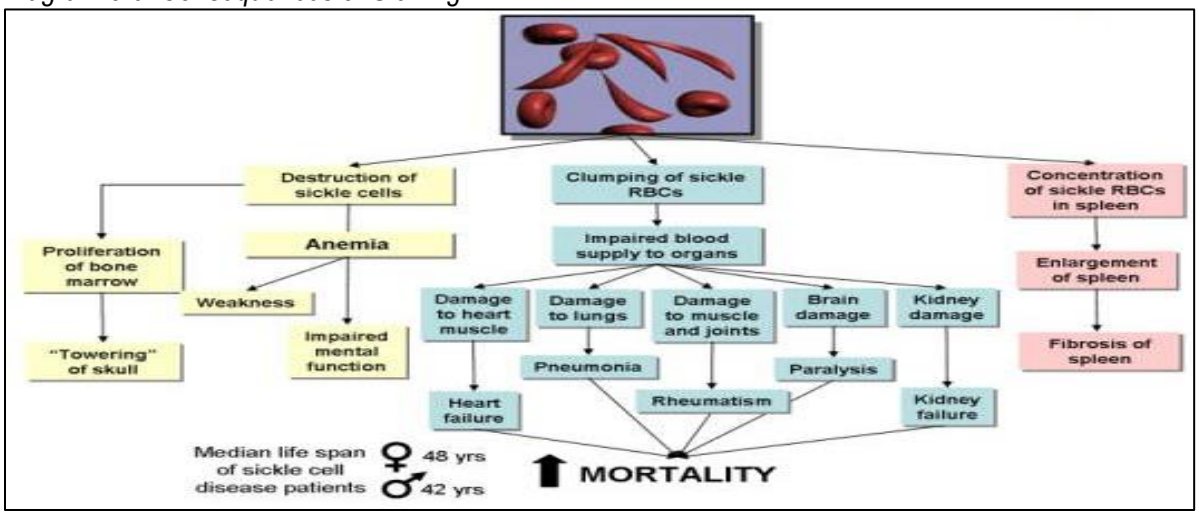
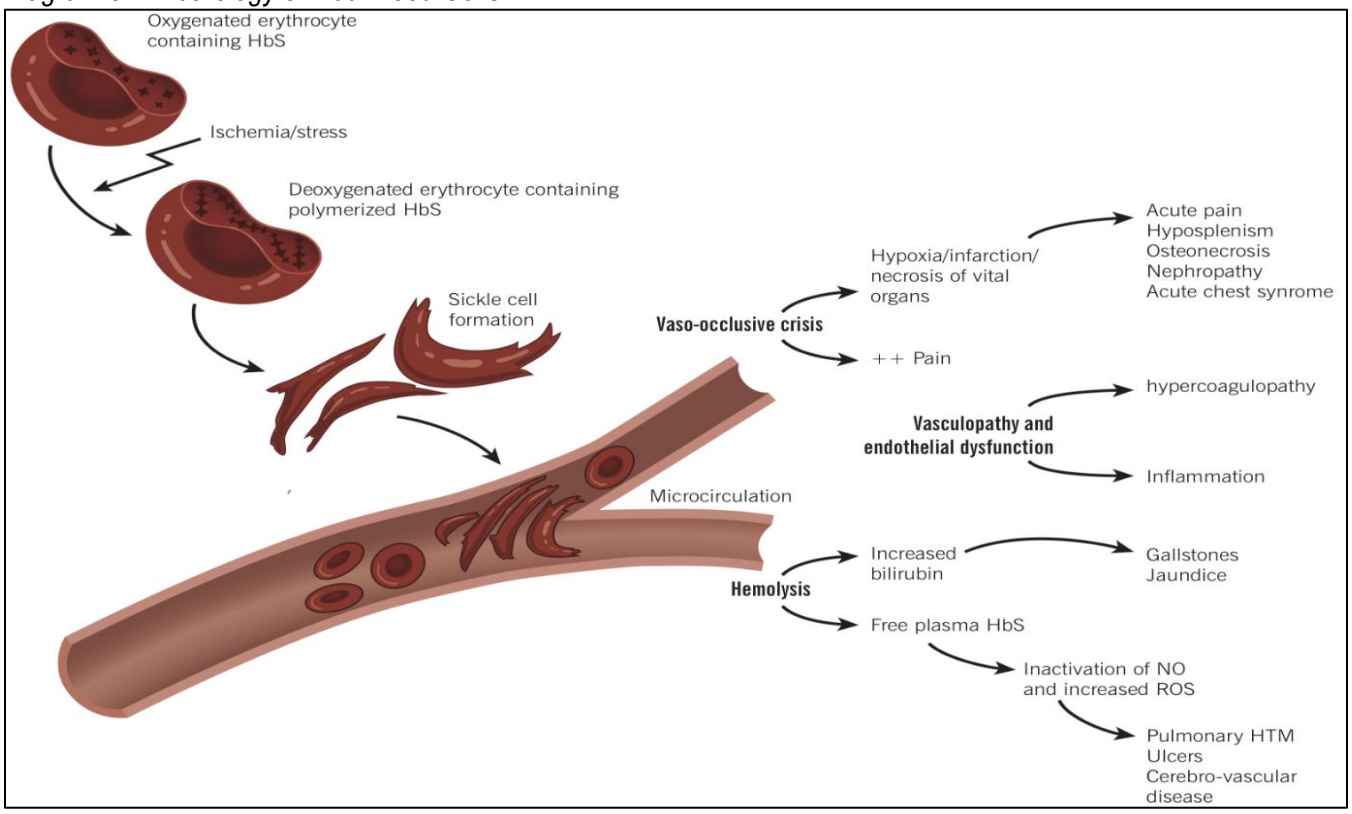


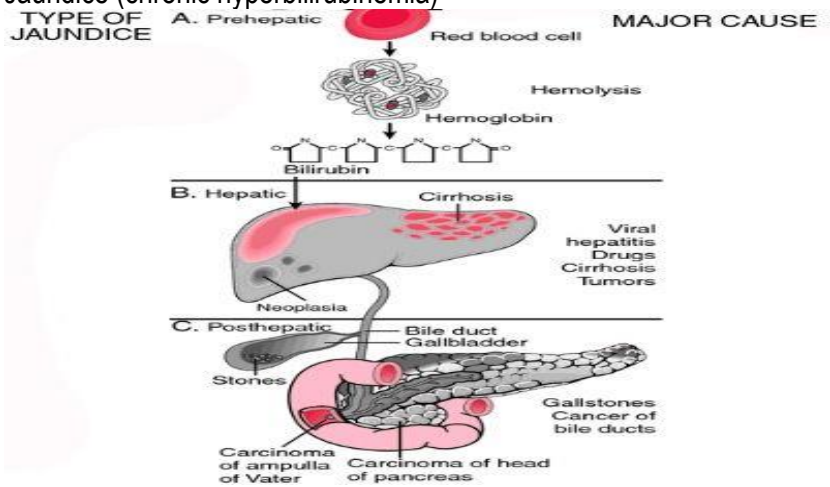
Diagram 3.7: Pathology of Red Blood Cells



Clinical Features

1) Severe anaemia – due to haemolysis and sequestration
   - Sickle cells are mechanically weak and are prone to intravascular haemolysis
   - More important mechanism leading to decreased red cell survival time is the extravascular haemolysis that occurs when inflexible cells are trapped in the spleen and phagocytized by the reticuloendothelial system
   - Bone marrow tries to compensate by increasing RBC production but it cannot match the rate of destruction
   - Complications of increased haemolysis include **cholelithiasis** due to excessive bilirubin production

2) Jaundice (chronic hyperbilirubinemia)



3) Infections
   i) **Encapsulated bacterial infections**
      - Splenic sequestration of sickle cells leads to splenic congestion, as manifested by splenomegaly, and reduced immune function
      - The spleen is important for macrophage phagocytosis of encapsulated bacteria, thus patients with SCD are prone to **bacteremia** with pathogens like *Streptococcus pneumoniae (S. pneumoniae), Haemophilus influenzae (H. Influenzae)* and *Neisseria meningitidis (N. Meningitidis)*
      - These pathogens, normally causing localized disease, may cause life-threatening sepsis in patients with sickle cell disease.
      - Patients with SCD develop **pneumonias**, predominantly from atypical organisms, such as, *Mycoplasma pneumoniae, Chlamydia pneumoniae* and *Legionella*. Respiratory viruses are also common causes of pulmonary infection
      - **Osteomyelitis and septic arthritis** can affect minority of patients with SCD due to both, bone damage and poor splenic function. Leading pathogens include *Salmonella*, *S. Aureus* and other gram-negative bacteria
   ii) **Auto-splenectomy**
      - Continued splenic dysfunction eventually leads to infarction and loss of splenic function, which is referred to as **autosplenectomy** or **functional asplenia**
   iii) Dysfunctional complement system has been proposed to contribute to the infectious complications in SCD

4) Crises
   i) Infarctive/vaso-oclusive/thrombotic
      - Results from blockage of small blood vessels causing ischemia and infarction
      - Hypoxia and infarction associated with pain in the affected region (pain crises)
      - Triggered by infection, dehydration, and acidosis
      - Common sites of involvement are bones (hand and foot syndrome a dactylitis of bones of the hands or feet, osteomyelitis), lungs, brain, liver, spleen and penis
      - Due to the deformed shape, HbS induces RBC membrane damage leading to calcium influx into the cell
      - Calcium influx leads to crosslinking of the membrane proteins and activating channels that allow for the efflux of potassium and water from the cell leading to RBC dehydration exacerbating the sickling
      - Vaso-occlusive crisis results from the sickle red cells obstructing and reducing blood flow to the vital organs leading to ischemia, necrosis and pain
      - Repeated episodes lead to **bone infarction and necrosis**; and **bone marrow degeneration** occurs overtime
      - Long bones are affected most commonly, but pain episodes can affect any bone marrow-containing structure, including the ribs, sternum, vertebral bodies, and skull
      - **Pulmonary fat embolism** can be a life-threatening complication of bone marrow infarction in patients with SCD and precipitate Acute Chest Syndrome (ACS)
      - Hemoglobin released from haemolyzed cells readily binds to and depletes NO, leading to vascular smooth muscle cell contraction and enhanced platelet aggregation
      - Occlusions lead to further hypoxia within the tissue, setting up conditions for a vicious cycle in which further sickling and hypoxia occur.

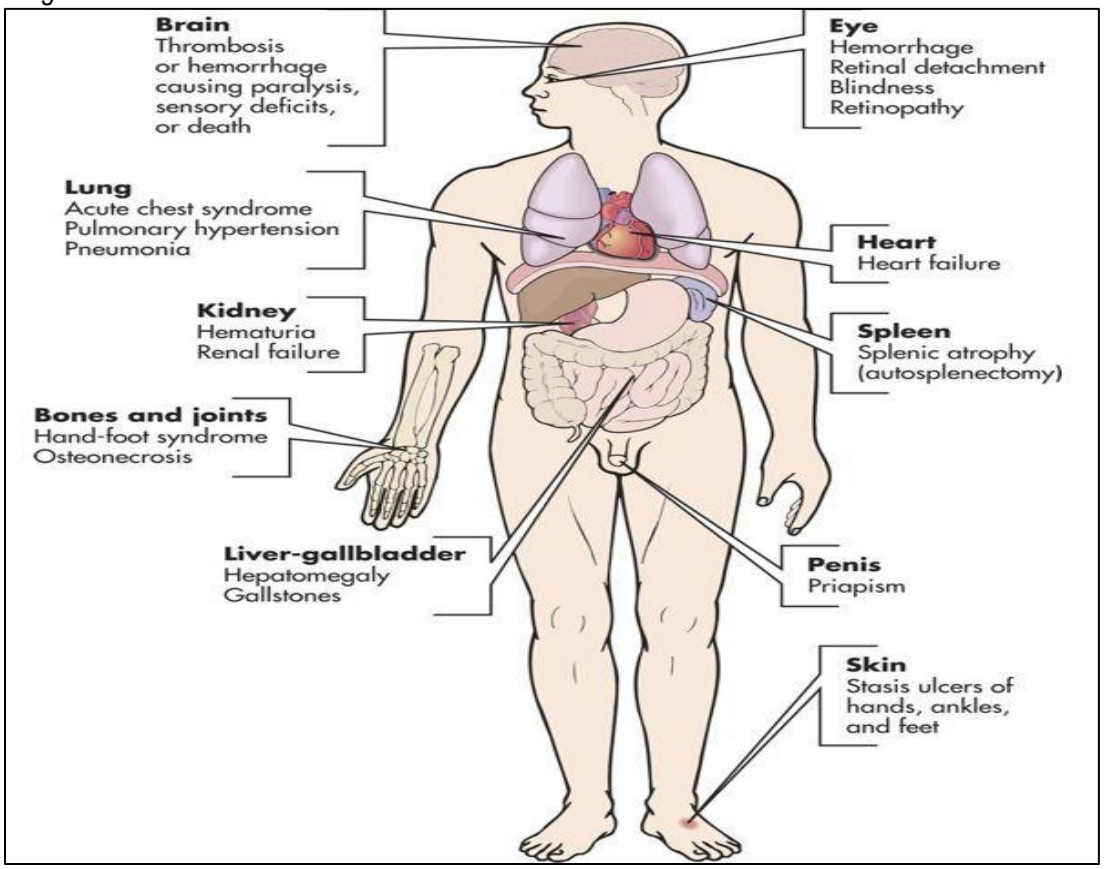
ii) Haemolytic crisis
- Results from accelerated rate of haemolysis usually peopled by infection and can also be part of the infective crises

iii) Anaplastic crisis
- Occurs due to bone marrow failure causing severe anaemia with associated infections
- There is reduced bone marrow erythropoiesis
- Reticulocytes disappear from the peripheral blood causing sudden and rapid worsening of anaemia

iv) Sequestration crisis
- Occurs in young children with an intact spleen
- There is sudden massive pooling of blood in the spleen resulting is severe anaemia and circulatory collapse

5) Acute chest syndrome
- Occurs when the lungs are deprived of oxygen during a crisis
- It can be very painful, dangerous, and even life threatening

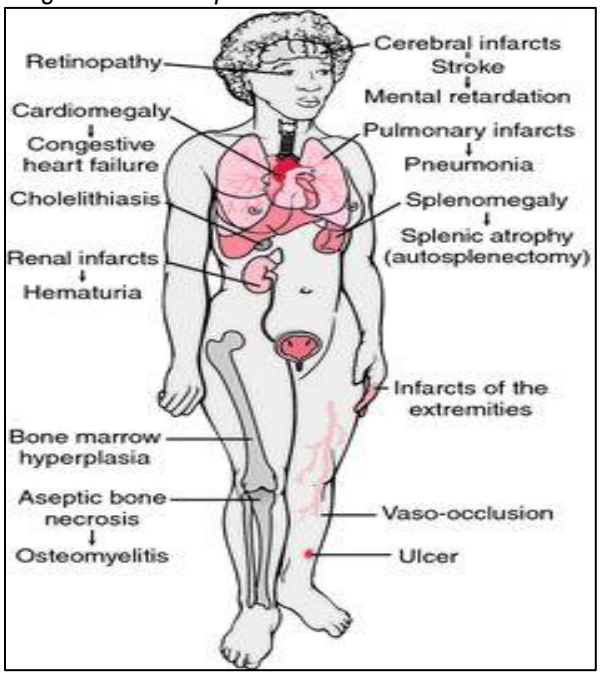
Diagram 3.8: Clinical Features of SCD



Complications

	Complication	Explanation
1.	Recurrent SCD crises	
2.	Acute infections	
3.	Haematological (Haemolytic anaemia)	
4.	Cardiopulmonary – cardiac failure, ischaemic heart disease, pneumonia,	
5.	Renal – renal failure, nephrotic syndrome	
6.	Reproductive system - obstetric/gynaecologic, priapism, delayed development of secondary sexual characteristics	
7.	Skeletal – dactylitis, osteomyelitis (Salmonella typhimurium, Salmonealla enteritidis, Salmonella choleraesuis, Salmonella paratyphi B, Staphylococcus aureus, Hemophilus influenzae,Escherichia coli, Enterobacter spp), Acute Painful (vaso-occlusive) crisis, Osteomyelitis, Septic arthritis, Bone infarcts and Dactylitis (Hand-foot disease); Chronic - Osteonecrosis or Avascular necrosis of Femoral or Humeral head, Chronic arthritis, Osteoporosis and Growth retardation/Skeletal immaturity	
8.	Skin – infections, abscess, ulcers	
9.	Reticulo-endothelial system – reduced immunity	
10.	Central nervous system – stroke, haemorrhage, convulsions	
11.	Hepatobiliary system – jaundice, liver failure, liver abscess, gall stones	

Diagram 3.9: Complications of SCD



TOPIC 4: AUTOSOMAL RECESSIVE DISORDERS (CYSTIC FIBROSIS & ALBINISM)

Objectives

At the end of the lesson the learner will be able to: -
1) Explain the pathology of single gene autosomal recessive disorders – cystic fibrosis and albinism

1.0. INTRODUCTION

- Require that both copies of the inherited gene carry mutations
- Mutations may be passed on by carriers
- Typically, not seen in every generation of an affected family

1) CYSTIC FIBROSIS

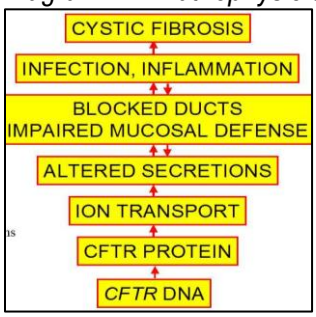
Introduction
- Life threatening disease associated with production of thick, sticky mucus that builds up in the lungs, digestive tract, and other areas of the body

Pathogenesis
- Inheritance of mutant transmembrane conductance regulator ***(CFTR)*** gene located on chrm 7

Pathophysiology

- Transmembrane conductance regulator ***(CFTR)*** gene encodes for a protein that functions as a chloride channel and regulates the flow of other ions across the apical surface of epithelial cells
- *CFTR* is regulated by cAMP[3] so its mutation result in abnormalities of cAMP-regulated chloride transport across epithelial cells on mucosal surfaces
- In non-cystic fibrosis individuals, the affected chloride channels are found in the cells lining the epithelium of the respiratory and gastrointestinal tract whereas in cystic fibrosis there are no chloride ion channels and the chloride ions are trapped within the cell
- There is decreased secretion of chloride and increased reabsorption of sodium and water across epithelial cells resulting in reduced height of epithelial lining fluid and decreased hydration of mucus results in formation of thick sticky mucus
- Secretions in the respiratory tract, pancreas, GI tract, sweat glands, and other exocrine tissues have increased viscosity, which makes them difficult to clear.

Diagram 4.1: Pathophysiology of Cystic Fibrosis



[3] cyclic adenosine monophosphate

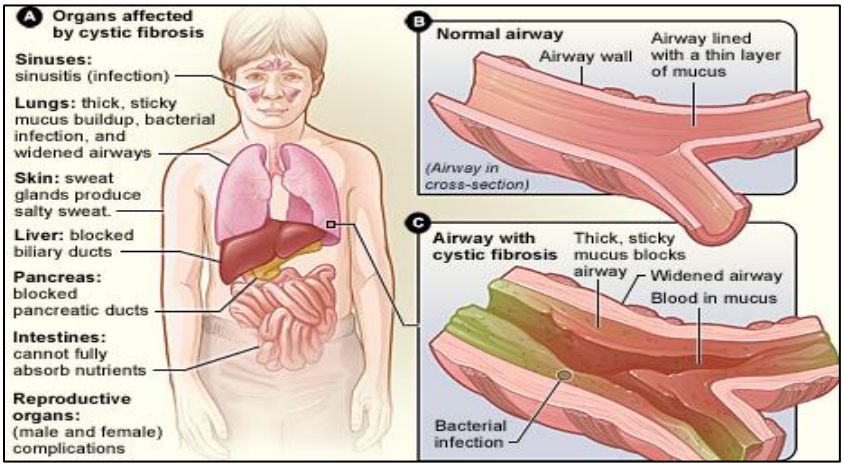
Pathology

- Abnormality of chloride channels and chloride transport system

Clinical Features

1) New-borns – delayed growth, failure to gain weight normally during childhood, no bowel movements in first 24 to 48 hours of life, salty-tasting skin
2) Bowel function - abdominal pain, abdominal distention, severe constipation, increased gas, bloating, nausea and loss of appetite, stools (mucoid, pale or clay coloured, foul smelling), weight loss
3) Lungs and sinuses - coughing or increased mucus in the sinuses or lungs, fatigue, nasal congestion caused by nasal polyps resulting in recurrent episodes of pneumonia
4) Infertility (in men)
5) Repeated inflammation of the pancreas (pancreatitis)

Diagram 4.2: Organs affected in Cystic Fibrosis



Complications

1) Respiratory system - recurrent chronic respiratory infection e.g. pneumonia, sinusitis, haemoptysis
2) GIT - such as gallstones, intestinal obstruction and rectal prolapse
3) Endocrine - Diabetes
4) Reproductive system - Infertility
5) Hepatobiliary system - liver failure, pancreatitis, biliary cirrhosis
6) Malnutrition
7) Musculo-skeletal system – osteoporosis and arthritis
8) Pneumothorax
9) Right-sided heart failure (cor pulmonale)

2) ALBINISM

Introduction

- A person has partial or complete loss of pigmentation (colouring) of the skin, eyes and hair
- Consists of a group of inherited abnormalities of melanin synthesis and are typically characterized by a congenital reduction or absence of melanin pigment
- Results from defective production of melanin from tyrosine through a complex pathway of metabolic reactions

Pathogenesis

- Inheritance of a mutation of **TYR gene** located on chromosome 11q and gene for P protein

Pathophysiology

- TYR gene gives instructions for synthesis of **tyrosinase enzyme** located in the **melanocytes**
- Tyrosine enzyme converts amino acid tyrosine into pigment molecules called **melanin** that gives colour to the skin, hair, and eyes
- Number of melanocytes is normal but melanin produced is reduced or absent
- P-protein is a melanosomal membrane protein involved in the transport of tyrosine prior to melanin synthesis
- Two other enzymes involved in the formation of eumelanin are tyrosinase-related protein 1 (TRP1; DHICA oxidase) and tyrosinase-related protein 2 (TRP2; dopachrome tautomerase) coded on chromosome 9
- Mutation to the *TRP1* gene causes OCA 3 and mutation to the *TRP2* gene does not produce albinism
- OCA1, or tyrosinase-related albinism, results from a genetic defect in an enzyme called tyrosinase
- OCA2, or P gene albinism, results from a genetic defect in the P protein that helps the tyrosinase enzyme to function.

