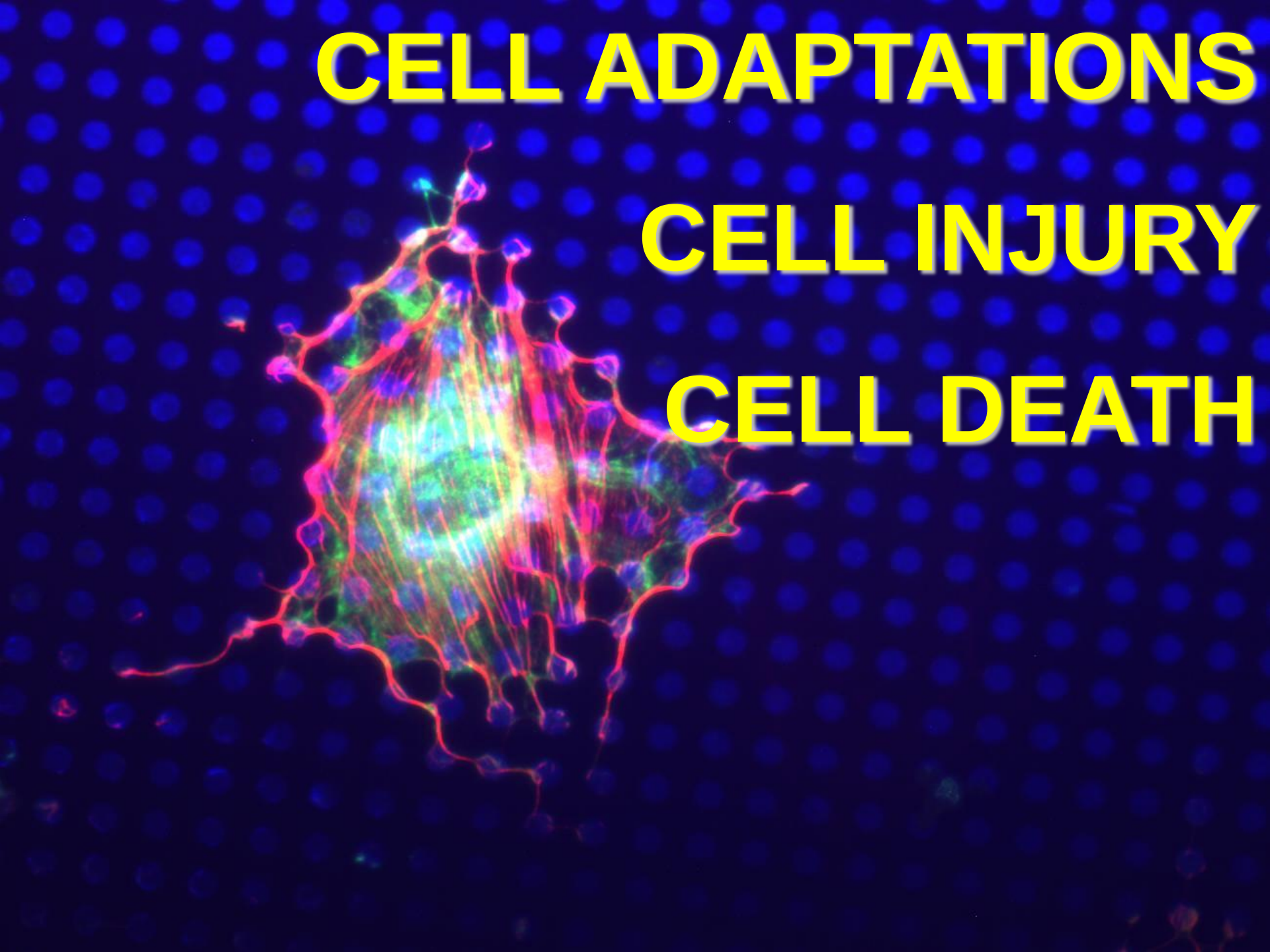
CELL ADAPTATIONS

CELL INJURY

CELL DEATH



OBJECTIVES

Understand the 3 main anatomic concepts of disease---Degenerative, Inflammatory, Neoplastic

Understand the concepts of cellular growth adaptations---Hyperplasia, Hypertrophy, Atrophy, Metaplasia

Understand the factors of cell injury and death---O2, Physical, Chemical, Infection, Immunologic, Genetic, Nutritional

OBJECTIVES

- Understand the pathologic mechanisms at the SUB-cellular level---ATP, Mitochondria, Ca++, Free Radicals, Membranes
- Understand and differentiate the concepts of APOPTOSIS and NECROSIS
- Understand SUB-cellular responses to injury---Lysosomes, Smooth endoplasmic reticulum, Mitochondria, Cytoskeleton

OBJECTIVES

- Identify common INTRA-cellular accumulations---Fat, Hyaline, CA++, Proteins, Glycogen, Pigments
- Understand aging and differentiate the concepts of preprogrammed death versus wear and tear.

PATHOLOGY

Pathos (suffering)

Logos

PATHOLOGY

- GENERAL
- SYSTEMIC

PATHOLOGY

- **ETIOLOGY (“Cause”)**
- **PATHOGENESIS (“Insidious development”)**
- **MORPHOLOGY (ABNORMAL ANATOMY)**
- **CLINICAL EXPRESSION**

Insidious - producing serious harm often stealthily and gradually.

ETIOLOGY

- **Cause**

vs.

- **Risk Factors**

PATHOGENESIS

"sequence of events from the initial stimulus to the ultimate expression of the disease"

MORPHOLOGY

- Abnormal Anatomy
  - –Gross
  - –Microscopic
  - –Radiologic
  - –Molecular

CLINICAL EXPRESSION

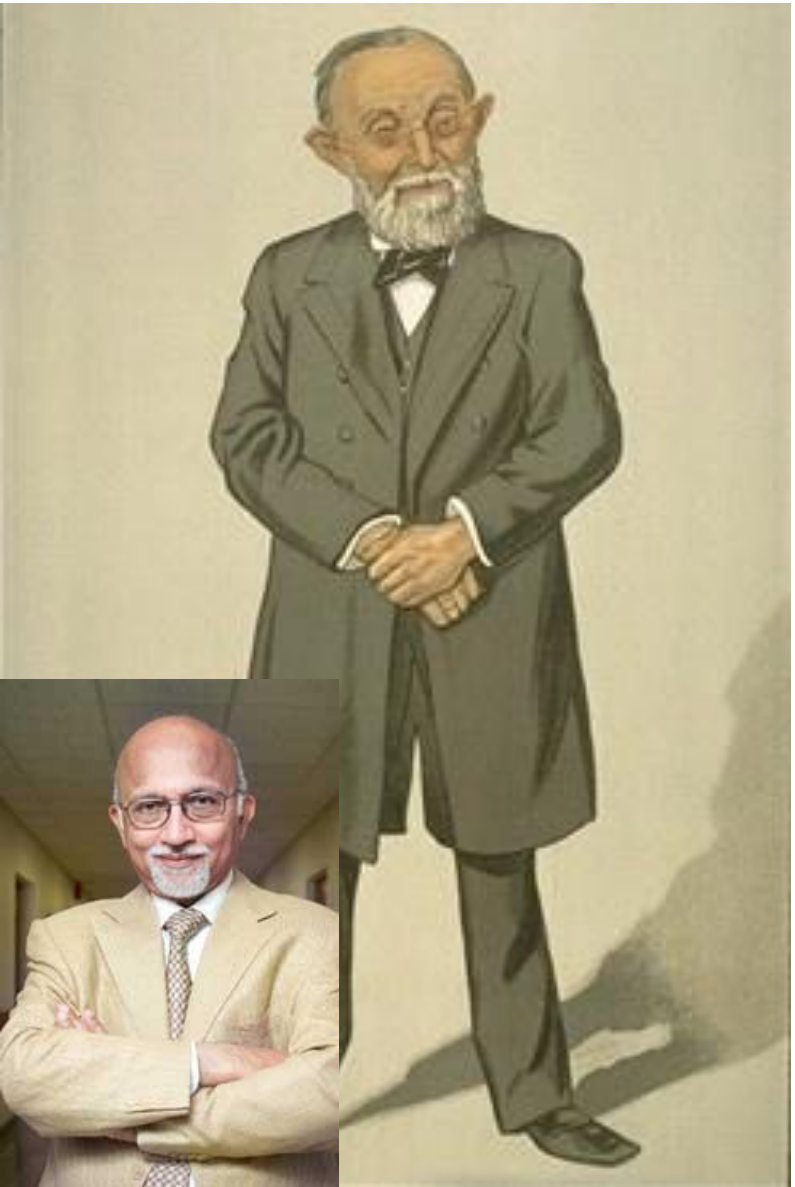
- **Ironically, even though “clinical expression” is not often present in subclinical diseases, it is the “pathos” of pathology.**

Most long term students of pathology, like myself, will strongly agree that the very best way for most minds to remember, or identify, or understand a disease is to associate it with a morphologic **IMAGE.**

This can be gross, electron microscopic, light microscopic, radiologic, or molecular.

In MOST cases it is at the **LIGHT MICROSCOPIC LEVEL.**

CLINICAL/FUNCTIONAL



Rudolph Virchow

1821-1902

The Father of Modern Pathology

FUNCTIONAL DEFINITION OF DISEASE

HOMEOSTASIS

CELL DEATH

- **APOPTOSIS** (“normal” death)
- **NECROSIS** (“premature” or “untimely” death due to “causes”

