CHS 2413
Pathology and Physiopathology

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บทที่ 2

Cellular Pathology

Summary

- This talk has covered….
  - Normal Functioning of Eukaryotic Cells
  - Cellular Changes
  - Intracellular Accumulations and Pigments
  - Cell injury

พยาธิวิทยากายวิภาค (Anatomical Pathology)

Boundary – Cell membrane (plasma membrane)

Composed of lipid molecules in bilayer

Phospholipids have hydrophobic tail

Phospholipids have hydrophilic heads

Also contains embedded proteins

proteins are important for cell-cell communication:

receptors for hormones

cell recognition

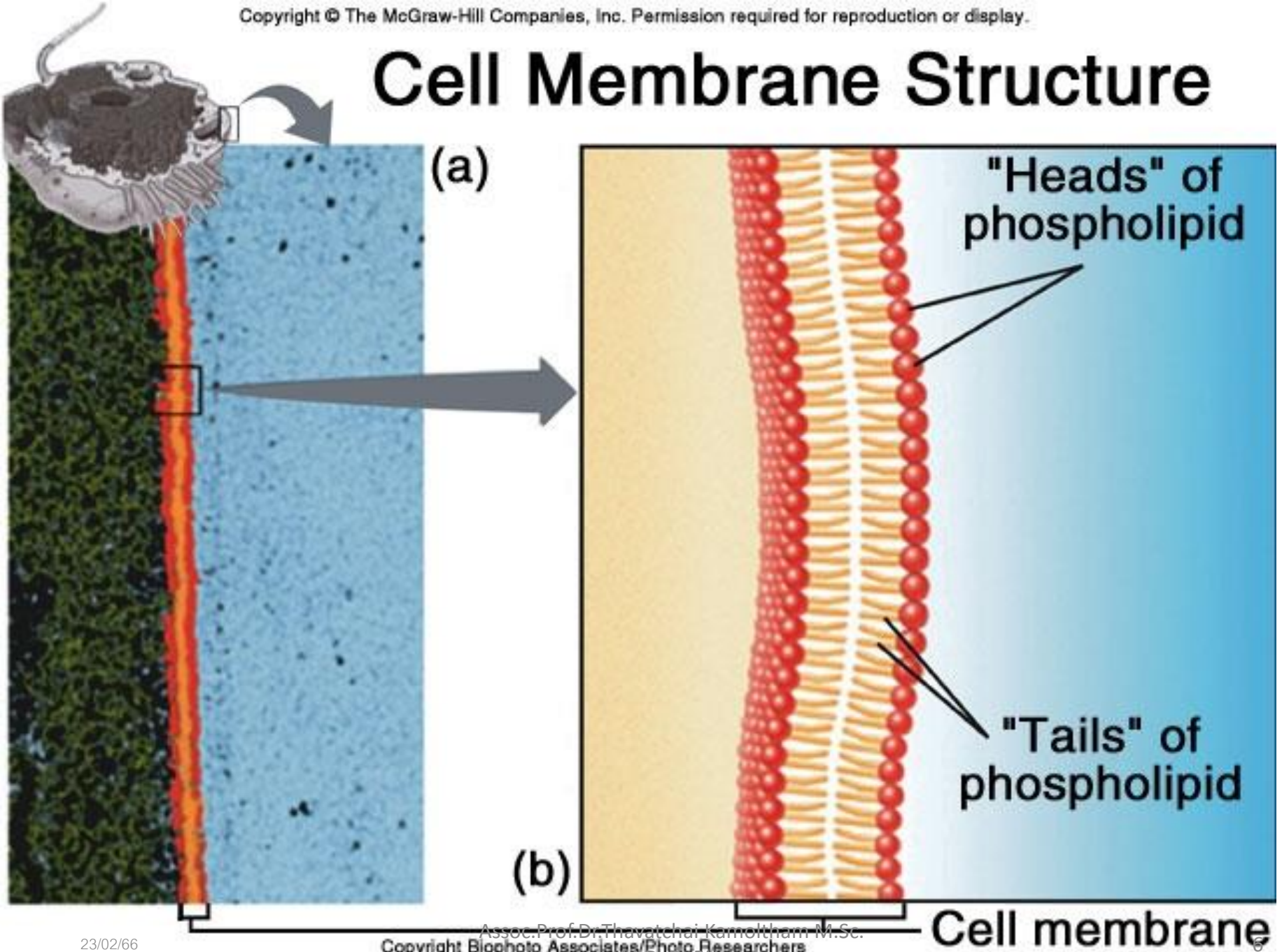
also important for metabolic processes inside the cell:

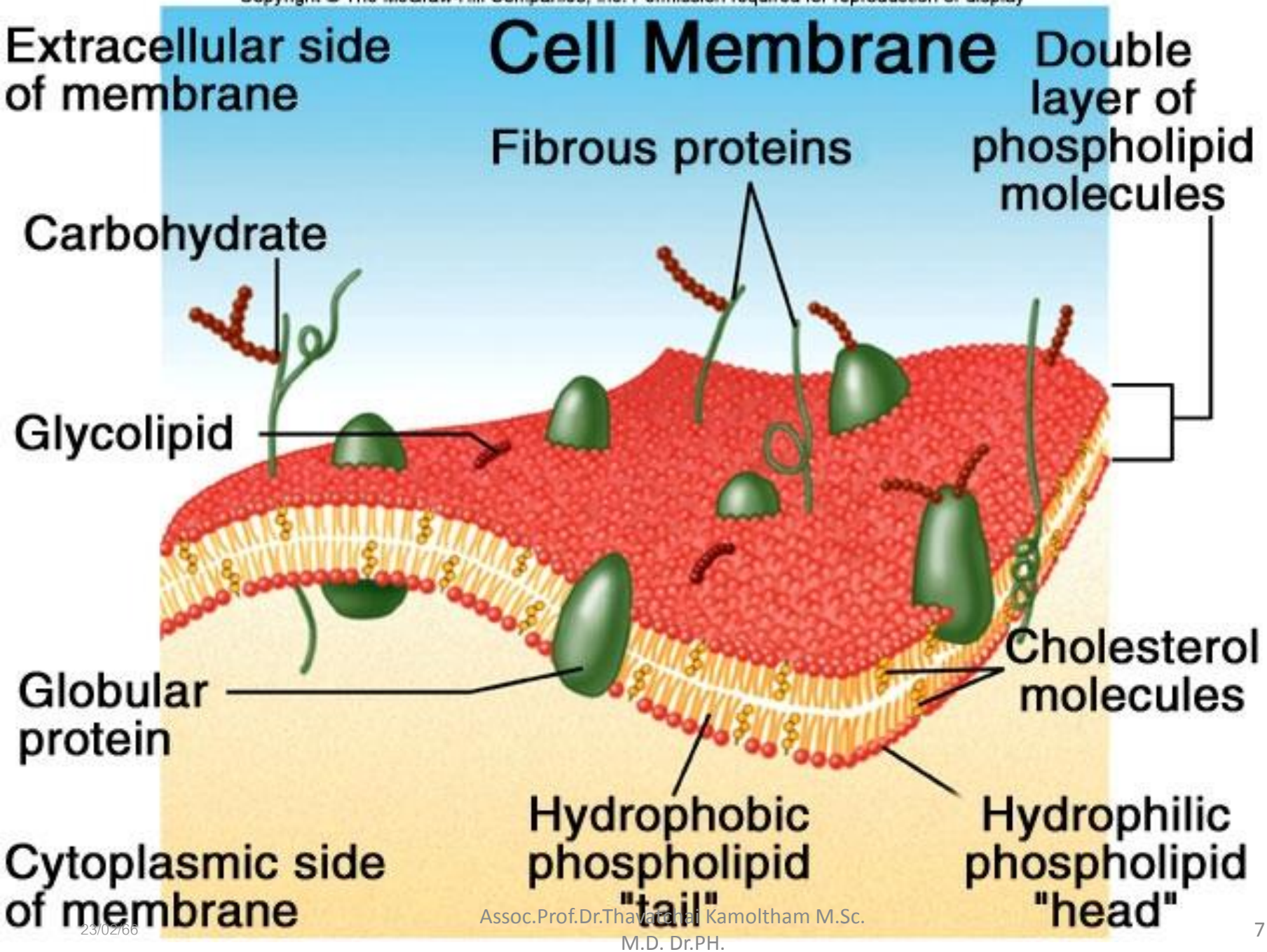
channels

pumps

enzymes

Cell Membrane Structure





Cytoplasm

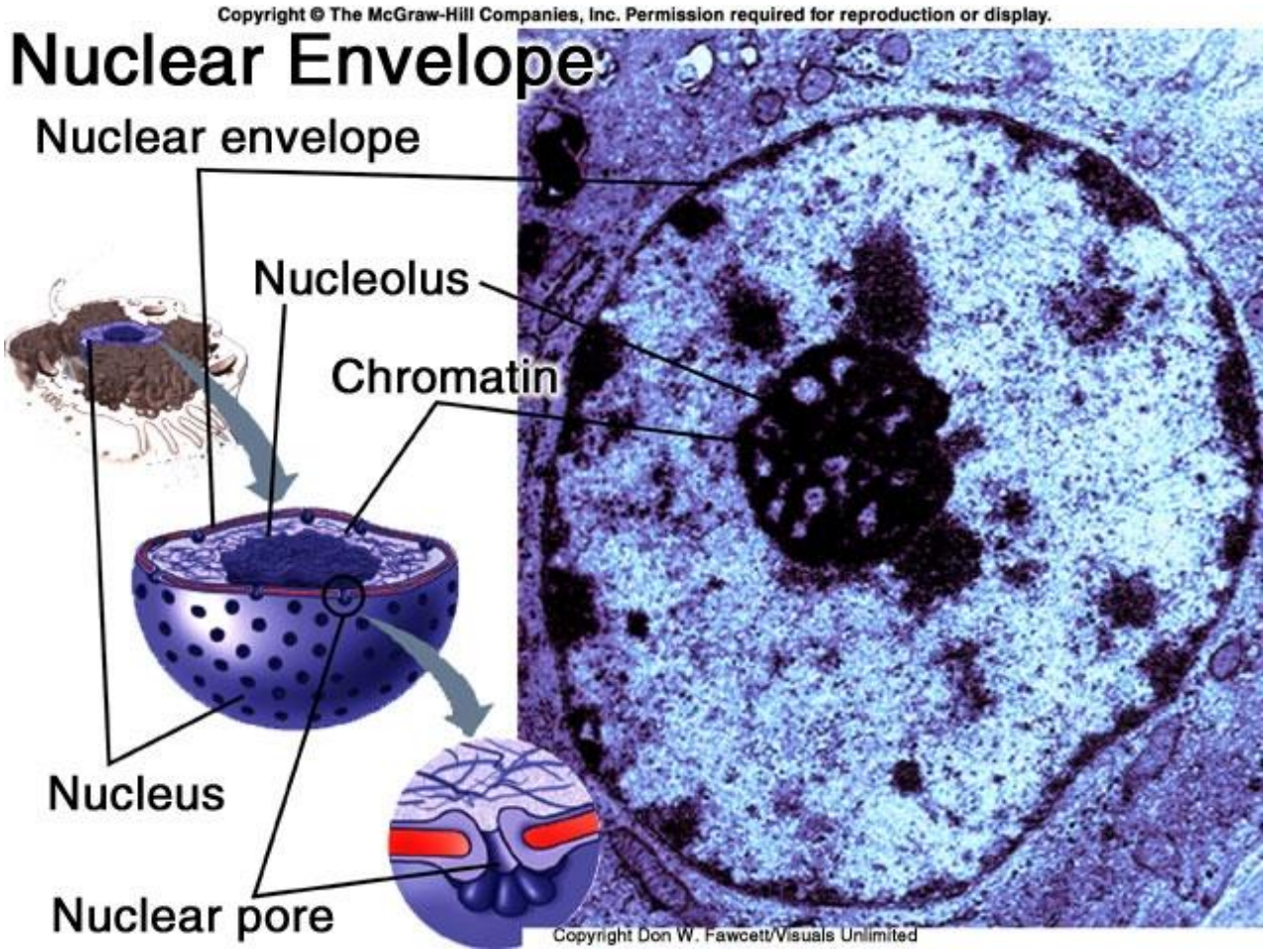
Cytosol – aqueous gel-like medium

Important metabolic processes occur here

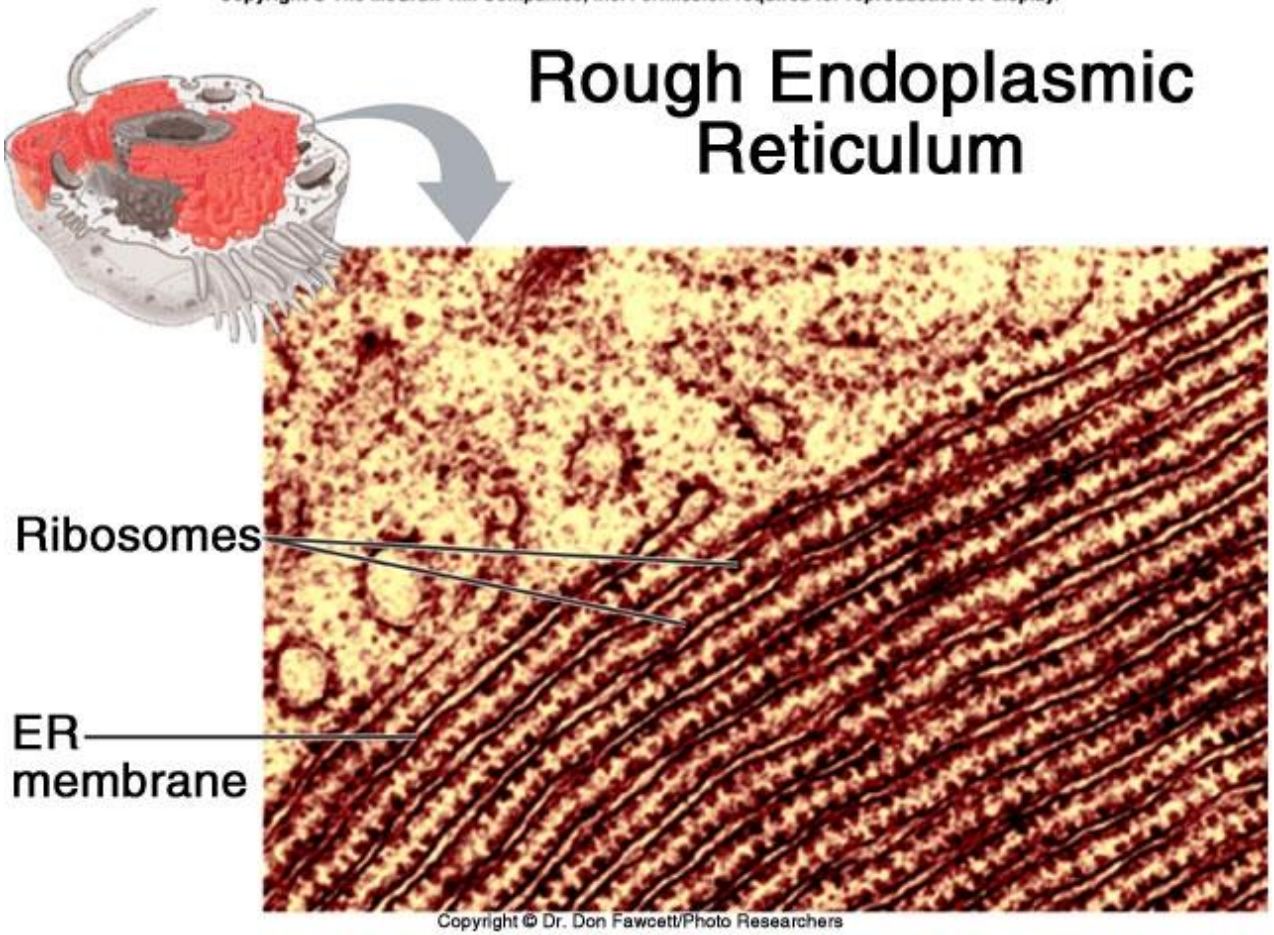
Organelles – membrane bound structures

Membranes provide compartments for separation of chemical reactions

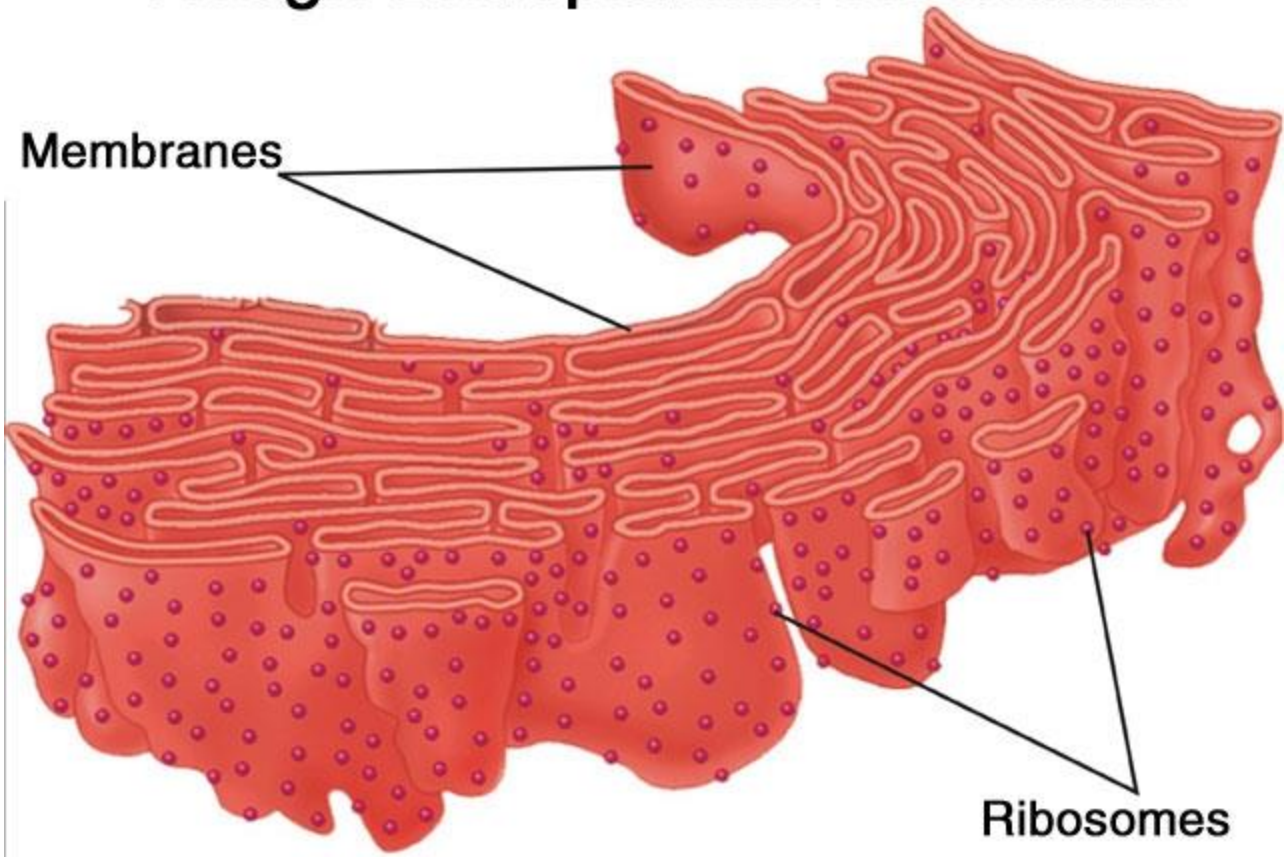
Nucleus
DNA codes for proteins



Rough Endoplasmic Reticulum
Contains ribosomes – make proteins

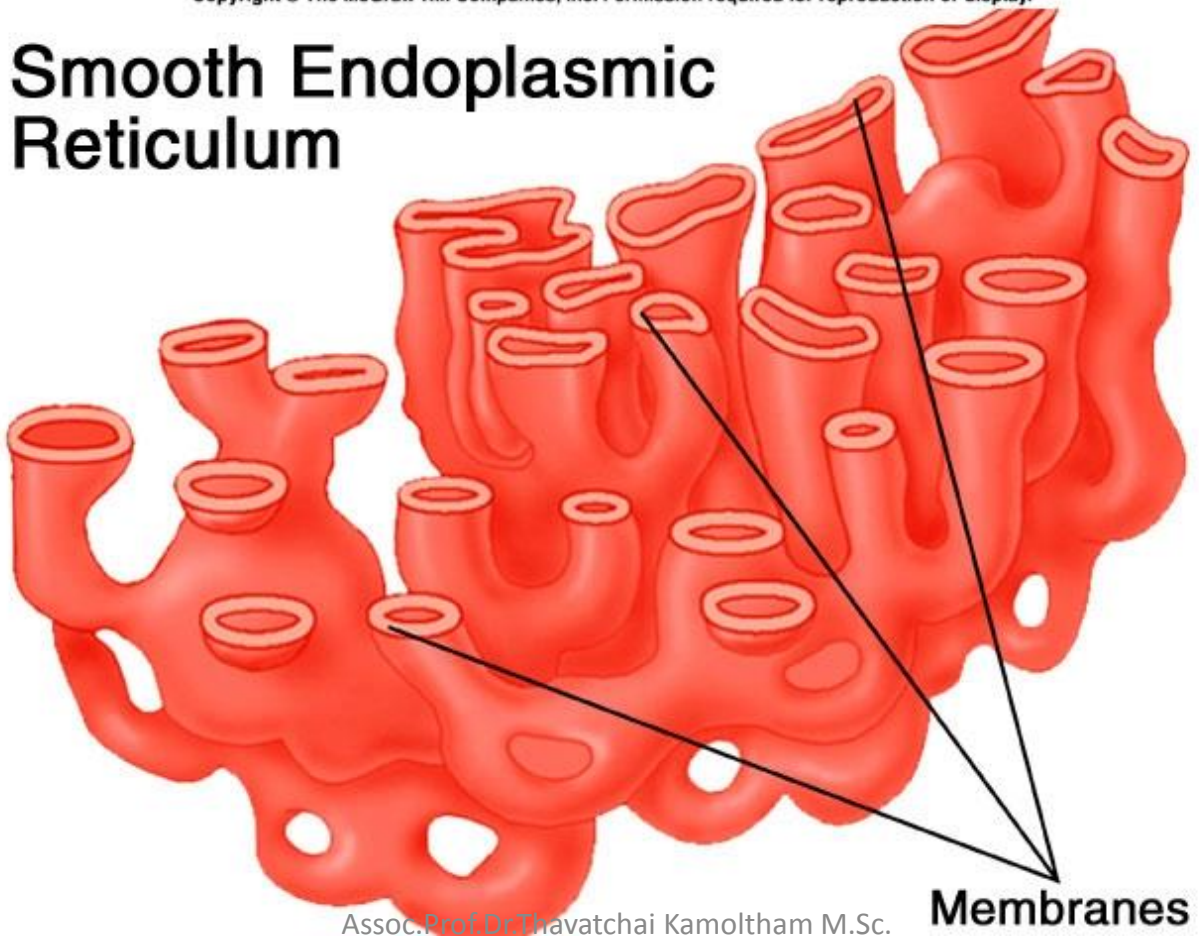


Rough Endoplasmic Reticulum

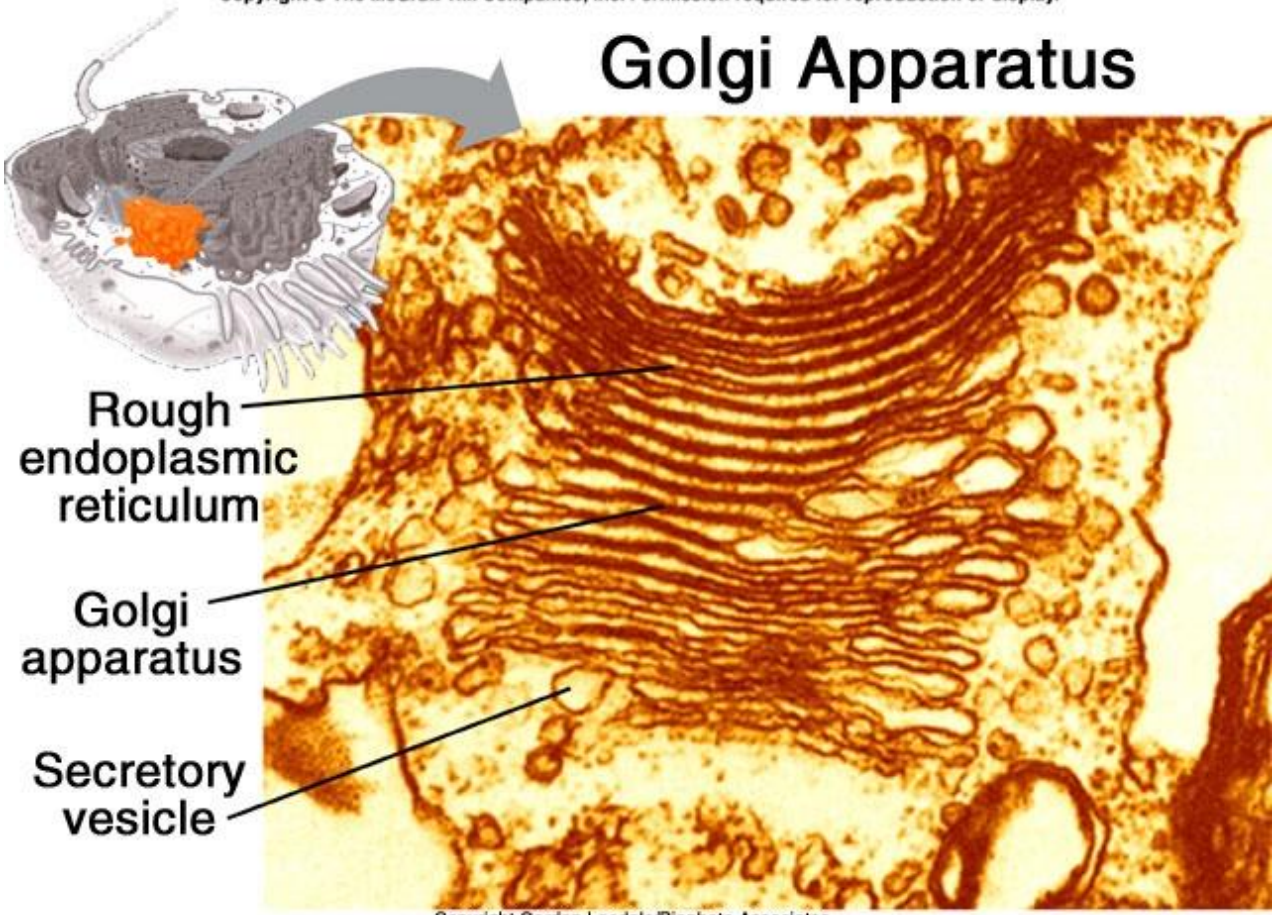


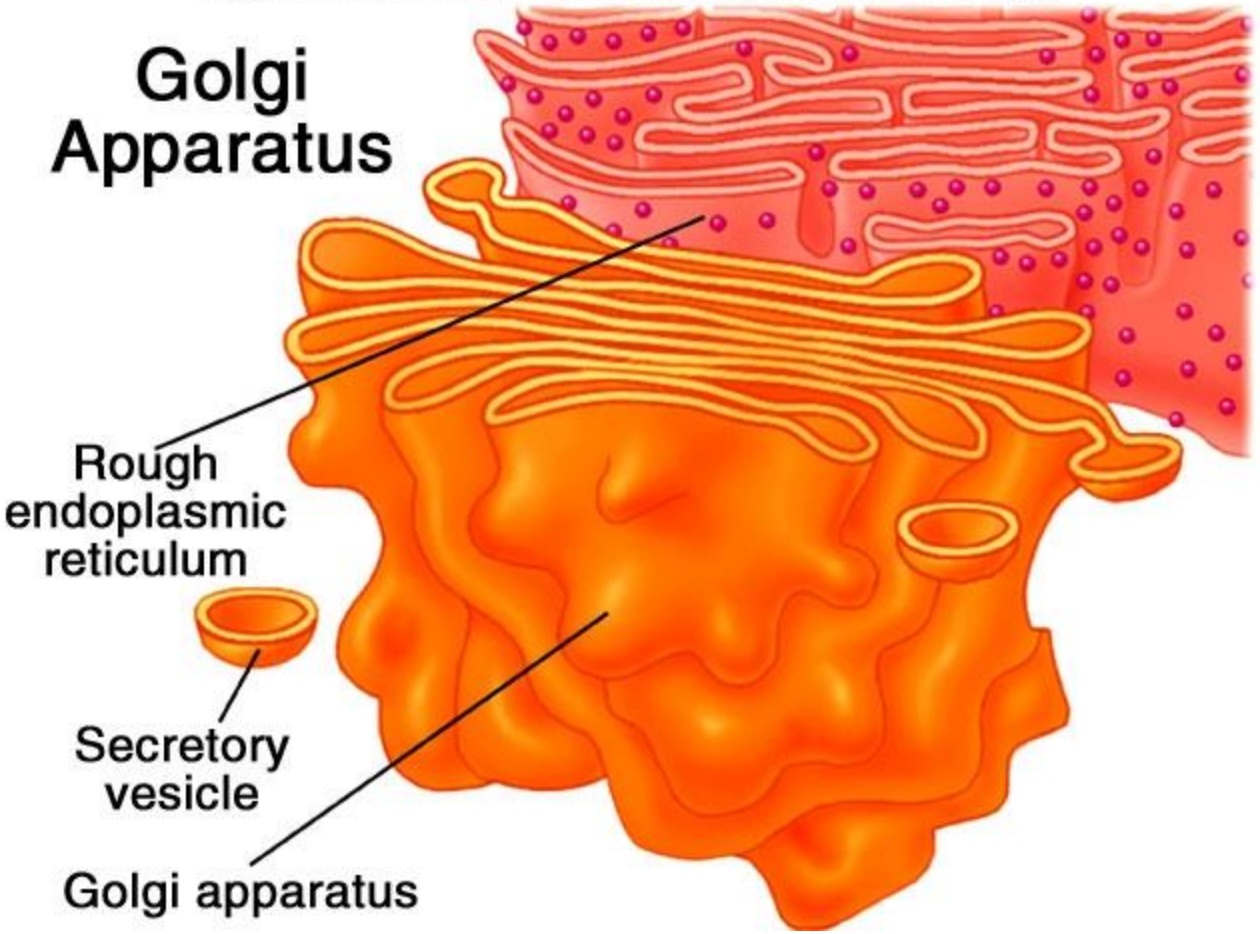
Smooth ER

synthesizes phospholipids
detoxifies

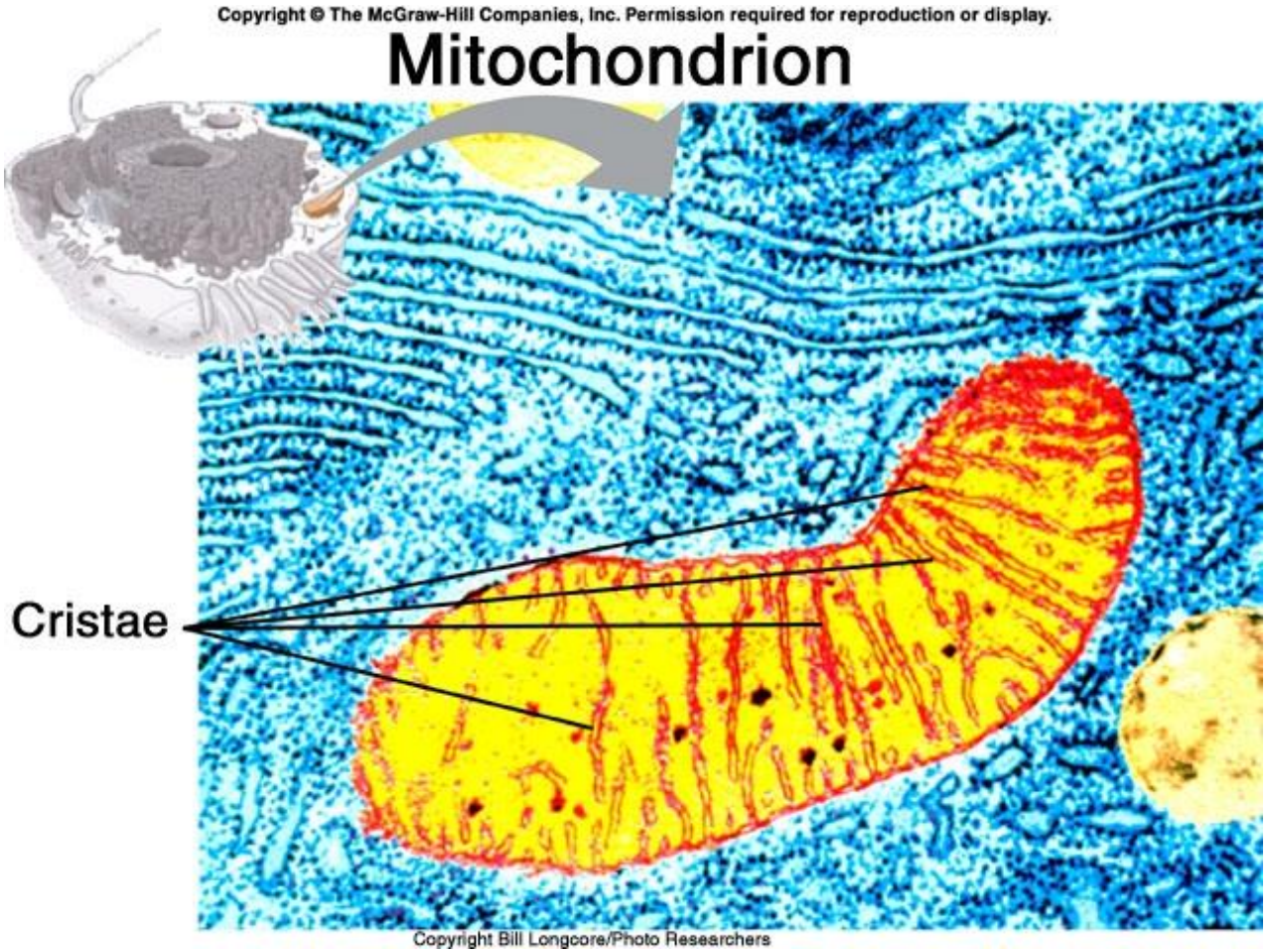


Golgi Apparatus
Packages protein for export

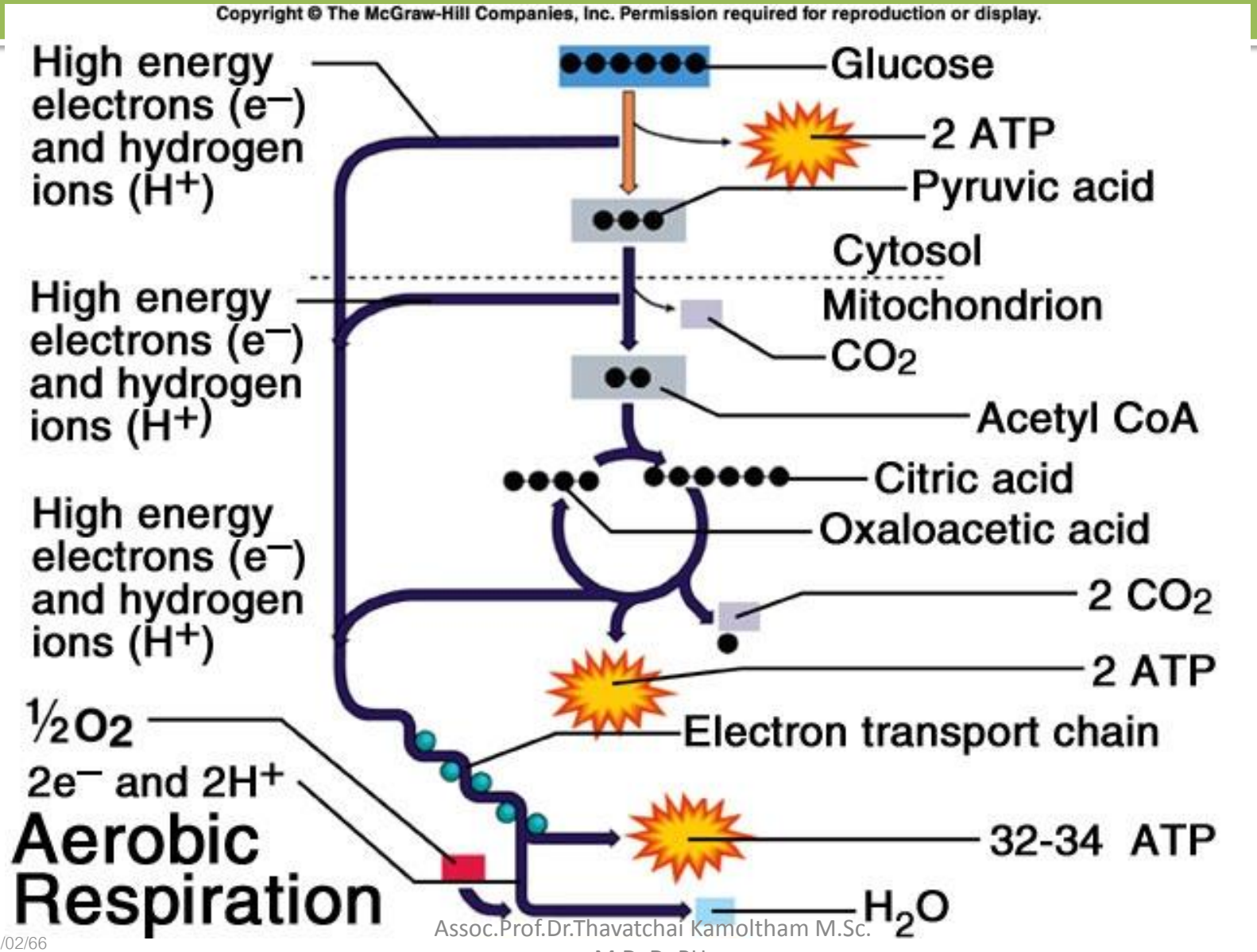




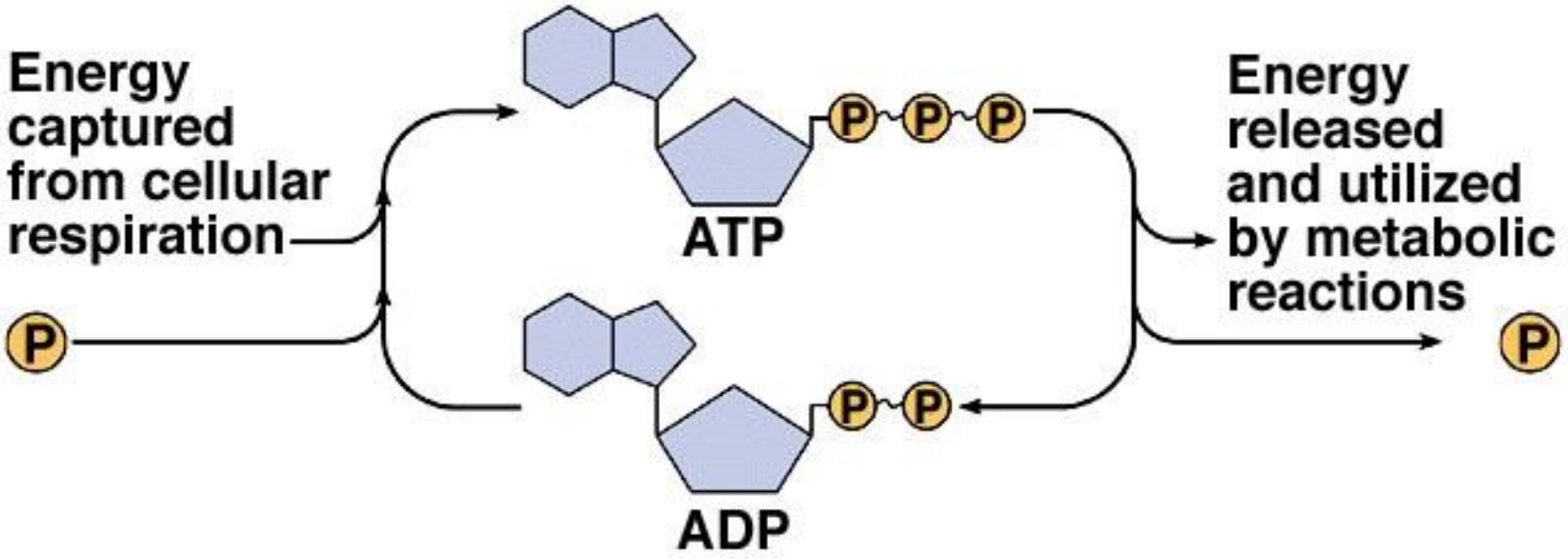
Mitochondria
The cell's power plant



Cellular respiration



ATP Regeneration



Vesicles

"sacs" that hold molecules within a cell
lysosomes –digestive enzymes
molecules to be exported

Inclusions

Temporary structures

- ribosomes
- filaments – cytoskeleton – protein strands
- other molecules without membranes:
- melanin
- lipids, etc.