Pathology

- Deficiency of melanin pigment in the body

Clinical Features

Ocular Albinism (OA)	• Hypopigmentation of the fundus with clearly visible choroidal vessels, foveal hypoplasia, hypopigmentation of the iris, strabismus, nystagmus, photophobia, absent stereoacuity and high refractive errors including hypermetropia , vision may be near normal but usually worse, reduced visual acuity
Oculocutaneous Albinism (OCA)	• Snow-white skin; snow-white hair, no pigment in their eyes, iris is a pale bluish pinkish colour, while the pupil may actually be red (from light entering the pupil and reflecting off of blood vessels in the retina, the light-sensitive layer of tissue lining the back of the eyeball • Seven forms – OCA 1 – 7 •

Complications

i. Non-melanoma skin cancers in keratinocytes
ii. Risk for squamous cell carcinoma
iii. Premature skin aging

TAKE HOME ASSIGNMENT

	Disease	Genetic link	Pathology	Main features
1.	Cystic fibrosis			
2.	Albinism			
3.	Thalassaemia			
4.	Sickle cell disease			
5.	Haemophilia			
6.	Gaucher's disease			
7.	Congenital deafness			

TOPIC 5: SEX LINKED SINGLE GENE DISORDERS

Learning Objectives

At the end of the lesson the learner will be able to: -

1) Explain the pathology of common sex-linked disorders

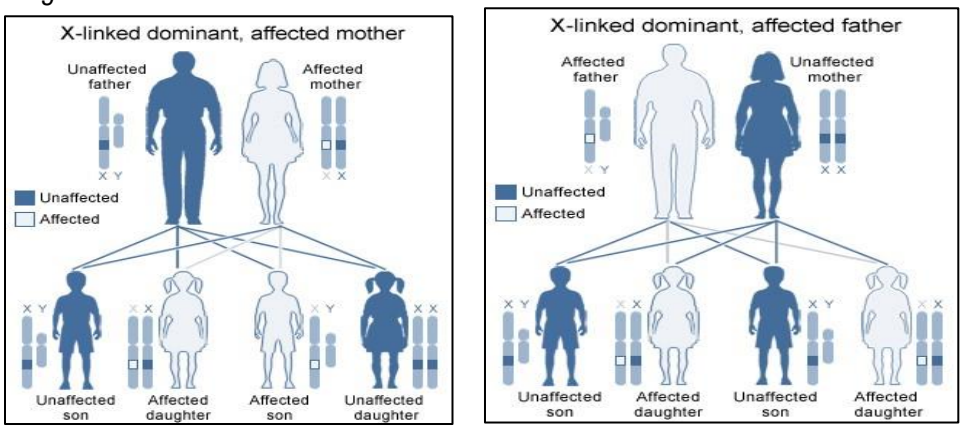
1.0. INTRODUCTION

- Females have a homogametic sex (XX) while males have a heterogametic sex (XY)
- The homologous "X" chromosome in the female protects them from mutant effects of the other "X") chromosome thus females will be normal carriers (heterozygous) and the males will be affected (homozygous)
- Males have a single "X" chromosome thus affected by any X-linked gene is mutant.
- Carrier mothers transmit the mutant gene to their sons or daughters while the affected father transmits it to the daughters
- Uneven distribution of sex chromosomes produces a characteristic pattern of inheritance of X-linked disorders

2.0. X-LINKED DOMINANT DISORDERS

- Very rare conditions characterised by expression in both sexes, but with a greater incidence in females due to the greater number of X chromosomes the female may be homozygous or heterozygous for the affected
- A positive mother will transmit the trait to half of her sons and half of her daughters affected males having a uniform severity of disorder, while females are affected to different degrees
- Examples - Xg blood group; Vitamin D resistant rickets; Rett's syndrome; Fragile X syndrome
- A positive father transmits the mutant gene to all of his daughters, but not his sons,

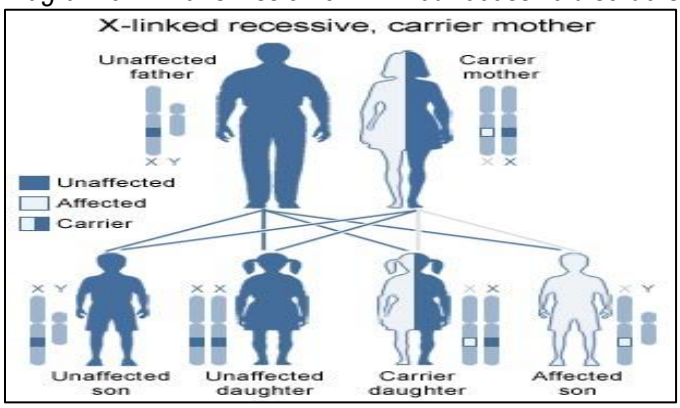
Diagram 5.1: Transmission of X-Linked Disorders



3.0. X-LINKED RECESSIVE DISORDERS

- Fully expressed in males because the mutant genes on the X-chromosome are not paired with alleles on the Y chromosome
- Females are carriers

Diagram 5.2: Transmission of X-linked recessive disorders



Examples

- Chronic granulomatous disease; Colour blindness; Congenital Aqueductal stenosis (hydrocephalus); Diabetes insipidus; Glucose-6-phosphate dehydrogenase (G6PD) deficiency; Haemophilia; Muscular dystrophy

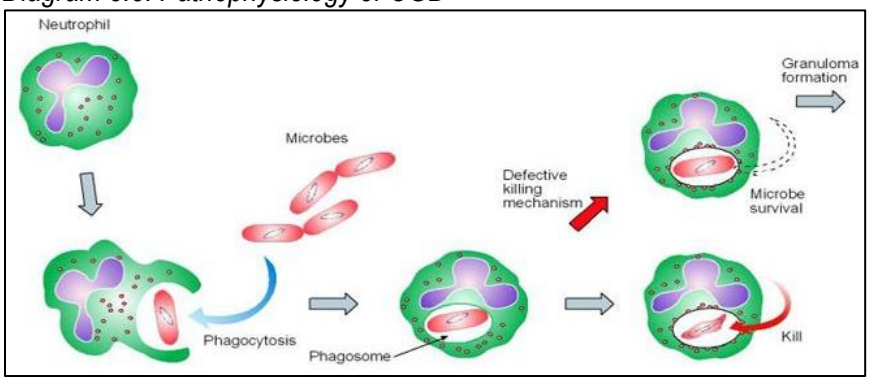
1. CHRONIC GRANULOMATOUS DISEASE

- A genetically heterogeneous condition characterized by recurrent, life-threatening bacterial and fungal infections and *granuloma* formation
- Recurrent and chronic infections occur due to inability of phagocytes to destroy micro-organisms

Pathogenesis

- Caused by mutations in the CYBB gene, making a protein called cytochrome b-245, p
- the protein is one part (subunit) of a group of proteins that forms an enzyme complex called NADPH oxidase in phagocytes
- Condition is inherited in an X-linked recessive pattern.
- Females show exhibit disease

Diagram 5.3: Pathophysiology of CGD



Pathophysiology

- Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase generates superoxide essential for intracellular killing of pathogens by phagocytes

- Gene mutation cause defects in NADPH oxidase enzyme complex that normally generates increased oxygen consumption essential for clearance of phagocytised micro-organisms which are killed by oxygen radicals (absent in CGD)
- There is inability of phagocytes to kill bacteria and fungi that they have ingested
- Repeated infections and formation of multiple abscesses result in formation of granulomas in the lungs, spleen, live and the skin

Pathology
- Defective intracellular killing of microbes due defective function of phagocytes

Clinical Features
- Skin infections; pneumonia and lung abscess; sepsis; osteomyelitis; diarrhoea; abscesses (anus, rectum, liver and spleen); granulomas; lymphadenopathy; hepatosplenomegaly

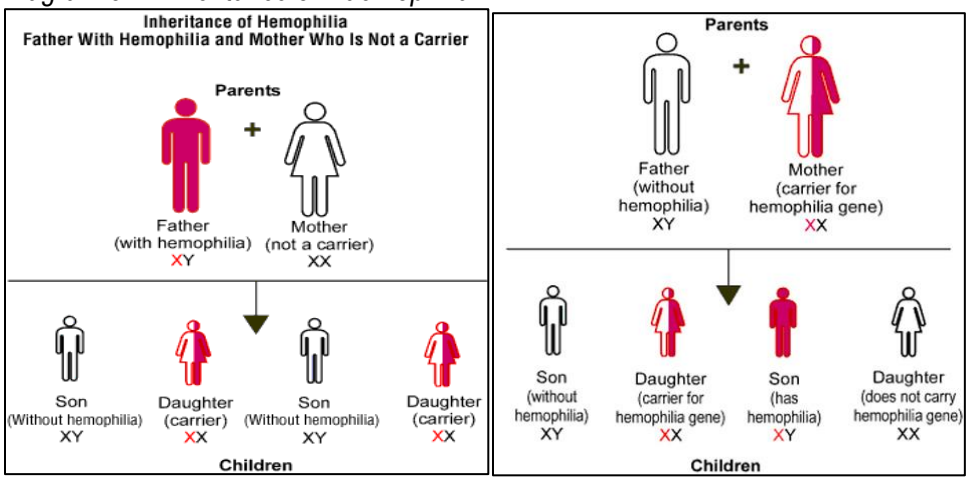
Investigations
- Total blood counts; Cultures – blood, pus, stool; X-rays

2. HAEMOPHILIA

- An inherited bleeding disorder that follows Mendelian pattern of inheritance
- Affects males while females are carriers
- Two types of haemophilia – Haemophilia A (classic) and Haemophilia B (Christmas disease)

Pathogenesis
- Inheritance of mutant genes for factors VIII and IX are located on the X chromosome
- Deficiency occurs following a mutation of gene F8 located on the X chromosome

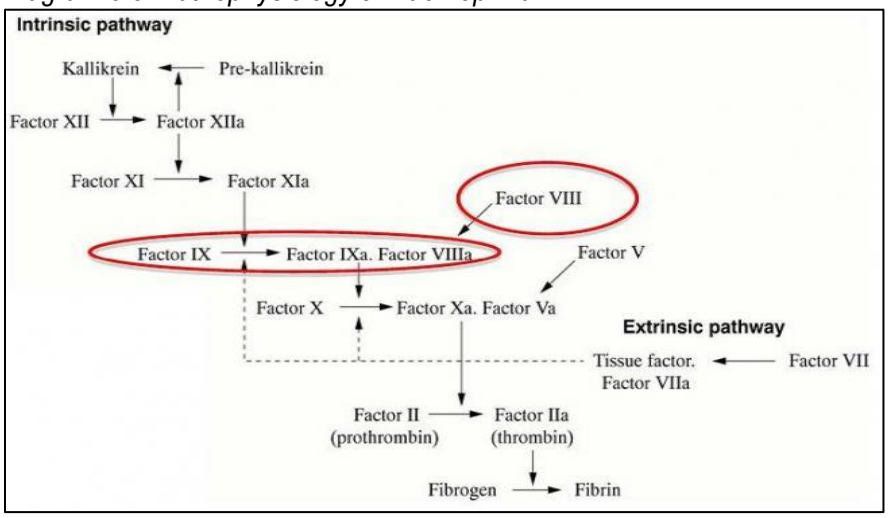
Diagram 5.4: Inheritance of Haemophilia



a) Haemophilia A (Classic)

Pathophysiology
- Due to lack of Factor VIII, there is a defective intrinsic coagulation pathway

Diagram 5.5: Pathophysiology of Haemophilia



Pathology

- Factor VIII deficiency (antihaemophilic factor) is a large protein synthesized in the liver and regulates activation of Factor X during the process of coagulation of blood

Clinical Features

1. Bleeding tendencies - Patients bleed easily following trauma, surgery, circumcision and tooth extraction; Haemarthrosis (weight bearing joints), muscles of the calf, thigh, fore arm and the iliopsoas sheath; microscopic haematuria, intracranial haemorrhage (low incidence), epistaxis, petechial haemorrhage, ecchymosis, neonatal cephalohematoma,
2. Intramuscular haematoma that can lead to ischemia, infarction, gangrene and paralysis
3. Unexplained GIT bleeding, haematuria
4. Prolonged bleeding

b) Haemophilia B (Christmas disease)

- Results from deficiency of clotting Factor IX which is a protein synthesized in the liver and requires vitamin K for activity and clinical presentation resembles that of Haemophilia A

Investigations in Haemophilia

- Total blood count (full haemogram); Coagulation screen – clotting time, bleeding time

3. DIABETES INSIPIDUS (Nephrogenic)

- Rare condition where patients produce large quantities of dilute urine (polyuria)

Pathogenesis

- Results from mutations in the AVPR2 **gene which** provides instructions for making a hormone called vasopressin or antidiuretic hormone (ADH).

Pathophysiology

- Kidney fails to respond to vasopressin (antidiuretic hormone, ADH) which controls the permeability of the renal collecting ducts to water and concentration of urine
- Results in failure of the kidneys to reabsorb water thus production of large amount of dilute urine (**polyuria**)

4. G6PD DEFICIENCY

- Is a disorder that presents of anaemia due to haemolysis of RBCs
- Glucose-6-phosphate dehydrogenase (G6PD) is a **cytosolic enzyme that facilitates anaerobic respiration** of the red blood cells hence takes part in provision of energy to the red blood cells

Pathogenesis

- Inheritance of mutant G6PD gene located on the female X chromosome, and encodes for glucose-6-phosphate dehydrogenase a cytosolic enzyme whose main function is to produce NADPH, a key electron donor in the defense against oxidizing agents and in reductive biosynthetic reactions
- involved in the normal processing of carbohydrates and plays a critical role in red blood cells, which carry oxygen from the lungs to tissues

Pathophysiology

- Results from the absence of G6DP enzyme due to mutation of the G6PD gene
- RBCs lack the energy to operate the Na/K pumps in the cell membrane resulting in accumulation of sodium and excess water in the cells
- RBCs become abnormally big and thus recognized as abnormal cells and it is destroyed by the spleen causing haemolysis (repeated and eventually anaemia)

Clinical Features

- Haemolytic anaemia and jaundice

5. MUSCULAR DYSTROPHIES

- Disorders produce weak muscles due to necrosis of muscle fibres and poor regeneration resulting in atrophy, fibrosis (scarring) and deposition of fatty tissues in the muscle fibres producing pseudo hypertrophy

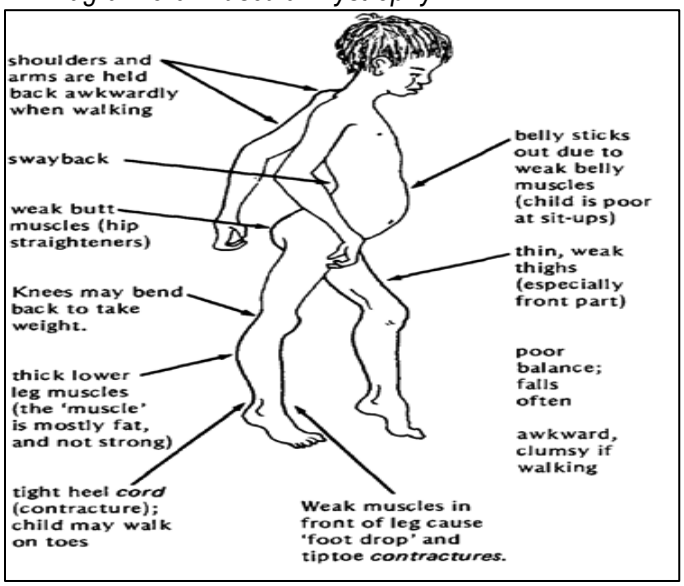
Pathogenesis

- Defect in gene coding for dystrophin on the short arm of X chromosome (Xp21.2).
- Dystrophin is a large, elaborate protein complex that links actin cytoskeleton to extracellular matrix in muscle.

Pathology

- Lack of dystrophin leads to cellular instability at these links, with progressive leakage of intracellular components and muscle membrane integrity
- Two types - Duchenne muscular dystrophy (severe form) and Becker muscular dystrophy (mild form)

Diagram 5.6: Muscular Dystrophy



6. COLOUR BLINDNESS

Assignment

1) What are the colours involved in colour blindness
2) Explain how individuals become colour blind
3) What the risks or challenges associated with colour blindness?

TAKE HOME ASSIGNMENT

	Disease	Genetic link	Pathology	Main features
1.	Chronic granulomatous disease			
2.	Haemophilia A			
3.	Haemophilia B			
4.	Diabetes Insipidus			
5.	G6PD deficiency			
6.	Muscular dystrophies			
7.	Colour blindness			

TOPIC 6: CHROMOSOMAL (CYTOGENIC) DISORDERS

Learning Objectives

At the end of the lesson the learner will be able to: -
1) Classify chromosomal disorders
2) Explain the pathology of chromosomal disorders

1.0 INTRODUCTION

- Are abnormalities result from alterations in the number or/and structure of the chromosomes
- Classification is based on the numerical and structural aberrations

2.0 PREDISPOSING FACTORS

1) Idiopathic
2) Advanced maternal age
3) Maternal hypothyroidism
4) Environmental factors – drugs, irradiation, maternal infections
5) Familial tendency

3.0 CLASSIFICATION

1) Numerical abnormalities - polyploidy and aneuploidy
2) Structural abnormalities - translocations, deletions and inversions

4.0 NUMERICAL ABNORMALITIES

- Somatic cells contain 46 chromosomes (diploid) and mature gametes have 23 chromosomes (haploid) i.e. 44 are autosomes and 2 sex chromosomes
- During cell division (meiosis and mitosis) mistakes may occur resulting in abnormal numbers of the chromosomes hence causing disease(s)

4.1. ANEUPLOIDY

- Caused by failure of paired chromosomes or sister chromosomes to disjoin during cell division (anaphase period) resulting in production of two cells – one with an extra copy of a chromosome (trisomy) and the other with a missing copy (monosomy)

Examples
1) Monosomy – Turner's syndrome
2) Trisomy – Down's syndrome (Mongolism), Klinefelter's syndrome, Triple X syndrome and XYY syndrome

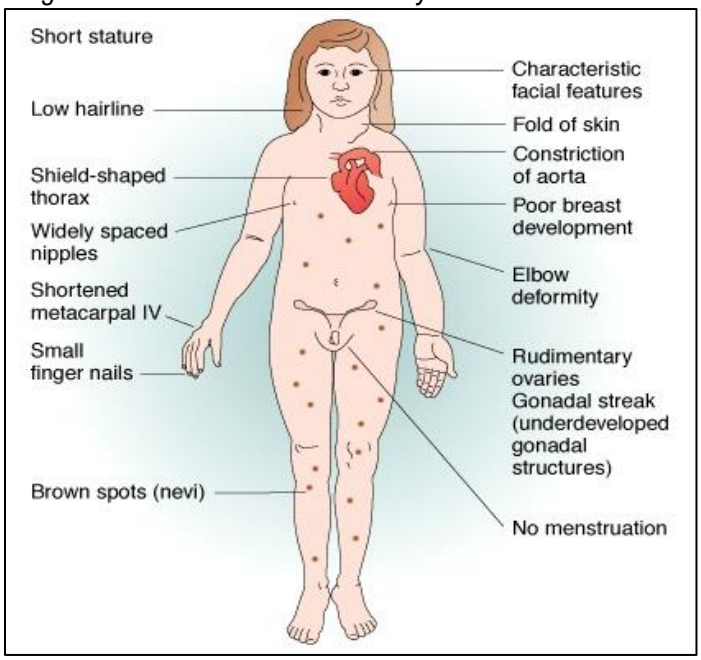
1. TURNER'S SYNDROME (45X0)

Pathogenesis
- A monosomy abnormality affecting female as result of loss of the X chromosome in the paternal meiosis

- Majority (99%) of the embryos are aborted early in pregnancy
- Also called gonadal digenesis

Clinical Features
- Body configuration is female
- Short stature, broad neck with prominent lateral skin folds, broad chest lacking breast development, widely spaced nipples, small uterus and ovaries are small fibrotic strands
- Sexual characteristics are not developed in adults (primary amenorrhoea, sexual infantilism)
- Abnormalities of the cardiovascular system

Diagram 6.1: Features of Turner's syndrome



2. DOWN'S SYNDROME (TRISOMY 21, Mongolism)

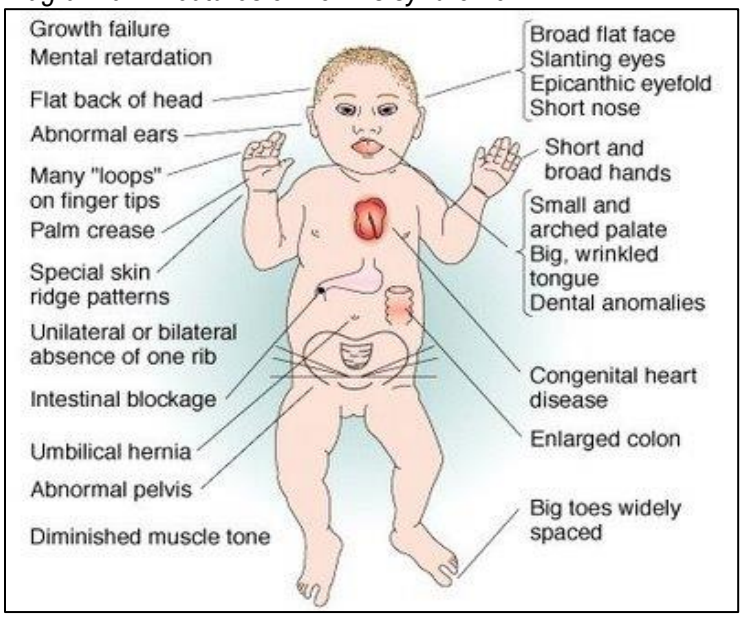
Introduction
- Common chromosomal disorder in humans with a wide range of manifestations
- Affects both sexes

Pathogenesis
- Caused by inheritance of 3 chromosomes 21, hence the name trisomy 21 (47XY+21 or 47XX+21)

Pathophysiology
- The individual inherits an extra copy of chromosome 21 from meiotic non-disjunction of failure of the chromosome pairs to separate during gamete formation (two copies from the mother and one copy from the father)
- Few do not inherit an entire extra chromosome 21, but just some extra chromosome 21 genes, which are attached to another chromosome (chr 14) in process called Robertsonian translocation.
- Few individuals with Down syndrome inherit additional genes from chromosome 21, but not in every cell of the body resulting in mosaic Down syndrome.

Features of Down's syndrome (Mongolism)

Diagram 6.2: Features of Down's syndrome



3. KLINEFELTER'S SYNDROME (47XXY)

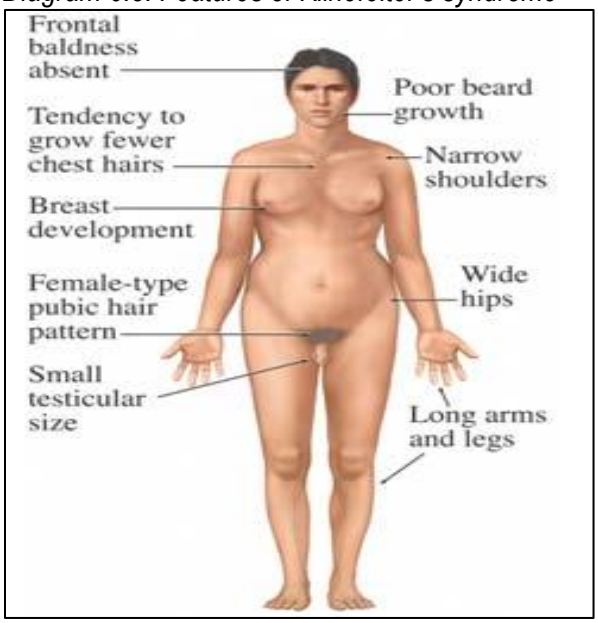
Pathogenesis

1. Sex-linked trisomy (XXY) that affects the males

Features

- The external genital organs are male, micro-orchidism (small testis) due to prepubertal testicular atrophy, azoospermia and sterility, body configuration is feminine with moderate breast hypertrophy, normal intelligence, reduced strength, osteoporosis and tooth decay

Diagram 6.3: Features of Klinefelter's syndrome



4. TRISOMY 18 (EDWARDS SYNDROME)

- Presents with multiple congenital malformations of many organs, low-set malformed ears, receding mandible, small eyes, mouth and nose with general elfin appearance, severe mental deficiency, congenital heart defects, horse shoe or double kidney, short sternum and posterior heel prominence

5. TRISOMY 13 (PATAU SYNDROME)

- Associated with severe mental deficiency, small eyes, cleft lip and/or palate, extra fingers and toes, cardiac anomalies, midline brain anomalies, genitourinary abnormalities

6. TRIPLE X (XXX) SYNDROME/Trisomy X

- There is presence of an extra X chromosome in the cell of the female
- Affects females
- Fertility and intelligence may either be normal or slightly reduced

7. XYY SYNDROME

- Presence of an extra Y chromosome (XYY)
- Affects males and is associated with some reduction in fertility and intelligence
- Individuals are taller than normal with no specific abnormality of the body configuration but some have aggressive and antisocial behaviour.

4.2. POLYPLOIDY

- There is addition of a complete set of chromosomes raising the total number of chromosomes to 69 (triploidy) or even 92(tetraploidy)
- Triploidy is usually aborted in early pregnancy (spontaneous arbortion)

5.0 STRUCTURAL ABNORMITIES

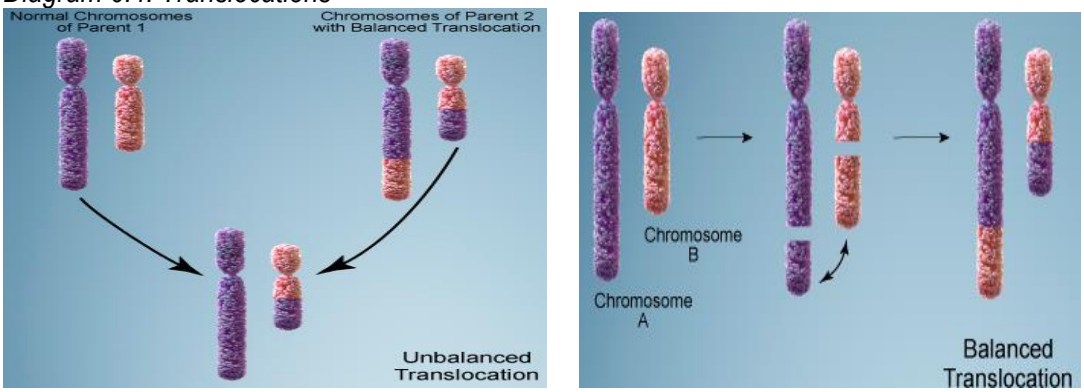
Introduction

- Occur during meiosis and mitosis as a result of breaks in the chromosomes
- When chromosomal breakage occurs at one site there is immediate repair of the unstable sticky ends of the chromosome but repair of many breakages may occur with translocation, deletion and inversion of chromosomal material.
- Can be balanced or unbalanced
- Unbalanced rearrangements result in significant clinical abnormalities due to loss, duplication or both
- Balanced arrangements are usually clinically normal if no essential chromosome material is lost and no genes are damaged by the breakage or re-union

Translocations

- Involve transfer of chromosomal material between chromosomes which does not usually result in DNA loss
- Individual is clinically normal
- Translocation may be **balanced** or **unbalanced** (produces repeated abortions and malformations in children)

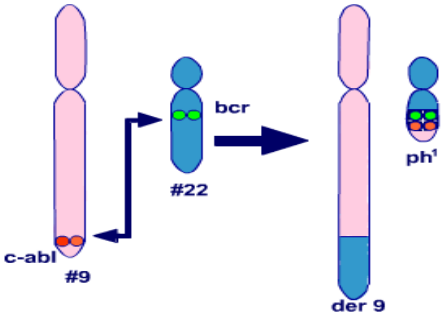
Diagram 6.4: Translocations



Examples

- Translocation of the long arm of chromosome 22 to long arm of chromosome 9 produces the Philadelphia chromosome which predisposes one to increased chances of getting Chronic myeloid leukaemia (cancer of white blood cells)

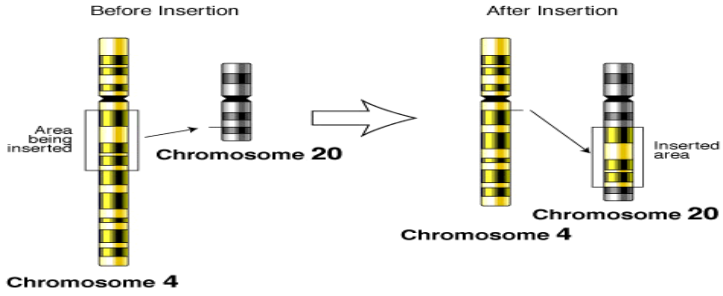
Diagram 6.5: Philadelphia Chromosome



Insertions

- Mutation resulting from the addition of extra nucleotides in a DNA sequence or chromosome.