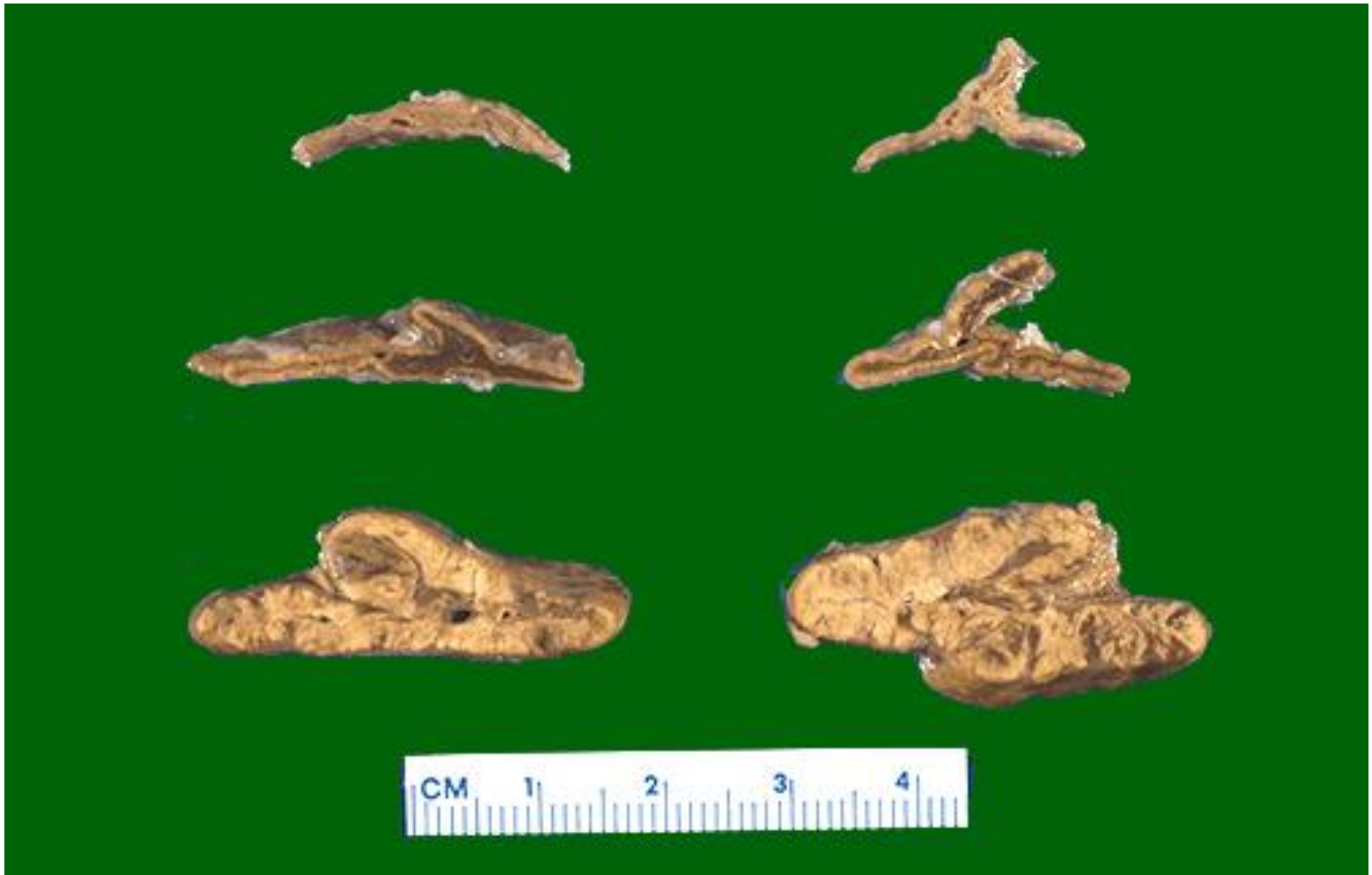
The –plasia brothers

- **HYPER-**
- **HYPO- (A-)**
- NORMO-
- **META-**

- **DYS-**
- **ANA-**
- “Frank” ANA-

HYPER-PLASIA

IN-CREASE IN NUMBER OF CELLS



HYPO-PLASIA

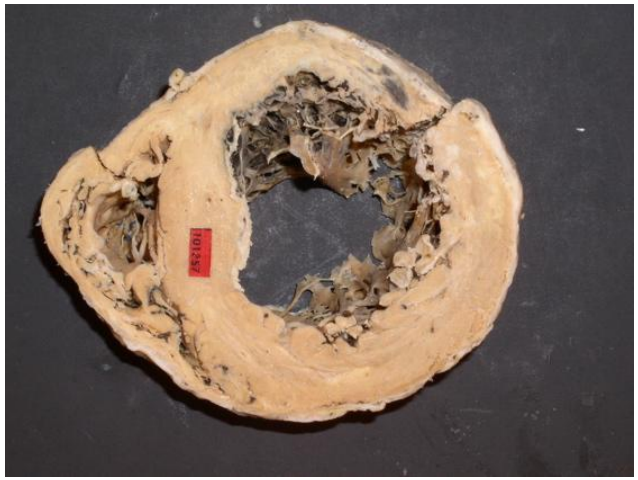
DE-CREASE IN NUMBER OF CELLS

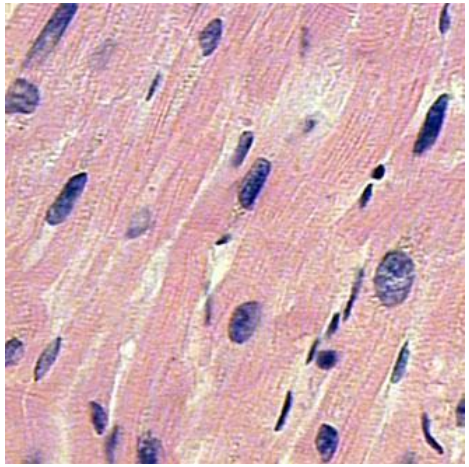
The –trophy brothers

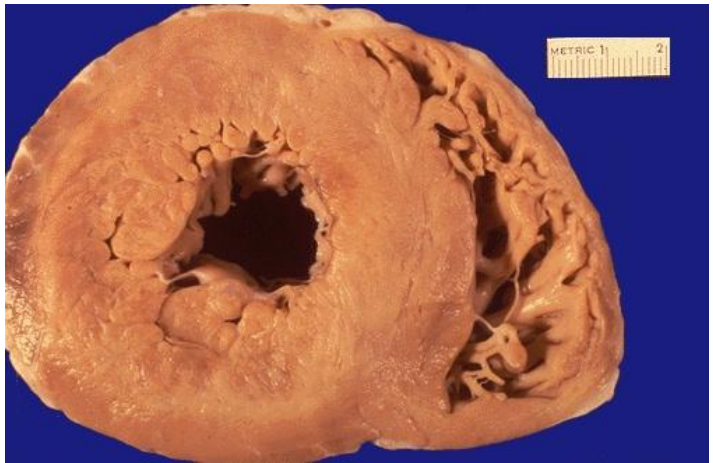
- **HYPER-**
- **HYPO- (A-)**
- **DYS-**

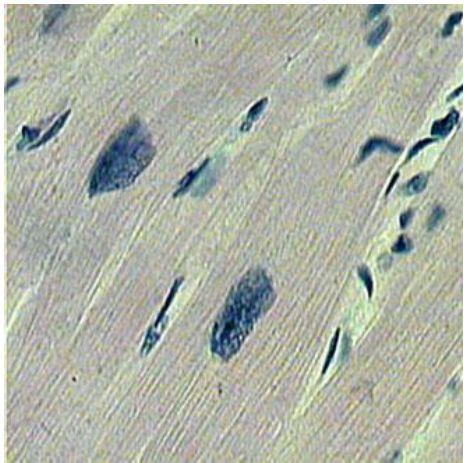
HYPER-TROPHY

IN-CREASE IN SIZE OF CELLS









HYPO-TROPHY?

DE-CREASE IN SIZE OF CELLS?

RARELY

USED

TERM

A-TROPHY?

DE-CREASE IN SIZE OF CELLS? YES

SHRINKAGE IN CELL SIZE DUE TO LOSS OF CELL SUBSTANCE

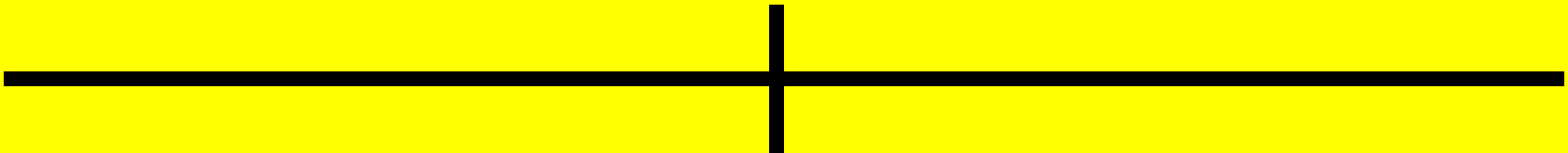
ATROPHY

- DECREASED WORKLOAD
- DENERVATION
- DECREASED BLOOD FLOW
- DECREASED NUTRITION
- AGING (involution)
- PRESSURE

METAPLASIA

- **A SUBSTITUTION of one NORMAL CELL or TISSUE type, for ANOTHER**
  - **COLUMNAR→ SQUAMOUS (Cervix)**
  - **SQUAMOUS→ COLUMNAR (Glandular) (Stomach)**
  - **FIBROUS→ BONE**

–WHY?



CELL DEATH

- APOPTOSIS vs. NECROSIS
- What is DEATH? (What is LIFE?)
  - –DEATH is IRREVERSIBLE

So the question is….

…NOT what is life or death, but what is REVERSIBLE or IRREVERSIBLE injury

REVERSIBLE CHANGES

- REDUCED oxidative phosphorylation
- ATP depletion
- Cellular “SWELLING”

IRREVERSIBLE CHANGES

- MITOCHONDRIAL IRREVERSIBILITY
- IRREVERSIBLE MEMBRANE DEFECTS
- LYSOSOMAL DIGESTION

REVERSIBLE = INJURY

IRREVERSIBLE = DEATH

SOME INJURIES CAN LEAD TO DEATH IF PROLONGED and/or SEVERE enough

INJURY CAUSES (REVERSIBLE)

THE

USUAL

SUSPECTS

But…WHO are the THREE WORST?

INJURY CAUSES (REVERSIBLE)

Hypoxia, (decreased O2)

PHYSICAL Agents

CHEMICAL Agents

INFECTIOUS Agents

Immunologic

Genetic

Nutritional

INJURY MECHANISMS (REVERSIBLE)

DECREASED ATP

MITOCHONDRIAL DAMAGE

INCREASED INTRACELLULAR CALCIUM

INCREASED FREE RADICALS

INCREASED CELL MEMBRANE PERMEABILITY

What is Death?
What is Life?

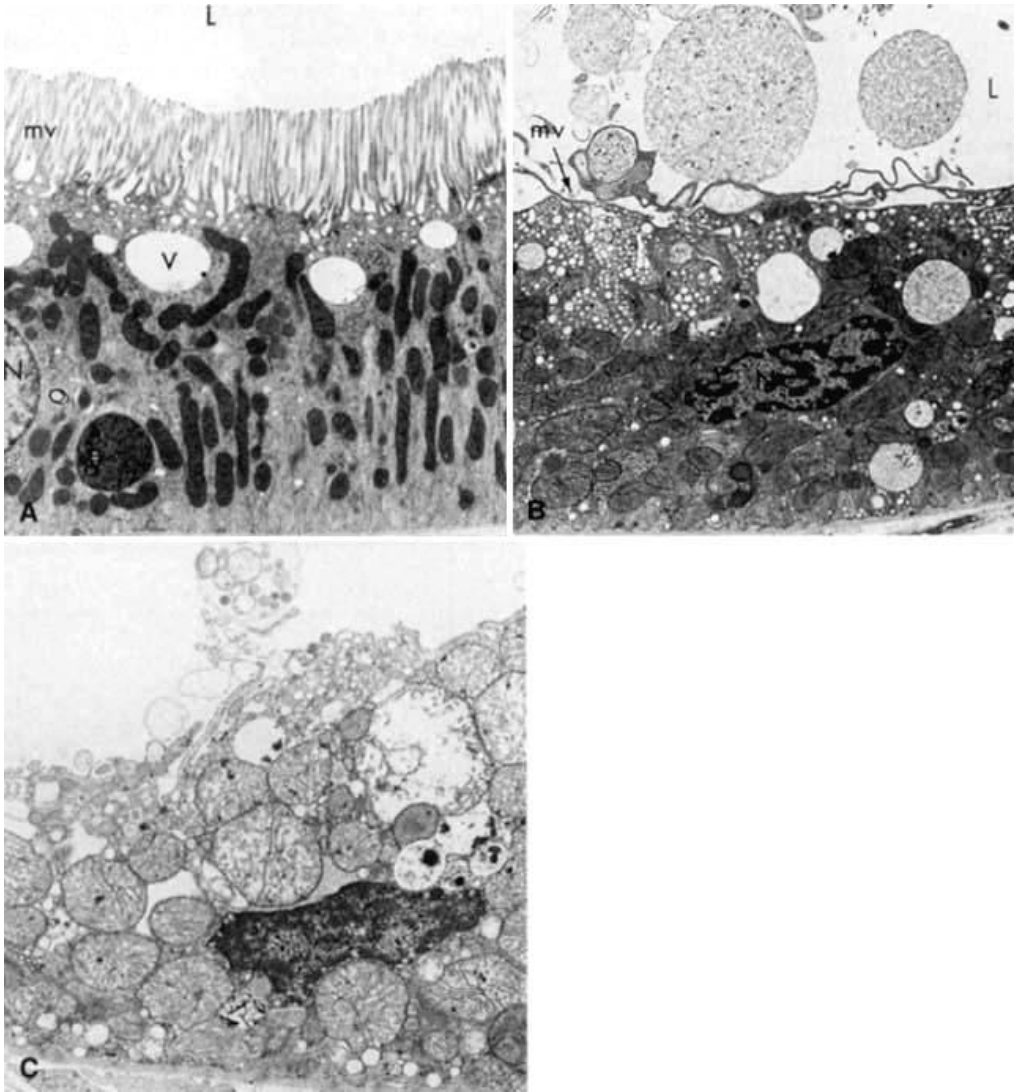
- **DEATH is**
  - **IRREVERSIBLE MITOCHONDRIAL DYSFUNCTION**
  - **PROFOUND MEMBRANE DISTURBANCES**