Tissues

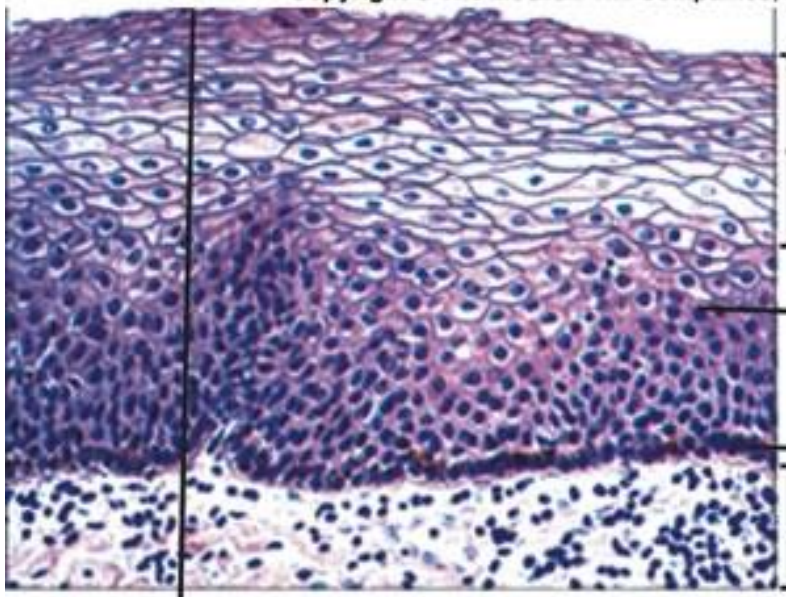
Tissues

Made up of cells with common function

Four major tissue types:

1. Epithelial
   - covering and lining
   - interacts with the body's environment
   - glandular tissue

Stratified Squamous Epithelium

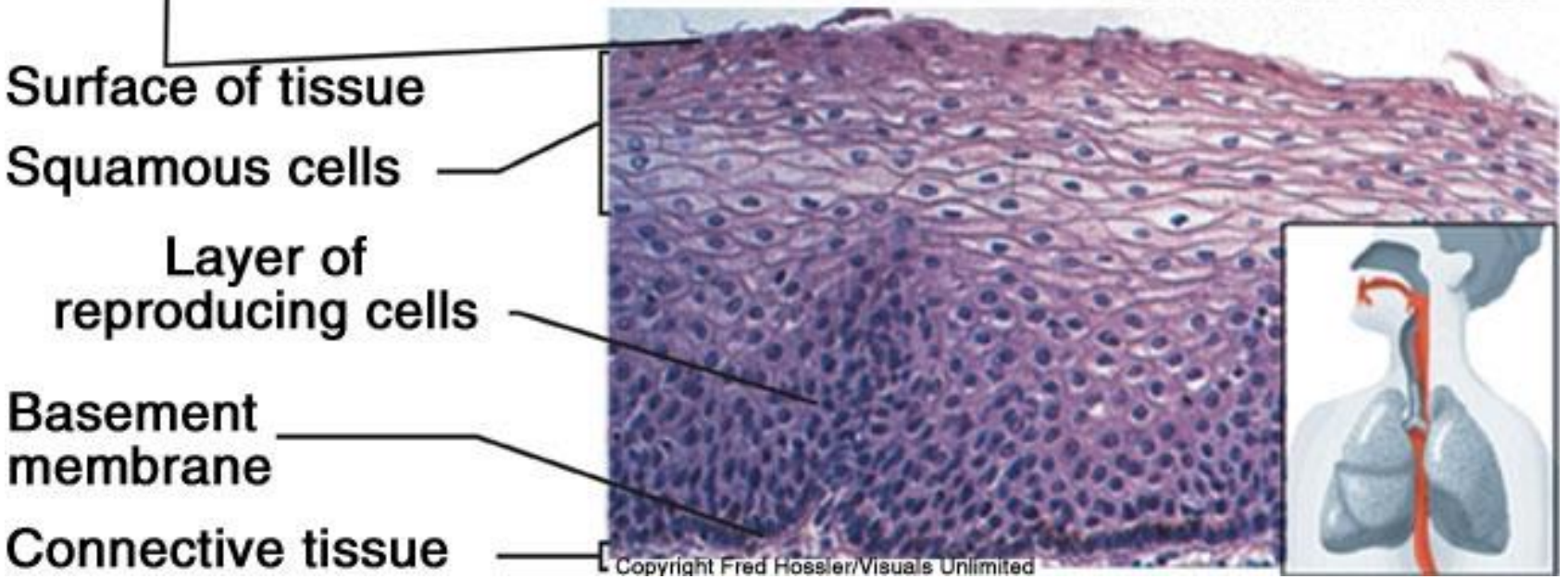


Squamous cells

Layer of reproducing cells

Basement membrane

Connective tissue



Surface of tissue

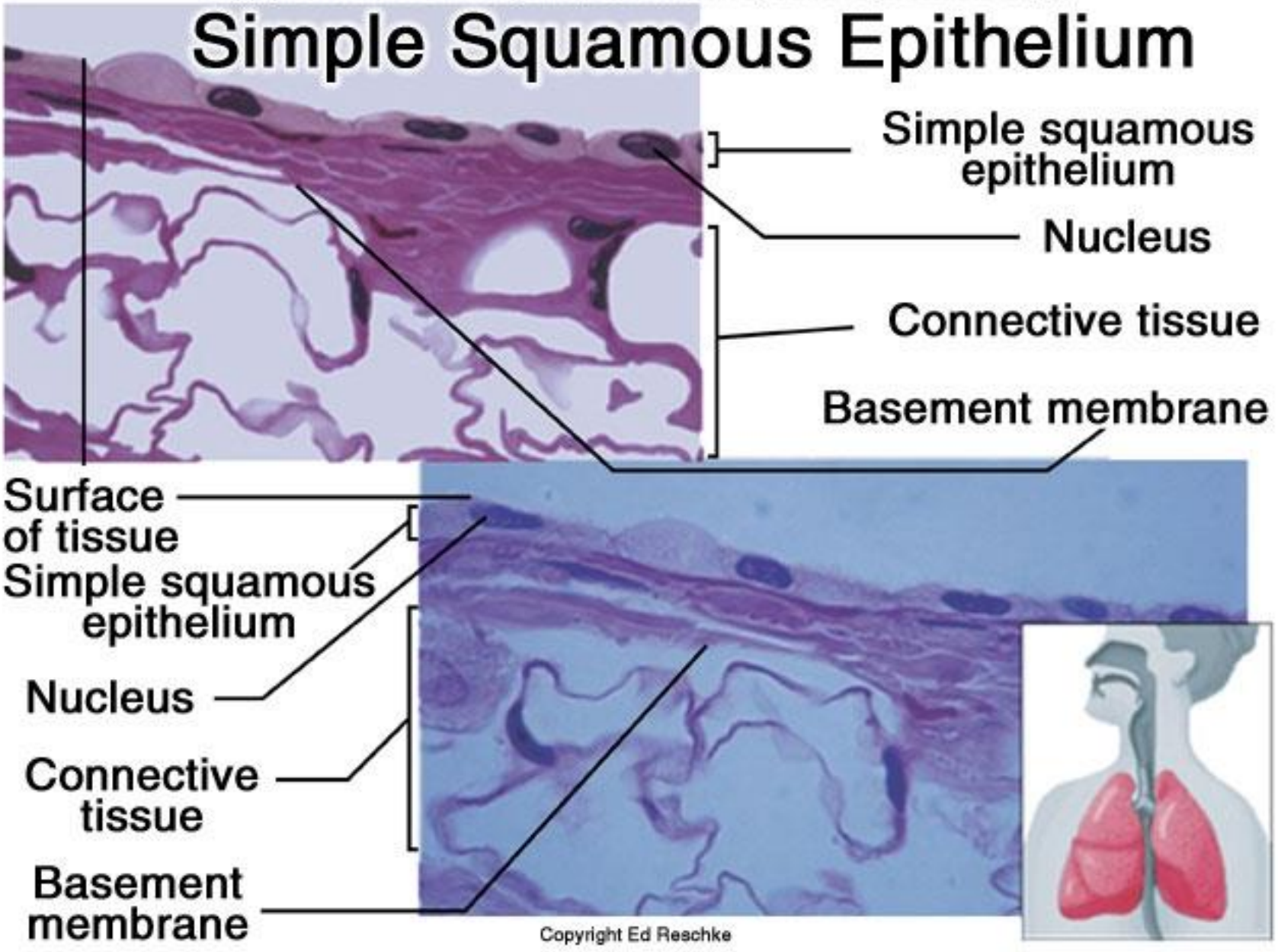
Squamous cells

Layer of reproducing cells

Basement membrane

Connective tissue

Simple Squamous Epithelium



2. Connective tissue

Important to structure , support and protection

3. Nervous tissue

Made up of neurons and supporting (glial) cells

receives info from outside (or inside) the body

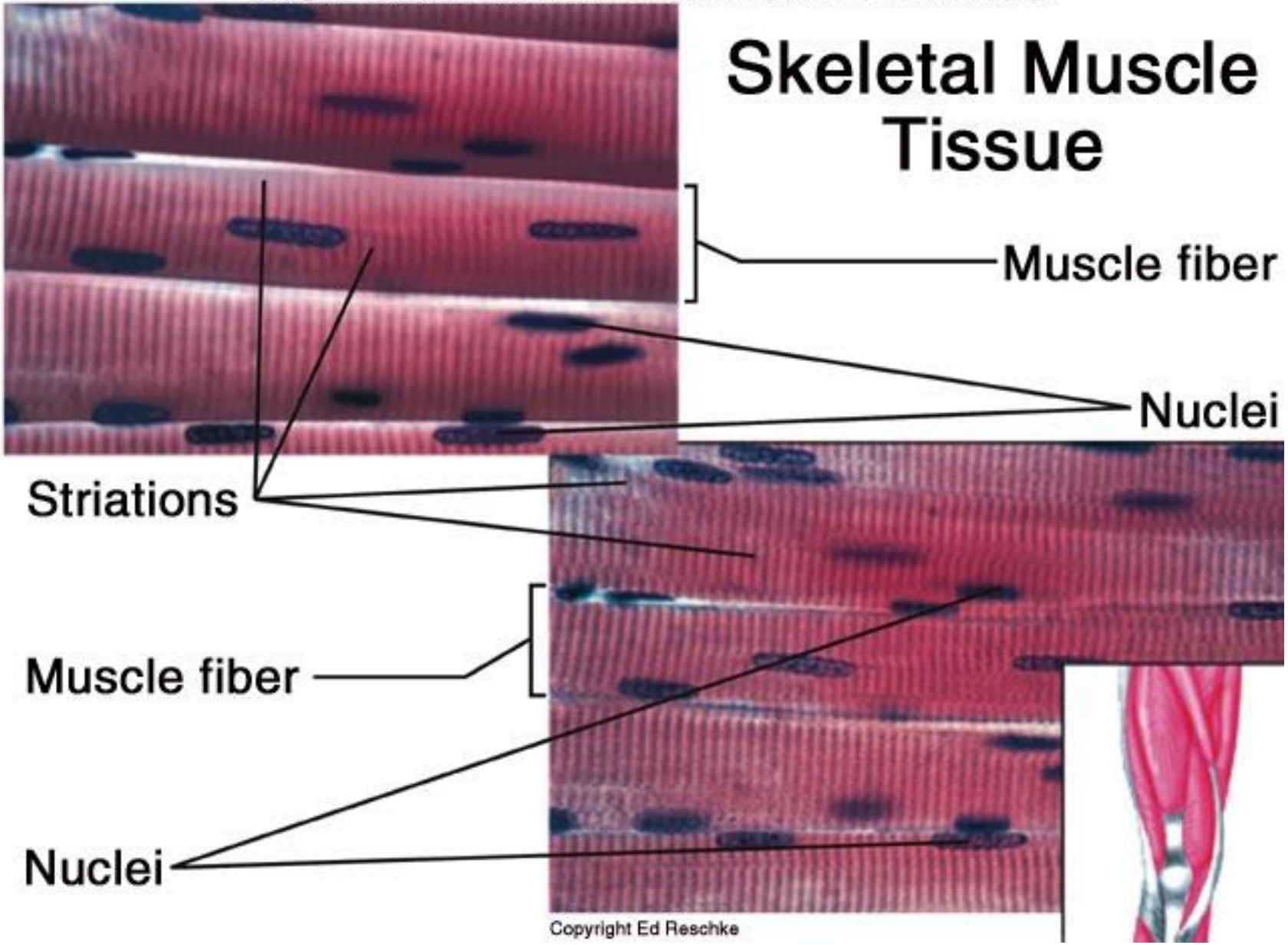
processes information

acts on the information through muscles, glands, etc.

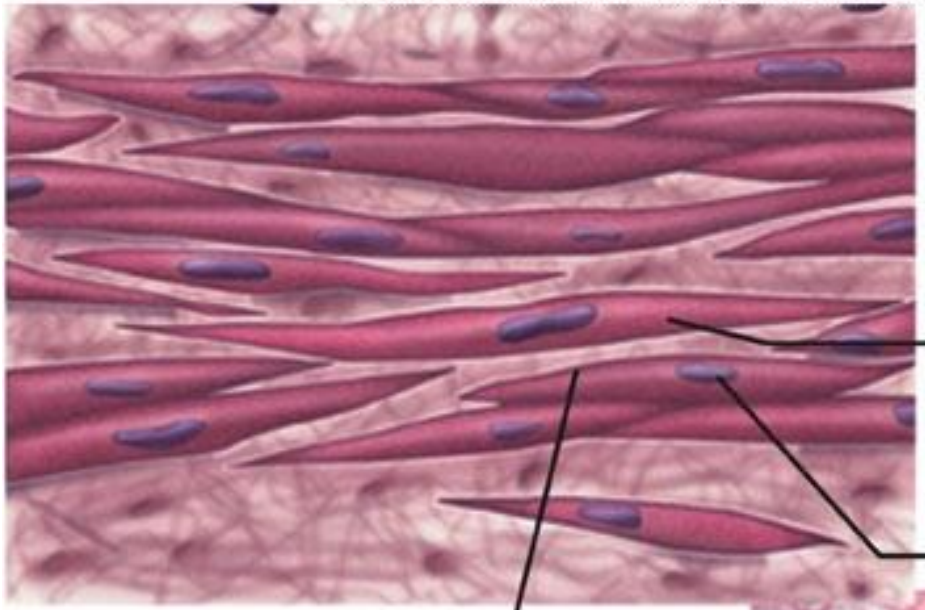
4. Muscle

- Important to movement
- Three types
  - Skeletal
  - Smooth
  - Cardiac

Skeletal Muscle Tissue



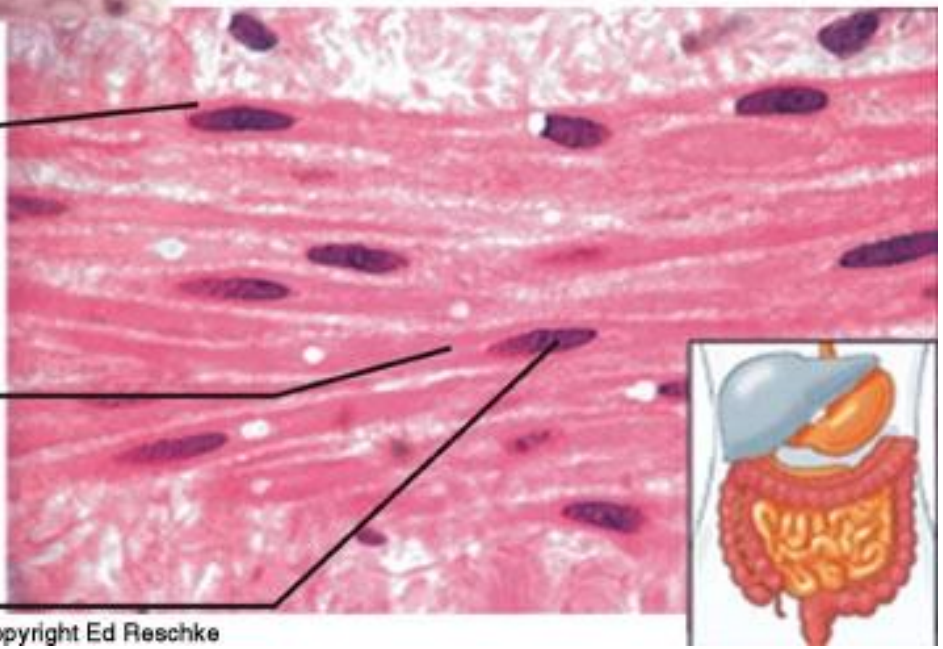
Smooth Muscle Tissue



Cytoplasm

Nucleus

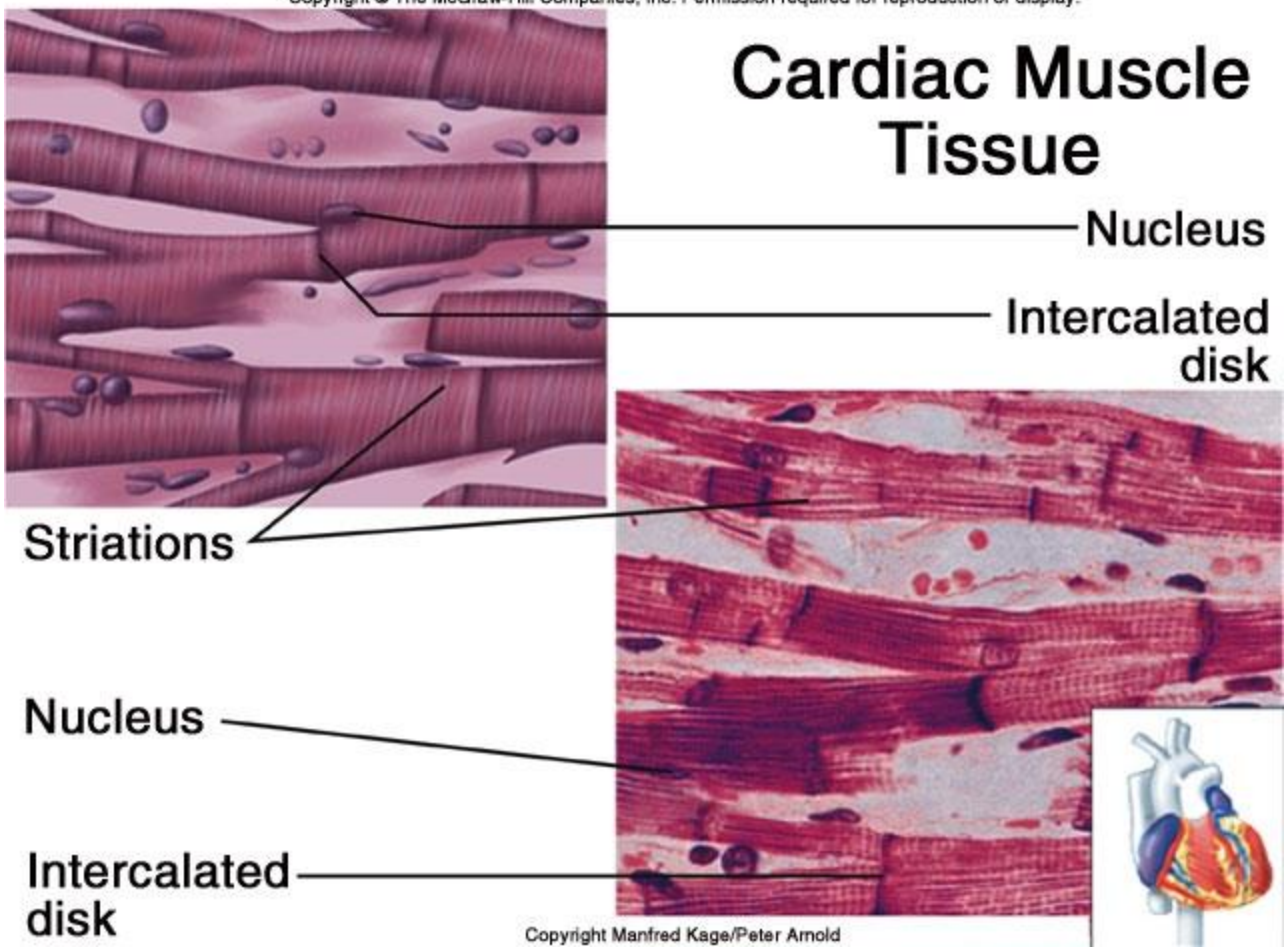
Cell membrane



Cytoplasm

Nucleus

Cardiac Muscle Tissue



PATHOLOGY

These are the four aspects about every disease you should keep in mind as a knee jerk reflex every time you hear the name of a disease.