Diagram 6.6: Insertions



Deletions

- Deletion is loss of genetic material from the chromosomes which may occur at the terminal or middle portion of the chromosome
- Deleted part lacks a centromere and it will be lost at the subsequent cell division.
- The breaks may occur in both arms of a chromosome with the two free terminal ends joining to form a ring (ring chromosome).

Diagram 6.7: Deletions

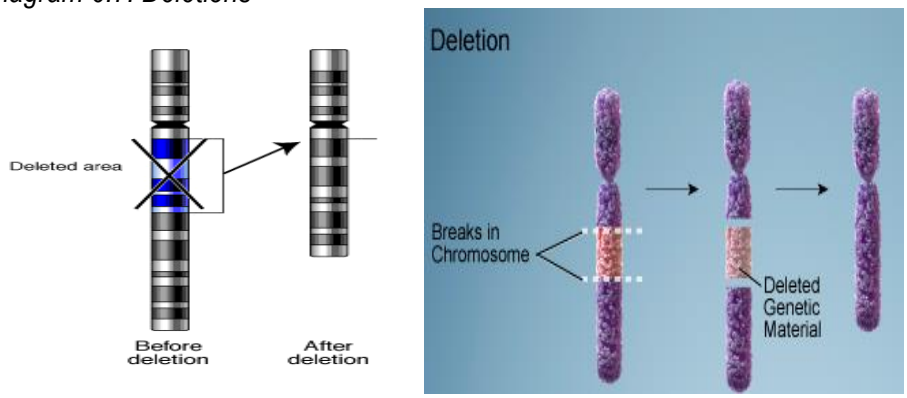
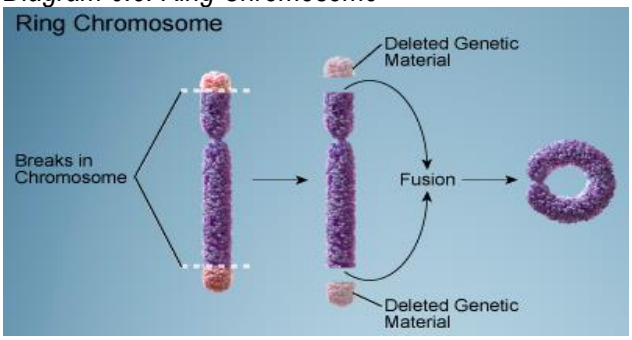


Diagram 6.8: Ring Chromosome



Examples

- Cri du Chat (Cry Cat syndrome) – results from deletion of the short arm of chromosome 5 producing this syndrome where the infant has a unique cry like that of a kitten
- These children have severe mental retardation, low birth weight, failure to thrive, microencephaly (small head), micrognathia (small jaw), moonfaced, poor development of organs e.g. larynx, hypospadias and crypto-orchidism
- Deletion of the long arm of chromosome 13 comes with heredity associated retinoblastoma (cancer of the retina)
- Deletion of the long arm of chromosome 11 predisposes one to developing Wilm's tumour (cancer of the kidney common in children)

Inversions

- There is rearrangement that involves breaks of a single chromosome with the pieces rotating 180^0 and joining the chromosome
- There is no clinical abnormality but there is a risk of producing unbalanced gametes which will then produce marked abnormalities.

TAKE HOME ASSIGNMENT

	Disease	Genetic link	Pathology	Main features
1.	Turner's Syndrome			
2.	Down's Syndrome			
3.	Klinefelter's syndrome			
4.				
5.				
6.				
7.				

TOPIC 7: POLYGENIC DISORDERS – BIRTH DEFECTS

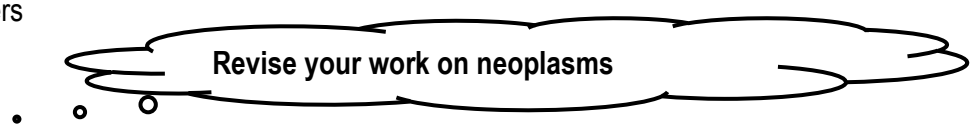
Objectives

At the end of the lesson the learner will be able to: -
1) Outline the pathology of common somatic cell and multifactorial disorders

1.0. INTRODUCTION

1.1. Somatic Cell Disorders

- Human body is made up of many **specialised** cells that perform **specific functions**
- Specialised cells arise from the **differentiation** of unspecialised cells during embryological development
- Somatic cells are the **differentiated** cells that form the different types of body tissue
- Examples of somatic cells include cardiac cells, epithelial cells, blood cells, nerve cells,
- Somatic cell disorders arise from mutations giving rise to abnormal cell division and growth e.g. the cancers



1.2. Multifactorial Inheritance Disorders

- Are disorders that result when environmental factors unmask mutant genes
- Include: -
  i) Birth defects - cleft lip and cleft palate, neural tube defects - spina bifida
  ii) Cardiovascular - coronary heart disease, hypertension, atherosclerosis, congenital heart disease, cardiomyopathy
  iii) Neurological – Alzheimer's disease, Schizophrenia, Bipolar disorders
  iv) Skin conditions – Psoriasis, eczema,
  v) Cancer – bowel, breast, ovarian, melanoma, prostate
  vi) Endocrine - diabetes mellitus
  vii) Musculoskeletal - rheumatoid arthritis, arthritis, gout, osteoporosis
  viii) Respiratory – asthma, allergies, emphysema
  ix) Immunological - atopic (allergic) disorders

2.0. BIRTH DEFECTS

Neural Tube Formation

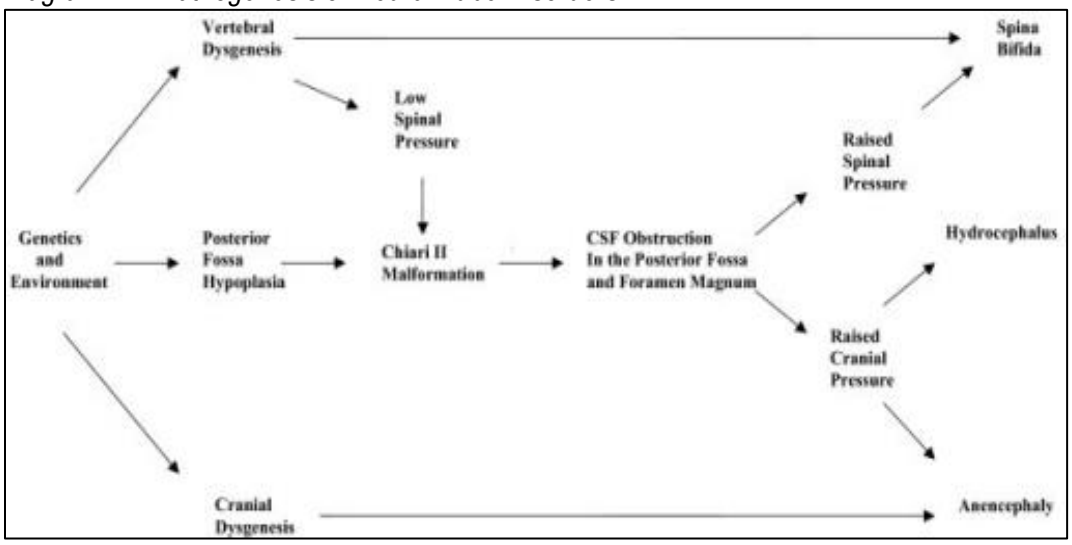
- Three weeks after conception, the first signs of the central nervous system appear in a human embryo in what is known as the neural plate
- Lateral edges of the plate elevate to form neural folds, turning in on each other and fusing together to create the neural tube
- Between the 23rd and the 26th day after conception, the closure of the cranial and then the caudal neuropore occurs
- The period of time directly after the closure, from the 26th to the 30th day, is the crucial moment for the formation of the neural tube and disruptions in the process can cause defects such as spina bifida, anencephaly and hydrocephalus

- Neural tube defects (NTDs) represent a common group of severe congenital malformations of the central nervous system.

Pathogenesis

- Is complex, involving environmental and genetic factors that interact to modulate the incidence and severity of the developing phenotype

Diagram 7.1: Pathogenesis of Neural Tube Disorders



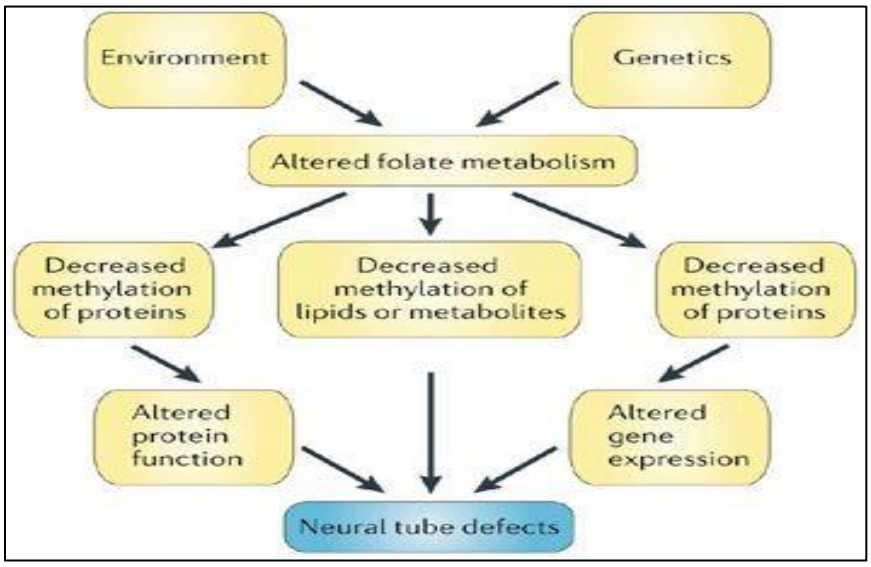
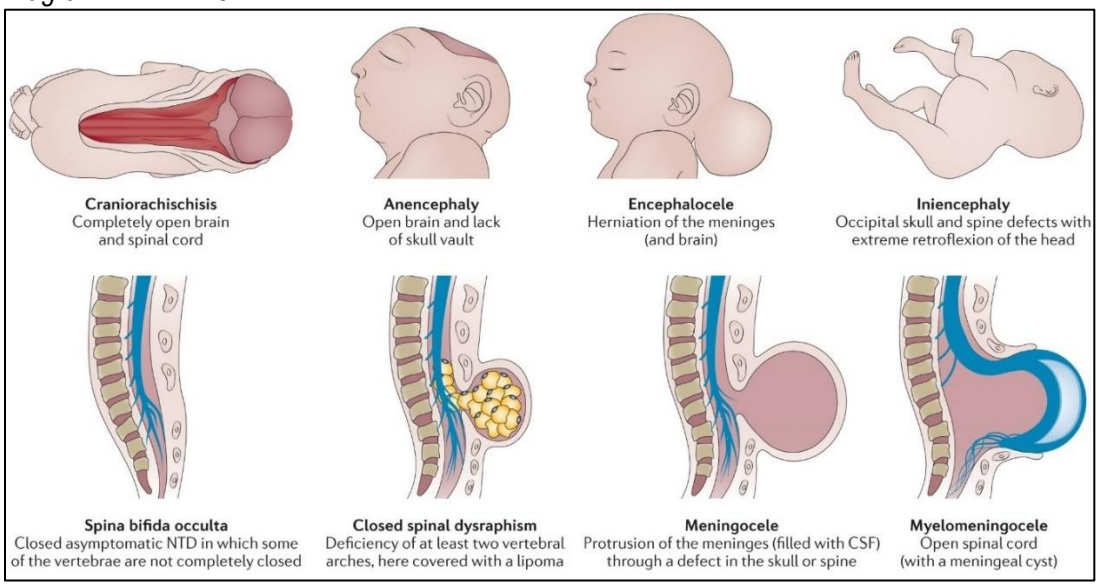


Diagram 7.2: MTDs



1. ANENCEPHALY

Introduction

- Anencephaly is a serious developmental defect of the central nervous system in which the brain and cranial vault are grossly malformed
- Cerebrum and cerebellum are reduced or absent, but the hindbrain is present. Anencephaly is a part of the neural tube defect
- Defect results when the neural tube fails to close during the third to fourth weeks of development, leading to foetal loss, stillbirth, or neonatal death

Pathogenesis

- Homozygous mutation in the **TRIM36 gene** on chromosome 5q22 and associated with trisomy 13. 18, Turner's syndrome
- Follows a multifactorial pattern of transmission, with interaction of multiple genes as well as environmental factors such as toxic effects, nutritional deficiencies, low socio-economic status
- In some cases, anencephaly may be caused by a **chromosome abnormality**, or it may be part of a more complex process involving single-gene defects or disruption of the amniotic membrane
- Associated with folding of the ears, cleft lip and congenital heart defects

Pathology

- Complete absence of the cerebral hemispheres with residual brain stem

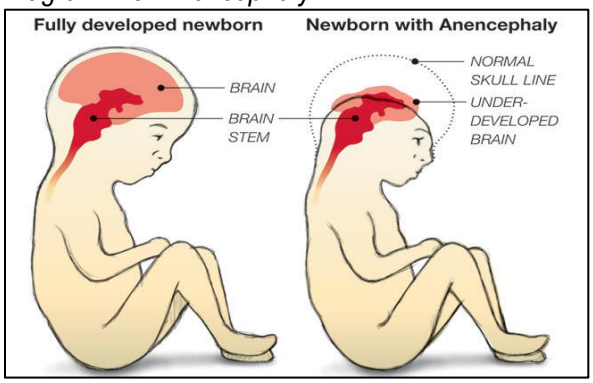
Clinical Features

- Include absence of the skull, absence of parts of the brain, facial feature abnormalities, heart defects

Investigations

i) Ultrasound during pregnancy
ii) Amniocentesis to look for increased alpha-foetal proteins (suggest neural tube defect)
iii) Urine outrival level

Diagram 7.3: Anencephaly



2. CLEFT LIP AND CLEFT PALATE

Introduction

- Are disorders where the clefts are unable to fuse normally resulting in cleft lip and/or cleft palate occur
- Sometimes a cleft occurs as part of a syndrome (in association with birth defects in other body parts)
- Both mothers and fathers can pass on a gene or genes that can contribute to the development of cleft lip or cleft palate
- Most critical time for the development of the lip and palate is 7 – 9 weeks and lasts up to 12 weeks of pregnancy (development of the lip and palate are separate events)

Pathogenesis

- A combination of both genetic and environmental factors (multifactorial inheritance)
- Risk factors include genetic factors (a family history of cleft lip and cleft palate) and environmental factors - teratogens (substances that can cause birth defects) such as - tobacco while you are pregnant, drinking alcohol, or using illegal or certain prescription drugs
- Several genes have been implicated including T-box transcription factor-22 (*TBX22*), poliovirus receptor-like-1 (*PVRL1*), and interferon regulatory factor-6 (*IRF6*

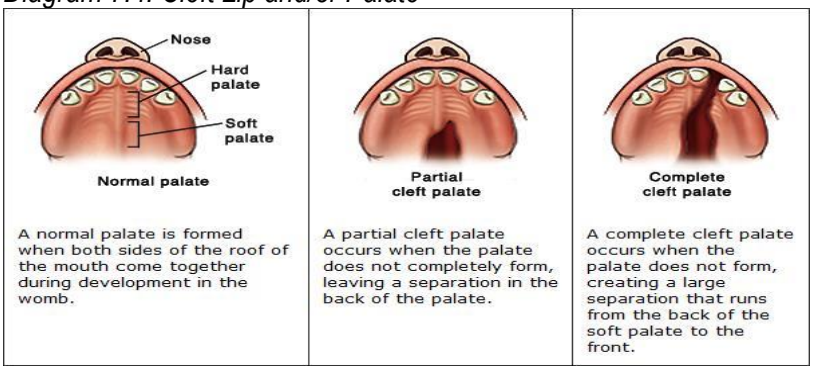
Pathophysiology

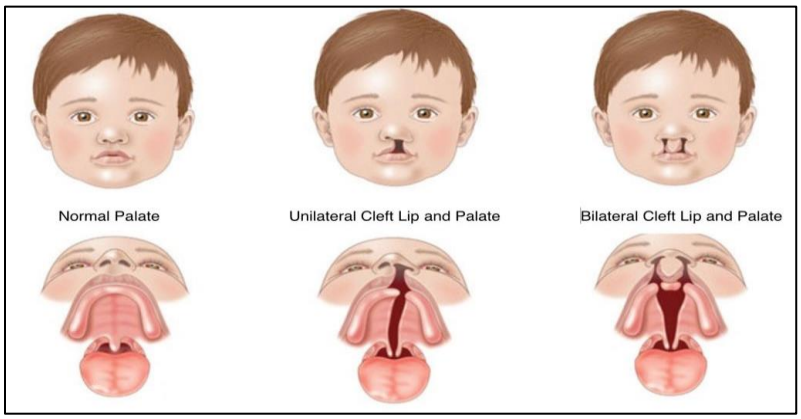
- Occurs between the 3rd and 8th week of gestation
- Lip development between the 3rd - 7th weeks and palate development between the 5th - 12th weeks
- Development of the upper lip and nose is a sequence of complex, programmed events involving fusion of 5 major facial prominences

Abnormalities

i) Cleft lip and/or palate
   - Results from interrupted fusion of the maxillary and median nasal prominences
   - In bilateral cleft lip with or without cleft palate, the arterial network and musculature of the lateral elements parallel that of the lateral segment of the unilateral deformity

Diagram 7.4: Cleft Lip and/or Palate

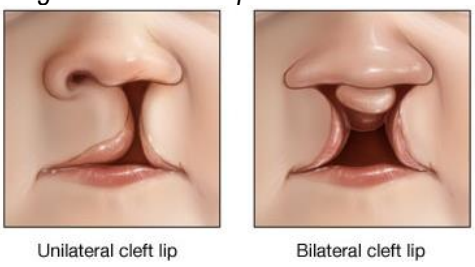




ii) Isolated cleft lip

- The orbicularis oris is a ring of concentric muscle that constricts and puckers the sphincter of the mouth
- The OO fibres on the cleft side insert into the nasal base, and the central (non-cleft) OO fibres abnormally insert into the nasal spine and septum
- This causes the base of the nose to splay laterally when the infant smile

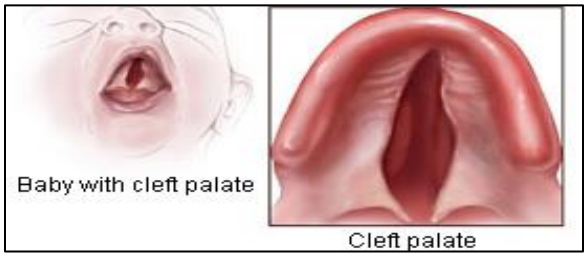
Diagram 7.5: Cleft Lip and Palate



iii) Isolated cleft palate

- Development of the palate involves fusion of the lateral palatal shelves and nasal septum in an anteroposterior direction from the incisive foramen to the uvula
- Formed when normal palatal development is interrupted before the 12th week of gestation
- Degree of clefting ranges from a complete isolated cleft palate to a bifid uvula
- Deformational cleft palate is associated with a small mandible (micrognathia) limits the space for the tongue, and the prominent tongue (glossoptosis) mechanically obstructs palatal fusion, leading to the classic triad of micrognathia, glossoptosis, and an isolated cleft palate.

Diagram 7.6: Cleft Palate



iv) Midline clefts of the nose and/or lip
- Are likely to arise from an interruption in the fusion of the paired median nasal prominences during embryological development
- Most median facial deformities represent developmental field defects and are sporadic with multiple aetiological factors.

Associated Problems

i) Feeding Problems - normally the palate prevents food and liquids from entering the nose thus there is difficulty sucking

ii) Middle Ear Fluid Build-up and Hearing Loss - prone to the build-up of fluid in the middle ear (caused by malfunction of the Eustachian tube) resulting in ear infections and hearing loss

iii) Dental Abnormalities
- Small teeth, missing teeth, extra teeth, or malpositioned teeth
- Defect in the gums or alveolar ridge (the bone that supports the teeth)
- Defects of the alveolar ridge can displace tip, or rotate permanent teeth, or prevent permanent teeth from coming in properly

iv) Speech Difficulties
- Fewer speech problems in cleft lip than cleft palate
- Excess nasality or hypernasality (palate normally separates the nose from the mouth for most sounds does not close adequately)
- Pronunciation e.g. age-related errors such as saying "wed" instead of "red."
- Distortion of some sounds particularly "s," "sh," "ch," and "j" sounds.

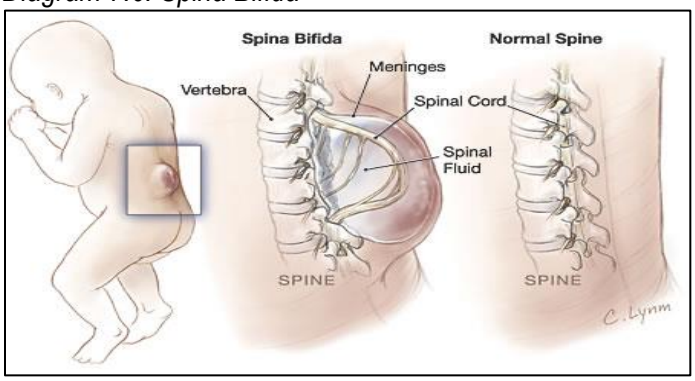
3. SPAIN BIFIDA

Introduction
- Spina bifida is the most common and complex central nervous system malformation in humans.
- Result from failure of fusion (incomplete closure) of neural arches are called **spina bifida and** one or more of the vertebral arches (rachiochisis)
- Vertebral defect is associated with defect in the neural tube structures and their coverings
- A portion of the neural tube fails to develop or close properly
- Bony defect may be of varying degrees
- Majority of these malformations occur in the lumbosacral region

Pathogenesis
- Genetic susceptibility is thought to play a role in the pathophysiology of spina bifida but environmental factors are also important.
- Involves multifactorial mutations of genes though the most linked is the is **MTHFR**, gene which provides instructions for making a protein involved in processing the vitamin folate

- Risk factors include - race, family genetic lines, folate, vitamin B-9, deficiency, administration of folic acid antagonists (including carbamazepine, phenobarbitone, phenytoin) diabetes and obesity are associated risk factors

Diagram 7.6: Spina Bifida



Pathophysiology

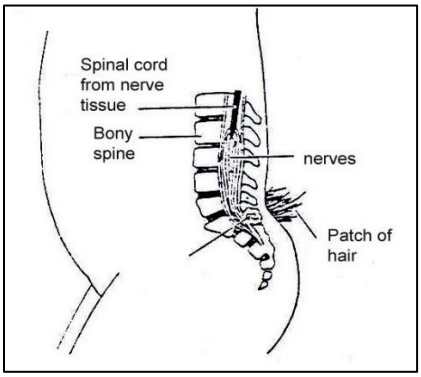
- There is failure of closure of the neural tube

Types

a) Spina Bifida Occulta (Closed)

- There is only vertebral bone defect with no abnormality of the spinal cord and its meninges
- It is limited to the lumbosacral region
- Site of the bone defect is marked by a small dimple covered by skin which may show abnormal pigmentation (mole), a hairy patch or a dermal sinus
- Majority are asymptomatic but neurological disturbances develop in adult life
- Indications include abnormal tuft of hair; collection of fat; small dimple or birthmark and slight to pronounced skin discoloration

Diagram 7.7: Spina Bifida



b) Spina Bifida Cystica (Aperta) - open

- Vertebral bony defect is large and the spinal cord and its meninges appear as a distinct cystic swelling over the affected site as revealed through the skin defect
- Defect in the skin allows herniation of the meninges or the spinal cord or both
- Has two types, meningocele and myelomeningocele (meningomyelocele)

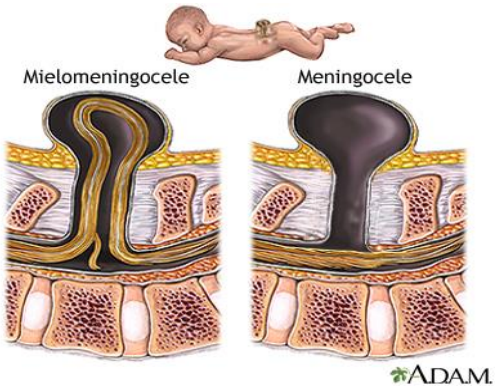
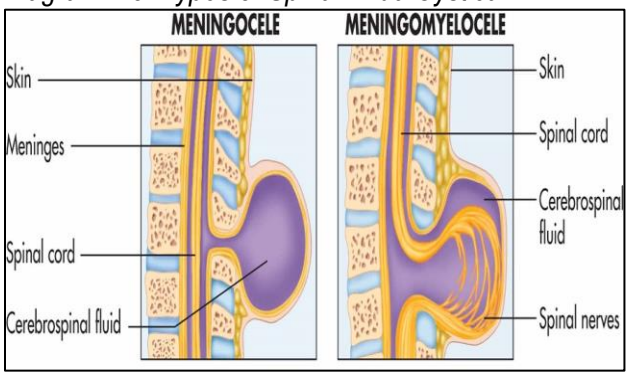


Diagram 7.8: Types of Spina Bifida Cystica



Clinical Features

- Signs and symptoms range from mild to severe depending on the location and extent of spinal cord involvement
- Neurological deficit e.g. weakness/paralysis, loss of sensation, urinary and feacal incontinence, hydrocephalus

Investigations

i) Maternal alpha foetal proteins screening
ii) Ultrasound

4. HYDROCEPHALUS

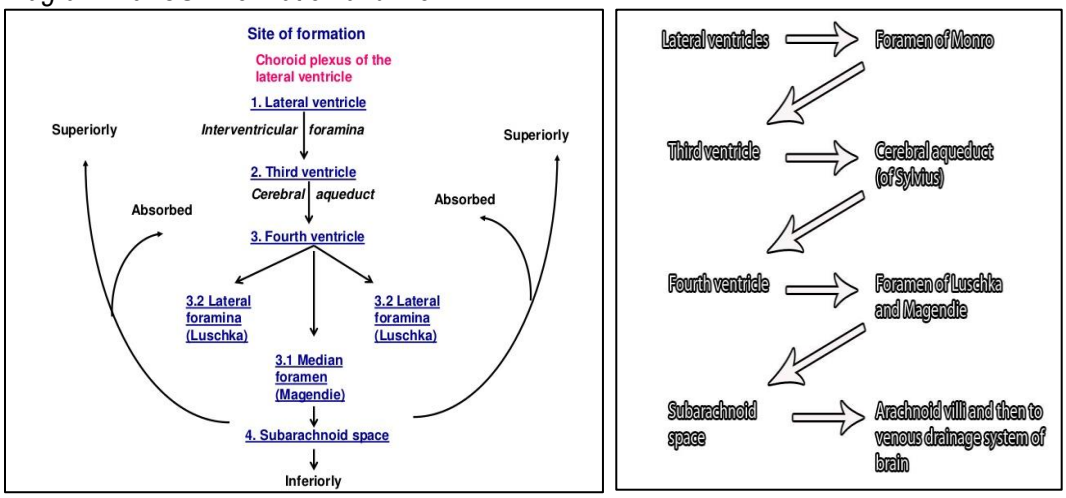
Introduction

- Means increased volume of CSF within the cranial cavity accompanied by dilatation of the ventricles
- Is a common medical condition that is characterized by abnormalities in the flow or resorption of cerebrospinal fluid (CSF), resulting in ventricular dilatation
- Hydrocephalus is characterized by abnormalities in the flow or resorption of cerebrospinal fluid (CSF), resulting in ventricular dilatation
- Can be classified into two clinical forms, congenital and acquired
- Hydrocephalus is one of the complex and multifactorial neurological disorders

CSF Formation and Circulation

- Majority of CSF is produced from within the two lateral ventricles
- From here, CSF passes through the interventricular foramina to the third ventricle, then the cerebral aqueduct to the fourth ventricle.