- **LIFE is……..???**

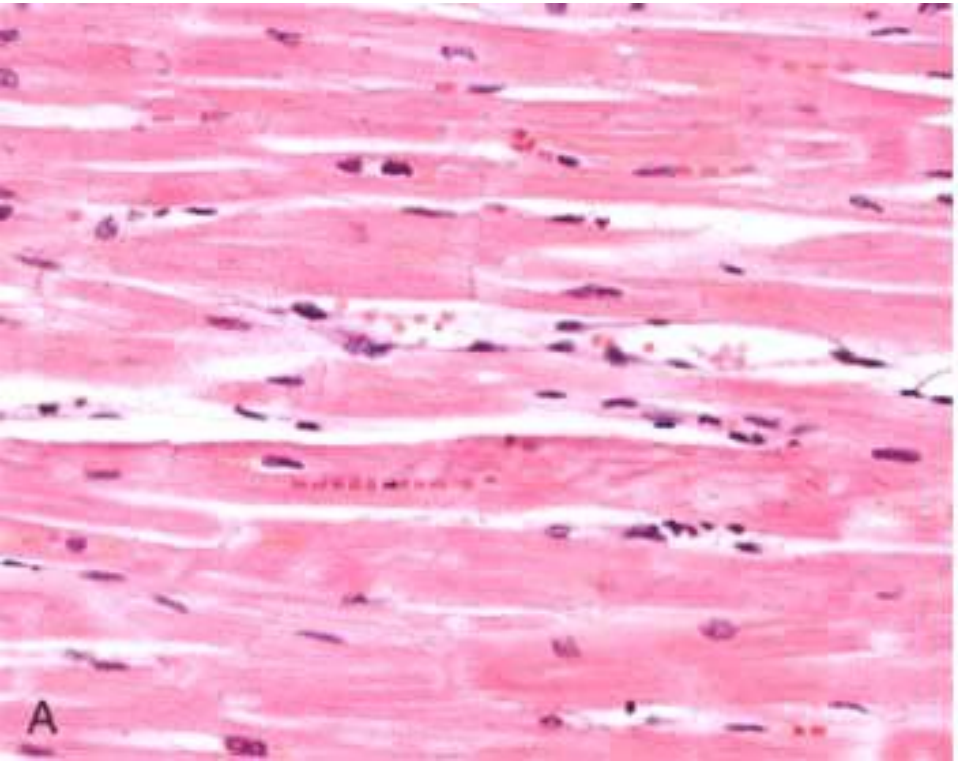
CONTINUUM

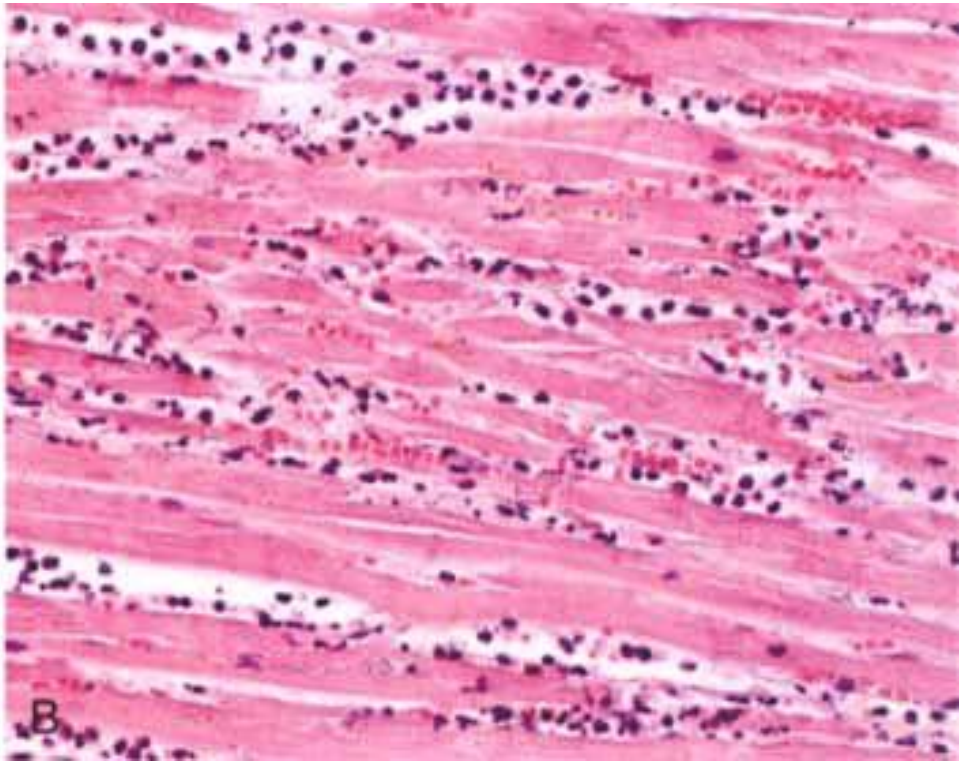
- REVERSIBLE →
- IRREVERSIBLE→
- DEATH→
- EM→
- LIGHT MICROSCOPY→
- GROSS APPEARANCES

DEATH:
ELECTRON MICROSCOPY



DEATH:
LIGHT MICROSCOPY

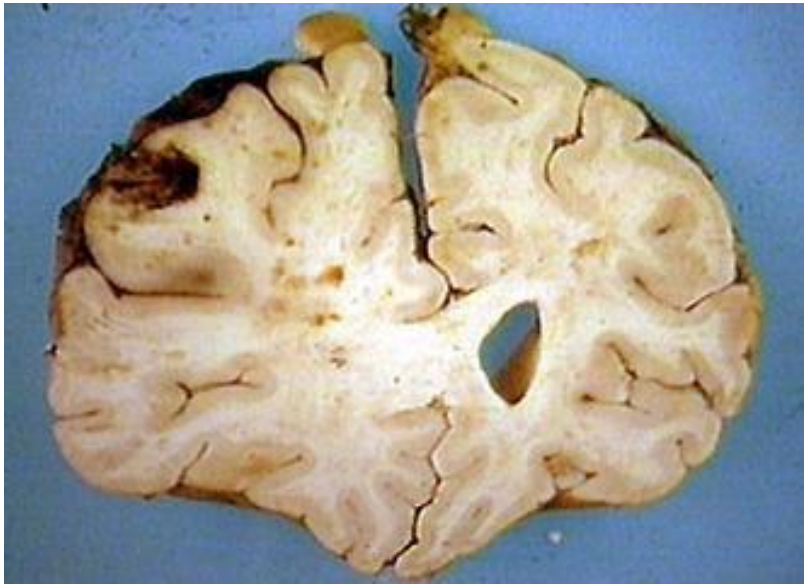


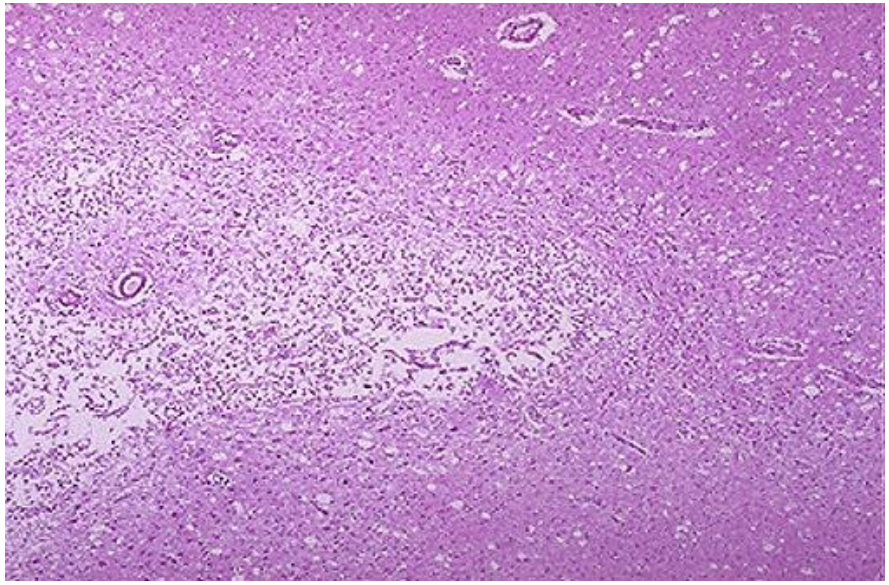


NECROSIS BROTHERS:

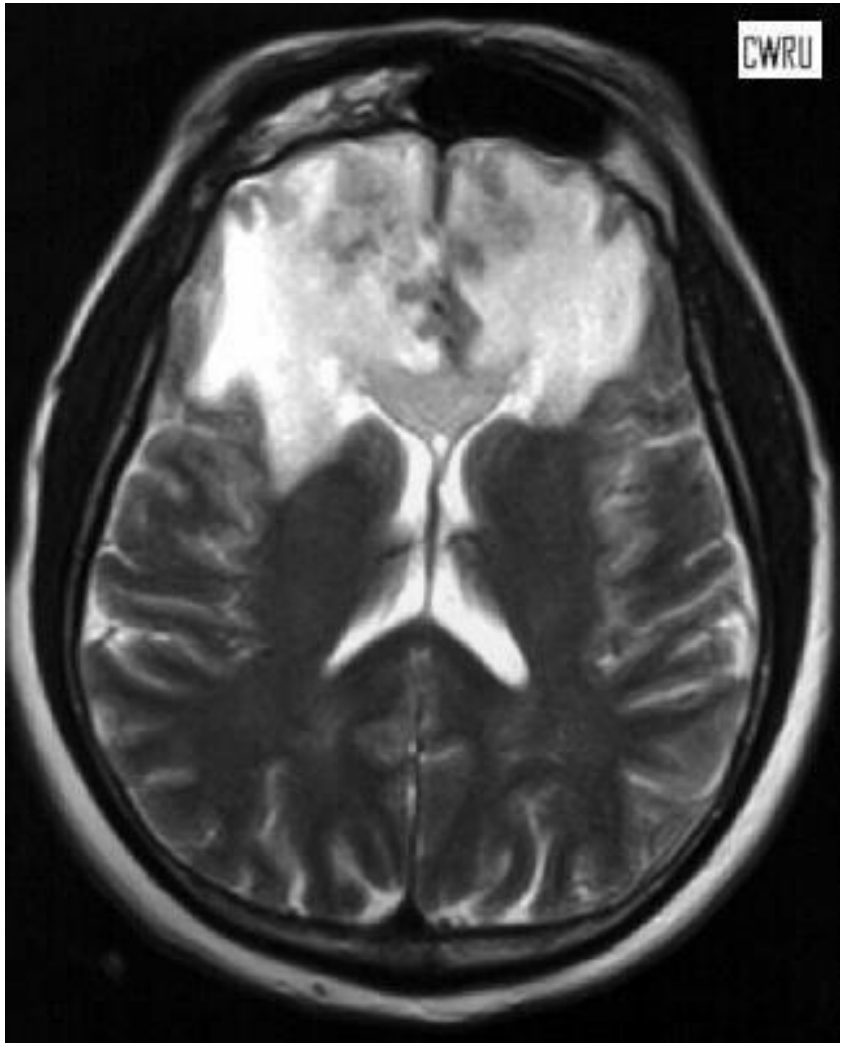
- **Liquefactive (Brain)**
- **Gangrenous (Extremities, Bowel, non-specific)**
  - **WET**
  - **DRY**
- **Fibrinoid (Rheumatoid, non-specific)**
- **Caseous (cheese) (Tuberculosis)**
- **Fat (Breast, any fat)**
- **Ischemic (non-specific)**
- **Avascular (aseptic), radiation, organ specific, papillary**
- **OneLook lists 153 terms preceding the word "necrosis":** http://www.onelook.com/?w=*necrosis&ls=a