- **ETIOLOGY ("Cause") Cause** vs. **Risk Factors**
- **PATHOGENESIS ("Insidious development") "sequence of events from the initial stimulus to the ultimate expression of the disease"**
- **MORPHOLOGY (ABNORMAL ANATOMY)**
  - **Gross**
  - **Microscopic**
  - **Radiologic**
  - **Molecular**
- **CLINICAL EXPRESSION "clinical expression" is not often present in subclinical diseases, it is the "pathos" of pathology.**

Cellular Changes

Cellular Changes
6 types

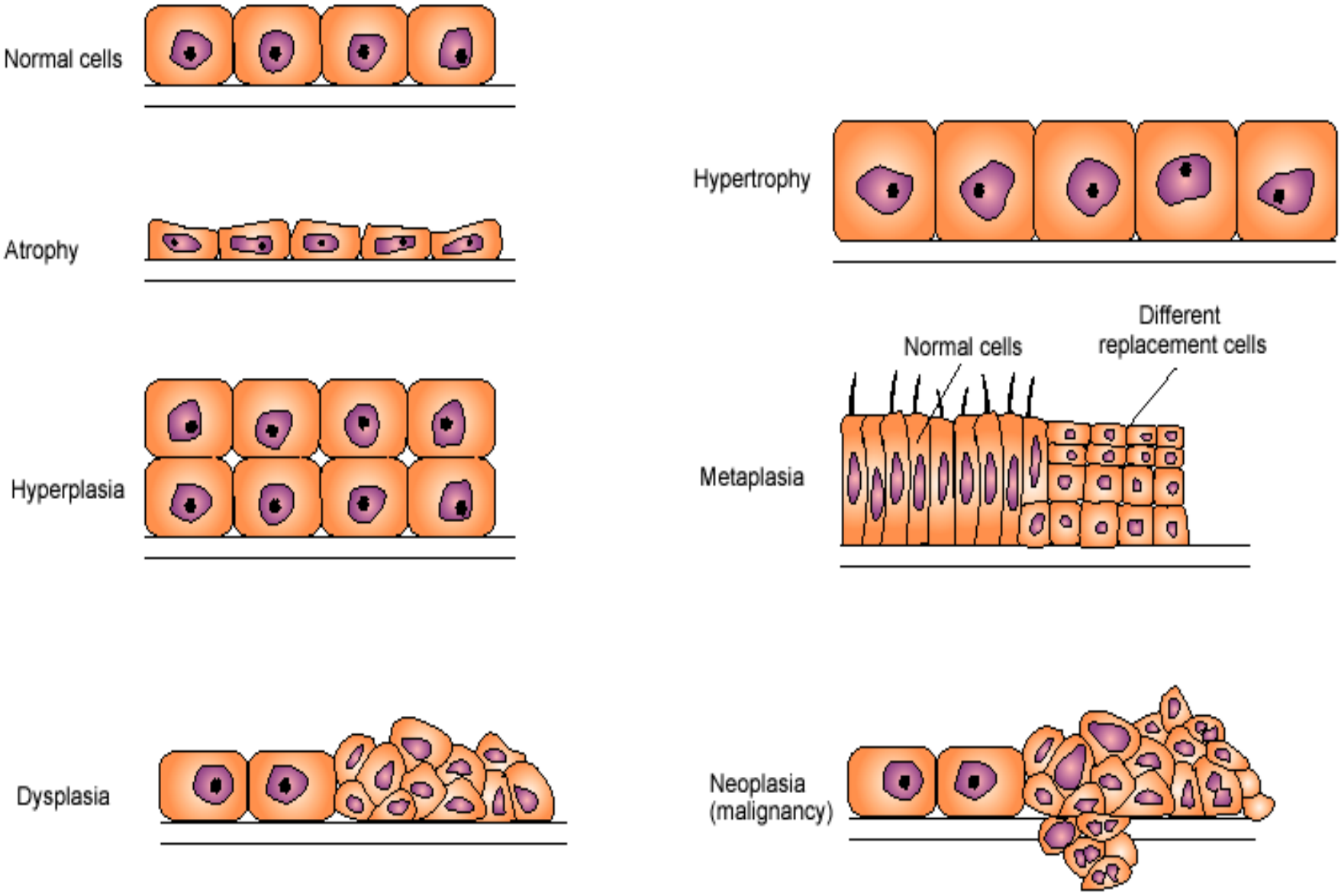
1. **Atrophy**- decrease in cell size
2. **Hypertrophy**- increase in cell size (increase muscle mass due to exercise)
3. **Hyperplasia**- increased number of cells (glandular proliferation of breast during pregnancy)
4. **Metaplasia**- one form changes to another (cells look different than before)
5. **Dysplasia**- cells vary in shape and size
   - Usually results from chronic infection or irritation
   - Pre-cancerous cells are detected (PAP smears)
6. **Neoplasia** = causes tumors

Changes in Growth

- Changes in **size** of individual cell
  - **Atrophy** = decrease in cell size
  - **Hypertrophy** = increase in cell size
- Changes in actual **number** of cells
  - **Hyperplasia, Dysplasia, & Anaplasia** = increase in rate of reproduction
  - **Hyperplasia** = increase in number of normal cells
  - **Dysplasia** = increase in number of atypical cells
  - **Anaplasia** = increase in number of frankly abnormal cells

Change in Type of Cell

- Change of one type of cell into another type **(metamorphoses)**
  - **Metaplasia =**change to different mature cell type


Normal cells
Atrophy
Hyperplasia
Dysplasia
Hypertrophy
Different
replacement cells
Normal cells
Metaplasia
Neoplasia
(malignancy)

- **Cell damage is the main reason to lose homeostasis**
  - **Deficiency of oxygen (hypoxia) = most common reason**
    - **Mechanism of progression:**

ischemia -to- necrosis -to- gangrene

- **Cell death**
  - **Once it occurs, lysis occurs with release of lysosomal enzymes**
    - **This causes inflammation**

- **After inflammation, the dead cells(tissue) is either:**
    - **Replaced by scar tissue**
    - **Regenerated to resemble original tissue**

Cells change to adapt to their environment

Atrophy* = *shrinkage = decrease in cell size.

Due to :

decreased use

decreased blood supply

decreased nutrition

Atrophy of tissues or organs may be due to cell shrinkage or due to cell death.

Hypertrophy* = *increase in cell size

We'll see this in heart, kidney (and others) w/ pathology

NOT due to increased cell volume or fluid

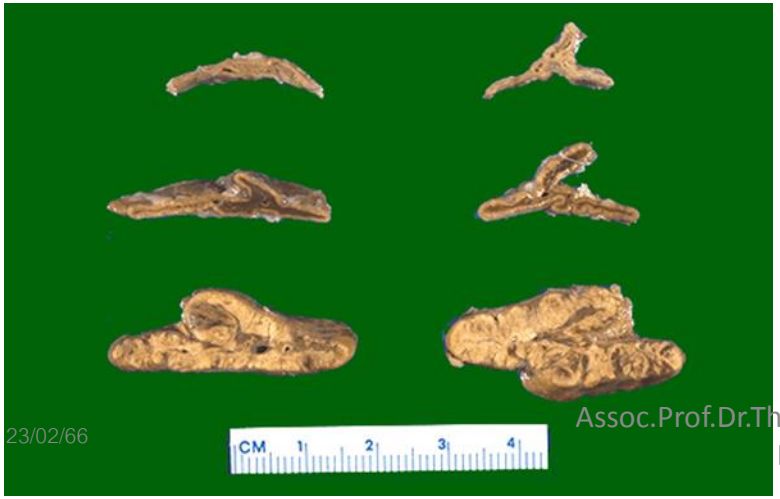
Rather, due to increased protein synthesis within the cell, or decreased protein breakdown

Result is increased protein in organelles

Hyperplasia* = *increase in cell number

Due to increased cell division

- Uterus and breast tissue
- Parathyroid gland in kidney failure
- Liver (compensatory hyperplasia)



Metaplasia = ***SUBSTITUTION of one NORMAL CELL or TISSUE type, for ANOTHER*** (Reversible)

An example:

-ciliated columnar epithelium replaced by stratified squamous epithelium(Cervix)

-SQUAMOUS → COLUMNAR (Glandular) (Stomach)

-FIBROUS→ BONE

Dysplasia = change in cell resulting in abnormal cell size, shape or organization

We'll see this in respiratory tract, cervix w/ pathology

In mature cells only

Immature cells would be expected to change in size, shape as they grow and mature

Considered a reversible change

Neoplasia = associated with a malignant tumor

The –plasia brothers

- HYPER-
- HYPO- (A-)
- NORMO-
- META-
- DYS-
- ANA-

The –trophy brothers

- HYPER-
- HYPO-
- A-
- DYS-

ATROPHY

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

Intracellular Accumulations and Pigments

Cells may be

- Producing the abnormal substance

  or

- Storing products of pathologic processes occurring elsewhere in the body

Intracellular Inclusions

- Normal cellular constituents in excess:
  - Water
  - Fat: Triglyceride, Cholesterol
  - Protein
  - Carbohydrate
- Abnormal substance
  - Mineral
  - Product of abnormal metabolism
- Pigment
- Infectious particles: Bacteria(Mycobacteria, Leishmania, Rickettsiae) Viruses, Prions

Significance Of Intracellular Inclusions

- Is the process reversible?
- Is the substance toxic?
- Does the substance result in cellular swelling, occupying a substantial amount of space?
- Should the substance be somewhere else?

3 Types Of Processes Result In Intracellular Accumulations

1) Normal endogenous substance produced at normal or increased rate, with inadequate rate of metabolism:
   - Hepatic fatty change
   - Plasma cell Russell bodies

2) Normal or abnormal endogenous substance accumulates because it cannot be metabolized or excreted:

   (a) Storage diseases

   Definition: Excess accumulation of complex substrates within lyzosomes as a result of a genetic enzymatic defect in a specific metabolic pathway i.e. Glycogen, Mucopolysaccharide, Sphingolipid

   (b) Disorders in protein folding (α-AT def/CF/Alzheimers)

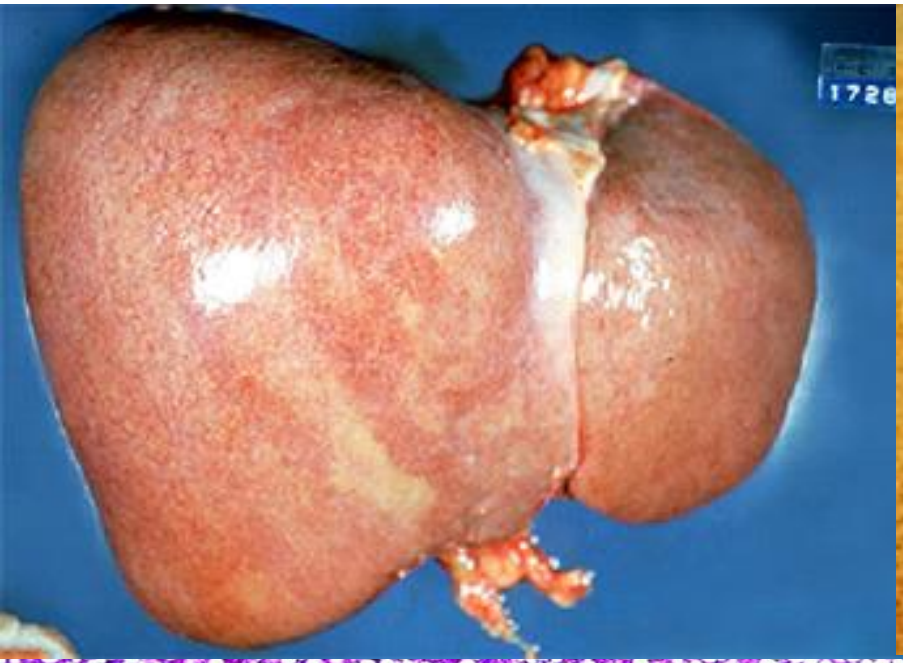
   (c) Cholesterol

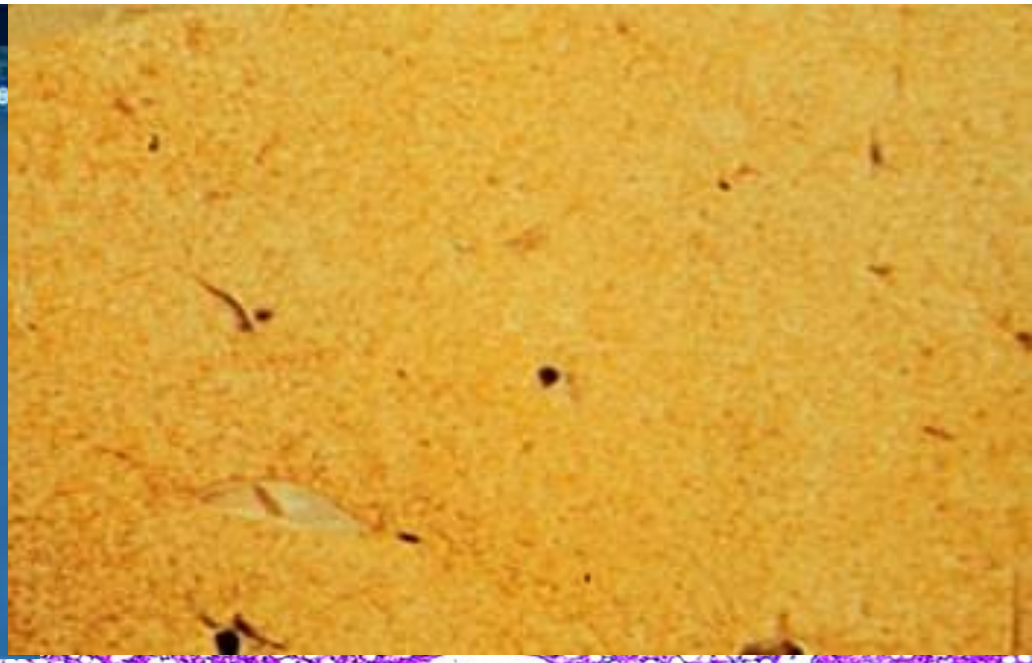
3) Abnormal exogenous substance accumulates due to inability of cell to metabolize the substance or to transport it to other sites

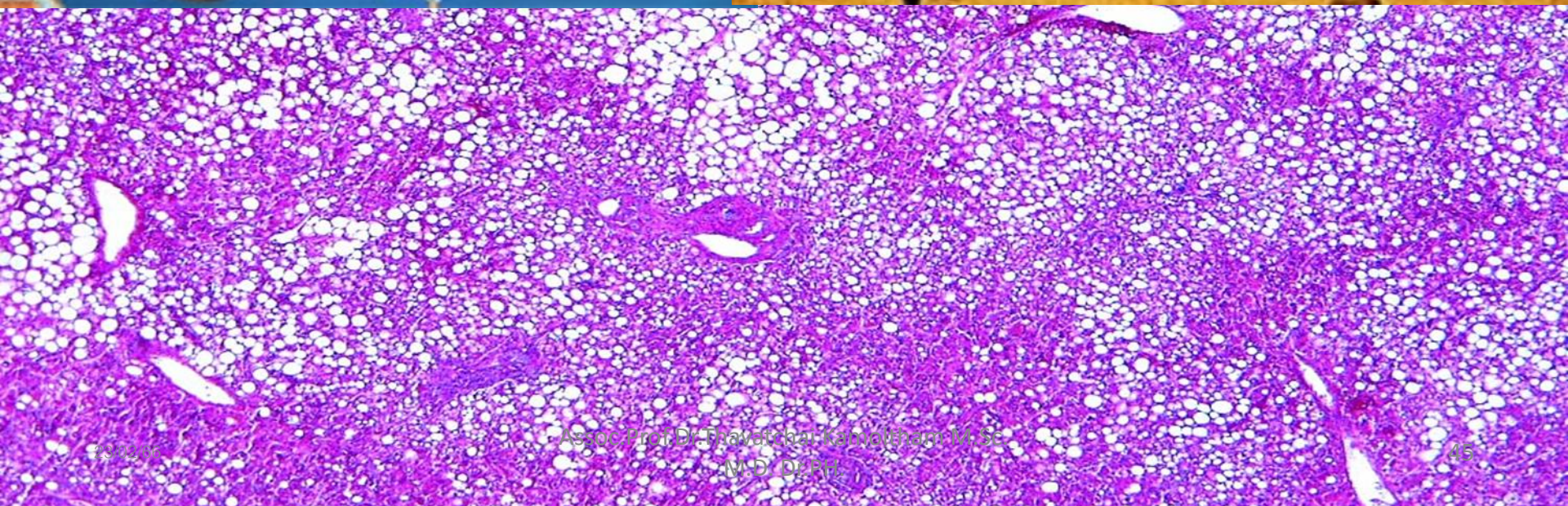
   (a) Inorganic particulate material: i.e. Carbon, silica, metals

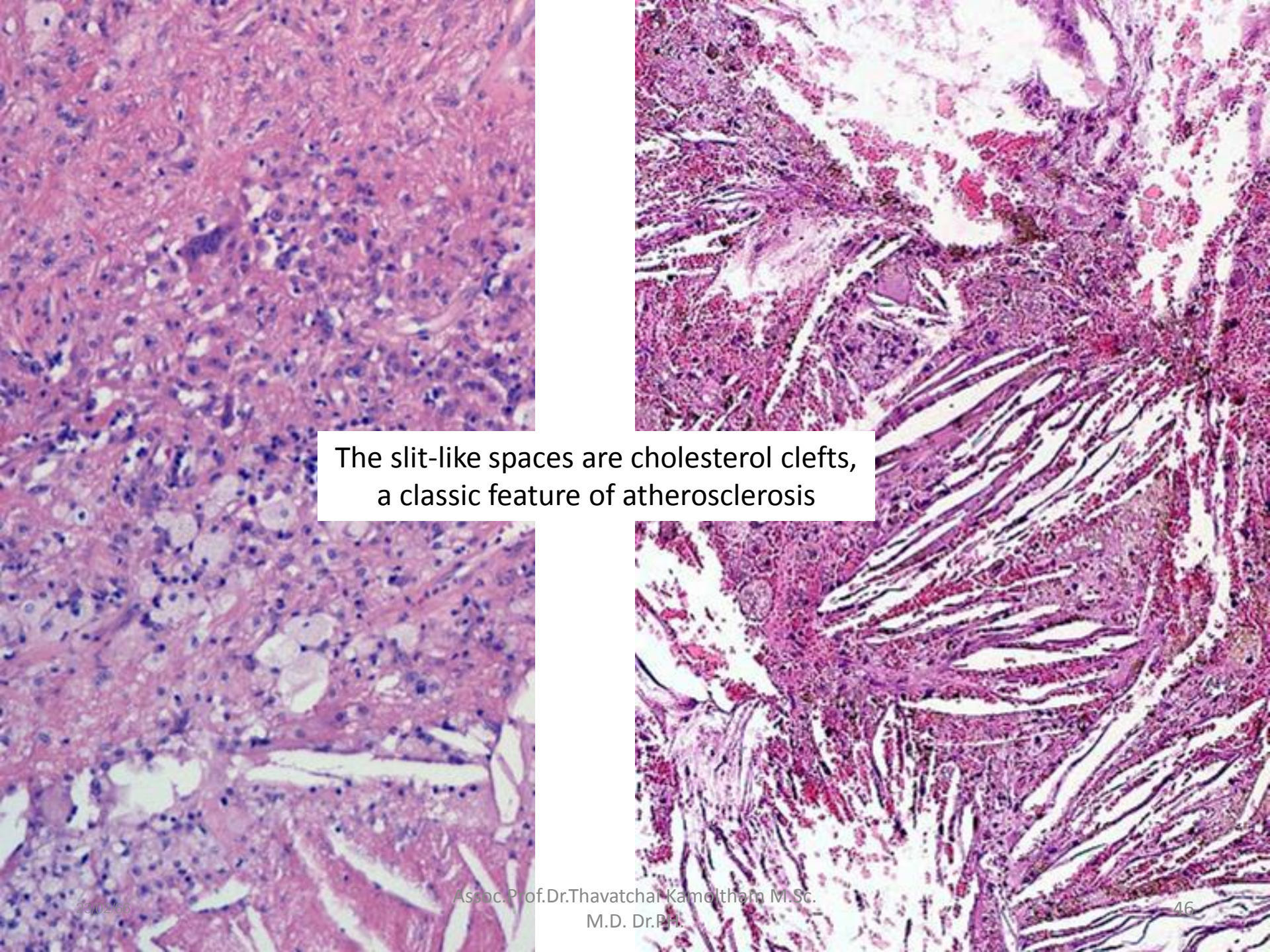
   (b) Infectious inclusions: i.e. Obligate intracellular bacteria, Viruses, Prions

FATTY LIVER





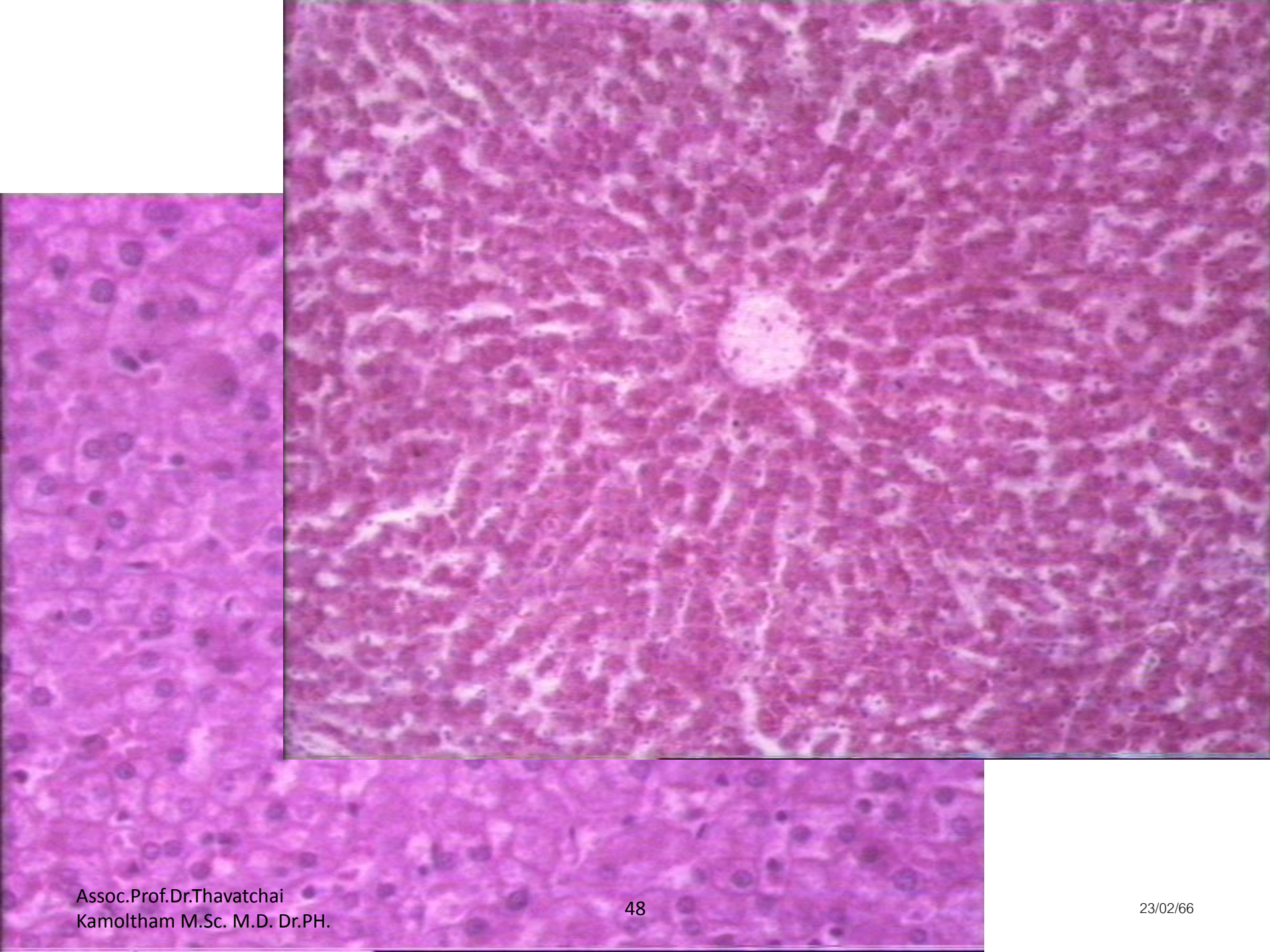




The slit-like spaces are cholesterol clefts, a classic feature of atherosclerosis