Diagram 7.9: CSF Formation and Flow



Pathogenesis

- Congenital hydrocephalus is the more common of the two forms of hydrocephalus
- Is probably the consequence of abnormal brain development and perturbed cellular function due to gene mutation?
- One hydrocephalus gene (X-linked) has been identified in humans

Causes of Hydrocephalus

1) Inherited - myelodysplasia, atresia of foramen of Monro, neural tube defects (encephalocele, spina bifida), genetic abnormalities (aqueduct stenosis, Dandy-Walker complex), cerebral and spinal malformations
2) Acquired - tumours, meningitis, infection, haemorrhage, arachnoid cyst, posterior fossa cyst, traumatic brain injury and idiopathic

Classification

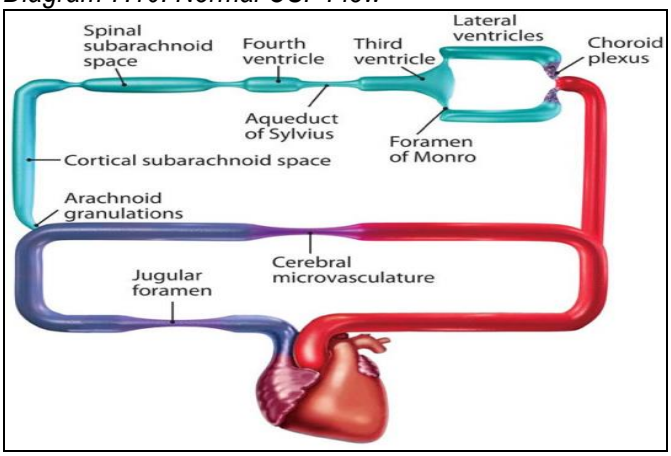
- Can be classified into two clinical forms, congenital and acquired
- Site of obstruction
  i) Internal hydrocephalus - increased volume of CSF within the ventricular system which becomes enlarged (dilated), associated with increased intracranial pressure
  ii) External hydrocephalus, excess CSF collects in the subarachnoid space
  iii) Communicating hydrocephalus - CSF can flow freely from the ventricular system
  iv) Non-communicating hydrocephalus - CSF does not circulate in the ventricular system
- Mechanisms of causation
  i) Primacy - involves actual increase in CSF volume within the cranial cavity with increased intracranial pressure due to obstruction of CSF flow (obstructive hydrocephalus)
  ii) Secondary Hydrocephalus - compensatory increase in CSF due to loss of neural tissue without increase in intracranial pressure e.g. flowing cerebral atrophy

Pathophysiology

- In hydrocephalus, the volume of CNS is increased and the ventricles are dilated
- In majority of the cases there is an increase in intracranial pressure
- Three main mechanisms
  1) Overproduction of CSF - the choroid plexus secretes more CSF to compensate for any external leak, but overproduction is not a cause of hydrocephalus

2) Obstruction of the flow of CSF (commonest) - sites vulnerable to obstruction are the aqueduct of Sylvius, foramina of Magendi and Luschka (4th ventricle to subarachnoid space) and the subarachnoid space between the midbrain and forebrain (interposition of tentorium cerebelli)
3) Defective or deficient reabsorption
   - Normally CSF is absorbed into venous sinus via the arachnoid granulation
   - Existence of pathology such as scarring following inflammation, haemorrhage obliterates the absorption sites reducing their absorption capacity

Diagram 7.10: Normal CSF Flow



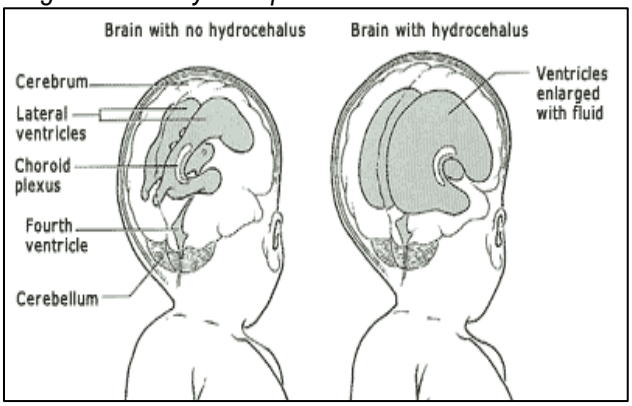
Pathology

- Ventricular dilatation, thinning and stretching of the brain, engorged scalp veins overlying the enlarged head and open fontanels

Clinical Features

- Infants - accelerated enlargement of the head, anterior fontanel –wide open and bulging, scalp vein are dilated, broad forehead, eyes may deviate downwards (sunset eyes sign)
- Older children - cranial sutures partially closed, skull percussion – "cracked pot" – Macewen sign – indicates separation of sutures

Diagram 7.11: Hydrocephalus



Investigations

- Plain Skull X-ray, CT scan and MRI

TAKE AWAY ASSIGNMENT

	Disease	Genetic link	Main pathology	Key features
1.	Anencephaly			
2.	Cleft lip and/or cleft palate			
3.	Spina bifida			
4.	Hydrocephalus			

TOPIC 8: POLYGENIC DISORDERS – CARDIOVASCULAR SYSTEM

Learning Objectives

- At the end of the lesson the learner will be able to explain the pathology of common multifactorial disorders of the cardiovascular system

1.0 CARDIOMYOPATHY

Introduction

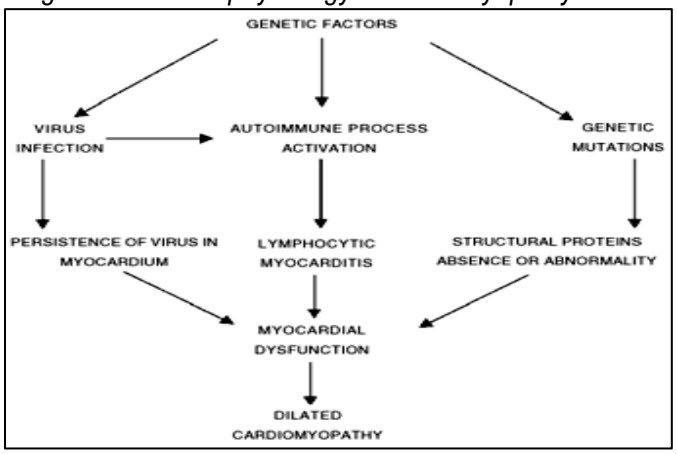
- Cardiomyopathy is a general term indicating disease of the cardiac muscle
- Can be primary cardiomyopathy (cause is unknown) or secondary cardiomyopathy (cause is known)
- WHO definition excludes heart muscles diseases of known aetiologies

Pathogenesis

- Familial DCM is associated with mutations in genes encoding sarcomeric proteins and proteins of the myocyte e.g., cytoskeletal or nuclear membrane, autosomal dominant
- Hypertrophic cardiomyopathies are mainly linked to mutations on genes encoding sarcomeric proteins, and beta myosin heavy chain and myosin binding protein C gene mutations
- Risk factors – Coxsackie's virus, HIV, alcohol toxicity and peri-partum, post viral myocarditis

Pathophysiology

Diagram 8.1: Pathophysiology of cardiomyopathy



Pathology

- Cardiomegaly, dilatation of the heart chambers, thickening of ventricular walls and thrombosis (mural), hypertrophy of heart muscle cells and degenerative changes

Clinical Features

- Cardiac failure, cardiac arrhythmias and embolism

Investigations

1) Chest X-ray – cardiac enlargement
2) ECG – diffuse non-specific ST segment and T wave abnormalities
3) Echocardiogram – dilatation of the left ventricle and/or right ventricle with poor global contraction
4) Full haemogram

2.0 ATHEROSCLEROSIS

Introduction

- **Atherosclerosis** is a disease of the **intima** associated with deposition of sterols, triglycerides and lipoproteins resulting in narrowing of the vessel lumen, thrombosis or obstruction in large and medium sized arteries
- **Arteriosclerosis** affects the **media** causing proliferation or hyaline changes that result in an increase in wall thickness and decreased vessel elasticity (arteriosclerosis = hardening of vessels)
- **Atheroma** is an **intimal plague** (patch) created by the focal deposition of lipids in the subendothelial connective tissue of the inner intima due to accumulation of lipids, proliferation of smooth muscle cells and formation of fibrosis tissue. They have a soft lipid rich part (*athere* = porridge) and a hard (sclerotic) fibrous component. The principal changes occur largely within the intima of the medium and large arteries

Pathogenesis

- A protein called **apolipoprotein E,** which can exist in several different forms, is coded for by a gene found on chromosome 19. It is important for removing excess cholesterol from the blood and does so by carrying cholesterol to receptors on the surface of liver cell
- Defects in apolipoprotein E sometimes result in its inability to bind to the receptors, which leads to an increase a person's blood cholesterol and consequently their risk of atherosclerosis.
- Risk Factors
  i) Major risk factors
     a. Constitutional– age (advancing age), sex (M > F up to the age of 55 years after which the incidence is the same), genetic factors
     b. Acquired (Hard risk factors) - hypertension, hyperlipidaemia, cigarette smoking and diabetes mellitus
  ii) Minor risk factors (Soft risk factors)
     - Have a lesser role in aetiology of atherosclerosis and include environmental factors (high prevalence in developed than developing countries), diet, hormonal factors, physical inactivity and stressful life style

Pathophysiology

- Change or damage to the vascular endothelium causes increased permeability of the vessel wall to proteins and lipids leading to aggregation of platelets and monocytes
- Aggregated platelets and monocytes release substances to promote smooth muscle proliferation and the influx of more leucocytes
- The leucocytes release various enzymes and growth factors which promote smooth muscle cell proliferation
- Monocytes migrate from the blood into the sub-endoethelial layers where they become macrophages and ingest lipids

Pathology

- Principal lesions are fatty streaks, fibrous plaque and complicated lesion
- Reduction of blood flow through arteries
- Predisposition to thrombosis
- Bleeding into a plaque – coronary arteries leading to myocardial infarction
- Weakening of vessel walls

Clinical Features

- Presents with hypertension, stroke, myocardial infarction and ischaemic heart disease

Investigations

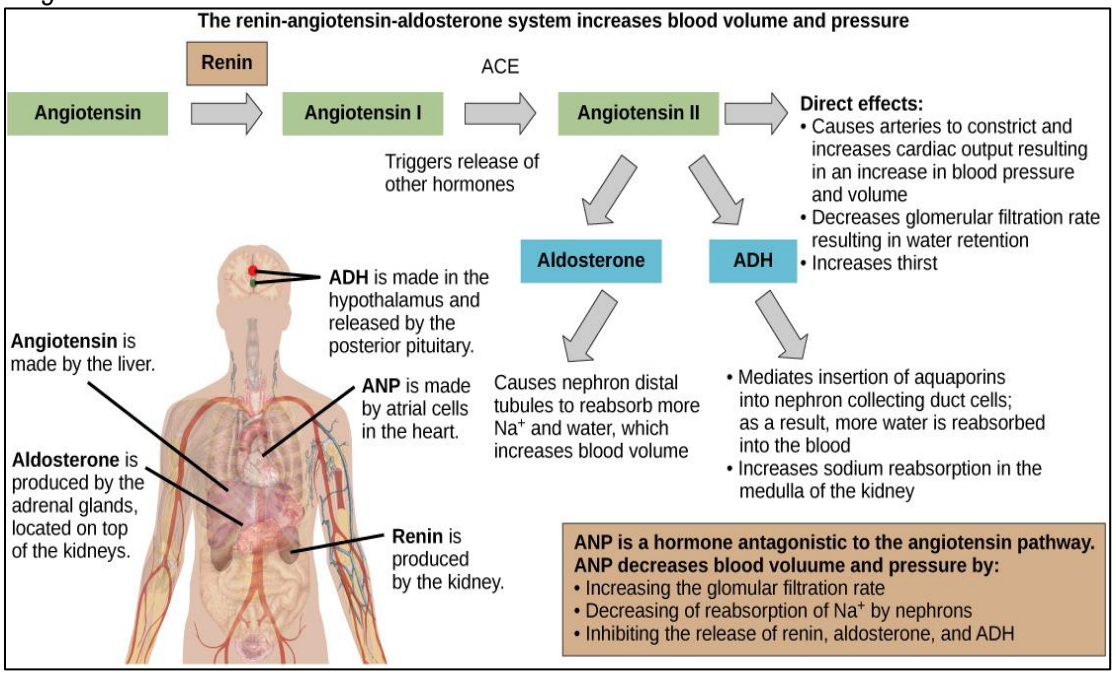
i) Serum lipid levels
ii) Ultrasound
iii) Renal function tests

3.0 HYPERTENSION

Introduction

- Blood pressure (BP) is a complex trait regulated by an intricate network of physiological pathways involving extracellular fluid volume homeostasis, cardiac contractility and vascular tone through renal, neural or endocrine systems
- Blood pressure control mechanisms include nervous, hormonal, renal and capillary shift mechanisms
- Hypertension is the most common risk factor for stroke and myocardial infarction and predisposes affected individuals to heart failure, ventricular arrhythmias, renal failure, blindness, and other serious medical problems
- Blood pressure (BP) is a complex trait regulated by an intricate network of physiological pathways involving extracellular fluid volume homeostasis, cardiac contractility and vascular tone through renal, neural or endocrine systems.

Diagram 8.2: Homeostasis of BP

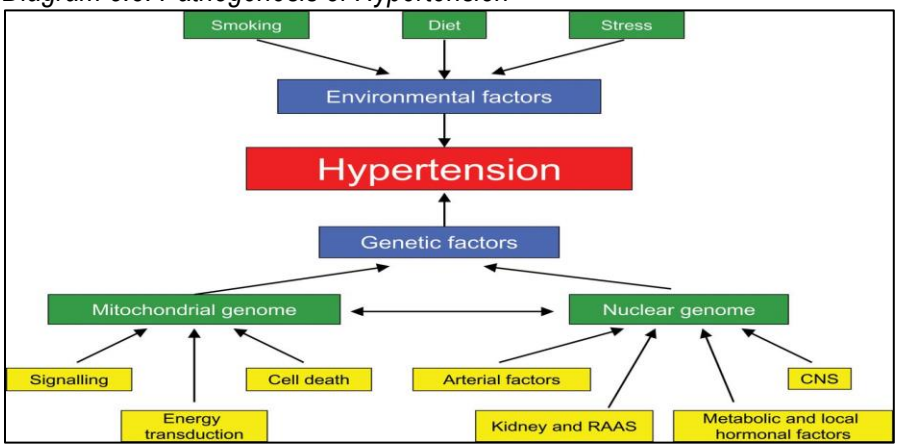


Pathogenesis

- Presence of risk factors and genetic predisposition involving the **angiotensinogen (AGT) gene** which favours retention of sodium and action of angiotensin II
- Advanced molecular biological technologies have identified as many as **17 independent mutations in genes associated with blood pressure - hypertension (8 genes) or hypotension (9 genes)**

- The RAAS plays a prominent role in the genesis of hypertension - polymorphisms of the genes coding for angiotensinogen, angiotensin-converting enzyme, angiotensin II type 1 and 2 receptors
- Others include aldosterone synthase, **the KLK 1 gene** of tissue kallikrein, gene variants of endothelial nitric oxide synthase and polymorphisms of the endothelin-1 gene, genes coding for inflammatory cytokines, adrenergic receptors and intracellular G proteins, which can activate Na+/K+ exchangers

Diagram 8.3: Pathogenesis of Hypertension



Classification

- Primary and secondary hypertension

Risk Factors

i) Non-modifiable – age, gender, **genetics**, race
ii) Modifiable - high BMI, lifestyle, smoking, alcohol, diabetes

Pathophysiology

- Revolves around volume loading and vasoconstrictor mechanisms

Pathology

- Includes destruction of blood vessels – narrowing and necrosis; heart enlargement; renal damage and brain damage

Investigations

i) Renal function tests
ii) Lipid serum levels
iii) Blood sugar levels

Complications

STUDY QUESTIONS

1) Explain the normal production and flow of CSF.
2) How does one develop hypertension?

TAKE AWAY ASSIGNMENT

	Disease	Genetic link	Main pathology	Key features
1.	Cardiomyopathy			
2.	Atherosclerosis			
3.	Hypertension			

TOPIC 9: POLYGENIC DISORDERS – RESPIRATORY AND IMMUNE SYSTEMS

Learning Objectives

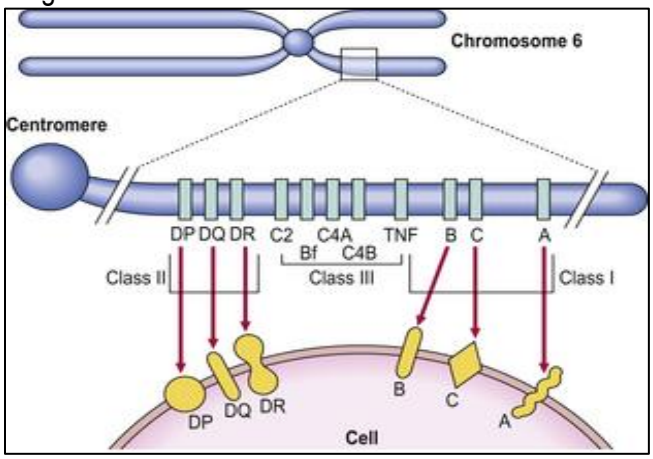
At the end of the lesson the learner will be able to: -

1) Outline the pathology of common multifactorial disorders of the respiratory system

1.0 THE IMMUNE SYSTEM - INTRODUCTION

- Histocompatibility antigens antigens play a fundamental role in the normal immune response by presenting antigenic peptides to T-cells.
- Human major histocompatibility complex (MHC) antigens are also known as human leukocyte antigens(HLAs)
- MHC antigens are cell surface glycoproteins of two basic types: class I and class II
- They exhibit extensive genetic polymorphism with multiple alleles at each locus
- As a result, genetic variability between individuals is very great and most unrelated individuals possess different HLA molecules

Diagram 9.1: MHC/HLA



2.0 ASTHMA

Introduction

- Bronchial asthma is a chronic relapsing inflammatory disorder characterized by increased responsiveness of the tracheobronchial tree to various stimuli resulting in widespread paroxysmal contraction of bronchial airways due to muscular spasms and plugging by increased thick mucus secretions from the mucosal glands
- Changes result in a state whereby the respiratory tree is drawn longer with a reduced diameter forming a physiological valve mechanism that leads to easy or normal inspiration but difficult and prolonged expiration
- The inheritance of asthma and allergy does not follow the classical Mendelian patterns of inheritance; however, rarely monogenic cases of atopic disease have been documented and the majority of atopic asthma is likely to be the result of numerous interacting genetic and environmental factors

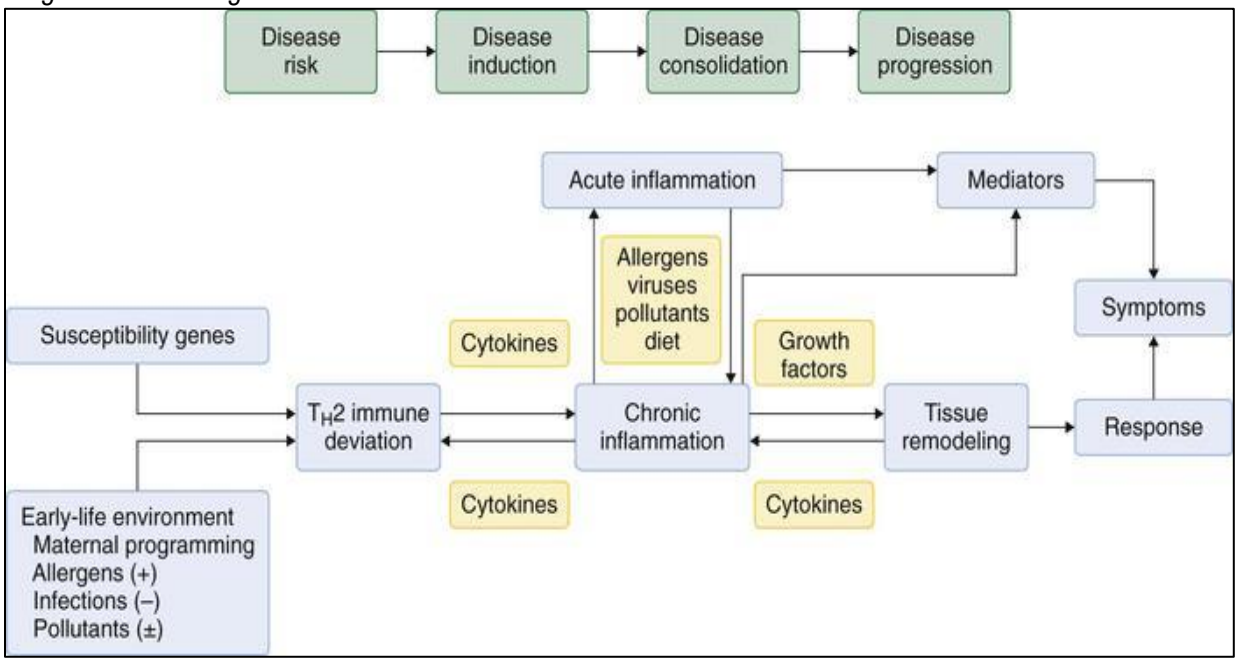
Classification

1. Extrinsic (atopic, allergic) asthma
2. Intrinsic (cryptogenic, non-atopic, idiosyncratic) asthma
3. Exercise induced asthma
4. Drug induced
5. Occupational asthma
6. Asthma associated with COPD

Pathogenesis

- Results from a hypersensitivity state caused by a combination of genetic and environmental factors
- Genetic studies indicate that multiple genes are involved in the pathogenesis of this disease, and chromosomal regions likely to harbour asthma susceptibility
- Eosinophils are believed to play important roles in the pathogenesis of asthma through the release of inflammatory mediators
- The immune response associated with asthma is characterized by infiltration of the bronchial mucosa with mast cells, eosinophils, macrophages, lymphocytes, & plasma cells
- Cytokines derived from T helper 2 (T_{H2}) lymphocytes and mast cells are implicated in the pathogenesis of asthma
- Other genes genes playing role in innate immune recognition and immunoregulation, antigen presentation, biosynthesis and regulation of lipid mediators, IgE synthesis and regulation, Th2 differentiation and effector function, and other pathological mechanisms have been identified; T helper cell differentiation play vital role in asthma pathogenesis; SPINK5, on chromosome 5q23-31, is another gene that might play an important role in **airway remodelling** as it is highly expressed in **bronchial epithelium** and consistently shows association with asthma