LIQUEFACTIVE NECROSIS, BRAIN

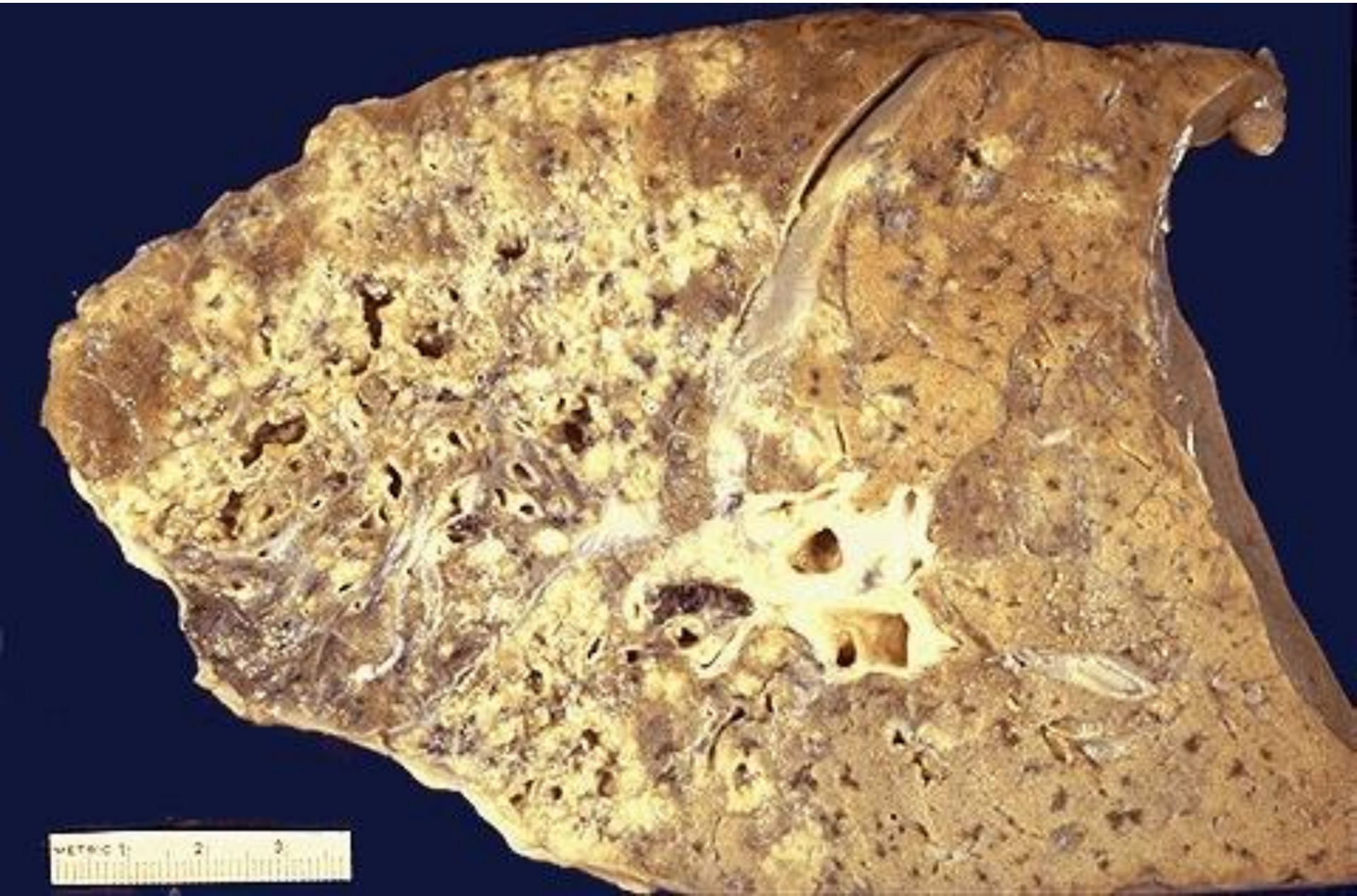




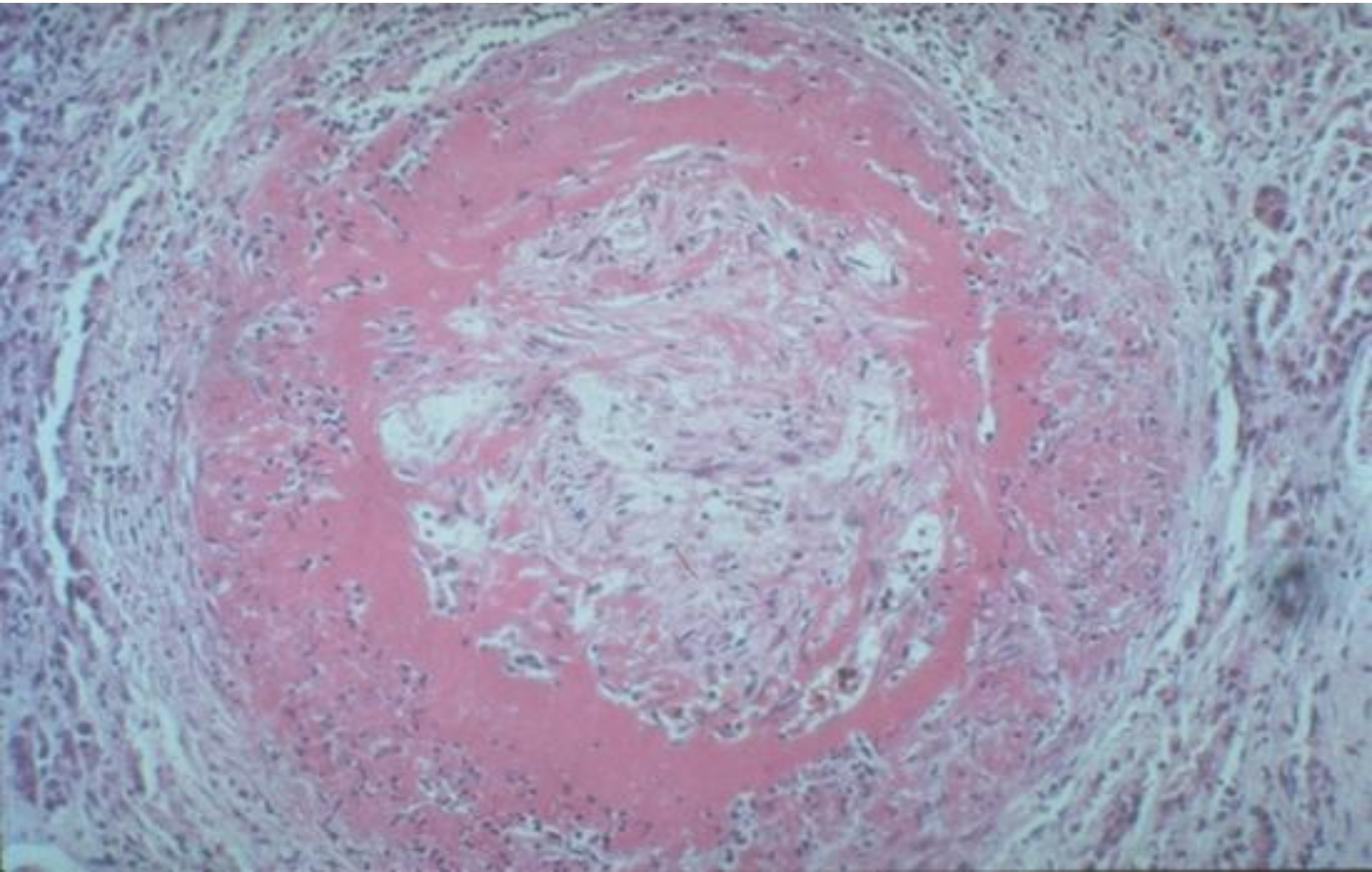
MORE LIQUID → MORE WATER → MORE PROTONS



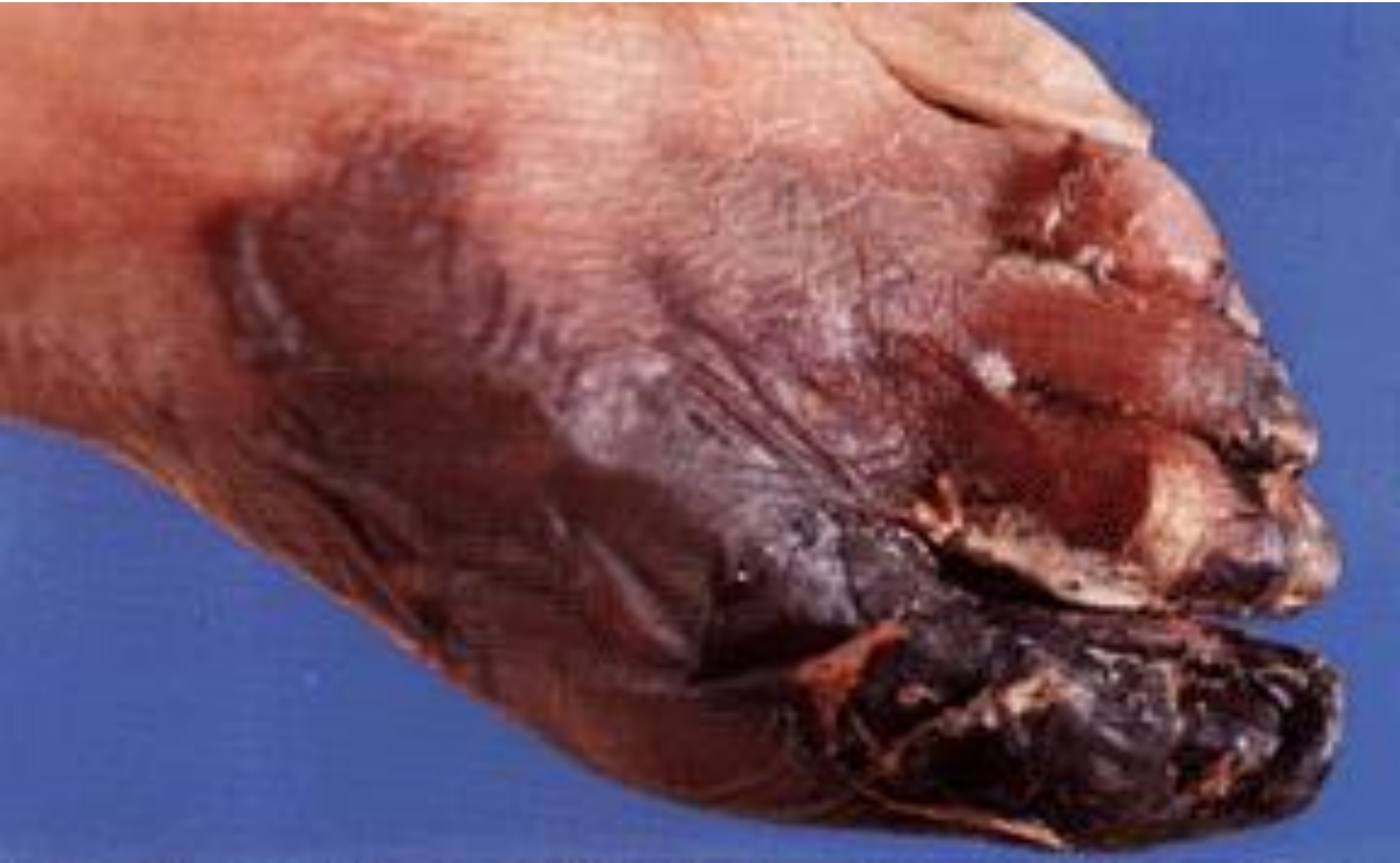
CASEOUS NECROSIS, TB



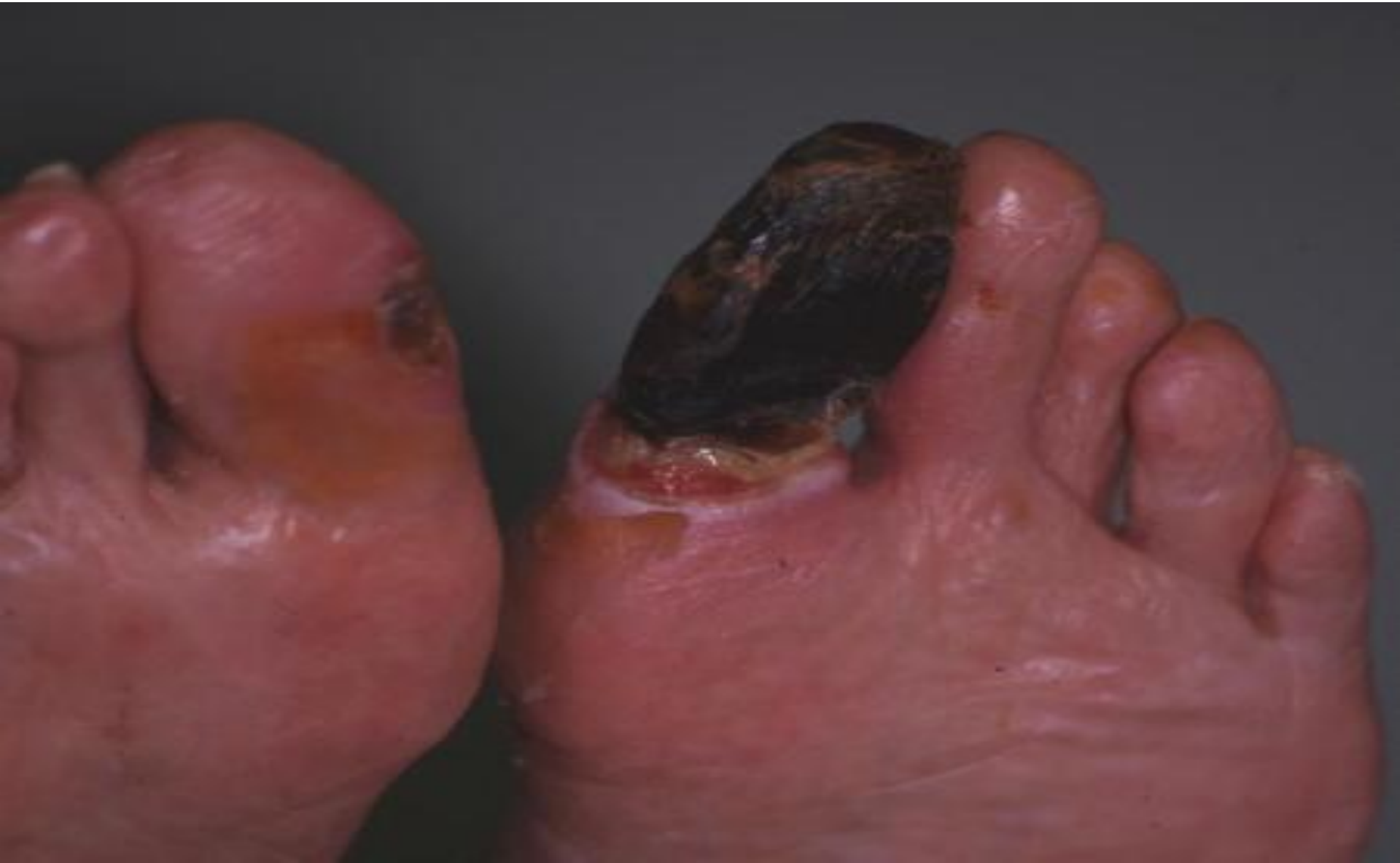
FIBRINOID NECROSIS



“WET” GANGRENE



“DRY” GANGRENE



EXAMPLES of Cell INJURY/NECROSIS

- Ischemic (Hypoxic)
- Ischemia/Reperfusion
- Chemical

ISCHEMIC INJURY

- REVERSIBLE→ IRREVERSIBLE
- DEATH (INFARCT)

ISCHEMIA/RE-PERFUSION INJURY

NEW Damage "Theory"

CHEMICAL INJURY

- "Toxic" Chemicals, e.g CCl_4