Glycogen

- Clear vacuoles in cytoplasm, PAS positive
- Diabetes mellitus
  - Distal portions of the proximal convoluted tubules
  - Descending loop of Henle
  - Hepatocytes
  - Beta cells of islets of Langerhans
  - Cardiac muscle cells
- Glycogen storage diseases
  - Liver, skeletal muscle, heart, brain



Complex lipids & polysaccharides

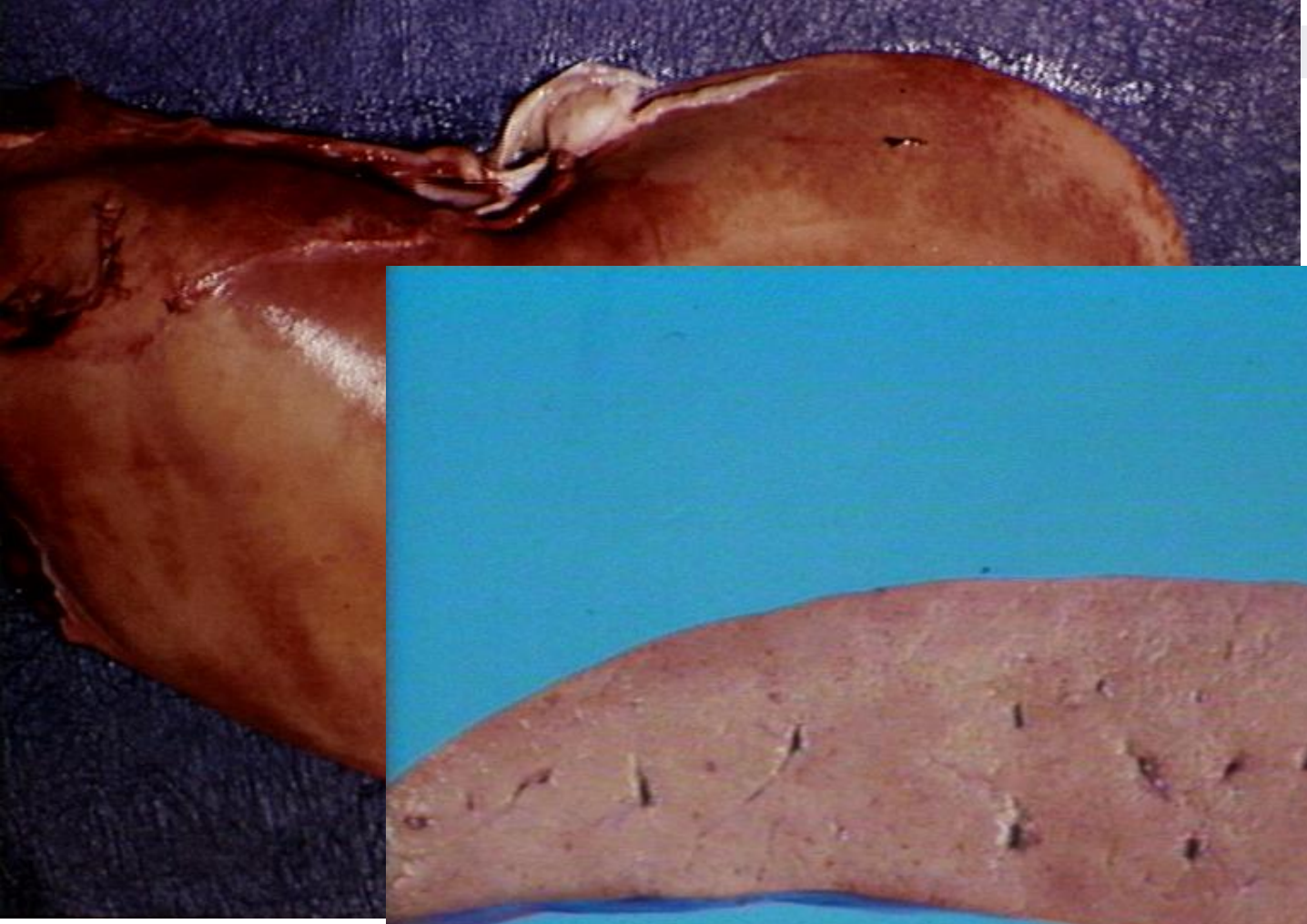
- Lysosomal storage diseases
  - Liver, nervous system (brain and retina), reticuloendothelial system (spleen, lymph nodes, bone marrow)
  - Sphingolipidoses
    - sphingomyelins, gangliosides
    - e.g. Tay-sachs, Gaucher, Niemann-Pick
  - Mucopolysaccharidoses
    - e.g. Hurlers, Hunters

Defective Protein Folding

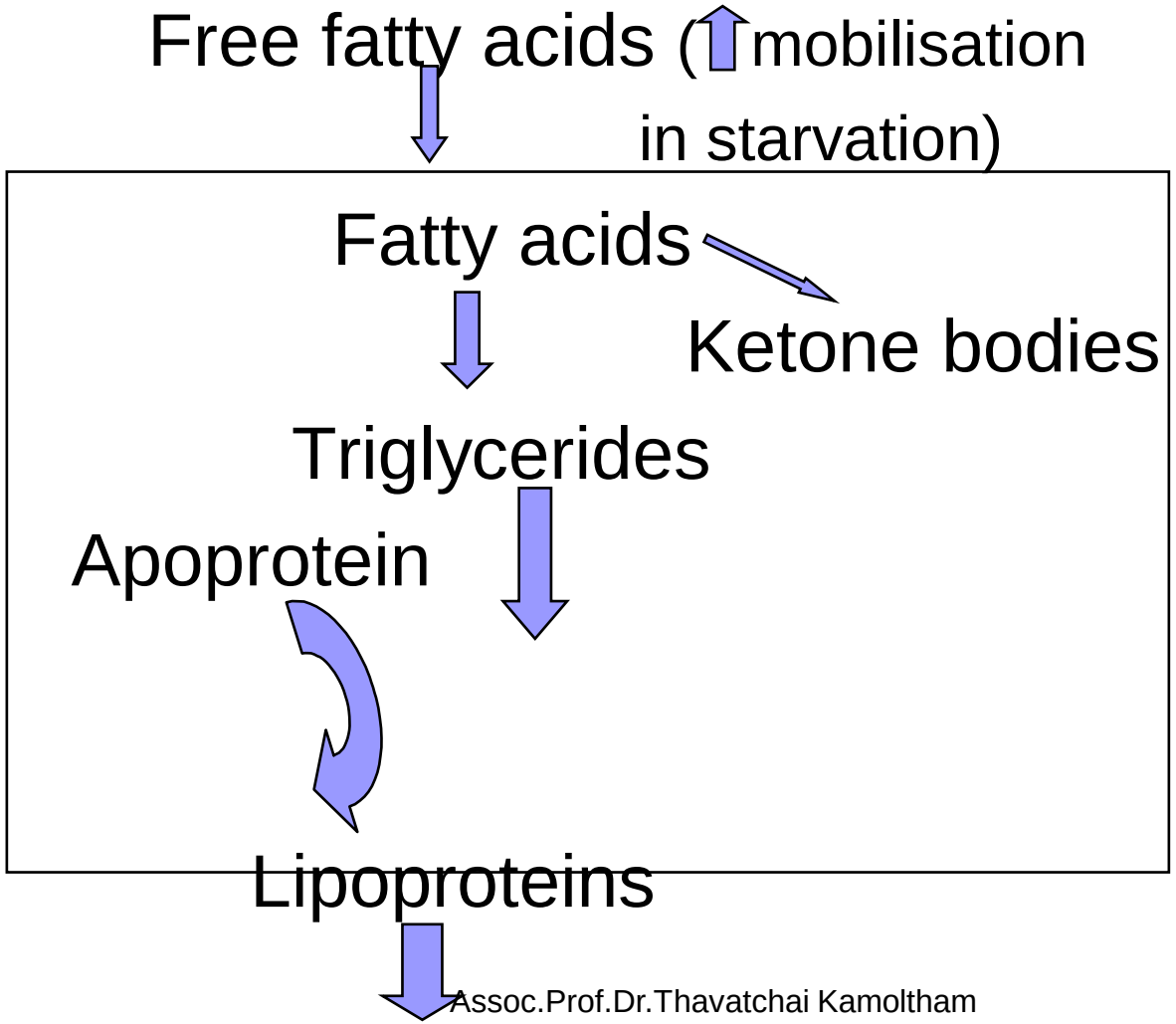
- Defective transport and secretion
  - Alpha-1 Antitrypsin deficiency
  - Cystic Fibrosis
- Toxicity of abnormal proteins
  - Neurodegenerative diseases (proteinopathies)
    - Alzheimers, Huntingtons, Parkinsons
  - Amyloidosis

Triglyceride

- Intracellular and extracellular vacuoles
- Liver
  - Alcohol, malnutrition, diabetes, obesity, drugs
- Heart
- Muscle
- Renal cortex



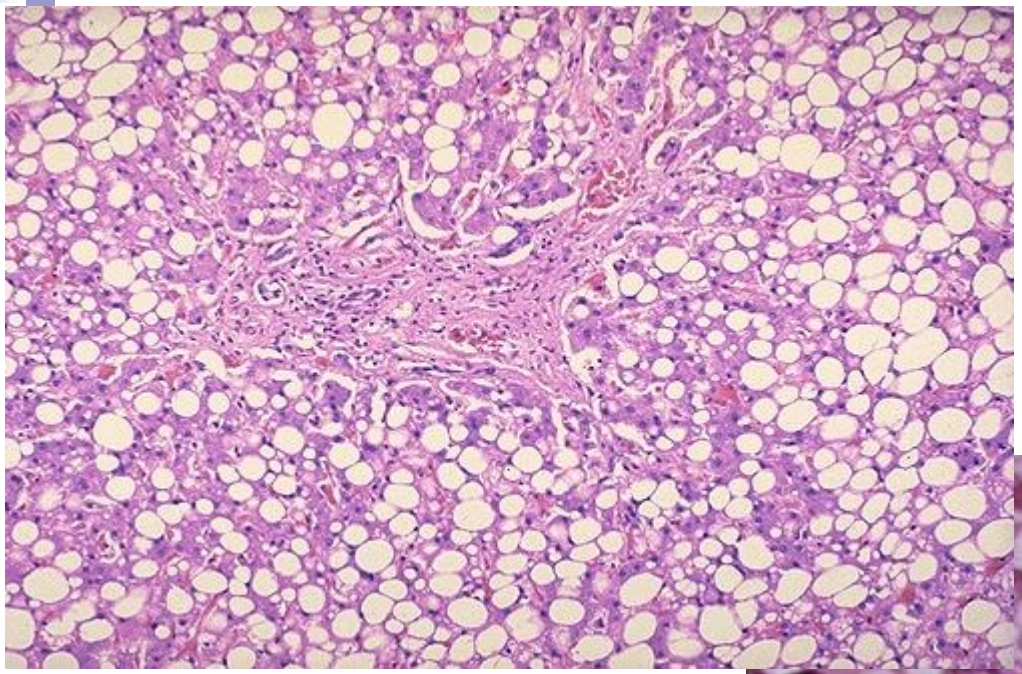
Mechanism of hepatic lipid accumulation

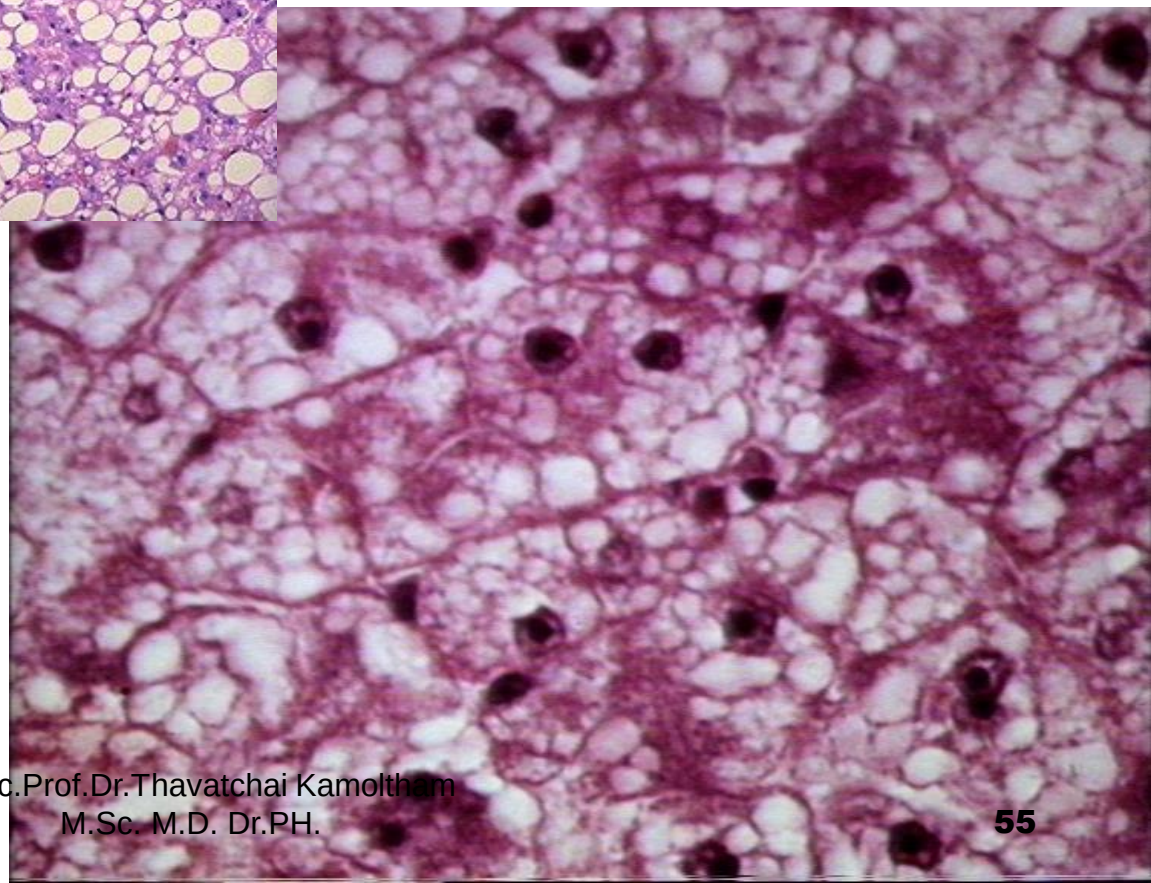


1. Excess entry
2. Decreased oxidation
3. Increased synthesis
4. Increased esterification to TG's
5. Decreased apoprotein synthesis
6. Impaired lipoprotein secretion

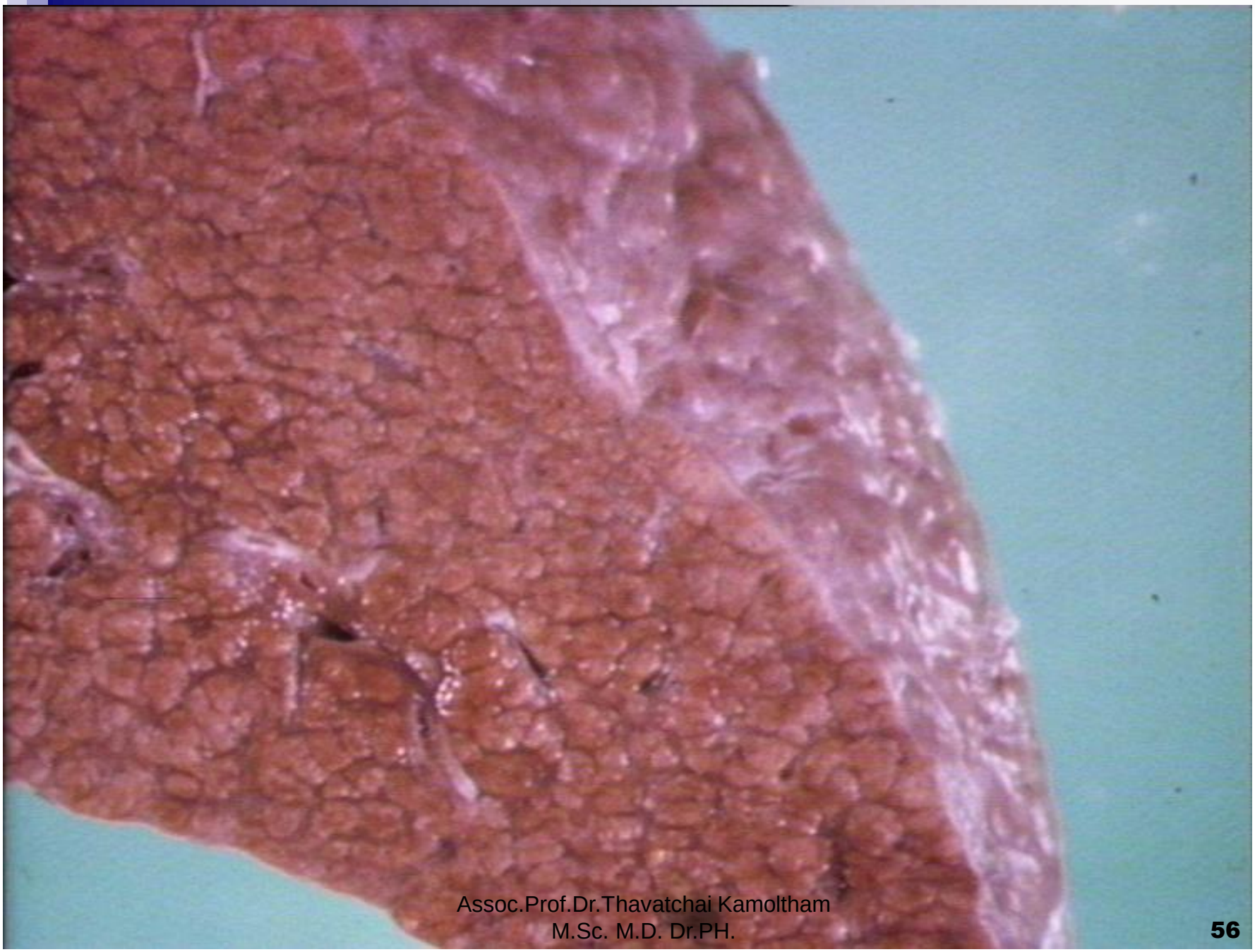
Mechanism of fat accumulation

- Ethanol:
  - Impaired assembly and secretion of lipoproteins
  - Increased peripheral fat catabolism
- Starvation: Mobilisation of free fatty acids
- Anoxia: Inhibition of fatty acid oxidation
- Carbon tetrachloride poisoning and protein malnutrition: Decrease synthesis of apoproteins
- Acute fatty liver of pregnancy, Reye's syndrome - rare fatal conditions (Defect in mitochondrial oxidation suspected)