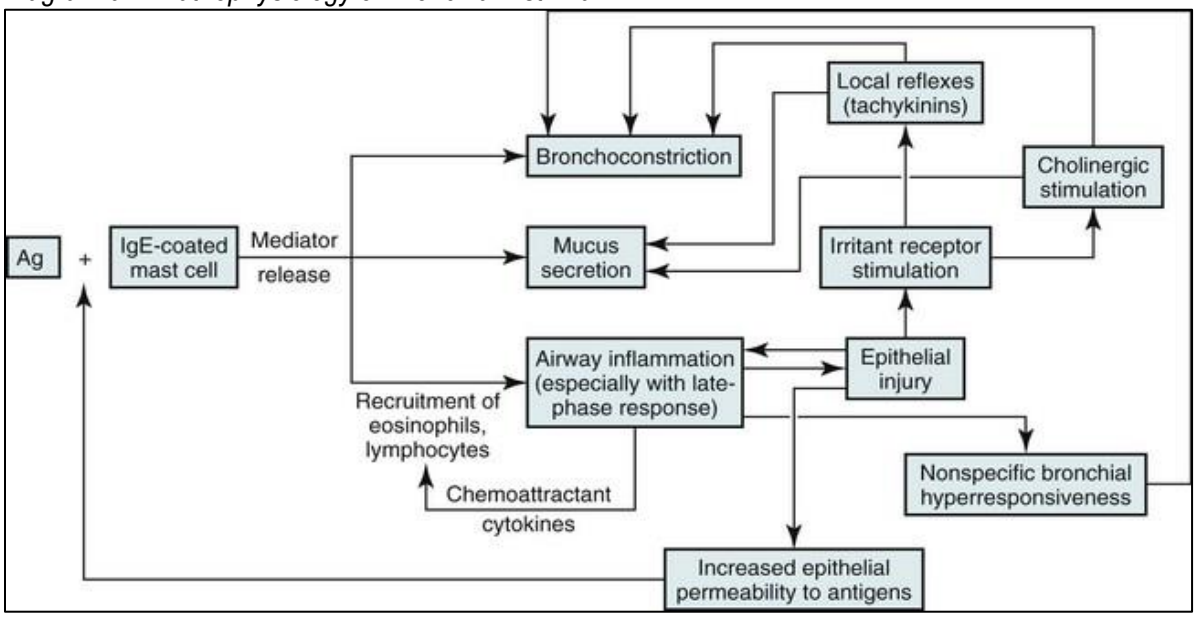
Diagram 9.1: Pathogenesis of Bronchial asthma



Pathophysiology

- This is an acute or immediate response, which consists of ***bronchoconstriction***, ***oedema***, ***mucous secretion*** and ***hypotension*** (in severe cases)
- The response is triggered by allergens or infection

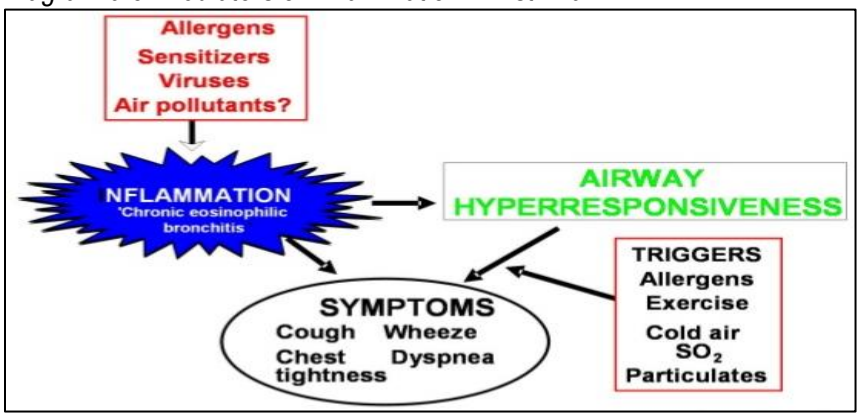
Diagram 9.2: Pathophysiology of Bronchial Asthma

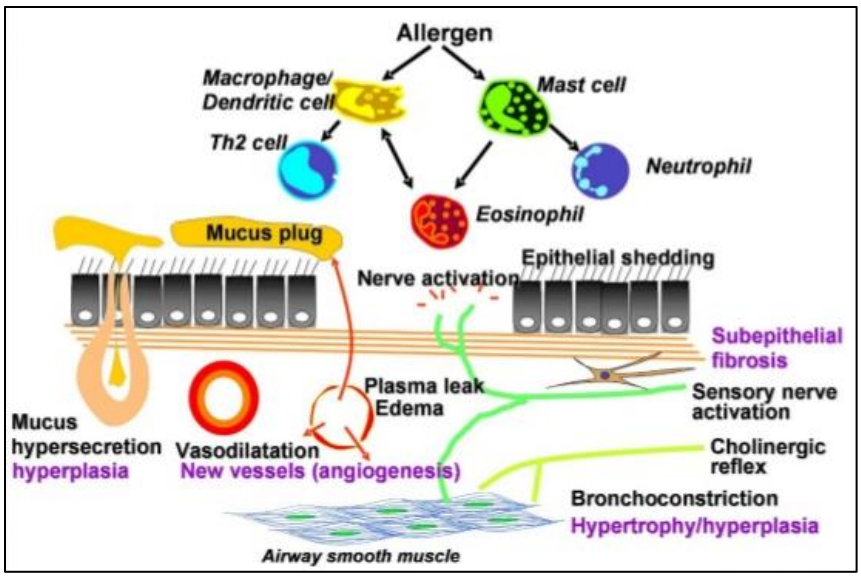


i) Hypersensitivity
- Pivots around airway hypersensitivity, inflammation and airway obstruction
- Exposure of pre-sensitized IgE coated mast cells to allergens (antigens) results in release of chemical mediators on the mucosal surface resulting in the opening of the intercellular tight junctions thereby enhancing penetration of the mast cells by antigens to reach the numerous submuocal mast cells

ii) Inflammation
- Mast cells release cytokines, which result in influx of leucocytes (**neutrophils**, **monocytes**, **lymphocytes**, **basophils** and **oesinophils**) which mediate the late phase reaction together with recruited chemotaxic factors
- Other sources of mediators of the late phase reaction include the vascular endothelium and airway epithelial cells (produce cytokines in response to infection, drugs and gases)
- Process of inflammation results in **oedema** formation on the bronchial walls and hyper secretion of **tenacious mucous**

Diagram 9.3: Mediators of Inflammation in Asthma



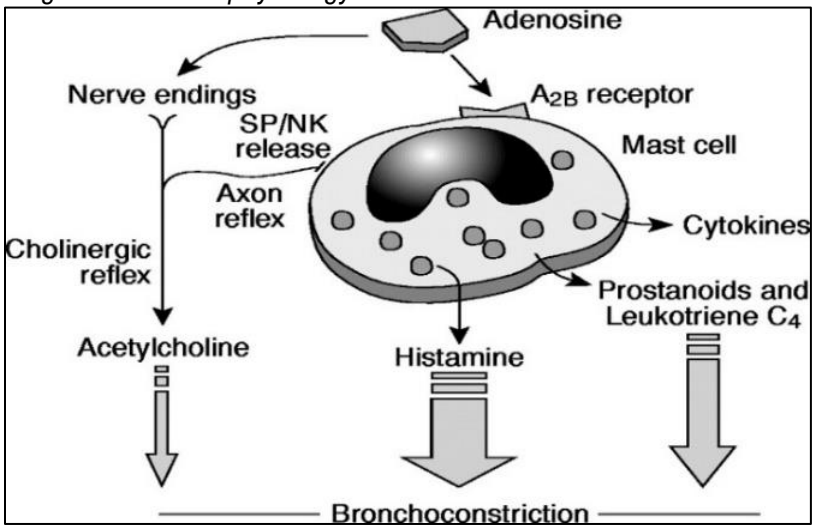


iii) Broncho constriction

- Direct stimulation of the sub epithelial vagal (parasympathetic) receptors provokes bronchoconstriction through both central and local reflexes
- There is release of histamine, acetylcholine (autonomic nervous system), prostaglandins and leukotrienes which are bronchoconstrictors

iv) Remodelling

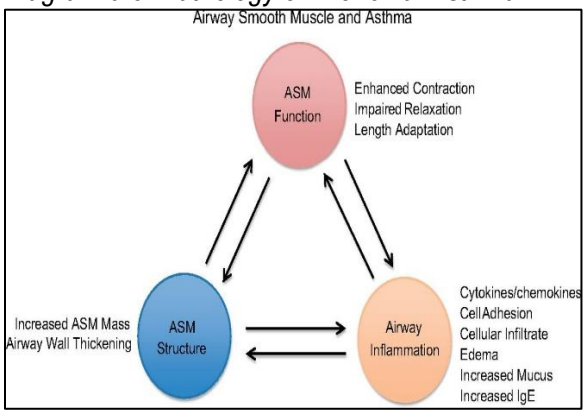
Diagram 9.4: Pathophysiology of Bronchoconstriction

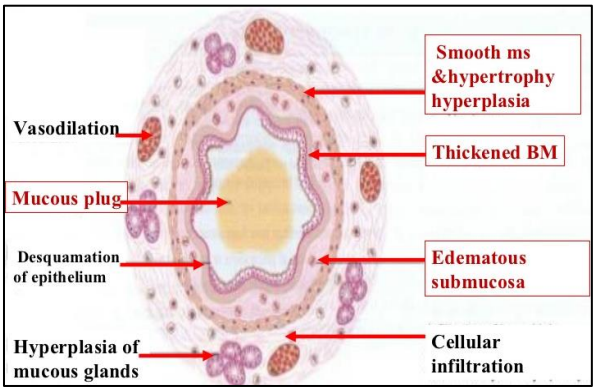


Pathology

- Bronchial obstruction due to bronchoconstriction, oedema
- Thick tenacious mucous containing Curshaman spirals, Charcot Leyden crystals and leucocytes
- Hyaline membrane thickening
- Hypertrophied bronchial muscle

Diagram 9.5: Pathology of Bronchial Asthma





Clinical Features

- Main Features include – cough, headache, difficulty in breathing, hyperventilation, wheezing and chest pain/tightness, paradoxical pulse

Investigations

i) Chest x-rays
ii) Lung function tests
iii) Hypersensitivity tests
iv) Spirometry
v) Total blood counts (haemogram)

3.0 EMPHYSEMA

Introduction

- Is abnormal permanent dilatation/enlargement of airspaces distal to the terminal bronchiole accompanied by destruction of the bronchiole walls without fibrosis

Aetiology

- Main factors are -
  i) Smoking – major risk factor that is dose related
  ii) α_1-antitrypsin deficiency – a protease inhibitor that prevents lung damage especially in smokers
  iii) Occupation – dusty environments e.g. coal mines

Pathogenesis

- Is due to imbalance between protease and anti-protease activities in the lung resulting in destruction of the alveolar walls
  - $\alpha-1-$antitrypsin ($\alpha-_1-$protease inhibitor) is a glycoprotein constituent of globulin in plasma is synthesised in the liver and is usually present in serum and tissue fluids
  - Protease inhibits proteolytic enzymes, which degrade elastin or neutrophil derived elastase. Increased neutrophil infiltration of the lung causes excessive production of elastase
  - Deficiency of $\alpha-1-$antitrypsin occurs in homozygous states however in smoking accelerates the damage in heterozygous situations

- Smoking - reduces anti-elastase and increases elastolytic protease in the lungs due to oxidants in cigarette smoke which inhibit $\alpha-1-$antitrypsin and smokers have increased phagocytes and neutrophils in the lungs
- After the damage the pressure inspired air expands the damaged portion into an emphysematous space
- With continued enlargement more pressure is required to cause further dilatation resulting in increased dilatation and damage
- Coughing in chronic bronchitis aggravates the situation

4.0 ALLERGIC (HYPERSENSITIVITY) DISORDERS

- Occur due to reactions emanating from the actions of the immune system

Type	Name	Genetic Link	Mechanism	Mediators	Examples
I	IgE-mediated hypersensitivity (Allergy) Atopic		Ag induces cross-linking of IgE bound to mast cells releasing vasoactive mediators	IgE Histamine	Systemic anaphylaxis, Local anaphylaxis; Hay fever; Asthma Eczema
II	Antibody-mediated cytotoxic hypersensitivity		Ab directed against cell-surface Ag mediates cell destruction via ADCC or complement	IgM or IgG (Complement)	Blood transfusion reactions; Haemolytic disease of the newborn Autoimmune Haemolytic anaemia
III	Immune-complex mediated hypersensitivity		Ag-Ab complexes deposited at various sites induces mast cell degranulation via Fcgamma RIII, PMN degranulation damages tissue	IgG (Complement)	Arthus reaction (Localised) Systemic reactions Disseminated rash, Arthritis, Acute Rheumatic fever Glomerulonephritis
IV	Cell-mediated hypersensitivity		Memory TH1 cells release cytokines that recruit and activate macrophages	T-cells	Contact dermatitis, Tubercular lesions

TAKE AWAY ASSIGNMENT

	Disease	Genetic link	Main pathology	Key features
1.	Bronchial asthma			
2.	Emphysema			
3.	Hypersensitivity disorders			

TOPIC 10: POLYGENIC - NEUROLOGICAL AND MUSCULOSKELETAL

Objectives

At the end of the lesson the learner will be able to: -
1) Outline the pathology of common multifactorial disorders of the brain and musculoskeletal system

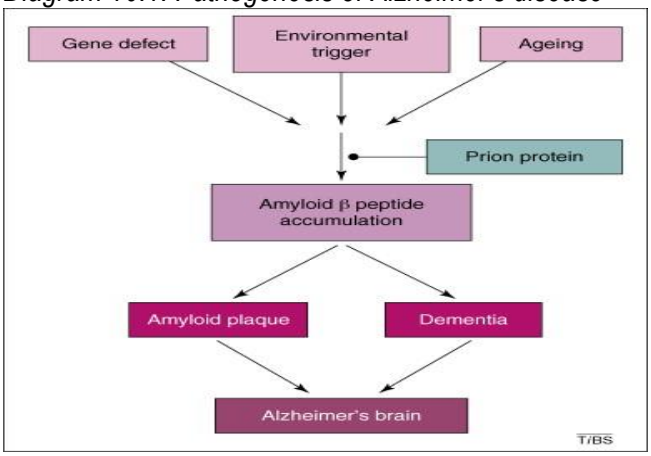
1.0 NEUROLOGICAL DISORDERS

1. ALZHEIMER'S DISEASE

Introduction
- Progressive mental deterioration that can occur in middle or old age, due to generalized degeneration of the brain
- It is the most common cause of premature senility
- The word dementia describes a set of symptoms that can include memory loss and difficulties with thinking, problem-solving or language

Pathogenesis
- Risk factors include aging process, family history, genetic, Down syndrome and environmental factors e.g. obesity, insulin resistance, vascular factors, dyslipidemia, hypertension and traumatic brain injury
- Results from mutations in the ***APP*** **gene on chromosome 21, presenilin-1 (*PS1* and presenilin-2 (*PS2*) genes on chromosomes 14 and 1 respectively**

Diagram 10.1: Pathogenesis of Alzheimer's disease

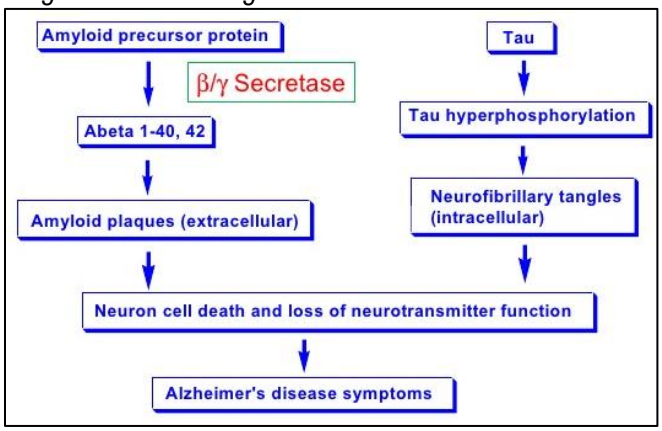


- The mechanisms include
  a) Two processes involving deposition of insoluble compounds
     i) Extracellular deposition of beta amyloid-Aβ peptide
        - Aβ is a 36 to 43 amino acid peptide, which is part of a larger protein, the Amyloid Precursor Protein (APP) - a transmembrane protein, made by neurons and other brain cells (The gene for APP is on chromosome 21)

     ii) Intracellular accumulation of tau protein
        - Neurofibrillary degeneration is characterized by the deposition in the neuronal body and processes of insoluble polymers of **over-phosphorylated microtubule associated protein tau**

b) Neuro-inflammation
c) **Free radicals- o**xidative stress, compounding with advancing age, causes mitochondrial DNA mutations, mitochondrial dysfunction and more oxidative stress. This process is accelerated in AD by the action of Aβ (a mitochondrial poison and free radical generator) and activated microglia, also a source of free radicals
d) Ischemia caused by cerebral amyloid angiopathy
e) Loss of cholinergic neurons in the basal forebrain, decreased **acetylcholine** (Ach) levels, and a decrease in the acetylcholine synthesizing enzyme **choline acetyltransferase** (CHAT) in the cerebral cortex

Diagram 10.2: Pathogenesis of Alzheimer's disease



Pathophysiology

- Affects the 3 processes that keep neurons healthy i.e. Communication, metabolism, and repair. Certain nerve cells in the brain stop working, lose connections with other nerve cells, and finally die
- The destruction and death of these nerve cells causes the memory failure, personality changes, problems in carrying out daily activities, and other features of the disease.
- The accumulation of senile plaques (SPs) primarily precedes the clinical onset of AD.
- Neurofibrillary tangles (NFTs), loss of neurons, and loss of synapses accompany the progression of cognitive decline

Pathology

- Senile plagues
- Neurofibrillary tangles (NFTs
- Cerebrocortical atrophy

Clinical Features

- Insidiously progressive memory loss, cognitive impairment, slowly progressive behavioural changes, language disorders (e.g., anomia), impairment in their visuospatial skills and executive functions, In later stages, many patients develop extrapyramidal dysfunction, progressive aphasia, spastic paraparesis, and impaired visuospatial skills,

2. SCHIZOPHRENIA

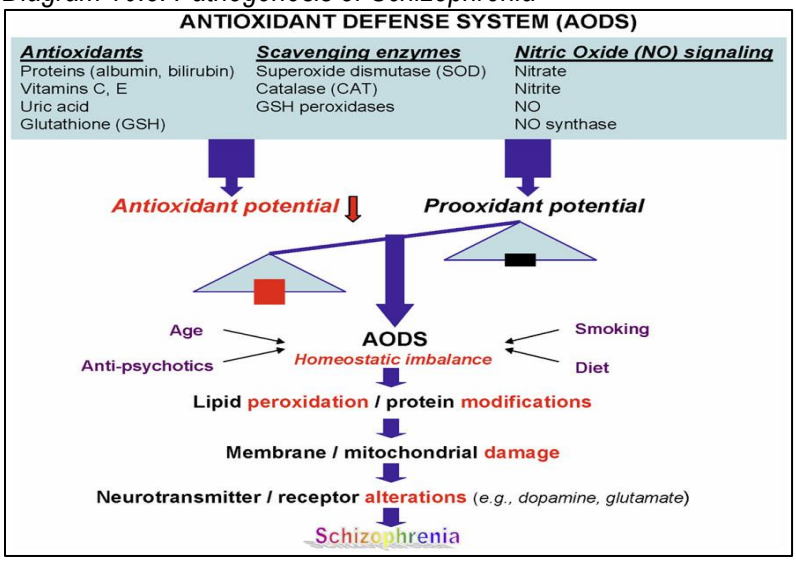
Introduction

- Schizophrenia is a mental disorder characterized by abnormal social, behavior psychological symptoms and failure to understand reality
- Schizophrenia is a brain disorder classified as a psychosis, which means that it affects a person's thinking, sense of self, and perceptions
- Typically becomes evident during late adolescence or early adulthood
- Individuals have difficulty distinguishing between what is real and what is imaginary; may be unresponsive or withdrawn; and may have difficulty expressing normal emotions in social situations.

Pathogenesis

- Genetics (Heredity) - tends to run in families and may be triggered by environmental events, such as viral infections or highly stressful situations or a combination of both
- Chemistry - genetics determine how the brain uses certain chemicals and people with schizophrenia have a chemical imbalance of brain chemicals (**serotonin and dopamine)** which are neurotransmitters
- These neurotransmitters allow nerve cells in the brain to send messages to each other

Diagram 10.3: Pathogenesis of Schizophrenia



Pathophysiology

- Imbalance of neurotransmitters affects the way a person's brain reacts to stimuli--which explains why a person with schizophrenia may be overwhelmed by sensory information (loud music or bright lights) which other people can easily handle.
- Problem in processing different sounds, sights, smells and tastes can also lead to hallucinations or delusions

Pathology

i) Structural brain abnormality – brain atrophy, ventricular enlargement, reduced size of specific brain structures
ii) Functional brain abnormalities
iii) Neurochemical brain abnormalities

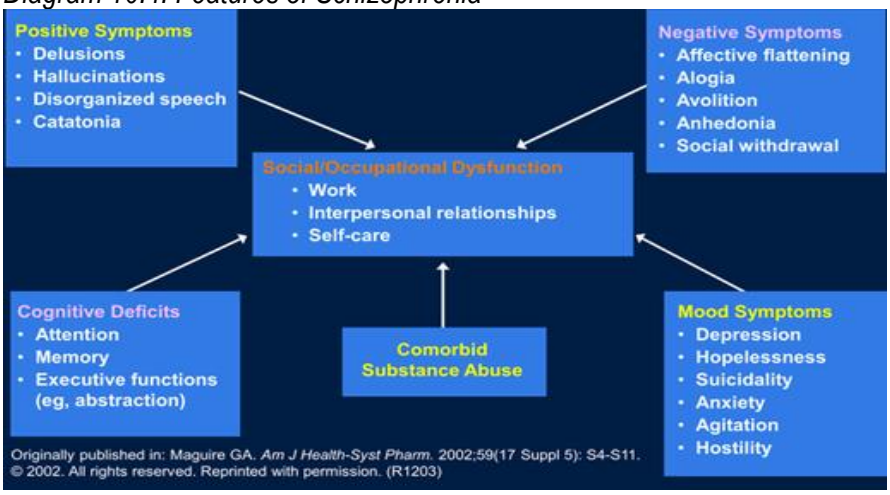
Types

i) Paranoid schizophrenia - a person feels extremely suspicious, persecuted, or grandiose, or experiences a combination of these emotions.
ii) Disorganized schizophrenia - a person is often incoherent in speech and thought
iii) Catatonic schizophrenia -a person is withdrawn, mute, and negative and often assumes very unusual body positions
iv) Residual schizophrenia - a person is no longer experiencing delusions or hallucinations, but has no motivation or interest in life
v) Schizoaffective disorder - a person has symptoms of both schizophrenia and a major mood disorder such as depression

Clinical Features

- Signs and symptoms of schizophrenia include false perceptions called hallucinations. Auditory hallucinations of voices are the most common hallucinations in schizophrenia, but affected individuals can also experience hallucinations of visions, smells, or touch (tactile) sensations. Strongly held false beliefs (delusions) are also characteristic of schizophrenia
- Positive symptoms are disturbances that are "added" to the person's personality including delusions (false ideas or beliefs), hallucinations (false perceptions –seeing, feeling, tasting, hearing or smelling something that doesn't really exist) and disordered thinking and speech (moving from one topic to another, in a nonsensical fashion. Individuals may make up their own words or sounds)
- Negative symptoms are capabilities that are "lost" from the person's personality include social withdrawal, extreme apathy, lack of drive or initiative and emotional unresponsiveness, suicidal tendencies

Diagram 10.4: Features of Schizophrenia



3. BIPOLAR DISORDER

Introduction

- Also known as manic-depressive illness
- Is a brain disorder that causes unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks
- Bipolar disorder is characterized by periods of deep, prolonged, and profound depression that alternate with periods of an excessively elevated or irritable mood known as mania

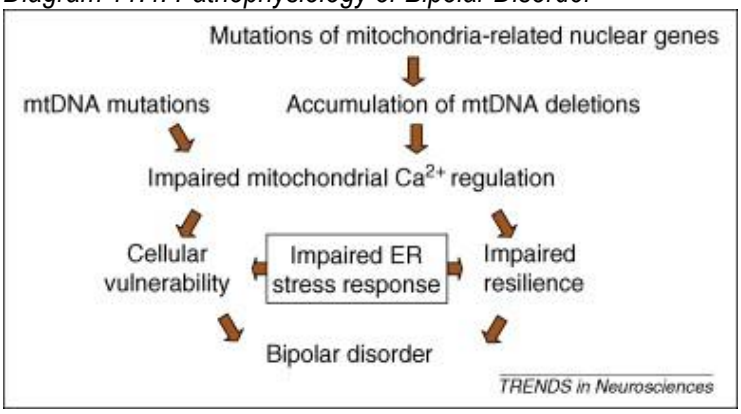
Pathogenesis

i) Genetic factors**-** involvement of the ***ANK3, CACNA1C,*** **and** ***CLOCK*** **genes**
ii) Biochemical factors - multiple biochemical pathways likely contribute to bipolar disorder including neurotransmitters and hormonal imbalances and disruptions of the hypothalamic-pituitary-adrenal axis involved in homeostasis and the stress response may also contribute to the clinical picture of bipolar disorder
iii) Neurophysiologic factors - functional and anatomic alterations in bipolar disorder in brain networks associated with the experience and regulation of emotions
iv) Environmental factors**-** external stresses or the external pressures may serve to exacerbate some underlying genetic or biochemical predisposition
v) Psychodynamic factors**-** manifestation of losses (i.e., the loss of self-esteem, sense of worthlessness)
vi) Pharmacological factors - there is the risk that antidepressant treatment may propel the patient into a manic episode.