- Drugs, e.g tylenol
- Dose Relationship
- Free radicals, organelle, DNA damage

APOPTOSIS

- **NORMAL (preprogrammed)**
- **PATHOLOGIC (associated with Necrosis)**

"NORMAL" APOPTOSIS

- Embryogenesis
- Hormonal "Involution"
- Cell population control, e.g., "crypts"
- Post Inflammatory "Clean-up"
- Elimination of "HARMFUL" cells
- Cytotoxic T-Cells cleaning up

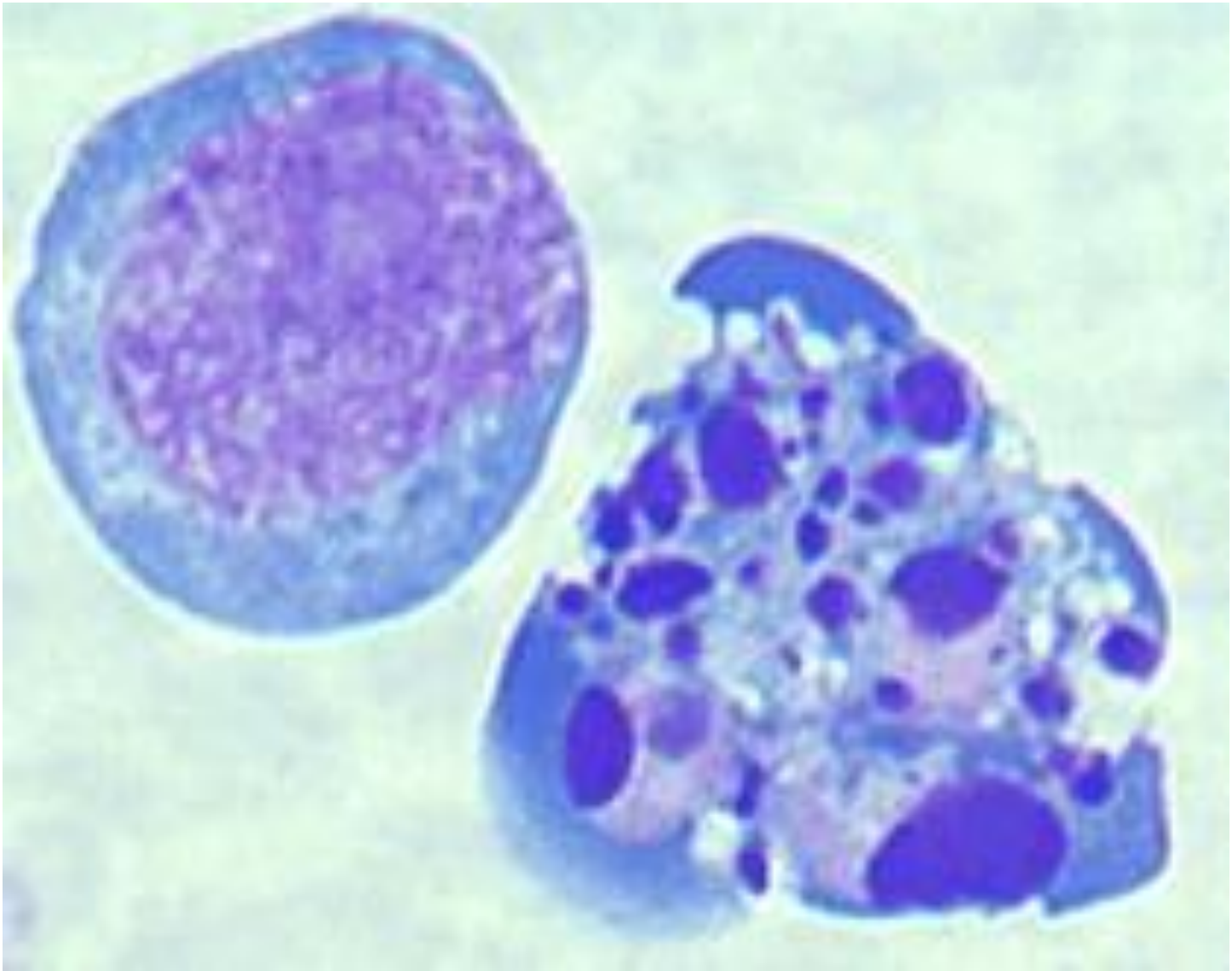
"PATHOLOGIC" APOPTOSIS

- "Toxic" effect on cells, e.g., chemicals, pathogens
- Duct obstruction
- Tumor cells
- Apoptosis/Necrosis spectrum