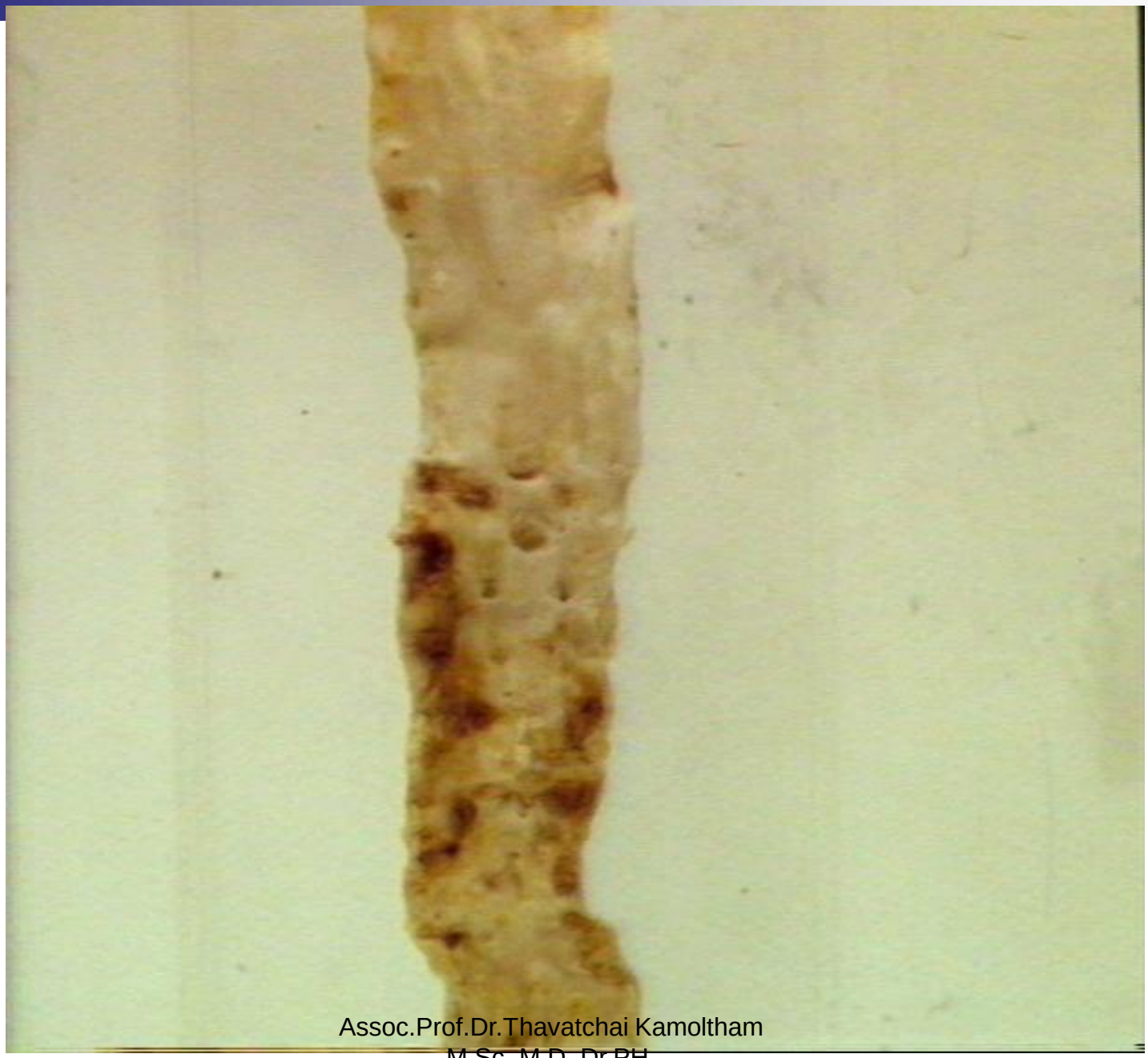


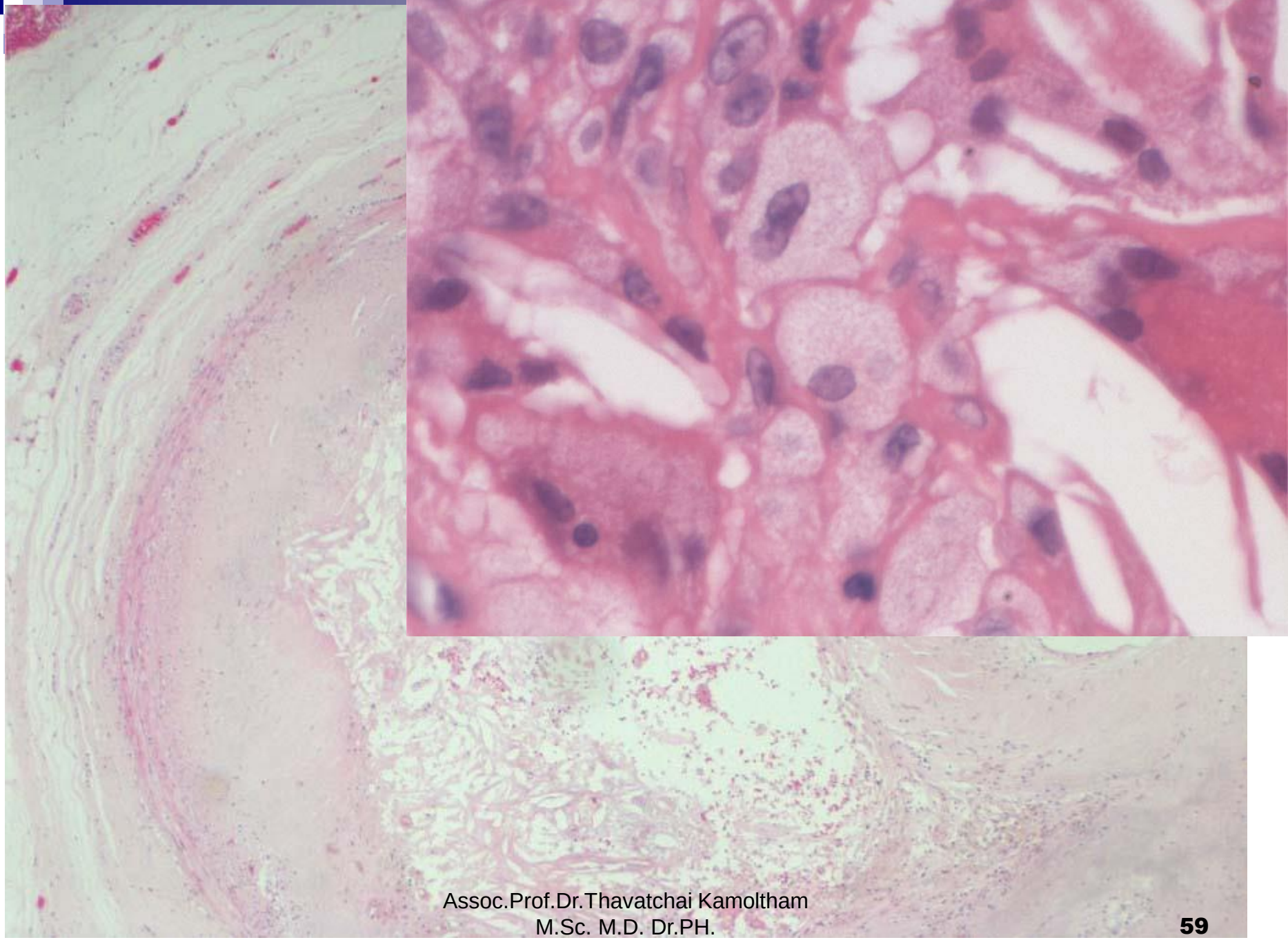
Intracellular accumulations of a variety of materials can occur in response to cellular injury. Here is fatty metamorphosis (fatty change) of the liver in which deranged lipoprotein transport from injury (most often alcoholism) leads to accumulation of lipid in the cytoplasm of hepatocytes.



Cholesterol and cholesterol esters

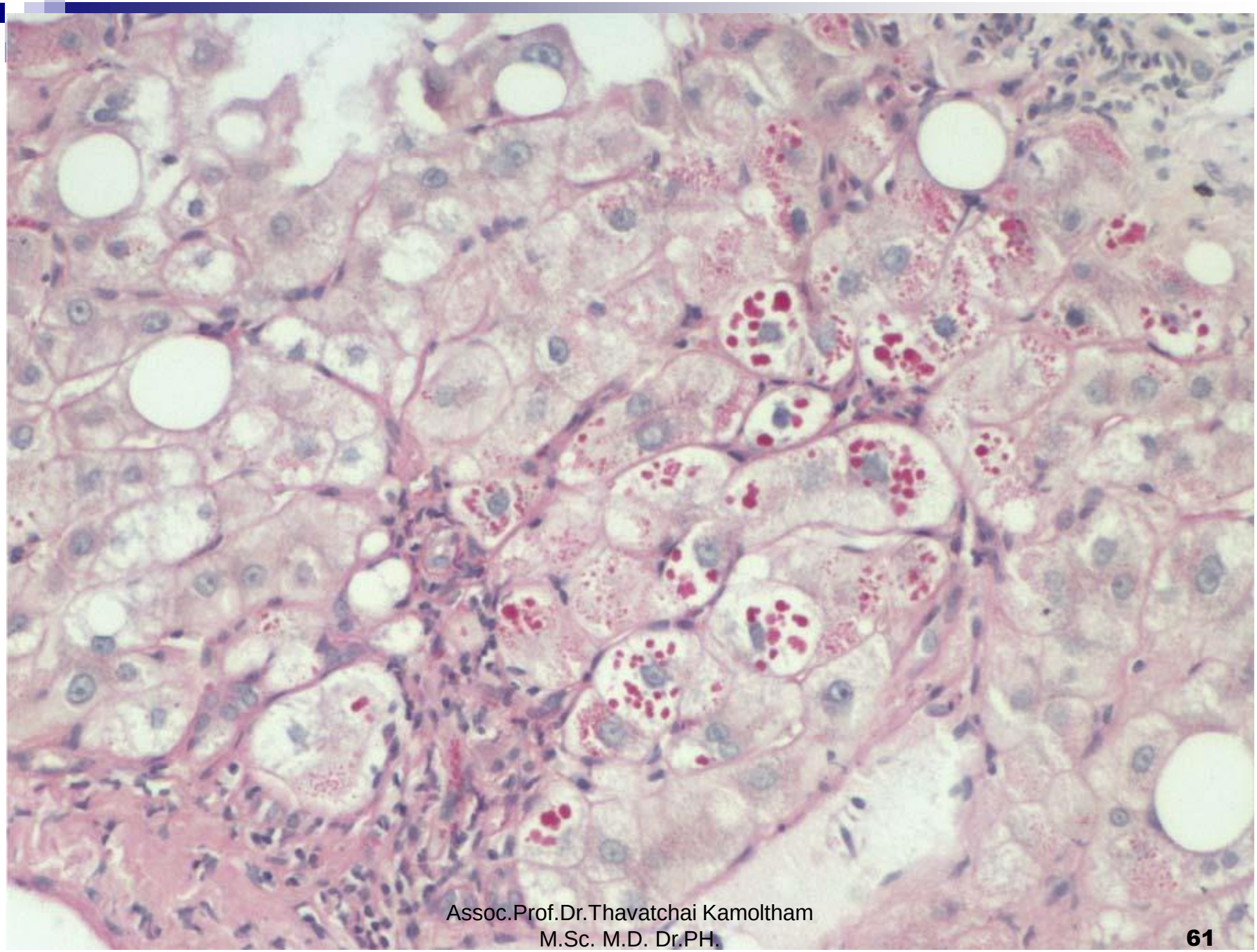
- Lipid-laden macrophages – 'Foam cells'
- Also extracellular cholesterol clefts
- Atherosclerosis: Intimal layer of aorta & large arteries
- Hyperlipidaemia: Xanthomas in subcutaneous connective tissue
- Inflammation & necrosis
- Cholesterolosis: Gallbladder





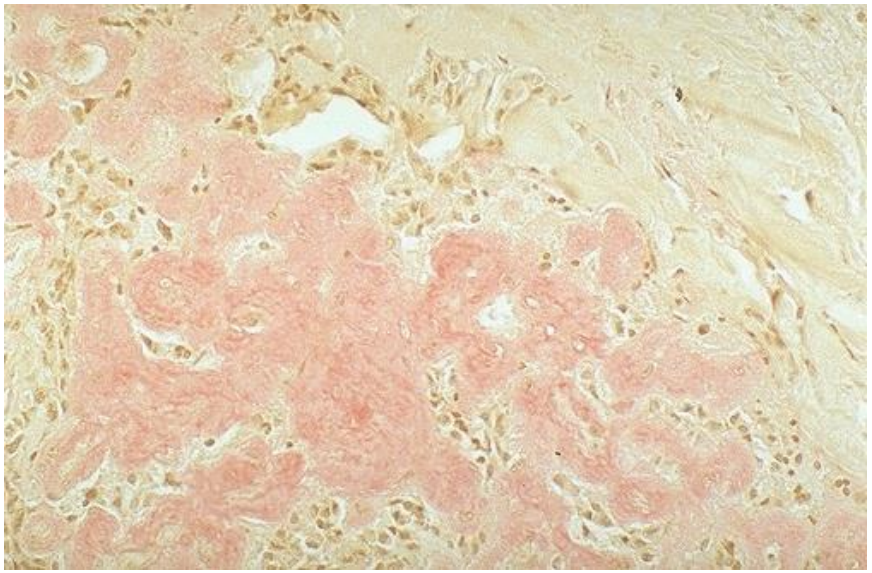
Proteins

- Cytoplasmic eosinophilic droplets
- Reabsorption droplets in proximal renal tubules - proteinuria
- Immunoglobulin in plasma cells (Russell bodies)
- Defective protein folding
  - Alpha-1 Antitrypsin deficiency
  - Neurodegenerative diseases

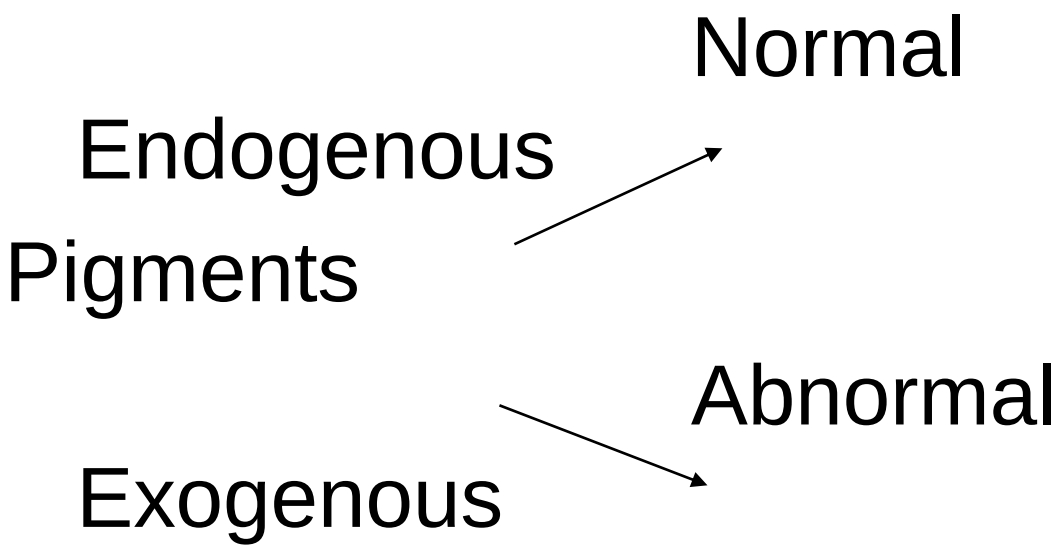


Amyloidosis

- This Congo red stain reveals orange-red deposits of amyloid, which is an abnormal accumulation of breakdown products of proteinaceous material that can collect within cells and tissues.
- e.g. Alzheimer disease



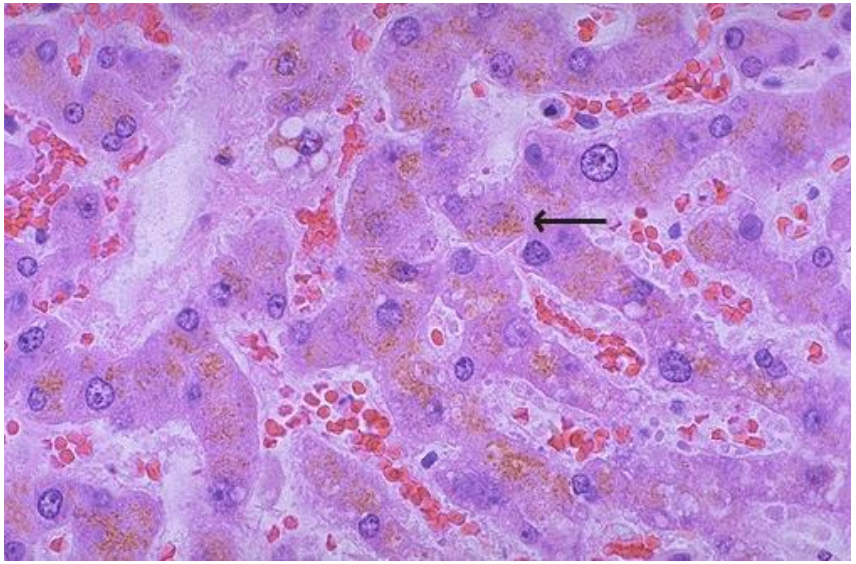
Pigments



Endogenous Pigments

- Lipofuscin (“wear and tear” pigment)
- Lipids and phospholipids complexed with protein
- Derived from lipid peroxidation of subcellular membranes - indicative of free radical injury
- Tissue sections: yellow brown finely granular intracytoplasmic peri-nuclear pigment
- Liver, heart and neurons of elderly

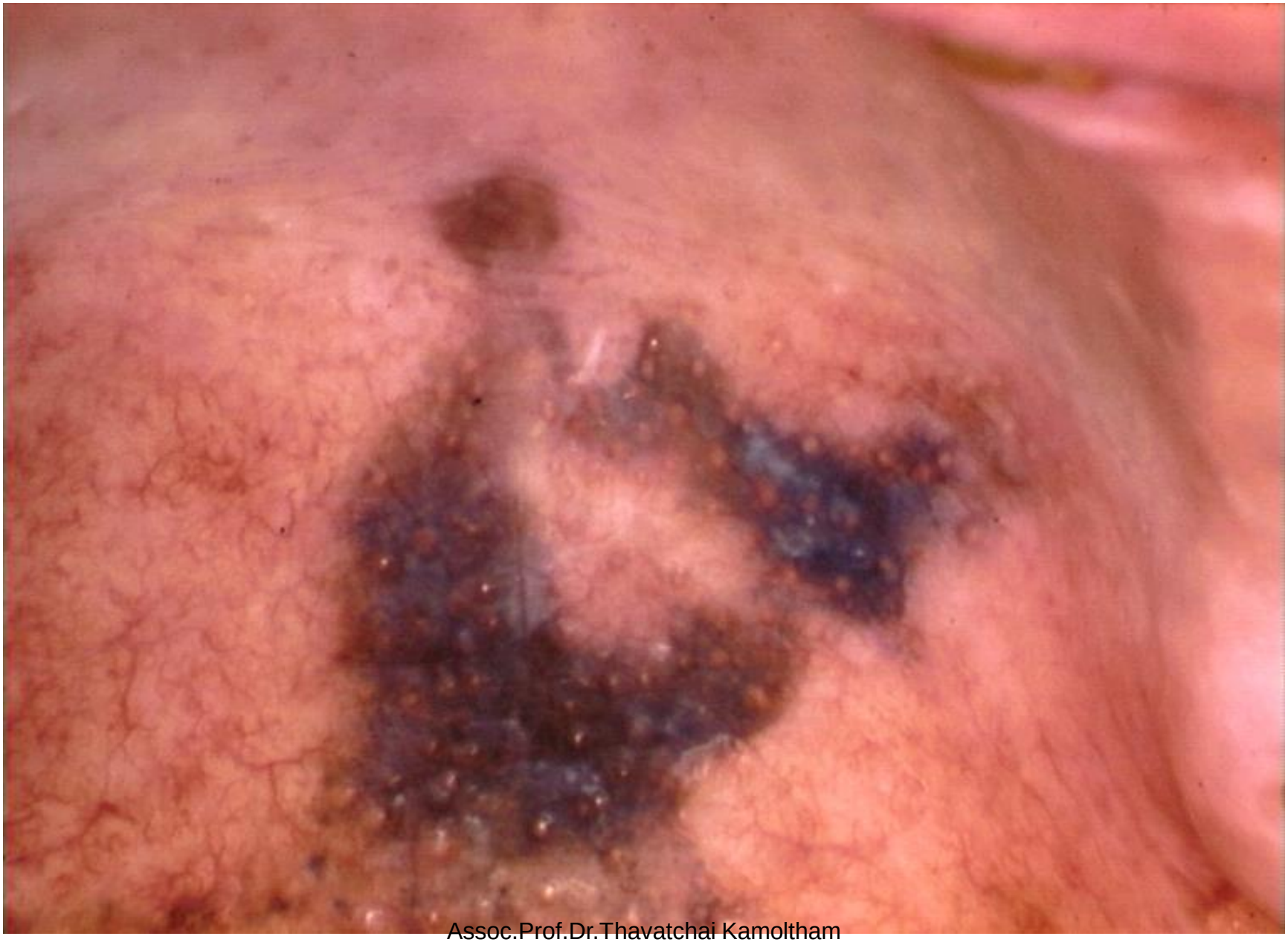
Lipofuscin

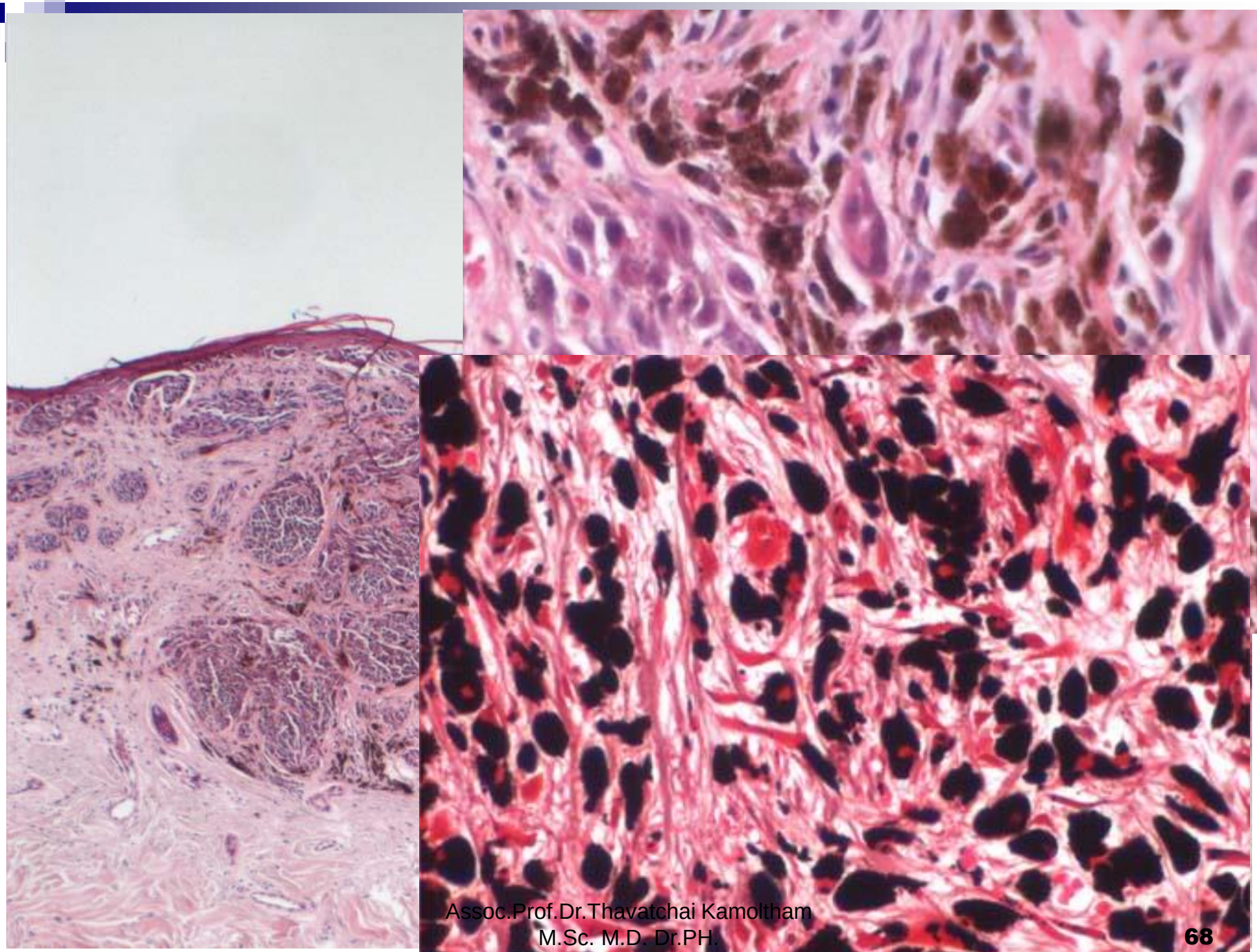


- The yellow-brown granular pigment seen in the hepatocytes here is lipochrome (lipofuscin) which accumulates over time in cells (particularly liver and heart) as a result of "wear and tear" with aging.
- It is of no major consequence, but illustrates the end result of the process of autophagocytosis in which intracellular debris is sequestered and turned into these residual bodies of lipochrome within the cell cytoplasm.