Pathophysiology

- Involvement of cortical, limbic, basal ganglia, and cerebellar structures in the brain
- Defects in mitochondrial energy production

Diagram 11.4: Pathophysiology of Bipolar Disorder



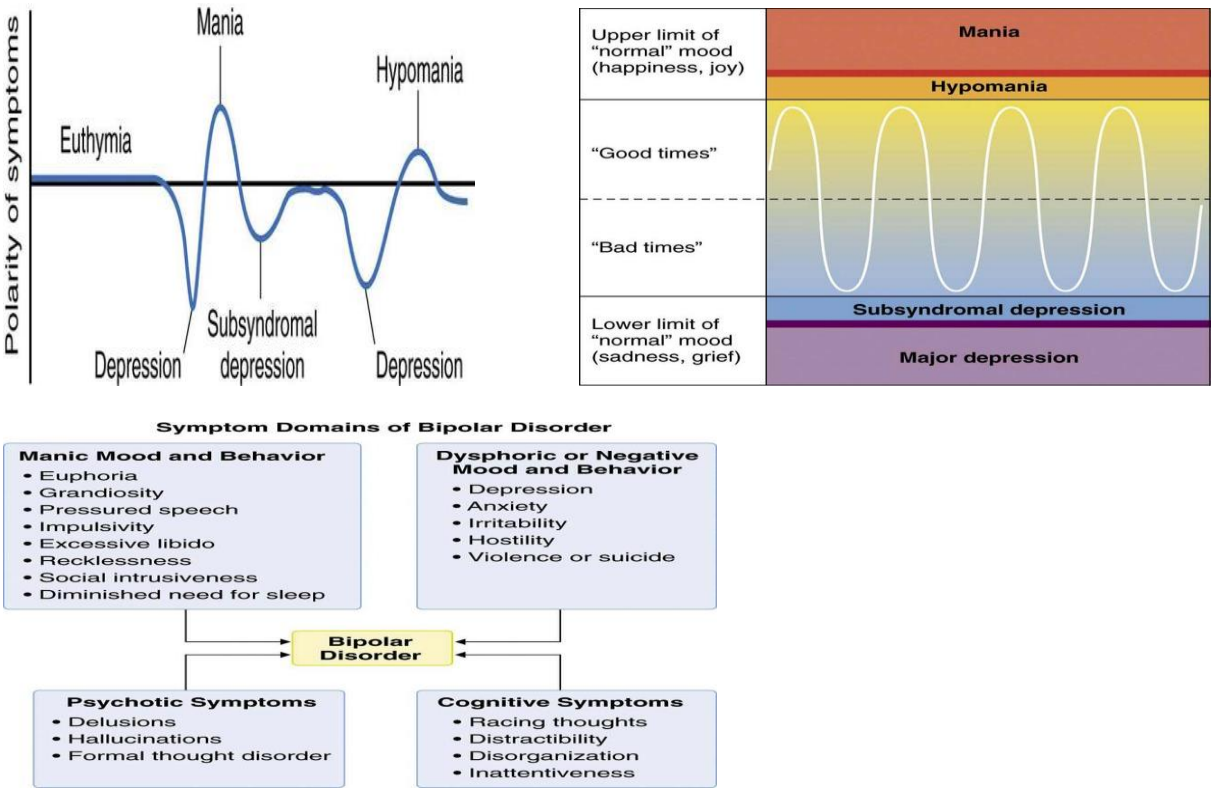
Pathology

- There is an underlying dysfunction of mitochondria
  i) Decreased mitochondrial respiration
  ii) Changes in mitochondrial morphology
  iii) Increases in mitochondrial DNA (mtDNA) polymorphisms and in levels of mtDNA mutations
  iv) Down regulation of nuclear mRNA molecules and proteins involved in mitochondrial respiration
  v) Decreased high-energy phosphates and decreased pH in the brain

Clinical Features

-

Diagram 10.5: Clinical Features of Bipolar Disease



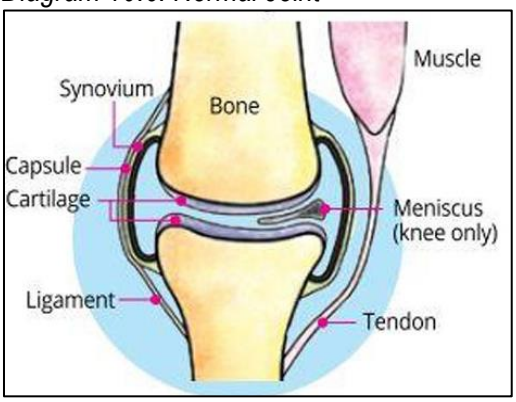
2.0 MUSCULOSKELETAL SYSTEM

1. RHEUMATOID ARTHRITIS (RA)

Introduction

- Most common inflammatory arthritis
- Is a systematic **autoimmune inflammatory joint** disorder affecting mainly synovial joints (linings, tendon sheets and bursae)
- MHC class III region contains genes that are involved in immune response, it has been suggested
- that these genes are good candidates for the development of RA. For example, HSP70 proteins have been suggested as playing a role in the self-surveillance and susceptibility to autoimmune diseases, including RA

Diagram 10.6: Normal Joint



Pathogenesis

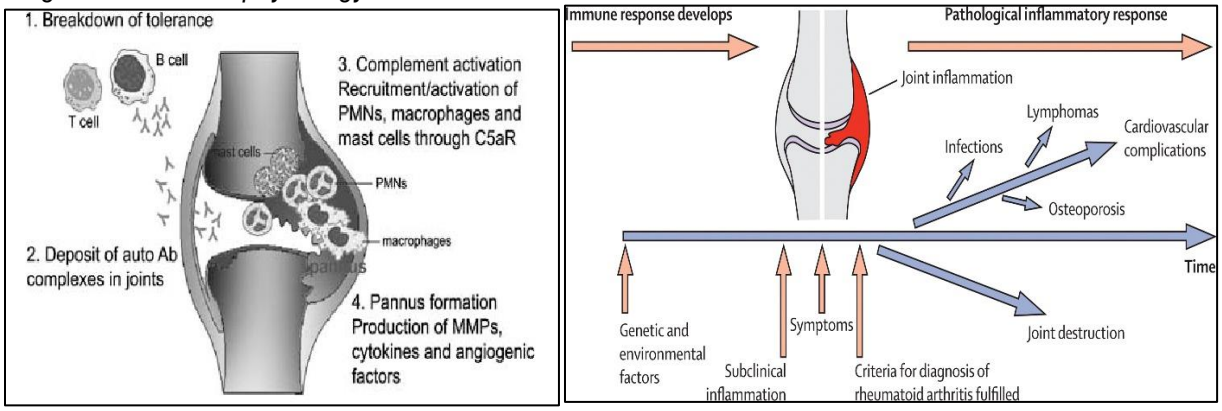
- Results from a complex interaction between genes and environment, leading to a breakdown of immune tolerance and synovial inflammation in a characteristic symmetric pattern
- RA genetic susceptibility factor is delivered via the human leukocyte antigen (HLA) locus on the MHC

- HLA-DRB1 gene encodes major histocompatibility complex (MHC) class-II β-chain molecules that take role in the presentation of antigen to CD4+ T helper cells and is known as one of the most polymorphic genes in the human genome
- MHC class III region contains genes that are involved in immune response e.g. HSP70 proteins play a role in the self-surveillance and susceptibility to autoimmune diseases, including RA
- Activation of T cells by unidentified antigens in the susceptible host commences the rheumatoid process
- The PTPN22 gene, located on chromosome 1p13, encodes a lymphoid-specific phosphatase (Lyp) protein which is a negative regulator of T cell activation
- Predisposing or risk factors - genetic, endocrine (common in females, null parity), infections (EBV, CMV and retrovirus), socio-economic status and life style factors

Pathophysiology

- Break in tolerance results in production of autoantibodies and formation of antibody antigen complexes
- Antibodies and T cells travel via blood to reach the joint
- Antibodies and Ag-Ab complexes are deposited in the joints and trigger inflammation of the synovial membrane (synovitis) under the influence of mediators of inflammation including TNF-α, IL-6, IL-8
- Breakdown of the joint cartilage by proteases and activated osteoclasts destroy the bone surface
- Bone and cartilage erosion
- Angiogenesis and the inflammatory chemokines reach the systems to cause systemic manifestations

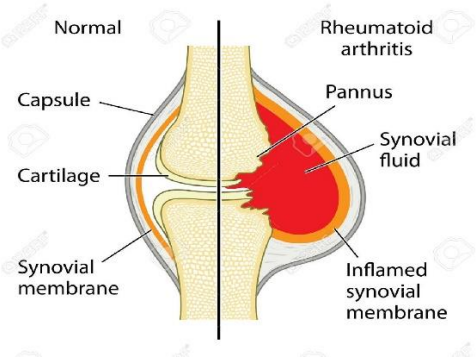
Diagram 10.6: Pathophysiology of RA



Pathology

- Joint destruction leading to deformities
- Inflammation leading swollen painful joints
- Destruction of other connective tissues

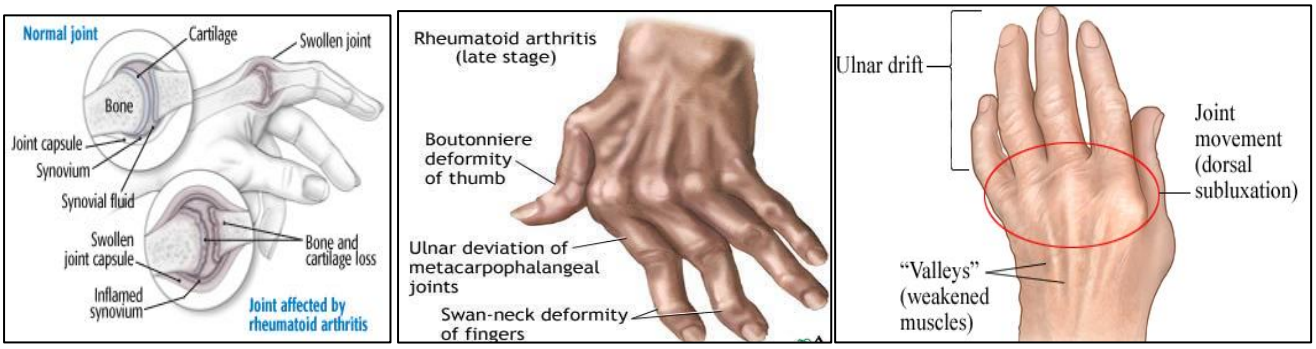
Diagram 10.7: Normal – Rheumatoid Arthritis Joint



Clinical Features

i. Articular - Joint involvement
- Swelling - small joints of the hands and feet including metacarpophalangeal (MCP), wrist, proximal interphalangeal (PIP), knee, metatarsophalangeal (MTP), shoulder, ankle, cervical spine, hip, elbow, and temporo-mandibular joints, DIPs are spared.
- Joint stiffness
- Deformities – Boutonniere, Z-deformity, ulna deviation

Diagram 10.8: Deformities



ii. Extra-articular manifestations
- Skin – subcutaneous nodules
- CVS – pericardial effusion, pericarditis, myocarditis, valvular disease, myocardial ischaemia
- Pulmonary - pleural effusion, interstitial fibrosis
- GIT – hepatomegaly, splenomegaly
- Haematological – chronic anaemia
- Neurologic – nerve entrapment
- Ocular – uveitis, kerato-conjuctivitis
- Syndromes -

Investigations

1) X-rays
2) Total blood count and Erythrocyte Sedimentation Rate (ESR)
3) CT scan
4) Ultrasound
5) ECG
6) ASOT
7) Rheumatoid Factor

8) C-Reactive proteins

2. GOUT

Introduction

- Is a form of inflammatory arthritis that results from the build-up of uric acid crystals in a joint
- Gout is an inflammatory reaction to monosodium urate crystals
- In the human body, urate is constantly near its limit of solubility, in a flux balance between production and elimination

Uric Acid Formation

- *Uric acid* is a heterocyclic compound of carbon, nitrogen, oxygen, and hydrogen with the formula $C_5H_4N_4O_3$
- Uric acid is formed by breakdown of purines from nucleic acids
- By two hydroxylation reactions, xanthine oxidase transforms hypoxanthine via xanthine to uric acid
- Uric acid is further metabolized to highly water-soluble allantoin by opening the larger of the two rings with the help of the enzyme uricase
-
-
- Nutrients high in purines include meat, especially offal, sea food and beer, which contains guanine

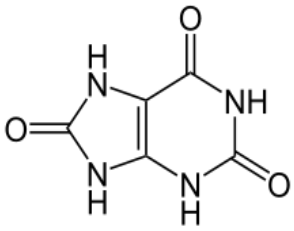
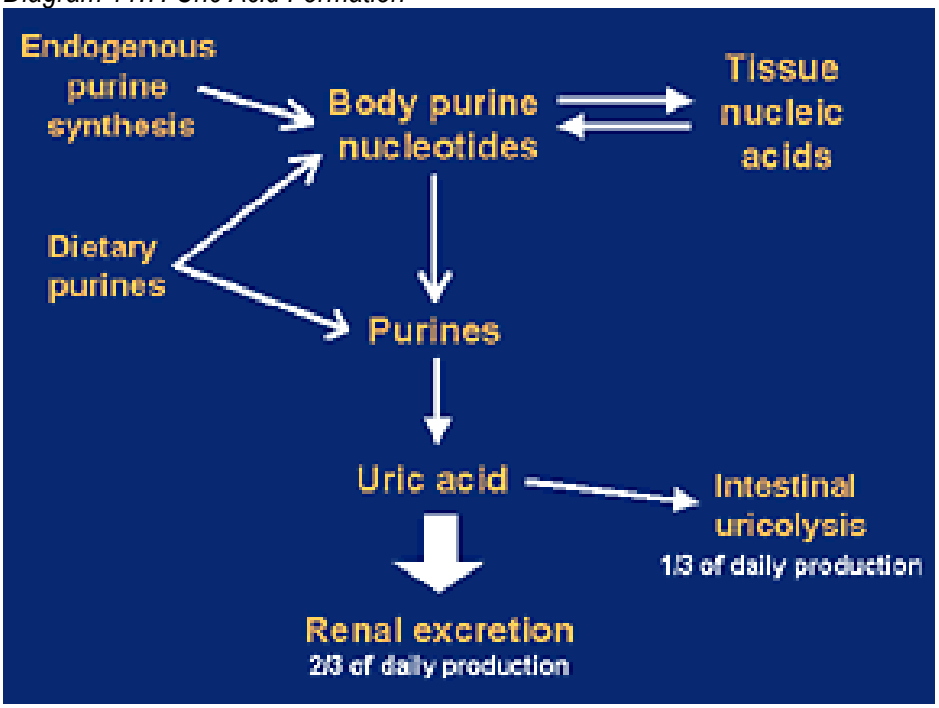


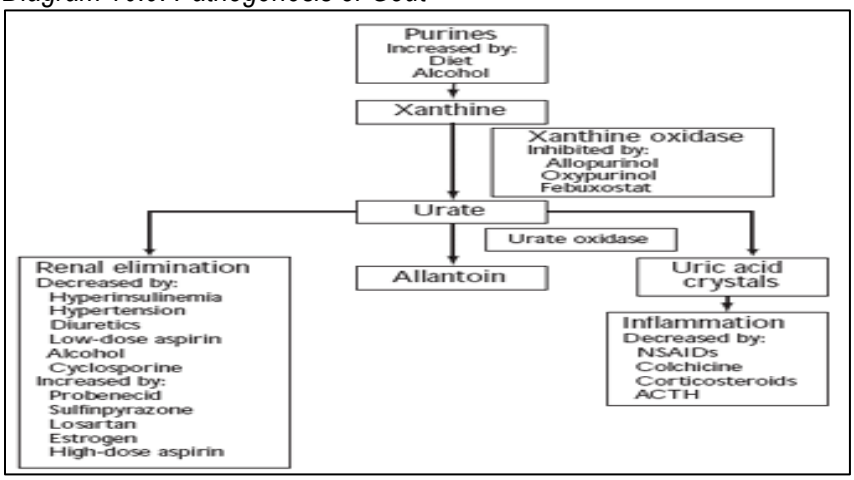
Diagram 11.7: Uric Acid Formation



Pathogenesis

- Gout is due to an inborn error of metabolism of uric acid.
- Two major regulators of hyperuricaemia- the **renal urate transporters SLC2A9 and ABCG2.**
- Risk factors - male gender, obesity,

Diagram 10.9: Pathogenesis of Gout

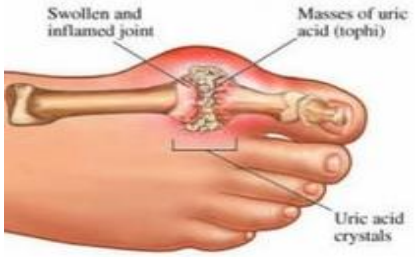


Pathophysiology

- Gout results from elevated urate concentrations in the blood (hyperuricaemia)
- When super-saturation of urate is reached, monosodium urate crystals form within the joint
- Accumulation of uric acid due to increased synthesis, poor metabolism and poor excretion
- There is formation of deposits (**tophi**) in joints, on tendons, bursae and in the surrounding tissues
- Naked crystals may break out of walled-off tophi due to minor physical trauma to the joint, medical or surgical stress, or rapid changes in uric acid levels
- This will trigger a local immune mediated inflammatory response as a result of phagocytosis of monosodium urate crystals
- Once crystals are deposited into a joint, they can be released into the joint space and initiate an inflammatory cascade causing acute **gouty** arthritis

Pathology (Lesions)

- Crystal formation (MSU)
- Inflammation
- Bone erosion
- Tophi



Clinical Features

- Typical gout attack is characterized by the sudden onset of *severe* pain, swelling, warmth, and redness of a joint
- Joint most commonly involved in gout is the first metatarsophalangeal joint (the big toe), and is called **podagra**
- Any joint may be involved in a gout attack (and it may be more than one) with the most frequent sites being in the feet, ankles, knees, and elbows

- Involvement of the kidneys – renal stones, gout nephropathy

Investigations

i) Blood - Serum uric acid levels (hyperuriceamia), Total blood count, Urea and electrolytes
ii) Synovial fluid aspirate – monosodium urate crystals (tophi)
iii) X-rays
iv) Urinalysis

3. OSTEOPOROSIS

Introduction

- Osteoporosis a medical condition in which the bones become brittle and fragile from loss of tissue, typically as a result of hormonal changes, or deficiency of calcium or vitamin D
- The bone becomes vulnerable to fractures
- Osteoporosis is a disease characterized by a deterioration of bone mass, architecture and quality leading to a decreased bone strength and increased risk for fragility fractures.
- Bone mineral density (BMD) is the major determinant for fracture risk but other factors such as bone turnover, connectivity and mineralization contribute to determining this risk by influencing bone quality

Normal bone formation and remodelling

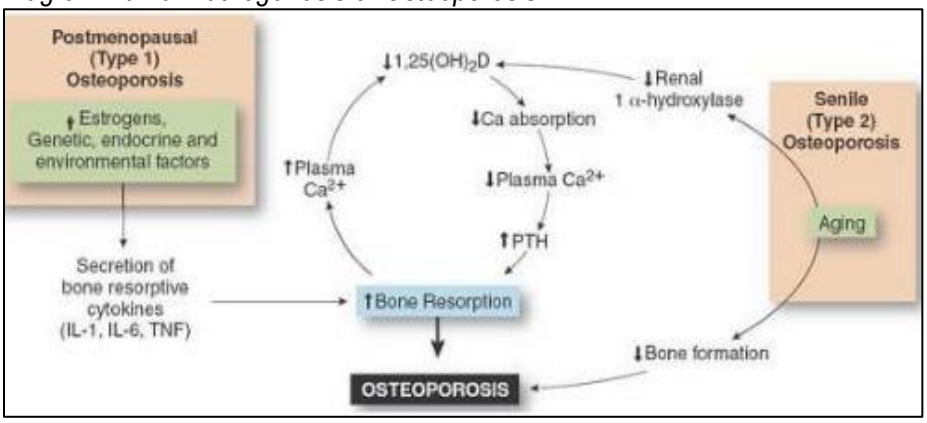
- Bone is continually remodelled throughout our lives in response to microtrauma
- Bone remodelling occurs at discrete sites within the skeleton and proceeds in an orderly fashion, and bone resorption is always followed by bone formation, a phenomenon referred to as coupling.
- Dense cortical bone and spongy trabecular or cancellous bone differ in their architecture but are similar in molecular composition
- Both types of bone have an extracellular matrix with mineralized and non-mineralized components
- Composition and architecture of the extracellular matrix imparts mechanical properties to bone
- Bone strength is determined by collagenous proteins (tensile strength) and mineralized osteoid (compressive strength)
- Osteoclasts, derived from hematopoietic precursors, are responsible for bone resorption, whereas osteoblasts, from mesenchymal cells, are responsible for bone formation
- Osteoblasts not only secrete and mineralize osteoid but also appear to control the bone resorption carried out by osteoclasts
- Osteocytes, which are terminally differentiated osteoblasts embedded in mineralized bone, direct the timing and location of bone remodelling. In osteoporosis, the coupling mechanism between osteoclasts and osteoblasts is thought to be unable to keep up with the constant microtrauma to trabecular bone. Osteoclasts require weeks to resorb bone, whereas osteoblasts need months to produce new bone.

Pathogenesis

- Pathogenesis of osteoporosis is complex and is the consequence of genetic, hormonal, dietary, lifestyle and physical factors
- Various genes coding for different interleukins influence genetic susceptibility to osteoarthritis.
- Oestrogen receptor α gene (ERα) is an important mediator in signal transduction and is expressed in different cells, including human chondrocytes (affect the progression of osteoarthritis)
- Vitamin D and its receptor (VDR) play an important role in bone metabolism, in response to the immune system, cancer and osteoarthritis

- Frizzled Related Protein gene (FRZB), which codes for the secretions of FRZB (FRZB3), is involved in both the bone formation and the negative regulation of the receptor-signalling pathway (inhibition is important in maintaining the structure of the cartilage)
- Asporins (ASP) are components of the extracellular matrix and expressed in high proportions in cartilage of osteoarthritic patients.
- The risk factors include genetics, aging, menopause, hormonal, calcium deficiency

Diagram 10.10: Pathogenesis of Osteoporosis



Pathophysiology

- The hallmark of osteoporosis is a reduction in skeletal mass caused by an imbalance between bone resorption and bone formation
- Under physiologic conditions, bone formation and resorption are in a fair balance
- A change in either—that is, increased bone resorption or decreased bone formation—may result in osteoporosis.

Pathology

- Reduced bone density
- Fractures

Clinical Features

- Presents with fractures

Investigations

i) Blood calcium level
ii) Total blood count
iii) X-rays

NOTE : Osteoporosis versus osteomalacia

- Osteoporosis may be confused with osteomalacia
- The normal human skeleton is composed of a mineral component, calcium hydroxyapatite (60%), and organic material, mainly collagen (40%). In osteoporosis, the bones are porous and brittle, whereas in osteomalacia, the bones are soft
- This difference in bone consistency is related to the mineral-to-organic material ratio
- In osteoporosis, the mineral-to-collagen ratio is within the reference range, whereas in osteomalacia, the proportion of mineral composition is reduced relative to organic material content.