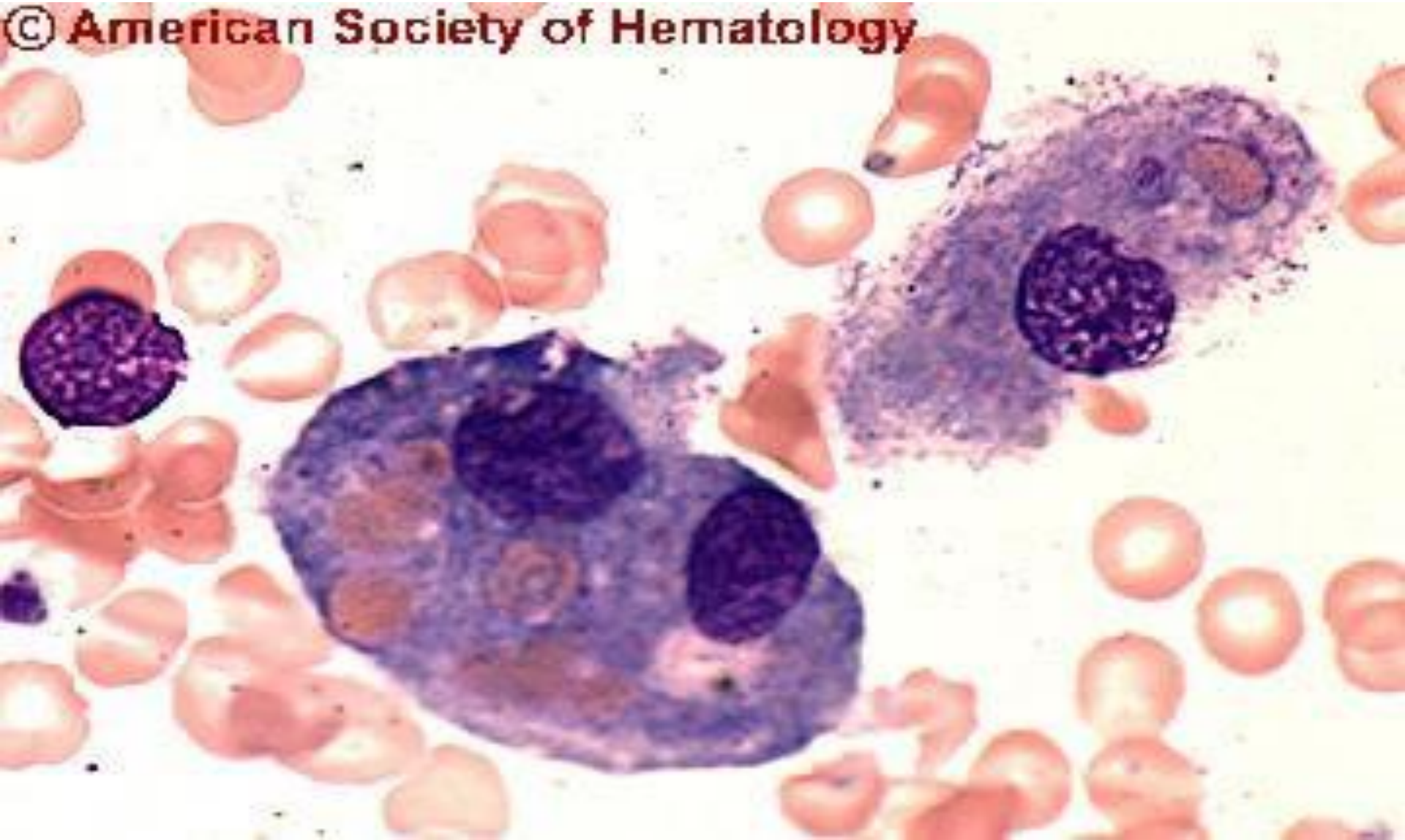
APOPTOSIS MORPHOLOGY

- DE-crease in cell size, i.e., shrinkage
- IN-crease in chromatin concentration, i.e., hyperchromasia, pyknosis→ karyorhexis→ karyolysis
- IN-crease in membrane “blebs”
- Phagocytosis

SHRINKAGE/HYPERCHROMASIA



PHAGOCYTOSIS



APOPTOSIS BIOCHEMISTRY

- Protein Digestion (Caspases)
- DNA breakdown
- Phagocytic Recognition

SUB-Cellular Responses to Injury (APOPTOSIS/NECROSIS)

- **Lysosomal** Auto-Digestion
- Smooth Endoplasmic Reticulum (**SER**) activation
- **Mitochondrial** "SWELLING"
- **Cytoskeleton** Breakdown
  - Thin Filaments (actin, myosin)
  - Microtubules
  - Intermediate Filaments (keratin, desmin, vimentin, neurofilaments, glial filaments)

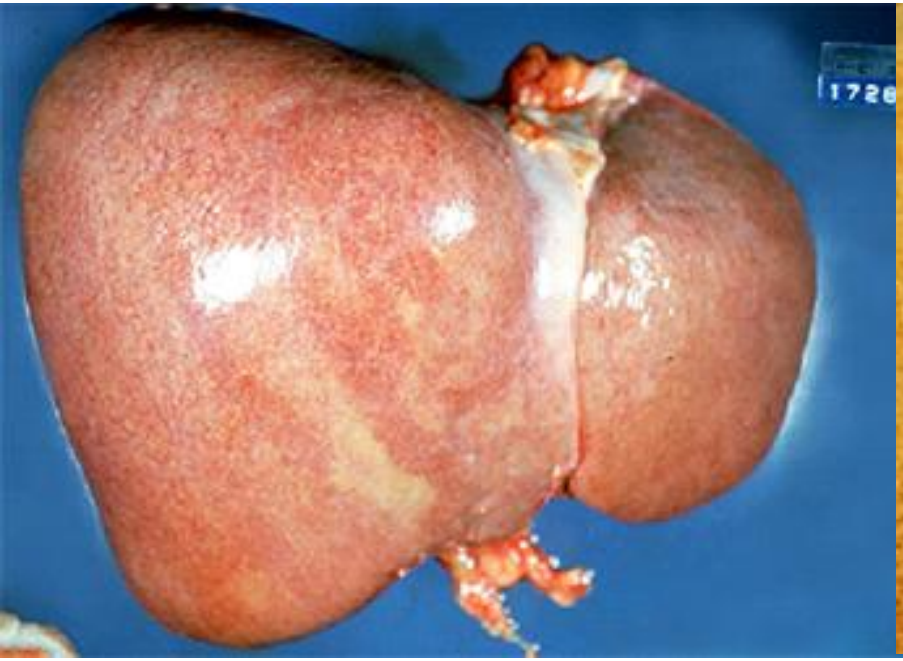
INTRAcellular ACCUMULATIONS

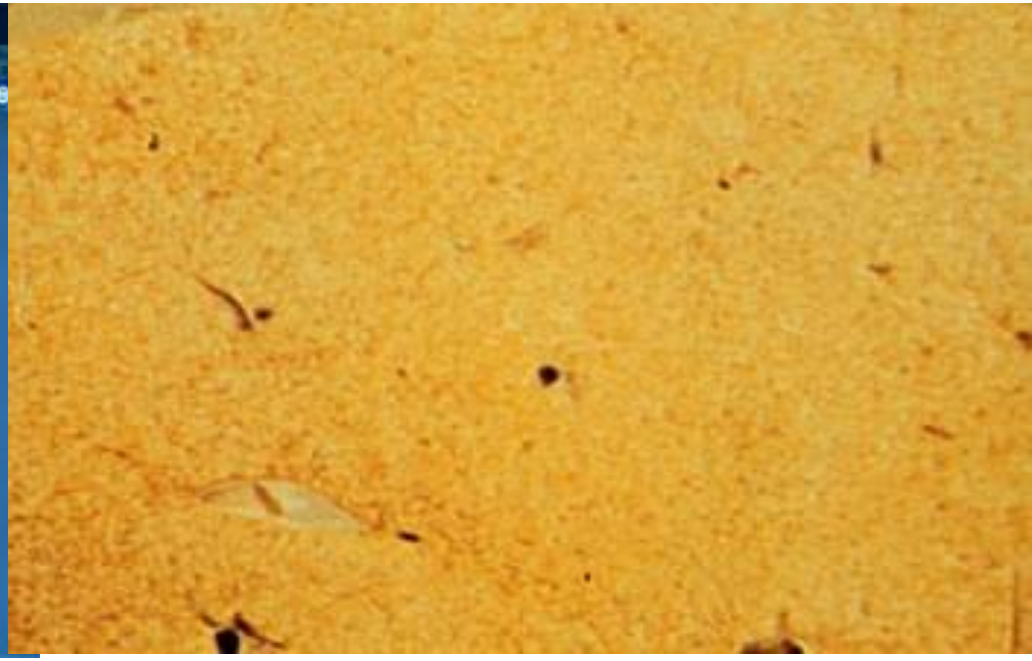
- Lipids
  - Neutral Fat
  - Cholesterol
- "Hyaline" = any "proteinaceous" pink "glassy" substance
- Glycogen
- Pigments (EXogenous, END-ogenous)
- Calcium

LIPID LAW

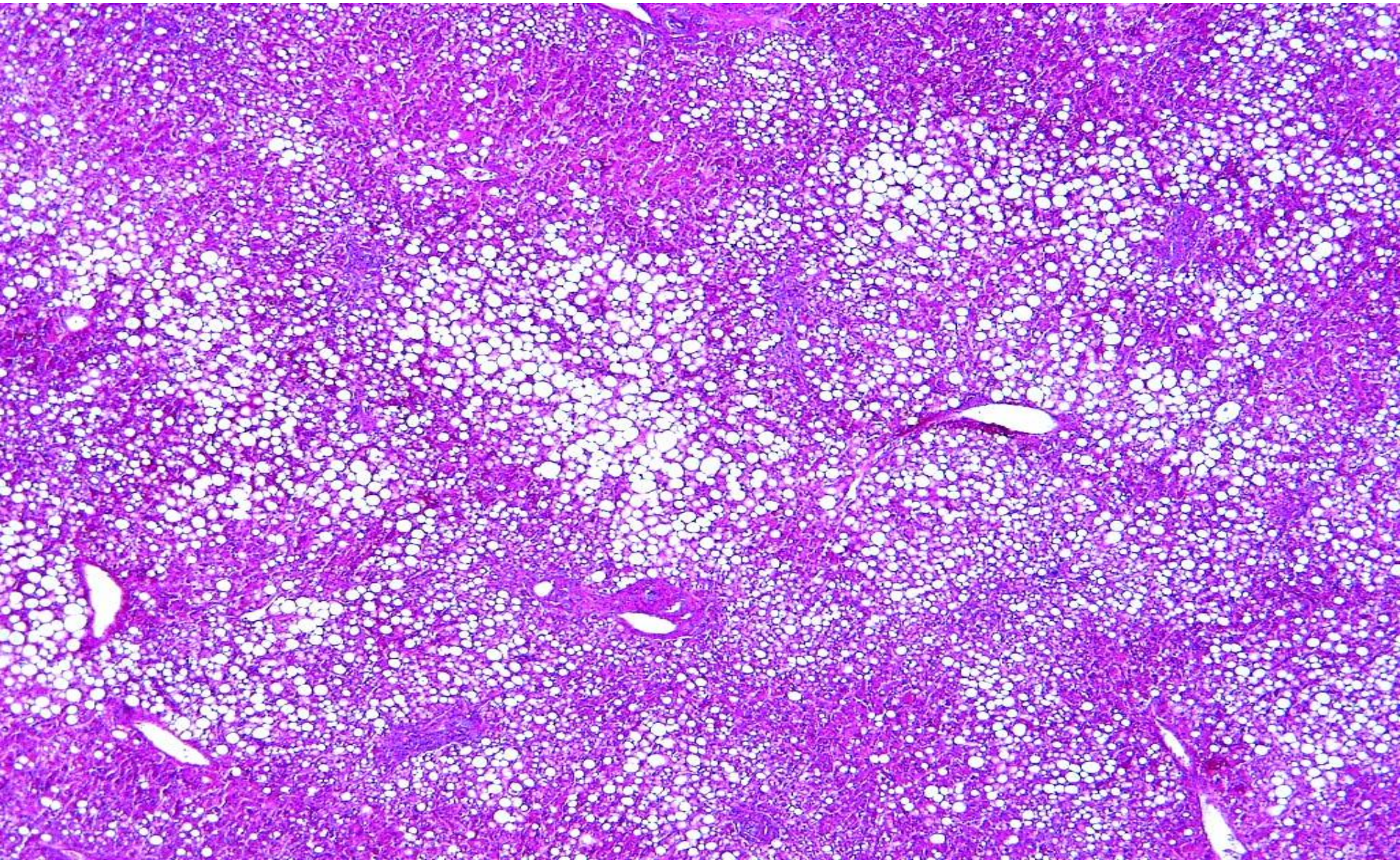
- ALL Lipids are YELLOW grossly and WASHED out (CLEAR) microscopically