Endogenous pigments cont'd

- Melanin: Brown black pigment found in melanocytes, Masson Fontana positive
- Endogenous screen against ultraviolet rays
- Tyrosine $\xrightarrow{\text{tyrosinase}}$ Dihydroxyphenylalanine $\downarrow$ Melanin
- Vitiligo – loss of pigment producing melanocytes within the epidermis
- Albinism – melanocytes are present but no melanin is produced because of a lack or defect in tyrosinase enzyme

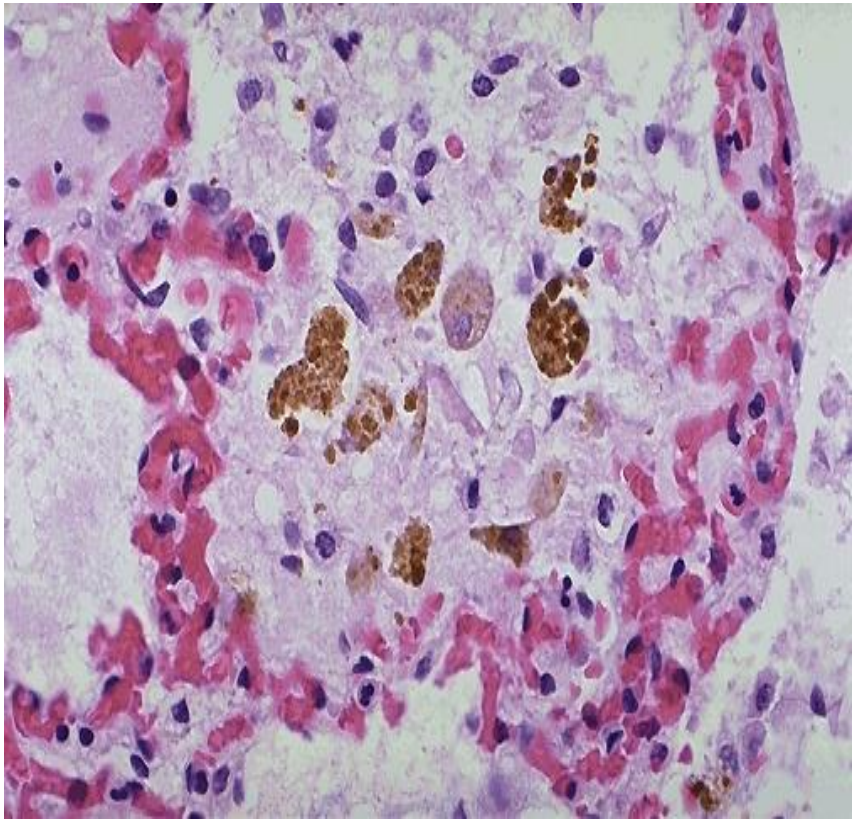




Endogenous pigments cont'd

- Haemosiderin
  - Haemoglobin derived
  - Golden yellow to brown granular pigment
  - Prussian blue positive
- In cells iron normally stored in association with a protein apoferritin → ferritin micelles
- Local or systemic excess of iron → aggregates of ferritin micelles = haemosiderin granules

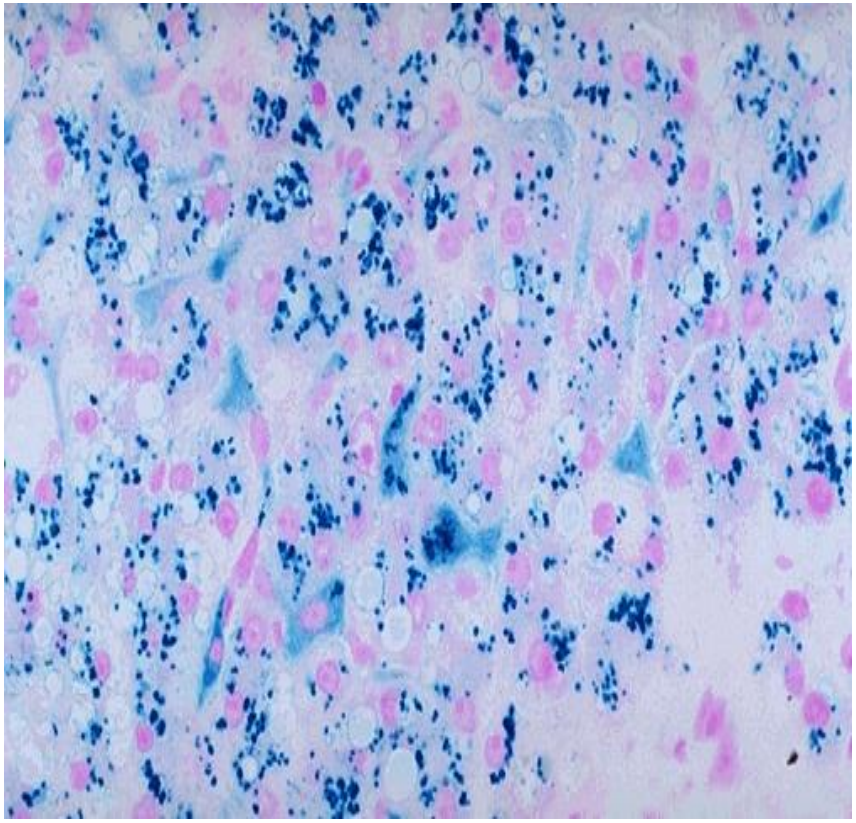
Haemosiderin

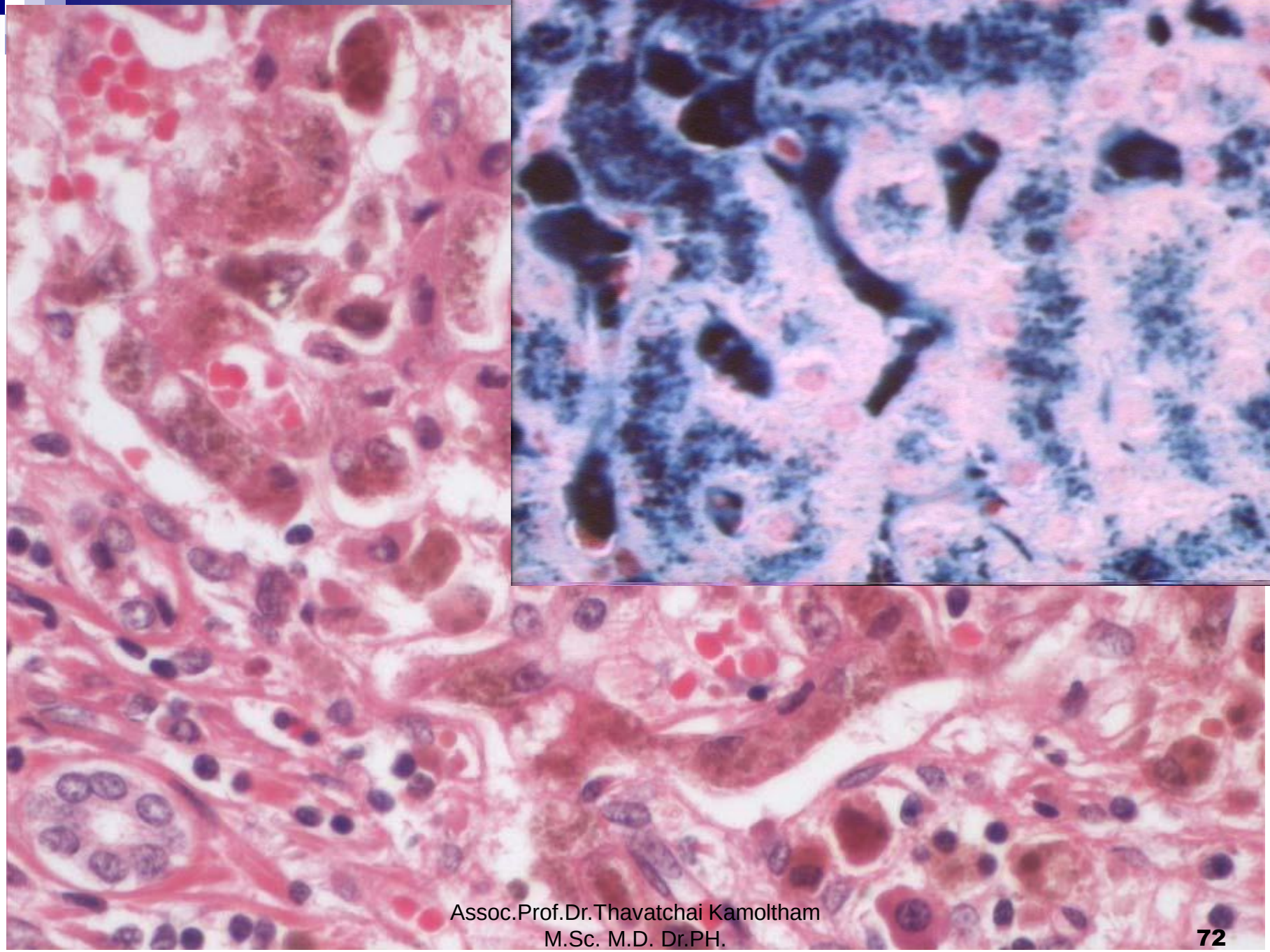


- The brown coarsely granular material in macrophages in this alveolus is hemosiderin that has accumulated as a result of the breakdown of RBC's and release of the iron in heme.
- The macrophages clear up this debris, which is eventually recycled.

Haemosiderin

- A Prussian blue reaction is seen in this iron stain of the liver to demonstrate large amounts of hemosiderin that are present within the cytoplasm of the hepatocytes and Kupffer cells.
- Ordinarily, only a small amount of hemosiderin would be present in the fixed macrophage-like cells in liver, the Kupffer cells, as part of iron recycling.





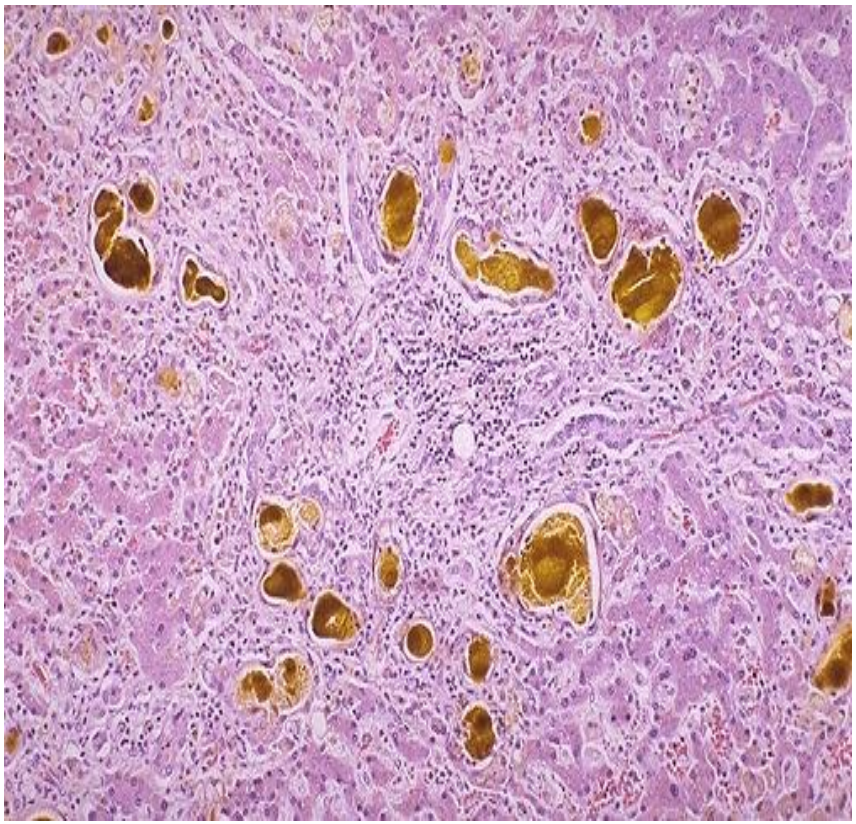
Endogenous pigments cont'd

- Normally small amounts of haemosiderin can be seen in mononuclear phagocytes of bone marrow, spleen and liver (all engaged in red cell breakdown)
- Common bruise → haemorrhage → lysis of erythrocytes → series of pigments → biliverdin → bilirubin → haemosiderin

Endogenous pigments cont'd

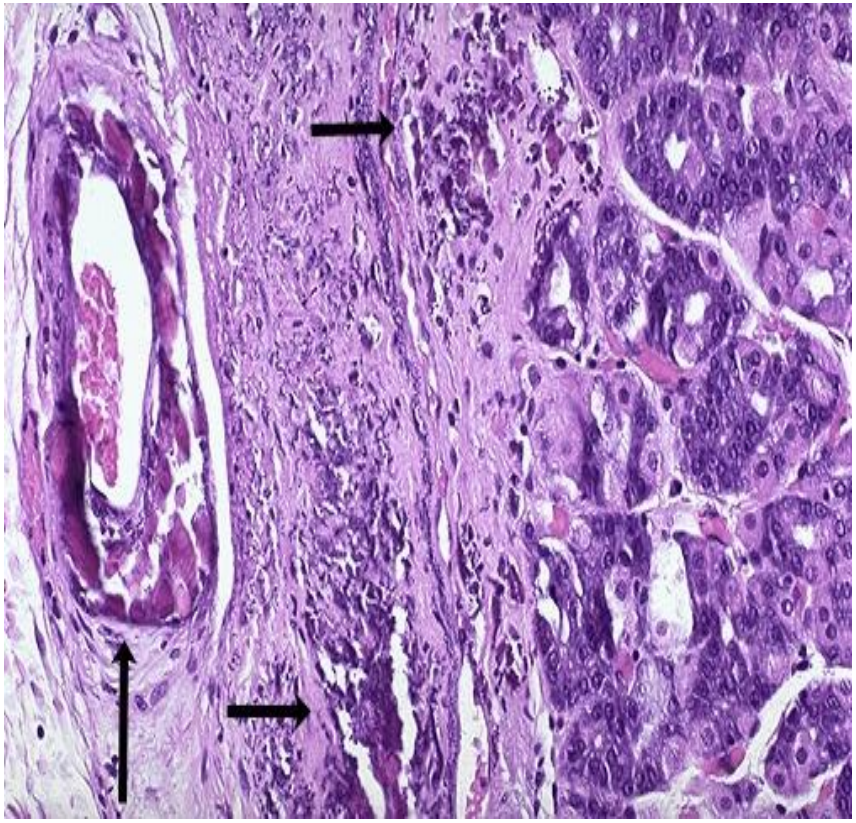
Systemic excess of iron

- Increased absorption of dietary iron
- Impaired utilization of iron
- Haemolytic anaemias
- Transfusions

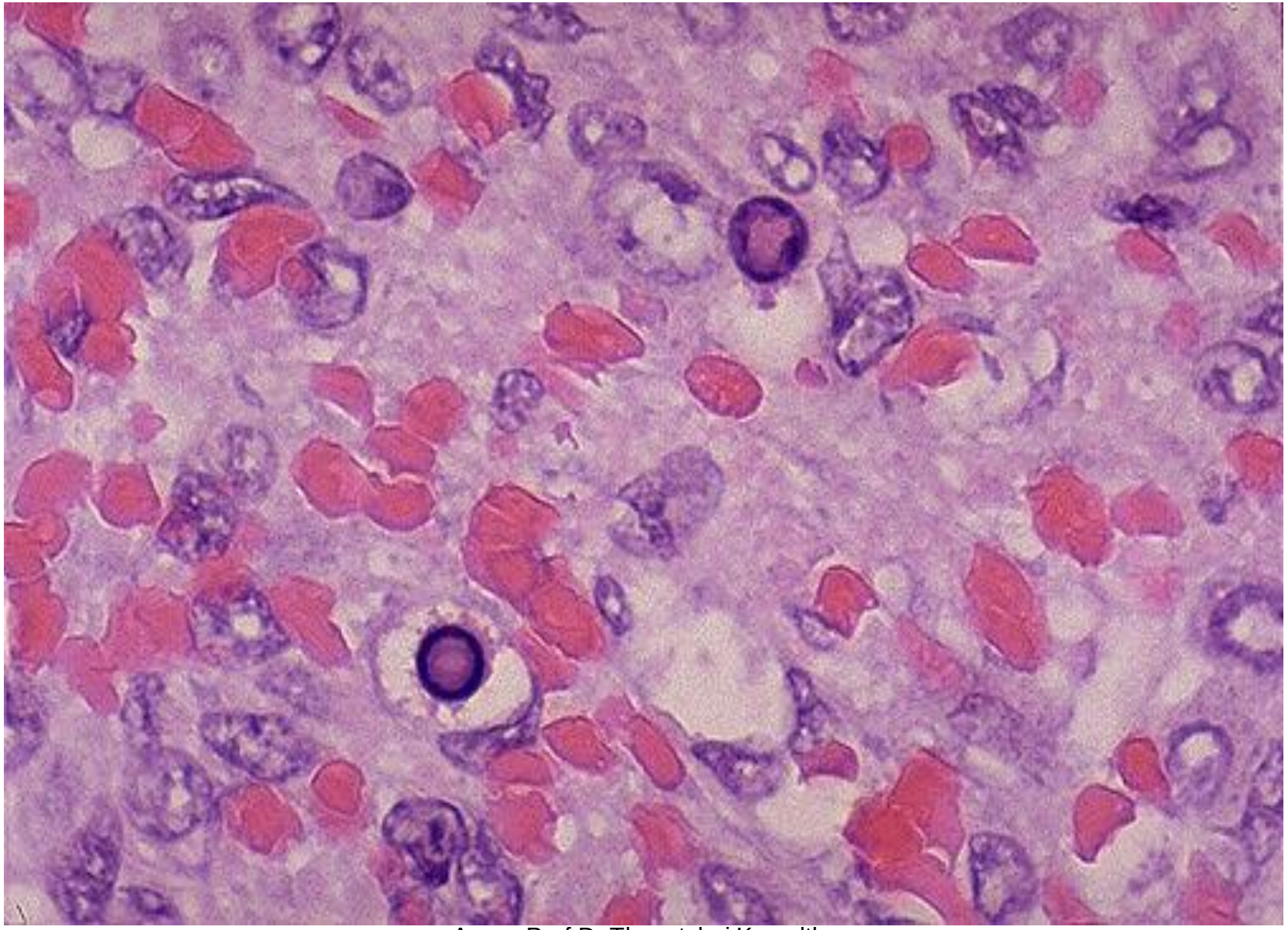


- The yellow-green globular material seen in small bile ductules in the liver here is bilirubin pigment.
- This is hepatic cholestasis.