TAKE AWAY ASSIGNMENT

	Disease	Genetic link	Main pathology	Key features
1.	Alzheimer's disease			
2.	Schizophrenia			
3.	Bipolar disorders			
4.	Rheumatoid arthritis			
5.	Gouty arthritis			
6.	Osteoporosis			

TOPIC 11: POLYGENIC DISORDERS - ENDOCRINE SYSTEMS AND THE SKIN

Objectives

At the end of the lesson the learner will be able to: -

1) Outline the pathology of common multifactorial disorders of the endocrine system and the skin

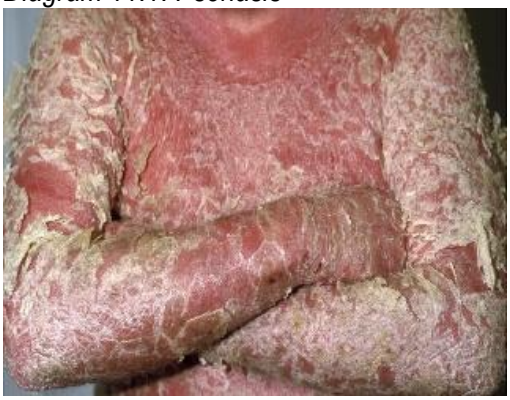
1.0 SKIN CONDITIONS

1. PSORIASIS

Introduction

- Psoriasis has a multifactorial onset – genetic and immune with strong association with HLA-C
- Psoriasis is a long-lasting autoimmune disease characterized by patches of abnormal skin which are typically red, itchy, and scaly
- A common skin condition that changes the life cycle of skin cells
- Psoriasis causes cells to build up rapidly on the surface of the skin
- A multi-systemic disorder associated with arthritis, myopathy, enteropathy and immunodeficiency

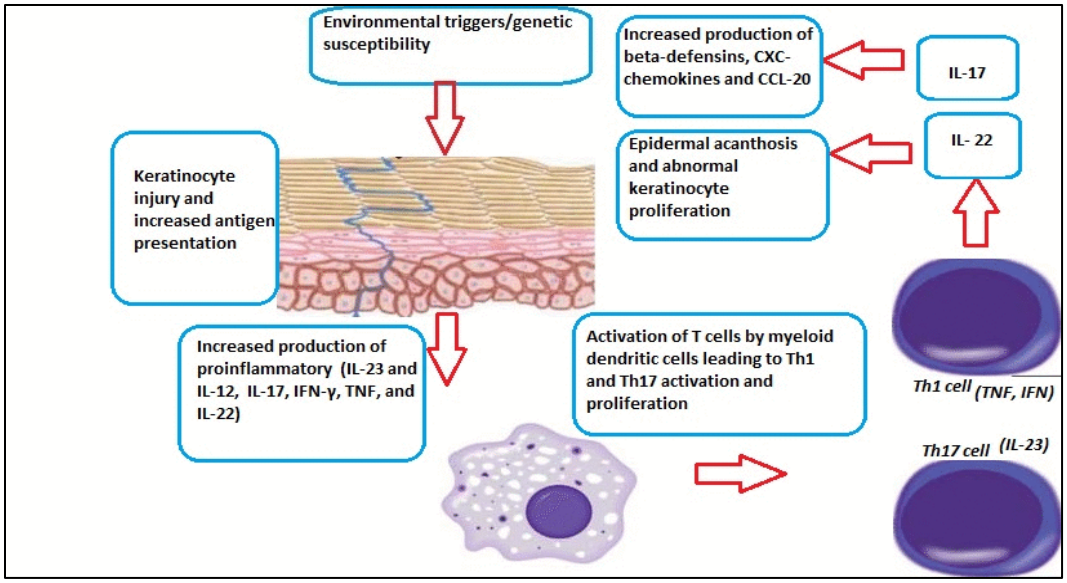
Diagram 11.1: Psoriasis



Pathogenesis

- **Psoriasis** is a complex immune-mediated inflammatory disease that occurs in genetically susceptible individuals and presents with the development of inflammatory plaques on the skin

Diagram 11.2: Pathogenesis of Psoriasis



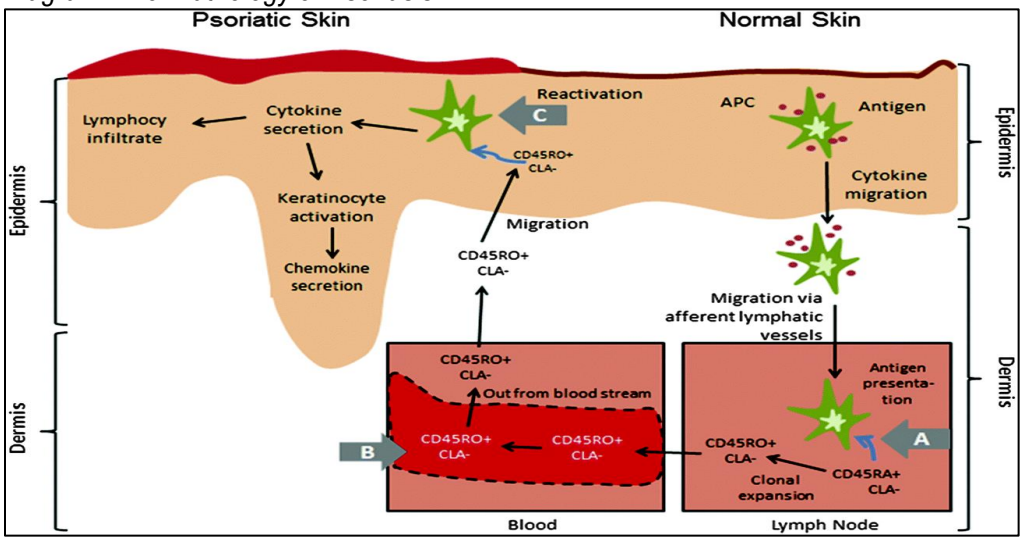
Pathophysiology

- Basal skin cells divide too quickly and the newly formed cells become profuse scales
- Rapid cell passage does not allow normal maturation and growth of the normal practice layers of the skin
- As underlying cells reach the skin's surface and die, their sheer volume causes raised, red plaques covered with white scales
- Sensitized T cells infiltrate the skin and secrete cytokines and growth factors
- This leads to inflammation, increased cell turnover, vascular proliferation angiogenesis
- Trauma precipitates the lesions

Pathology

- Presents with scales and crusts on the skin, inflammation and infection

Diagram 11.3: Pathology of Psoriasis

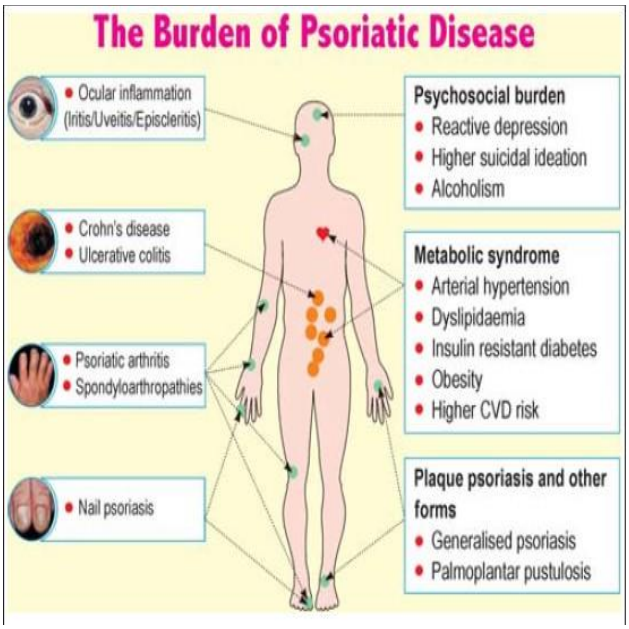


Clinical Features

- Psoriasis vulgaris, the common form of psoriasis, is characterized by red, scaly, raised plaques. Classic psoriasis vulgaris has a predilection for certain areas such as elbows, knees and the scalp

- There are clinical variants of psoriasis

Diagram 11.4: Features of Psoriasis

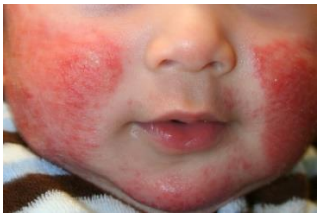


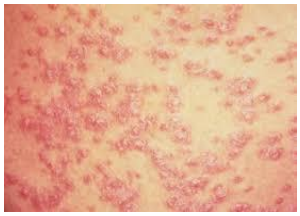
2. ECZEMA

Introduction

- A medical condition in which patches of skin become rough and inflamed, with blisters that cause itching and bleeding, sometimes resulting from a reaction to irritation (eczematous dermatitis)
- The skin to becomes itchy, red, dry and cracked
- Atopic dermatitis is a chronic pruritic inflammatory skin disease that occurs most frequently in children, but also affects adults

Diagram 11.5: Eczema





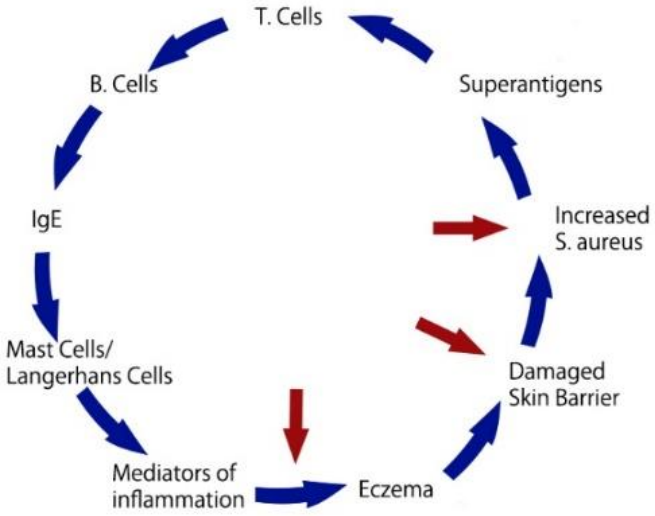
Pathogenesis

- A hypersensitivity reaction resulting from an interplay of genetic and environmental factors

Pathophysiology

- Initial exposure to an antigen, the antigen is processed by Langherns cells and presented to the T cells in the lymph node resulting in T cell activation
- Re-exposure to the antigen results in quick response leading to inflammation, urticarial, erythema - wet eczema
- Persistence of antigen stimulation resulting in chronic inflammation, which leads to acanthosis, hyperkeratosis (lichenification) – dry eczema

Diagram 11.6: Pathophysiology of Eczema



Types

- Includes atopic eczema, drug eczema, photo eczema, contact dermatitis and primary irritant dermatitis

Pathology

- Inflammation of the skin - thick, scaly skin

Clinical Features

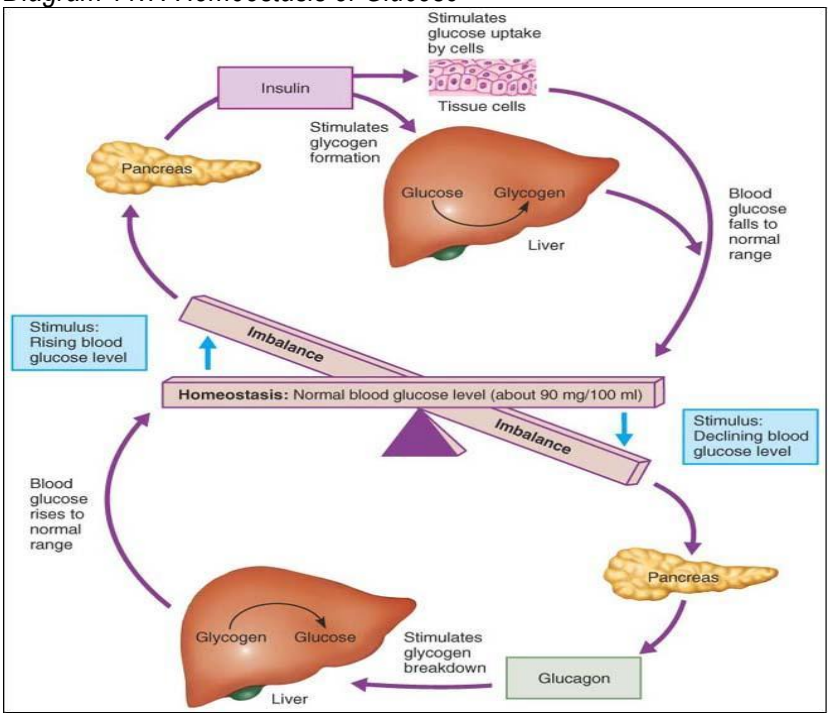
- Acute stage – red, oozing, crusty rash and intense pruritus
- Sub-acute stage – redness, blisters, excoriations, scaling, flaking, plaques or pustules. Fine scales may give a silvery appearance
- Chronic stage – the skin becomes dry, thickened, scaly and brownish grey

2.0 ENDOCRINE – DIABETES MELLITUS

2.1. Introduction

- Normal glucose homeostasis is tightly regulated by three interrelated processes – glucose production in the liver; glucose uptake and utilization by peripheral tissues (mainly skeletal muscle) and actions of insulin and counter-regulatory hormones such as glucagon on glucose
- Normal glucose homeostasis is regulated by 3 interrelated processes
  i) Glucose production in the liver
  ii) Glucose uptake and utilization by peripheral tissues (mainly skeletal muscle)
  iii) Actions of insulin and counter-regulatory hormones such as glucagon on glucose

Diagram 11.7: Homeostasis of Glucose



2.2. Definition

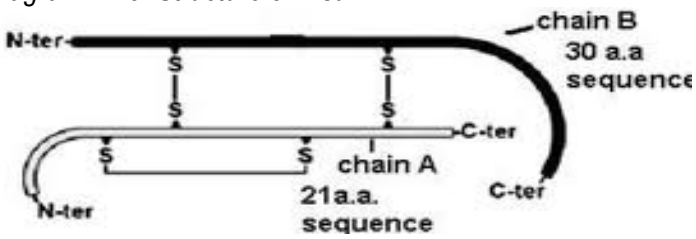
- Diabetes mellitus (DM) is a syndrome characterized by disordered metabolism and abnormally high blood sugar (hyperglycaemia) resulting from low levels of the hormone insulin with or without abnormal resistance to insulin effects
- Is a multisystem disease with both biochemical and anatomical consequences
- Is a chronic disorder of impaired metabolism of glucose & other energy yielding fuels

2.3. Insulin

- Insulin coded for on chromosome 11 is a major anabolic hormone synthesized by pancreatic beta cells
- Secretion of insulin is regulated by the concentration of glucose, which is transported to the beta cells bound on GLUT 2 protein in liver and GLUT 4 in the muscles

i) Insulin consists of α and β chains linked by disulphide bonds.

Diagram 11:8: Structure of Insulin



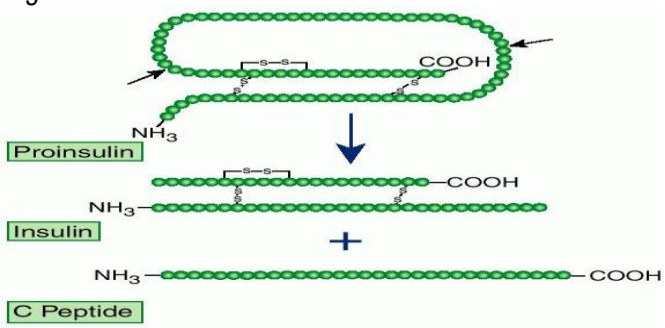
2.4. Functions of Insulin

1) Regulation of glucose metabolism through increased glucose uptake, use and storage
2) Stimulates lipogenesis and diminishes lipolysis
3) Increased protein synthesis and amino acid transport into cells
4) Increased fat storage
5) Exerts effects similar to growth factor

2.5. Insulin Synthesis

- Biosynthesis and release of insulin from cells involve: -
  i) Production of proinsulin due to presence of glucose (proinsulin is a single chain of 86 amino acids consisting and chains linked by a C-peptide).
  ii) Proinsulin is transferred to the Golgi complex where C-peptide is split off releasing insulin, which is stored as zinc-insulin crystals

Diagram 11.9.: Proinsulin and Insulin



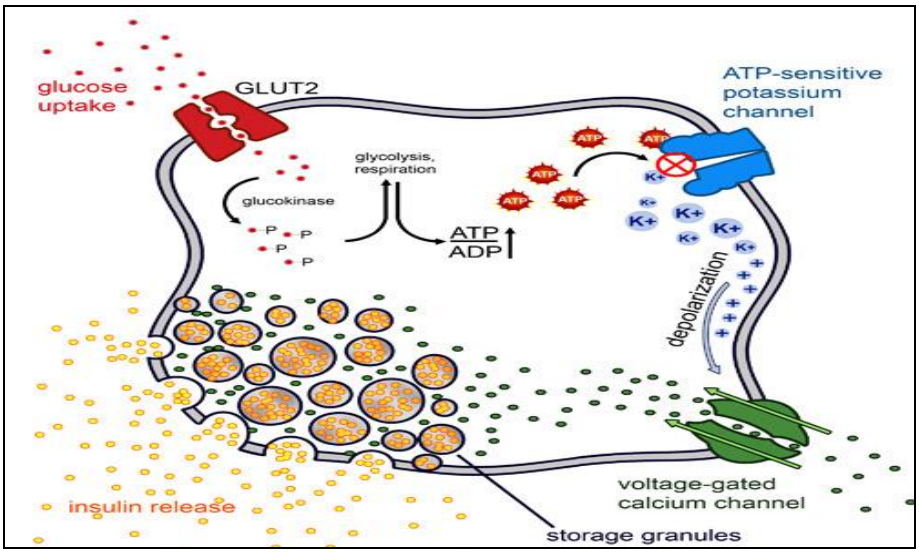
2.6. Insulin Release

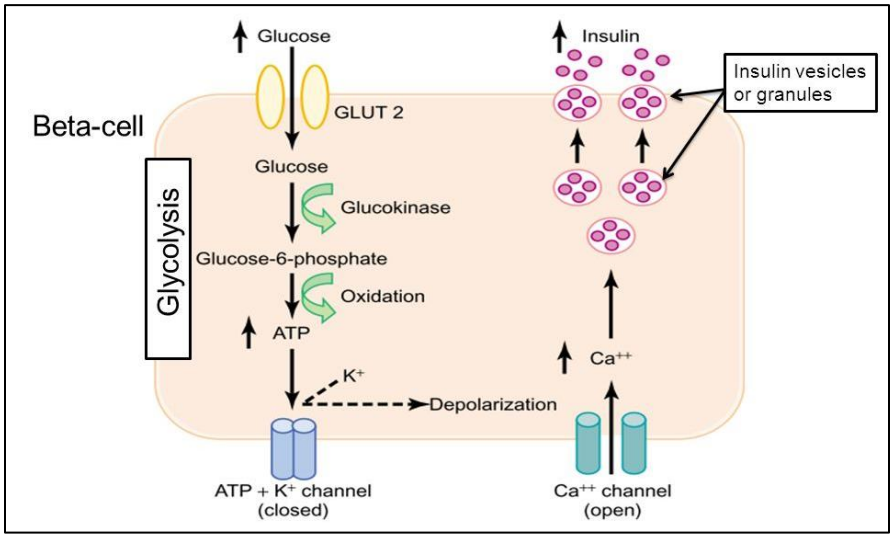
i) Insulin is released in two phases
   - First phase in response to a rise in blood glucose level
   - Slow second phase that continues until blood glucose level returns to normal
ii) Sacs containing zinc-insulin crystals and C-peptide are brought to the surface of the plasma membrane of the β cells a process that requires intracellular calcium.
iii) Release of β granules containing insulin and C-peptide into the extracellular space into the islets and then the systemic circulation
iv) Metabolism of glucose entering the β cells generates ATP which closes potassium channels in the cell membrane

v) The cell membrane becomes depolarized allowing calcium ions to enter the cell through the selective calcium channels in the membrane

vi) This rise in intracellular calcium triggers activation of calcium-dependent phospholipids *protein kinase* which causes phosphorylation and fusion of insulin containing granules with the cell membrane and exocytosis of the insulin rich granule contents.

Diagram 11.3: Insulin Secretion Mechanism

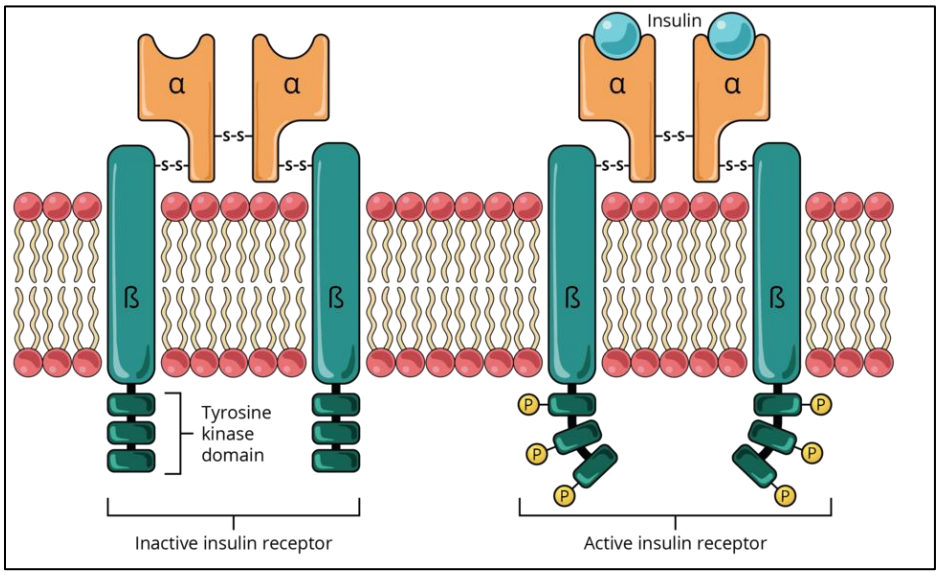




2.7. Insulin Receptor

- Is a glycoprotein which is coded for on the short arm of chromosome 19, which overlaps the cell membranes of many cells
- Consists of 2 α–subunits which have binding sites for insulin and 2 β subunits which traverse the cell membrane
- Once insulin binds to the α subunits it induces conformational changes in the β subunits resulting in activation of tyrosine kinase and initiation of a cascade response of intracellular reactions.

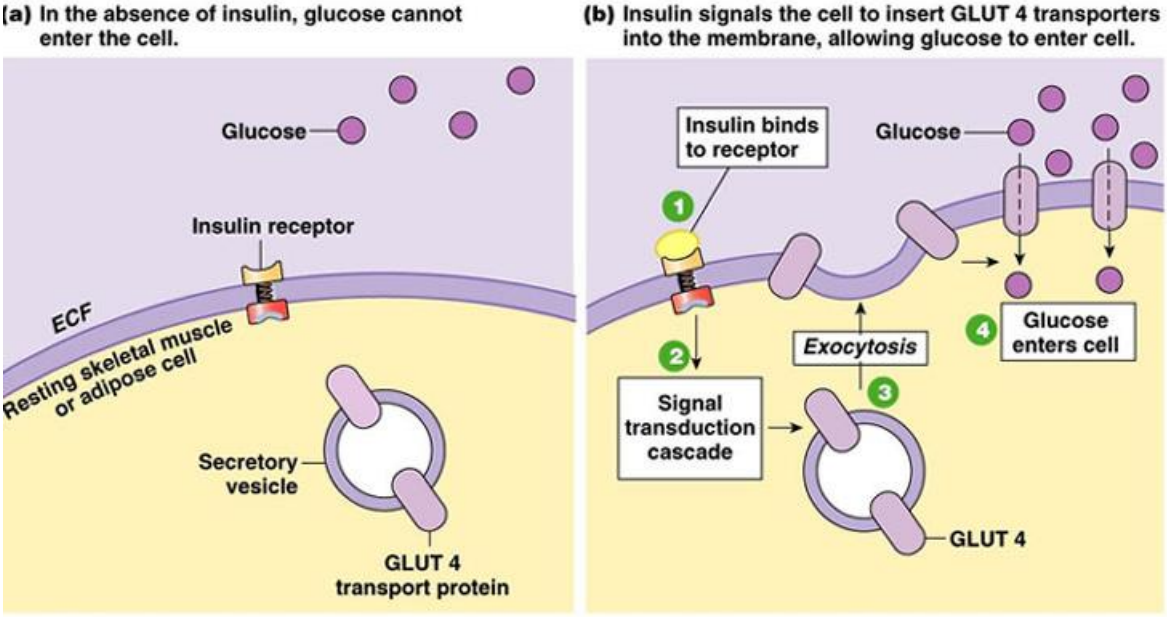
Diagram 11.10: Insulin Receptor

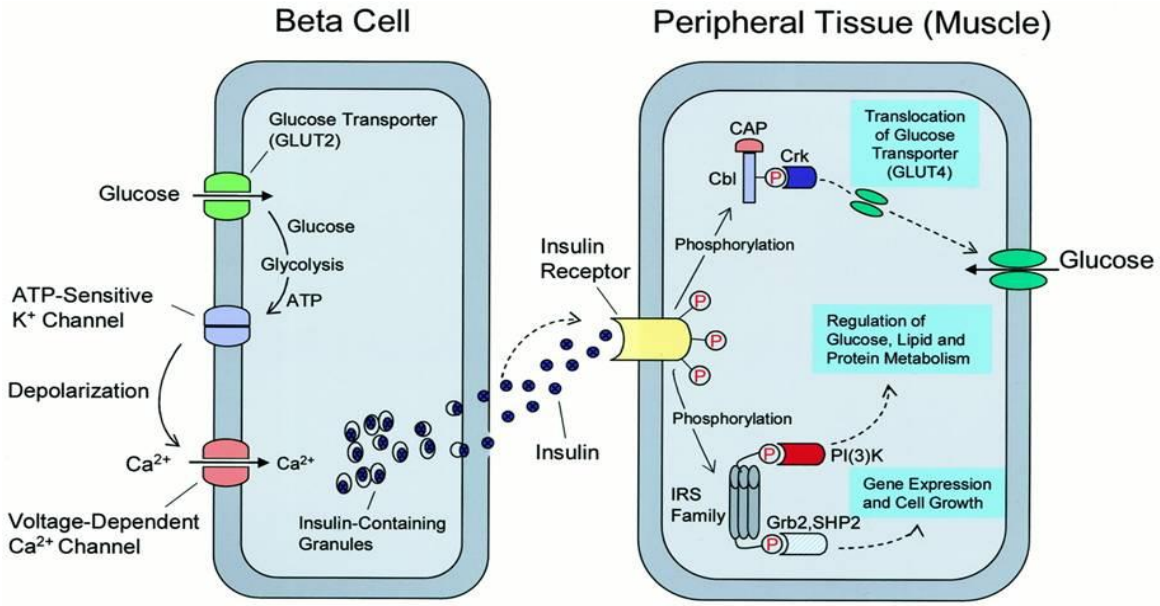


2.8. Insulin Metabolism

- After secretion insulin enters the portal circulation and is carried to the liver which is its prime target
- About 50% of insulin is extracted and degraded in the liver and the residue is broken down by the kidneys
- The C-peptide is partially extracted by the liver and hence it is degraded by the kidney.