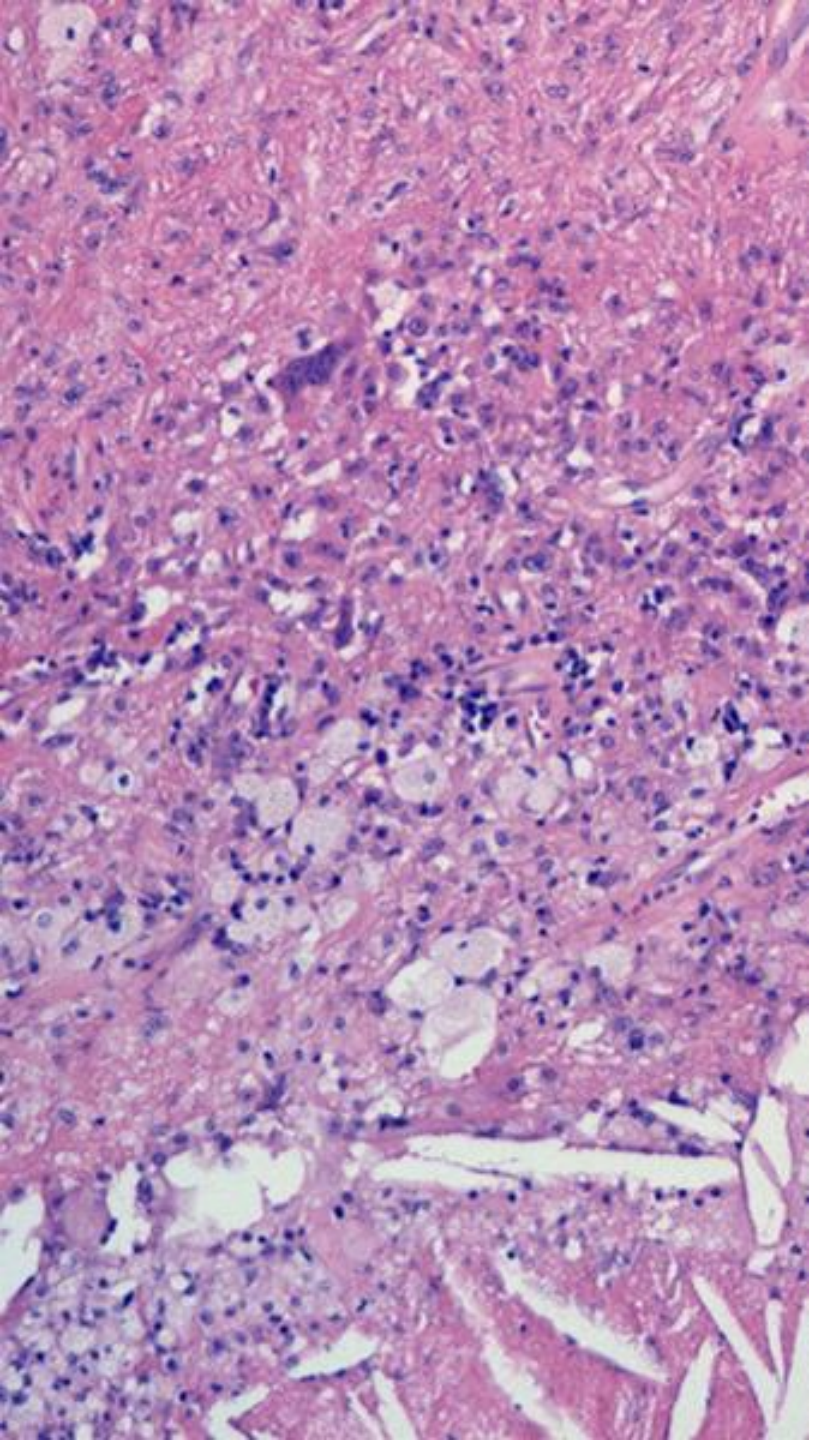
FATTY LIVER

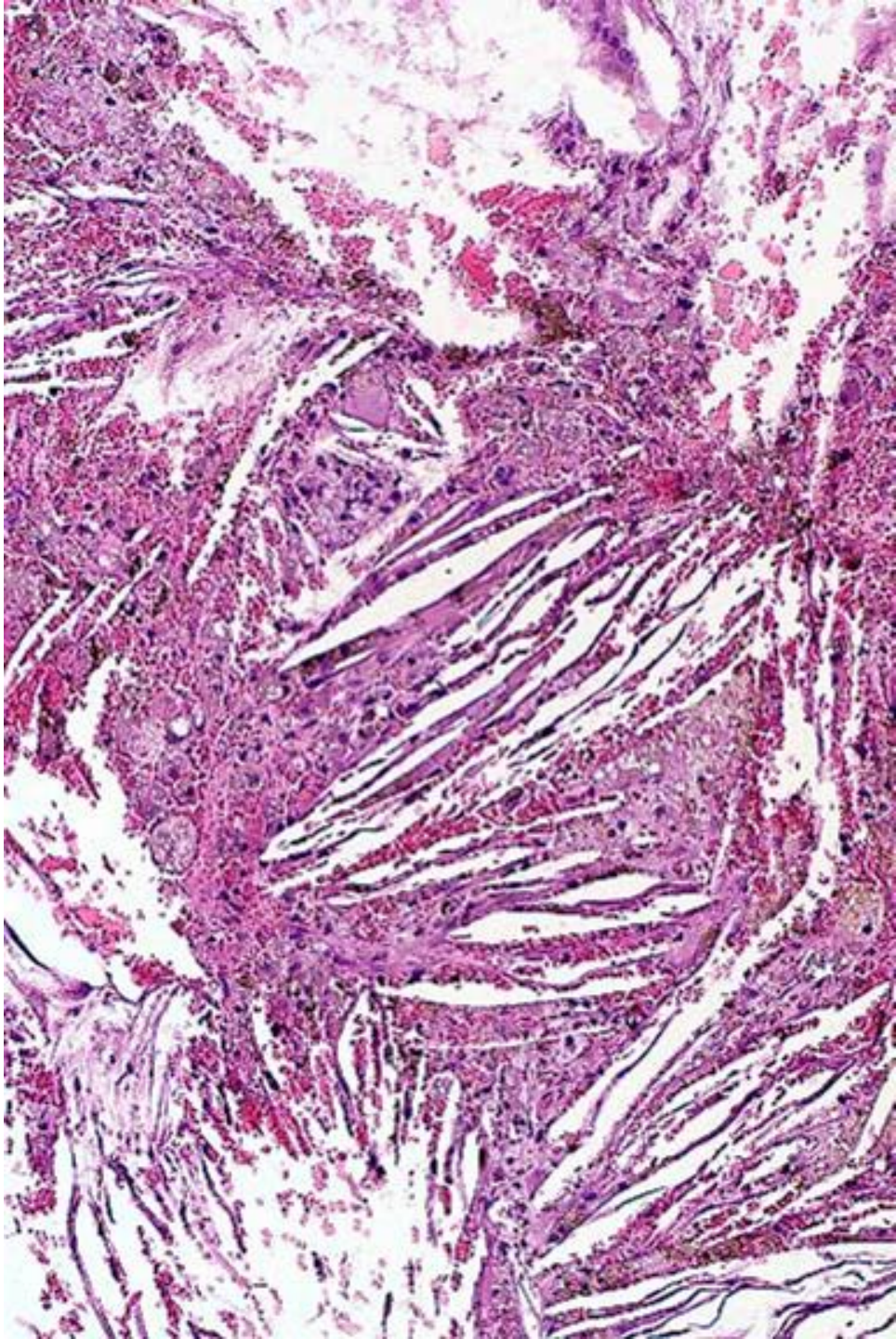




FATTY LIVER





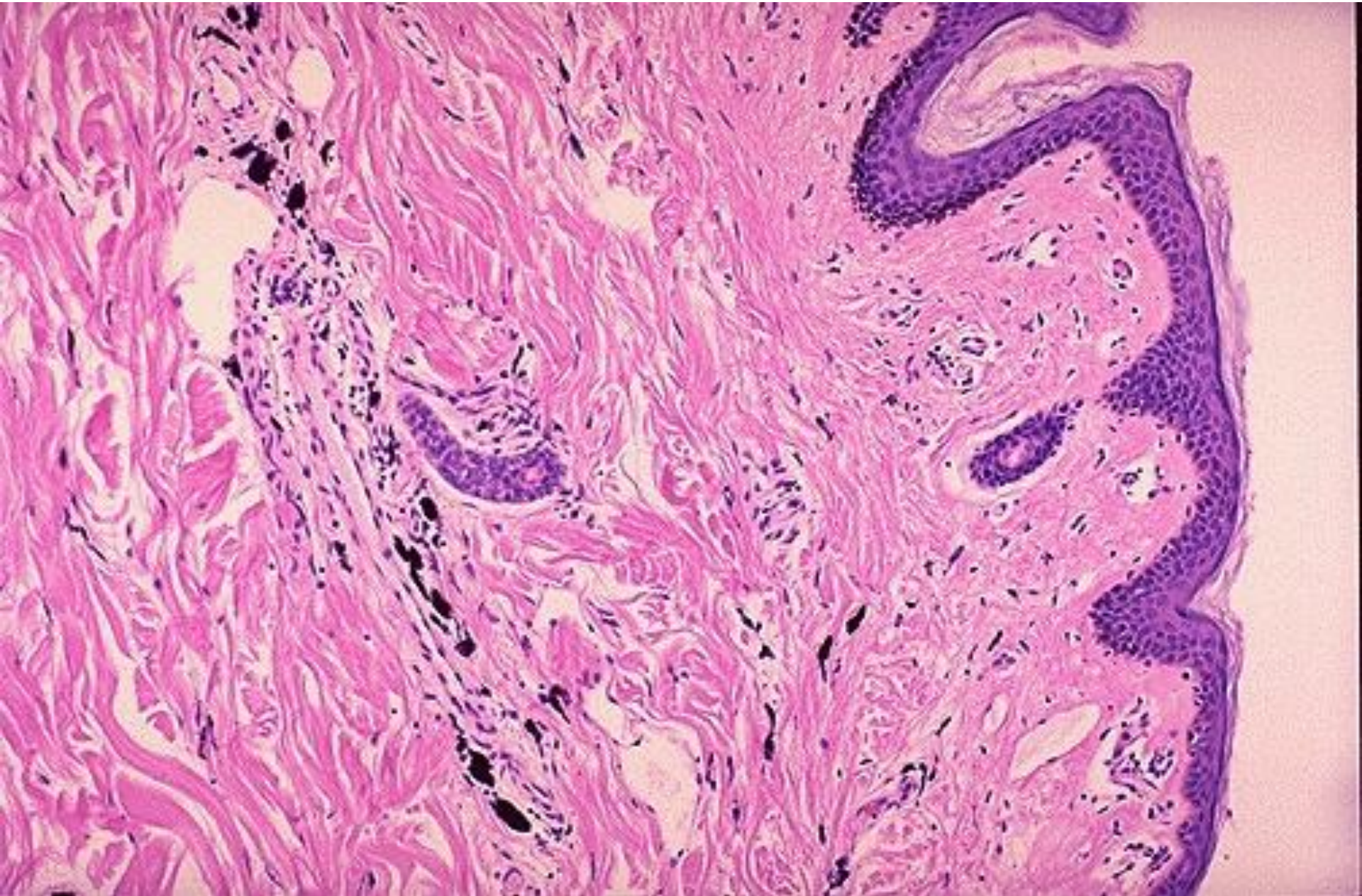


PIGMENTS

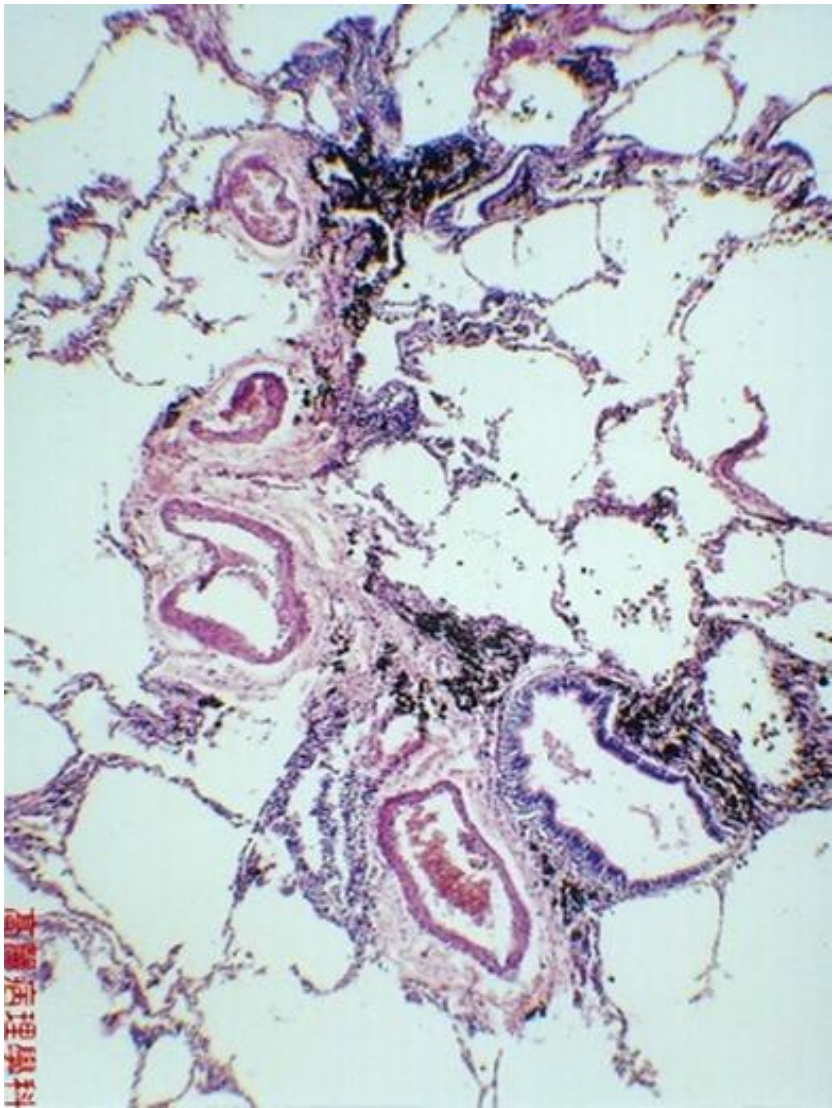
EXogenous--- (tattoo, Anthracosis)

END-ogenous--- they all look the same, (e.g., hemosiderin, melanin, lipofucsin, bile), in that they are all golden yellowish brown on "routine" Hematoxylin & Eosin (H&E) stains

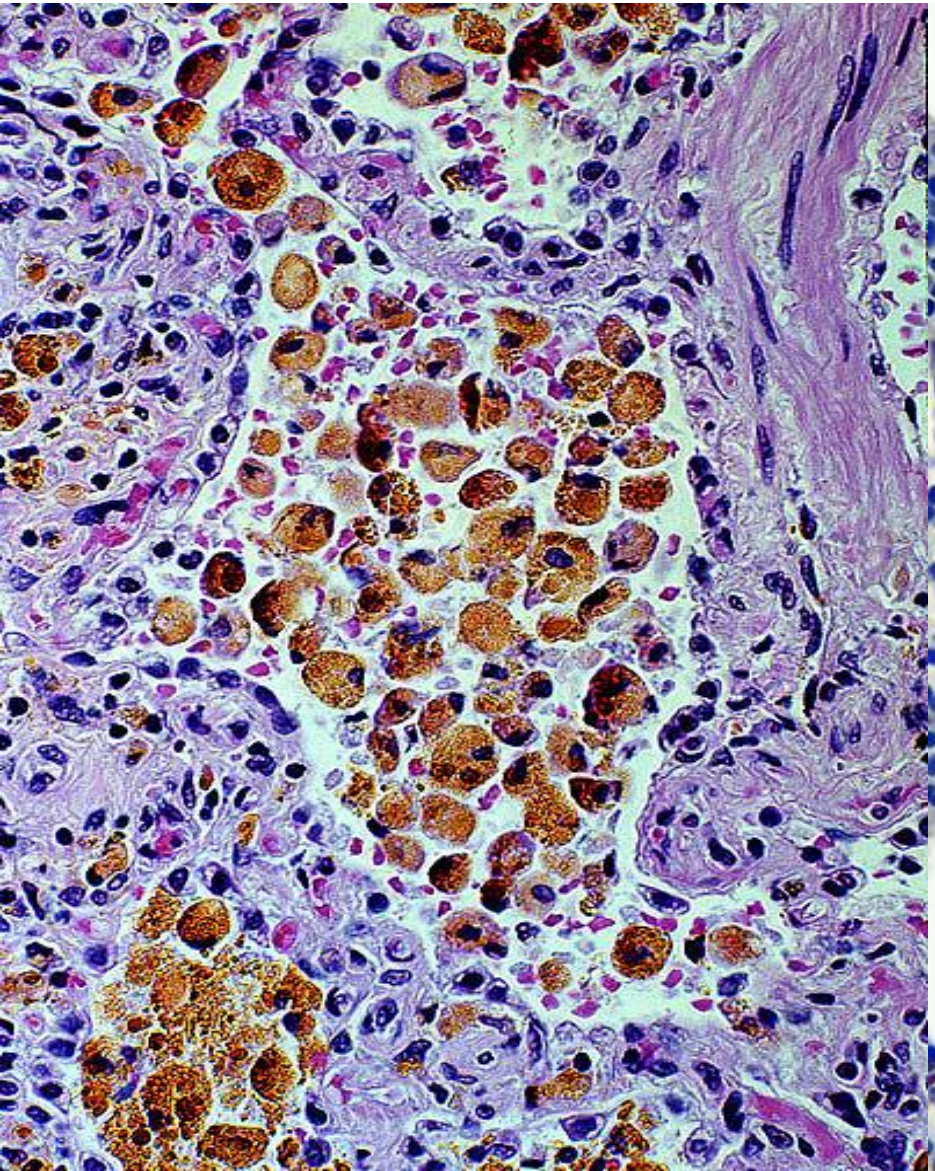