Figure 11.11: Action of Insulin





2.9. Classification of Diabetes

	Type	Description
1.	Type 1	• IDDM (insulin dependent diabetes mellitus); • Previously called juvenile onset diabetes (JOD) • Caused by absolute deficiency of insulin secretion • Type 1A (Immune mediated); Type 1B (Idiopathic)
2.	Type 2	• NIDDM (non-insulin dependent diabetes mellitus); • Previously called maturity onset diabetes (MOD) • Caused by resistance to insulin &inadequate compensatory secretory response
3.	Type 3	• Secondary with a known cause
4.	Type 4	• Develops in pregnant women due to changes during pregnancy and they revert back to normal glycaemia after delivery but remain prone to develop DM later in life

2.10. Pathogenesis

2.10.1. Type 1 DM

- Genetic susceptibility, multiple genetic predisposition with a strong association with HLA[4] (DR_3, DR_4 and DQ locus) genes on chromosome 6 (MHC) affect potential immune responsiveness to a pancreatic β–cell antigen
- Cell mediated autoimmune destruction of the beta cells (autoimmunity to islet β–cells resulting in insulitis)
- Destruction of beta cell by circulating IgG cytotoxic antibodies results in impaired insulin release causing absolute insulin deficiency
- Environmental factors - infections act as trigger agents e.g. viral infections (mumps, measles, Coxsackie virus, cytomegalovirus, Epstein Barr virus) and chemical toxins
- Mechanisms of β-cell Destruction
  i) T-lymphocytes react against β–cell antigens and cause cell damage

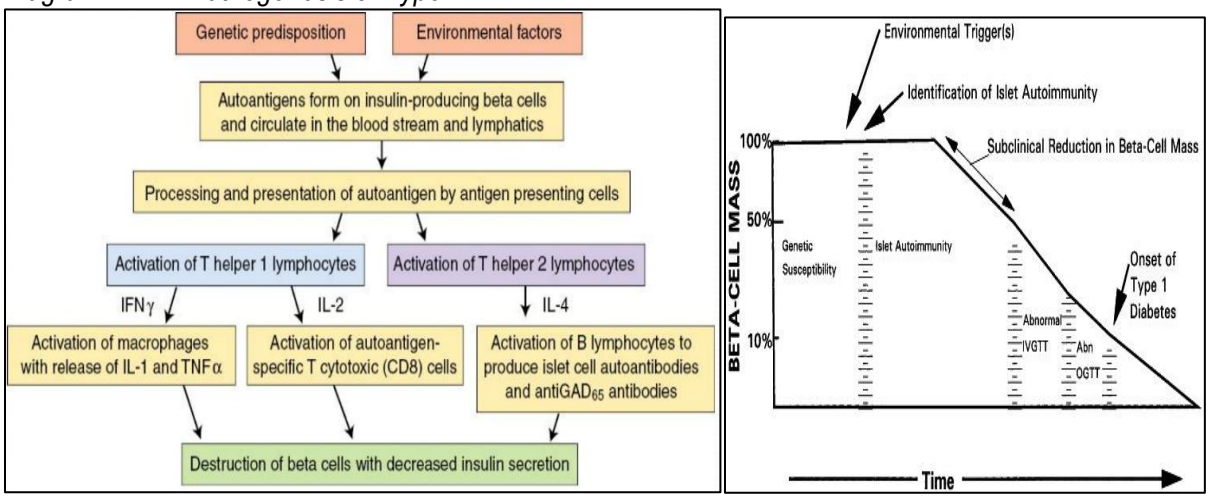
[4] *HLA – Human Leucocyte Antigen*

ii) CD4+ T_H cells cause tissue injury by activating macrophages and CD8+ cytotoxic T lymphocytes which directly kill β cells and secrete cytokines that activate macrophages.

iii) Damage of β cells by locally produced cytokines such as IFN-g (T cells) and TNF and IL-1 (macrophages)

iv) Auto-antibodies against islet cells and insulin

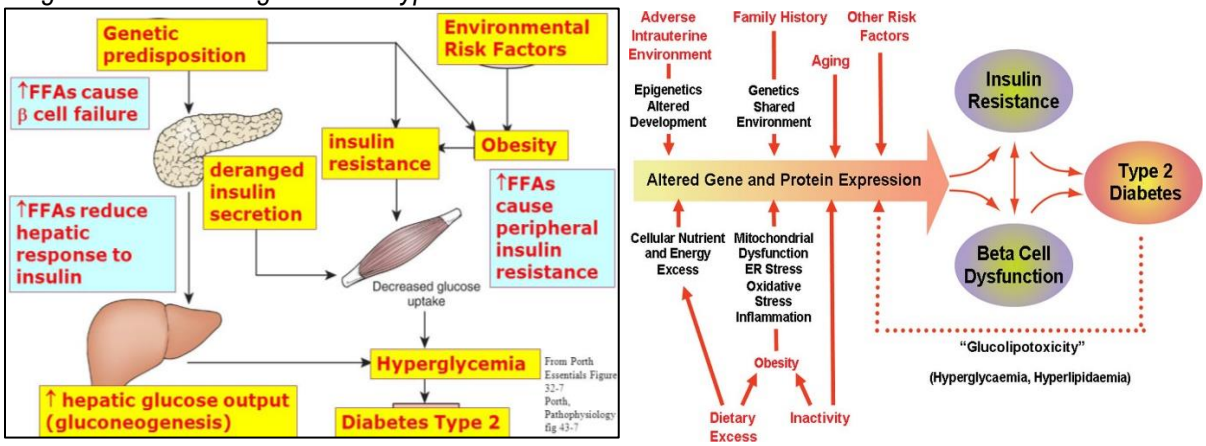
Diagram 11.12: Pathogenesis of Type I DM



2.10.2. Type 2 DM

1) Genetic Factors
   - Strong genetic predisposition
   - Patients have insulin resistance, impaired insulin (defects and secretion) and relative insulin deficiency (due to increased gluconeogenesis)
   - Physiologic events include deranged βcell secretion of insulin, insulin resistance, obesity and chromosomal disorders on chromosome 7, 12 and 20.
2) Constitutional factors
   - Obesity, hypertension, physical inactivity plays a contributory role and modulate the phenotyping of the disease

Diagram 11.13: Pathogenesis of Type 2 DM



3) Insulin resistance

- Lack of responsiveness of peripheral tissues to insulin especially skeletal muscles and liver
- Obesity is strongly associated with insulin resistance (as a result of decreased number of insulin receptors and intracellular signalling)
- Resistance to insulin impairs glucose utilization and hence hyperglycaemia.
- There is increased hepatic synthesis of glucose
- Mutations which can give rise to insulin resistance fall into 5 different classes:
  i) Decreased rate of receptor biosynthesis
  ii) Inhibition of the intracellular transport of receptors on the cell surface (e.g. alanine 1135 mutation to glutamic acid prevents the processing of the pro-receptor and transport to the cell surface)
  iii) Reduction in the affinity of the receptor for insulin
  iv) Inhibition of the insulin receptor tyrosine kinase
  v) Accelerated receptor degradation

4) Impaired insulin secretion
   - Occurs due to failure if β-cell function which results from compensatory hyperinsulinaemia in an attempt to bring glucose level to normal

5) Increased hepatic glucose synthesis

2.10.3. Type 3 DM

- Has a known aetiology
  i) Diseases of exocrine function – chronic pancreatitis, pancreatic tumours, post pancreactomy
  ii) Endocrinopathies – acromegaly, Cushing's syndrome, pheochromocytoma
  iii) Drugs or chemical induced – steroids, thyroid hormone, thiazides, beta blockers
  iv) Genetic diseases – Down's, Klinefelter's and Turner's syndromes
  v) Infections – congenital rubella, cytomegalovirus

2.10.4. Type 4 DM (GDM)

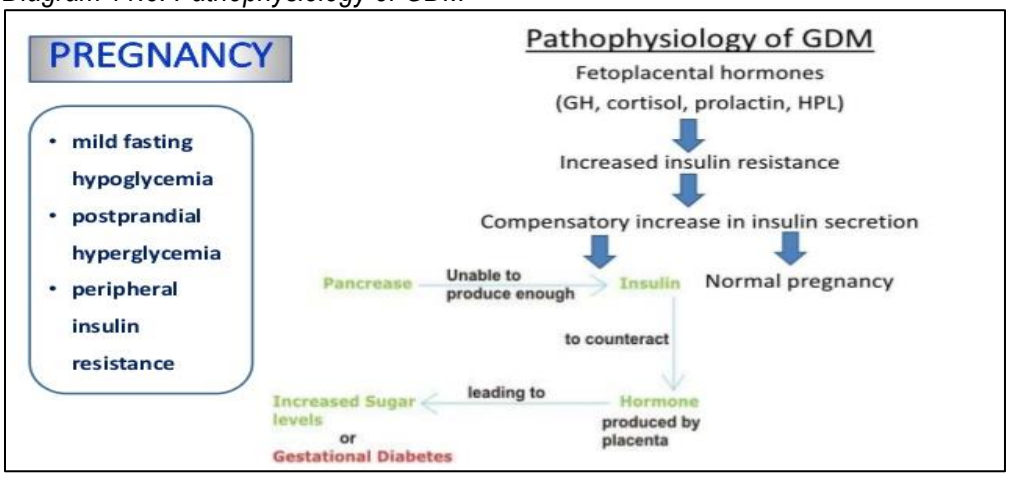
- A decrease in insulin sensitivity (increase in insulin resistance) normally occurs during pregnancy due to placental hormones to in order spare glucose for the foetus
- Placenta synthesizes pregnenolone and progesterone from cholesterol
- Steroid hormones (cortisol, oestrogen and progesterone) have anti-insulin activity increase steadily during pregnancy.
- Cortisol causes decrease in glucose tolerance while the others increase insulin resistance in late pregnancy
- Human placental lactogen (LPL) – human chorionic somatomammotropin (hCS) similar to human growth hormone (HCH) has diabetogenic effects by stimulating lipolysis to increase circulating free fatty acids for maternal use and spare glucose and amino acids for foetal use
- FFA interfere with insulin-directed entry of glucose into cells

2.11. Pathophysiology of DM

- Depends on the type of diabetes

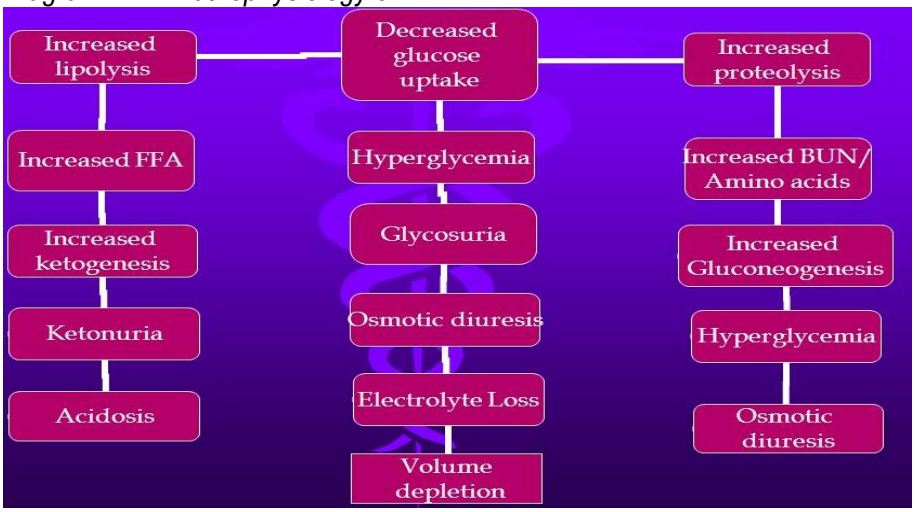
- Pathophysiology revolves are reduced insulin secretion, decreased glucose use by the body and increased glucose production
- Destruction of the beta cells resulting in reduced insulin secretion causing absolute insulin deficiency which affects metabolism of glucose, lipids and proteins
- Characterized by peripheral insulin resistance, impaired regulation of hepatic glucose production, and declining β-cell function, eventually leading toβ -cell failure
- Affects metabolism of carbohydrates, lipids and proteins

Diagram 11.3: Pathophysiology of GDM



2.12. Pathophysiology of DKA (Chemical pathology)

Diagram 11.4: Pathophysiology of DKA



1) **Euglycaemia**
   - After a meal, serum glucose level rises and stimulates beta cells resulting in insulin production
   - Insulin increases permeability of peripheral cells such as liver and muscle cells for glucose to enter and be stored as glycogen or utilized to provide energy, consequently serum glucose level falls to normal – **euglycaemia**
   - During fasting, adipose tissues are changed to fatty acids which are broken down to release energy and ketones while muscles protein is broken down to energy and urea

2) Hyperglycaemic States

a) Hyperglycaemia
- Insulin deficiency impairs peripheral uptake of glucose by the peripheral cells resulting in **hyperglycaemia** due to reduced rate of removal of glucose from the blood by the tissues supposed to utilize glucose & increased absorption from the gut
- Poor glucose utilization leads to fatigue

b) Gluconeogenesis and glycogenolysis
- Inability of cells to get glucose is perceived as if there is no glucose in circulation hence there is breakdown of other tissues to produce glucose (**gluconeogenesis**) as a compensatory reaction due to the influence of insulin antagonists and glycogen is broken down (**glycogenolysis**) further releasing glucose
- The sugar is not utilized further worsening the **hyperglycaemia**

c) Polyuria and Polydipsia
- Increased plasma glucose alters the osmotic gradient and water is taken up from the cells into the circulation reaching the kidney causing osmotic diuresis
- Osmotic diuresis results in excretion of large amounts of water (**polyuria**) causing dehydration of body cells a situation sensitizing the hypothalamus to trigger the thirst mechanism hence excessive intake of water (**polydipsia**)
- The polyuria is profound at night

d) Glycosuria
- Increased glucose in blood surpasses the renal threshold allowing glucose to appear in urine (**glycosuria**) due to overproduction of urine (polyuria)

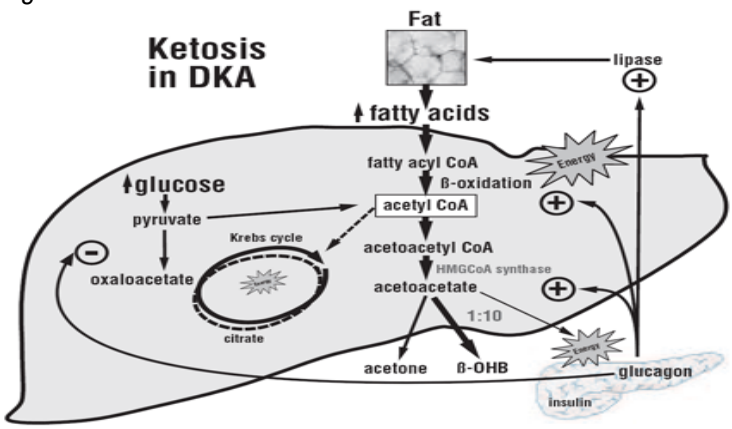
e) Dehydration and Electrolyte Imbalance
- Hyperglycaemia causes a profound osmotic diuresis leading to **dehydration** and electrolyte loss, particularly of sodium and potassium
- Excessive water loss facilitated by osmotic diuresis leads to **electrolyte imbalance** (Na^+, K^+, HCO_3^-, Cl^-)
- Metabolic **acidosis** forces hydrogen ions into the cells displacing potassium ions which may be lost through urine or vomiting

3) Hyperketonaemia and Metabolic Acidosis
- There is increased rate of cholesterol synthesis and breakdown of fats (lipolysis) yields free fatty acids, which are converted to Acetyl CoA[5] in the liver and taken up by the Kreb's cycle to provide energy
- Excess acetyl CoA is converted into ketone bodies in the mitochondria or they are re-esterified to form triglycerides
- Accumulation of ketones in blood results in **ketonaemia** which causes metabolic acidosis
- Ketone bodies (acetone, aceto acetone and β–hydroxybutyric acid) increase plasma osmolarity causing withdrawal of water from the cells
- Ketones are excreted in urine (aceto acetone and β–hydroxybutyric acid) resulting in **ketonuria** and in breath (acetone) producing a distinctive smell similar to that of **acetone**
- The acids formed are capable of releasing H^+ ions reducing plasma bicarbonate resulting in **acidosis**

[5] Acetyl CoA enzyme

- Progressive dehydration impairs renal excretion of H+ ions and ketones aggravating the acidosis leading to **keto acidosis- diabetic keto acidosis (DKA**)

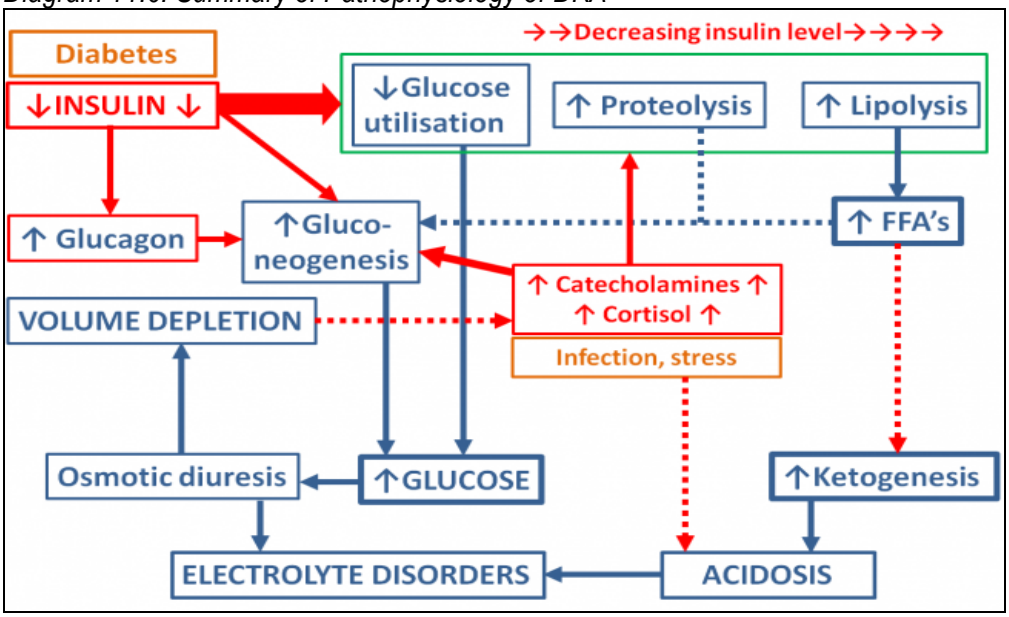
Diagram 11.5: Ketosis in DKA



4) Increased Proteolysis

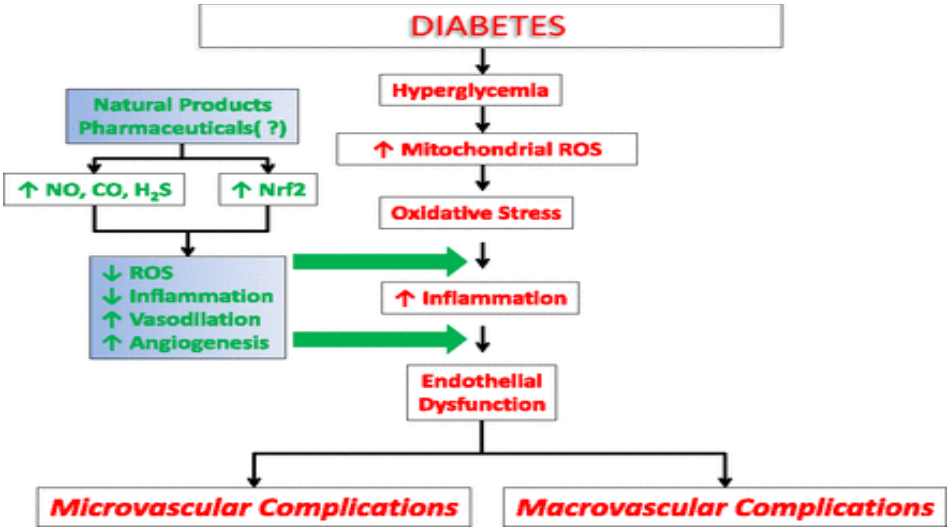
- There is breakdown and poor synthesis of proteins leading muscle wasting and production of urea which contributes to fatigue

Diagram 11.6: Summary of Pathophysiology of DKA



2.13. Pathology

- Biochemical changes
- Structural changes that occur due to biochemical derangement are encountered in many tissues and organs.
- Destruction involves mainly blood vessels **(macroangiopathy and microangiopathy)**
- This is the main stay of the legion complications of diabetes and involves mainly glycosylation of proteins and endothelial cell proliferation



2.14. Clinical Features

What are the clinical features of diabetes mellitus?

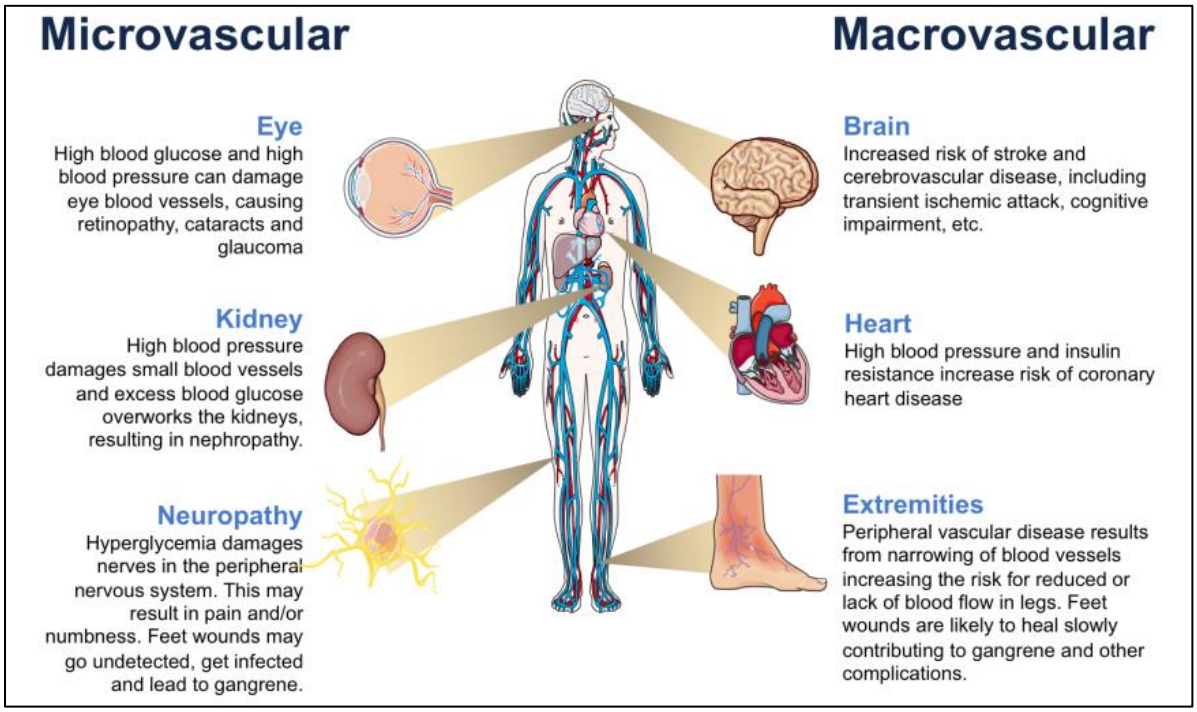
2.15. Investigations

	Investigation	Possible Findings
1.	Plasma glucose (blood sugar)	• RPG > 11.1 mmol/litre; FPG > 7.1 mmol/litre; 2 hours post-prandiol (PP) > 7.11 mmol/litre • RPG > 11.1 mmol/litre after OGTT; RPG – 7.1 – 11 mmol; After 2 hours > 11.1 mmol/L; RPG 7.1
2.	Urinalysis	• Glycosuria, Ketonuria, Proteins, Pus cells
3.	Full haemogramme and ESR	•
4.	Urea and Electrolytes	•
5.	Blood	• Ketonaemia
6.	Liver Function Tests(LFT)	•
7.	Serum cholesterol and triglycerides	•
8.	HbA_{1C} or HbA_1 (Glycosylated Hb)	• HbA_{1C} is expressed as a percentage of normal haemoglobin (4 – 8% in 6 weeks) • $HbA_{1C} = \frac{\text{Glycosylated Hb X 100}}{\text{Total Hb}}$ • Normal 4 – 8 % (< 7% good); ≥ 20% - poor control of glucose. Glycosylated HbA_{1C} gives the average blood glucose concentration over the life of the Hb molecule (2 – 3 months). It is unreliable in cases of reduced life span or abnormal haemoglobins

9.	Glycosylated protein (albumin)	•
10.	Chest X-ray/X-rays	•
11.	ECG	•
12.	Ultrasound	•

2.16. Complications

	State	System	Complications
1.	Early, acute	Nervous	Comas -
2.	Late, Chronic	Cardiovascular system	Arterial disease (microangiopathy and macroangiopathy), hypertension and myocardial infarction
		Renal	Nephropathy – renal failure
		Nervous	Neuropathy – burning sensation in the legs (glove and stocking distribution)
		Reproductive	Sexual dysfunction
		Skin/extremities	Skin infections, Peripheral ulcers, Diabetic limb – ulcer and gangrene



TAKE AWAY ASSIGNMENT

	Disease	Genetic link	Main pathology	Key features
1.	Diabetes Mellitus			
2.	Psoriasis			
3.	Eczema			