TATTOO, MICROSCOPIC

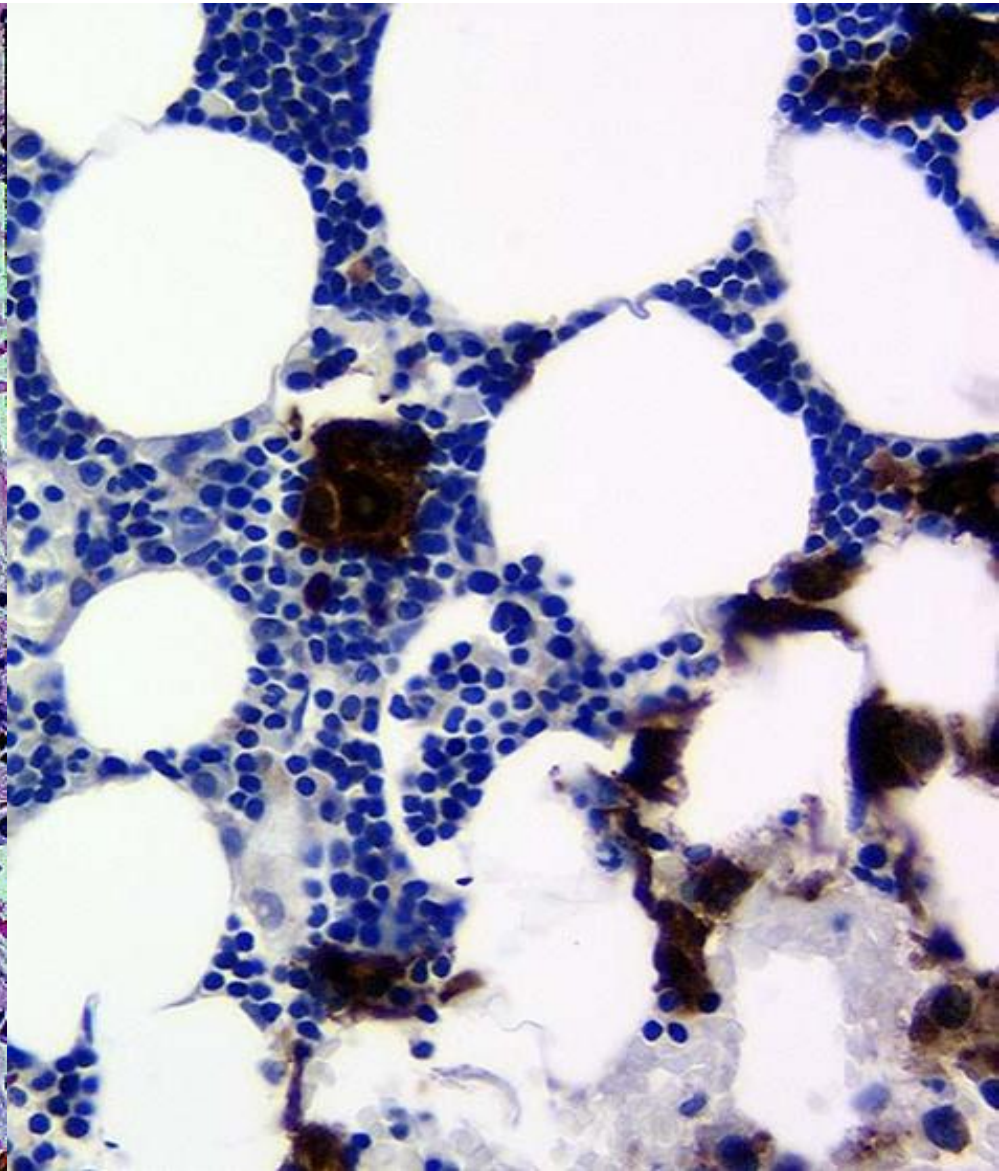


ANTHRACOSIS



Hemosiderin/Melanin/etc.





CALCIFICATION

- **DYSTROPHIC (LOCAL CAUSES) (often with FIBROSIS)**
- **METASTATIC (SYSTEMIC CAUSES)**
  - **HYPERPARATHYROIDISM**
  - **"METASTATIC* " Disease**

***NOT to be confused with "metastatic" calcification**

CELL AGING parallels ORGANISMAL AGING

PROGRAMMED THEORY (80%)

vs.

WEAR AND TEAR THEORY (20%)