Calcification



- This is dystrophic calcification in the wall of the stomach. (LOCAL CAUSES) (often with FIBROSIS)
- At the far left is an artery with calcification in its wall.
- There are also irregular bluish-purple deposits of calcium in the submucosa.
- Calcium is more likely to be deposited in tissues that are damaged.
- METASTATIC CALCIFICATION (SYSTEMIC CAUSES) e.g. HYPERPARATHYROIDISM



Exogenous pigments

- Carbon or coal dust

  inhaled → macrophages in alveoli

  ↓

  lymphatic channels

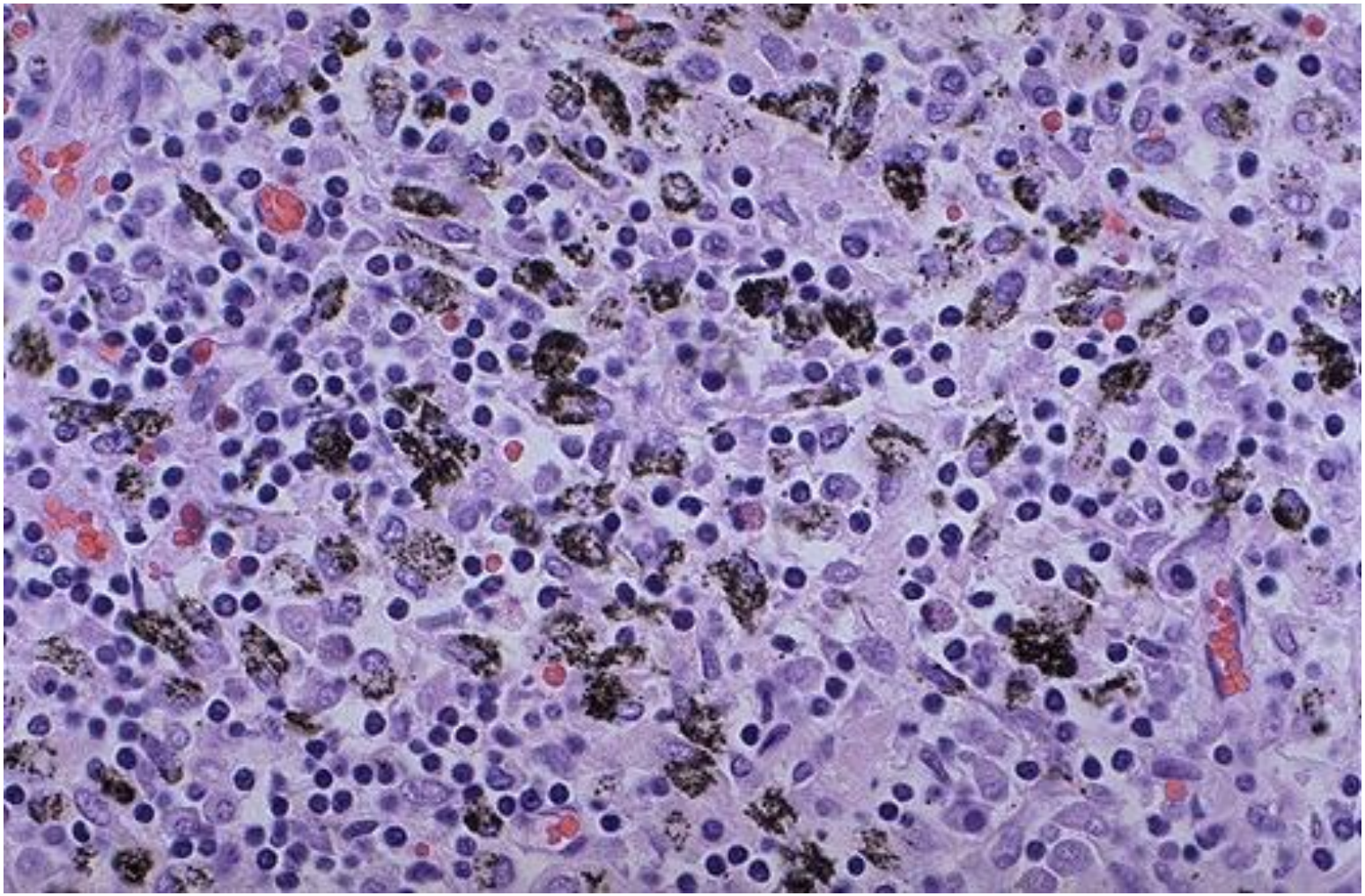
  ↓

  regional lymph nodes

  ↓

  anthracosis (blackening of lung)

  Heavy pollution → fibroblastic reaction, emphysema, coal workers' pneumoconiosis



-Anthracotic pigment in macrophages in a hilar lymph node.
-Anthracosis is an accumulation of carbon pigment from breathing dirty air.
-Smokers have the most pronounced anthracosis.

Exogenous pigments cont'd

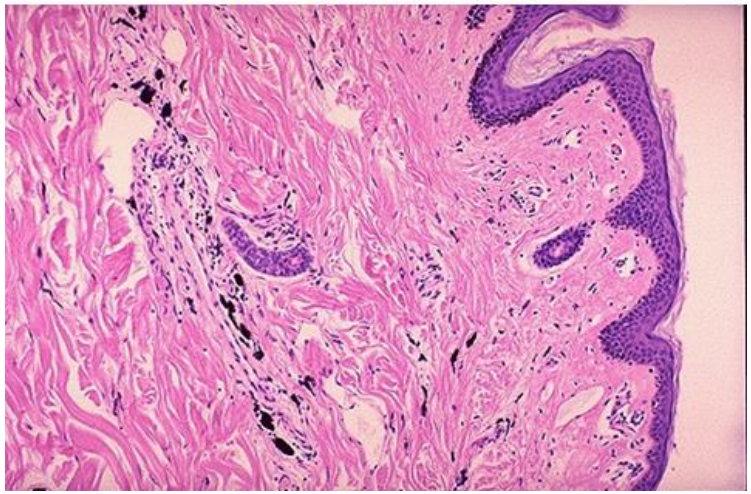
2) Tattooing

Pigments inoculated → phagocytosed by dermal macrophages

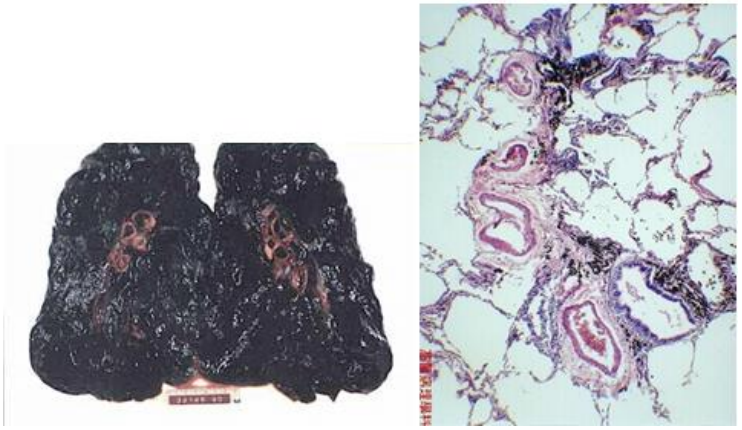
PIGMENTS

- **EX-ogenous--- (tattoo, Anthracosis)**

TATTOO, MICROSCOPIC

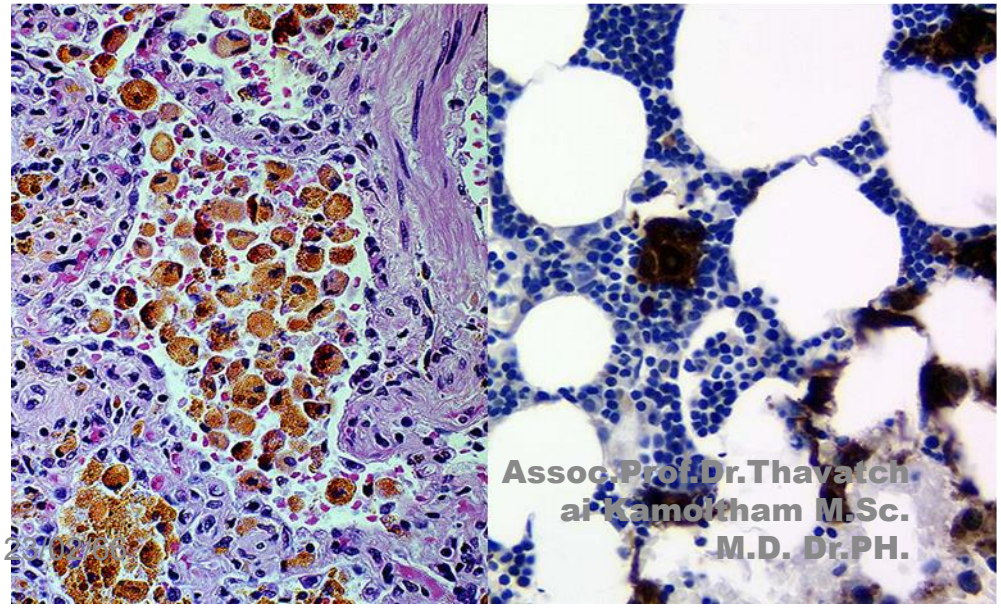


ANTHRACOSIS



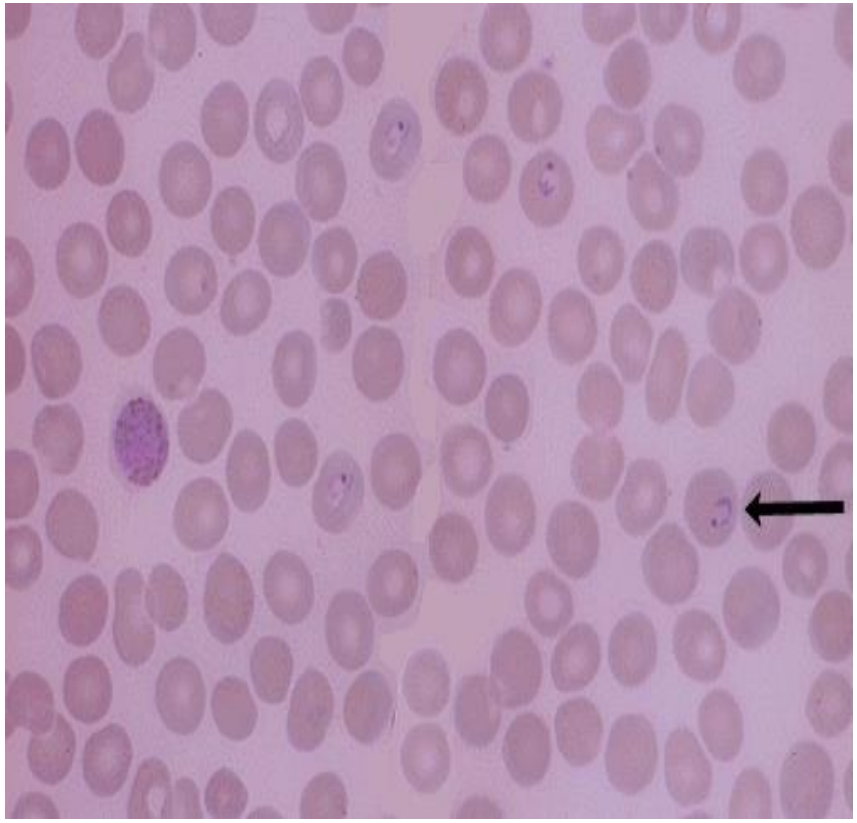
Hemosiderin/Melanin/etc.

- **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**



Parasitic infection

- This peripheral blood smear comes from a patient with malaria.
- This infection happens to be with *Plasmodium vivax*. At the arrow is a RBC with a malarial parasite in the shape of a ring.
- Three other RBC's in this smear are also infected with a ring trophozoite.
- At the far left is a gametocyte of this species.



CELL INJURY

Cellular injury
– cell unable to maintain homeostasis

- **Causes of cell injury:**
- **Deficiency** – lack of a substance necessary to the cell. Deficiency in oxygen most important
- **Intoxication or poisoning** – presence of a toxin or substance that interferes with cell functioning
- **Trauma** – physical injury and loss of cell's structural integrity

Hypoxia

Hypoxia = deficiency in oxygen at cell

Due to :

- *Decreased oxygen in air*
- *Decreased hemoglobin or decreased oxygen transported to cells*
- *Diseases of the respiratory and/or cardiovascular system*

Ischemia is inadequate blood supply to a cell or tissue. Ischemia can cause hypoxia.

Important to cell because of oxidative phosphorylation, which results in the production of ATP

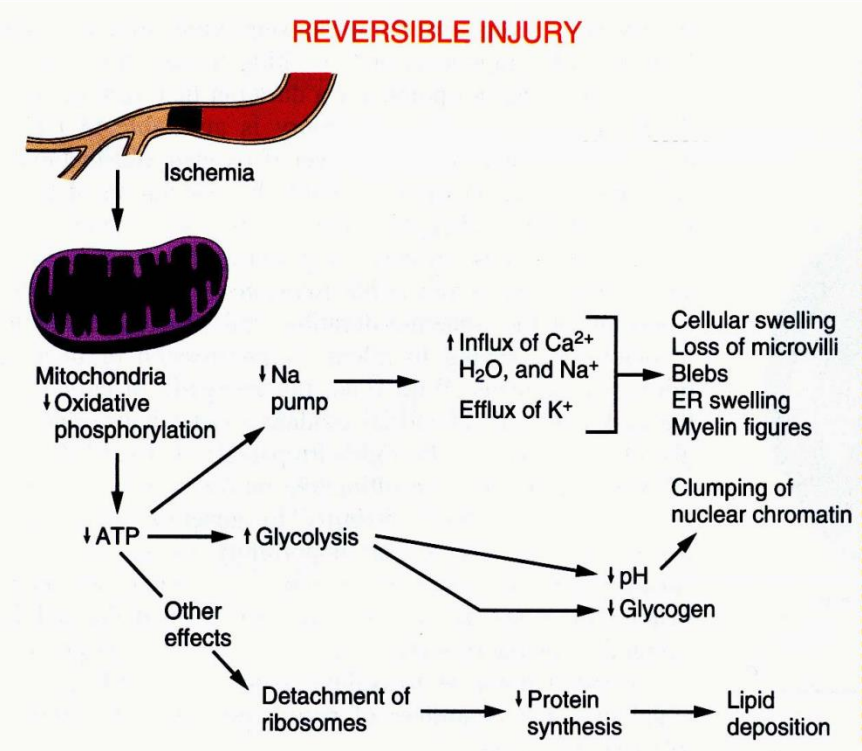
- *Oxidative: need oxygen to produce ATP*
- *ATP: needed by cell for metabolism, cell life*

Cellular response to hypoxia

- Decreased mitochondrial reactions → decreased ATP produced → decreased energy
- Ion pumps cease, so can't regulate ions into/out of cell (ATP needed for this)
- Can't pump Na^+ and water out of cell, so get cell swelling → organelle swelling →cell death

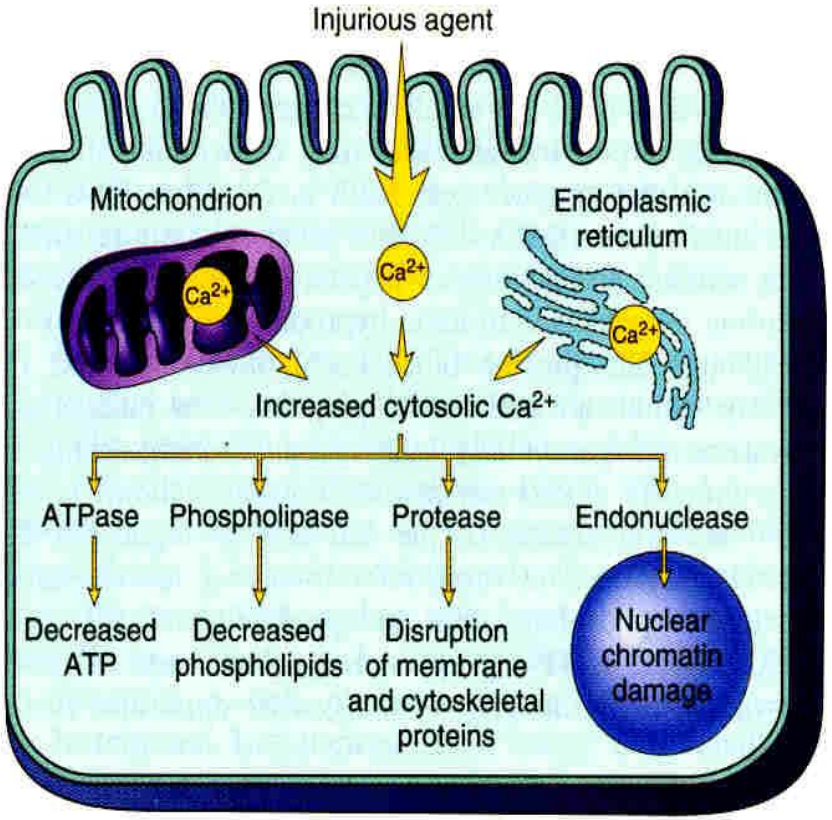
Pathogenesis of cell injury - hypoxia

- Reversible
  - Loss of ATP
    - Failure of Na/K pump
  - Anaerobic metabolism
    - Increased lactic acid and phosphate
  - Reduced protein synthesis



Pathogenesis of cell injury - hypoxia

- Irreversible
  - Massive intra-cytoplasmic calcium accumulation
  - Enzyme activation



Causes of cell injury

- Hypoxia
- Chemical
- Physical
- Infection
- Immune
- Nutritional deficiency (or excess!)

Types of insult - hypoxia

- Ischaemia
  - Local e.g. embolus
  - Systemic e.g. cardiac failure
- Hypoxaemia
  - Oxygen problems e.g. altitude
  - Haemoglobin problems e.g. anaemia
- Oxidative phosphorylation
  - E.g. cyanide poisoning

Types of insult - chemical

- Many of the common poisons (arsenic, cyanide, mercury) interfere with cellular metabolism. If ATP levels drop below critical levels, affected cells will die.

- The list of pharmaceuticals that may have toxic effects on cells is enormous. Some act directly, but most have their effect through breakdown metabolites. Metabolism of alcohol (a type of drug) to acetaldehyde is one example.

- Intoxication (or introduction of toxins into the cell)

  Effect on cell depends on toxin and on cell

  Some examples:

  Lead -- injures nervous system

  CO -- deprives body of oxygen

  Ethanol -- effects central nervous system

Types of insult - infections

- Infections agents

Microorganisms can invade and harm cells

- Fungi, Rickettsiae, Bacteria and Viruses
  - E.g. viruses can take over protein translation machinery and subvert it entirely to the production of new virions.

Types of insult - Physical

- Direct Physical Effects
  - Exposure of tissue to extreme heat or cold results in direct injury that is often irreversible, resulting in a pattern of coagulative necrosis (see later).
  - Sudden changes in pressure can cause cellular disruption (e.g. a hammer blow to the thumb).
  - Electrical currents can cause direct breakdown of cellular membranes that may be irreversible.
  - Cell injury can have effects on the entire body

    Examples: fever, pain, increased heart rate
  - Trauma -- physical disruption of cells

    Ex: abrasion, cutting, burns, microorganisms etc.

Types of insult –immune

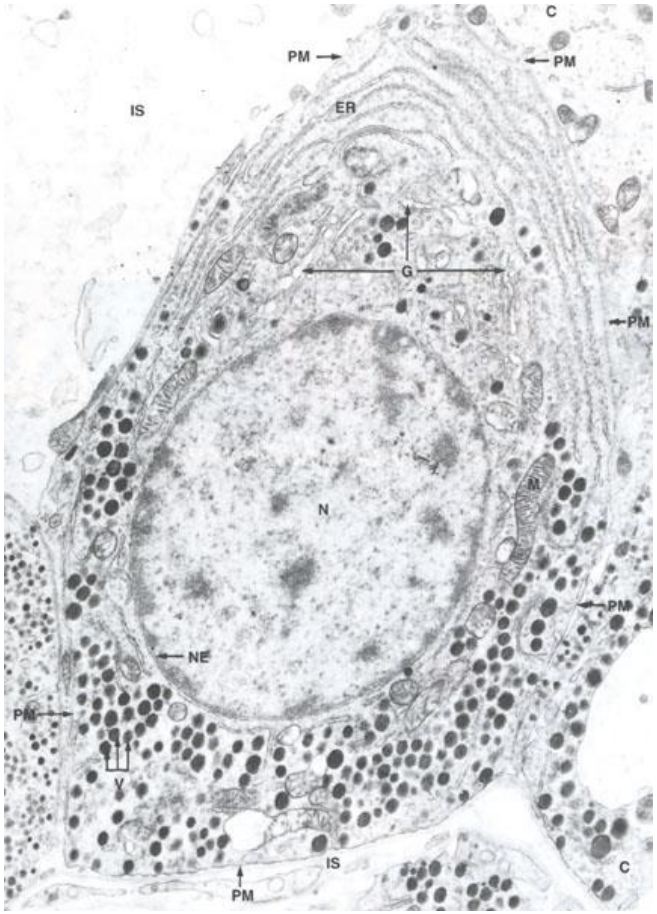
- Inflammatory mediators such as *interferons* and *interleukins*
  - can alter both gene expression and cellular metabolism. The effects are designed to help cells combat an infectious process, but the resulting stress to the cells can be highly injurious and sometimes deadly.
- Activation of *complement*
  - can result in direct attack on a cell's surface membrane.
- Cytotoxic T-cells and NK cells
  - can mediate a direct attack on a target cell's and initiate the self-destruct cascade within a target cell.

Types of insult - nutrition

- Dietary insufficiency
  - of protein, vitamins and/or minerals can lead to injury at the cellular level due to interference in normal metabolic pathways.
- Dietary excess
  - can likewise lead to cellular and tissue alterations that are detrimental e.g. fat is the biggest offender, or excess ingestion of "health supplements"

Principle structural targets for cell damage

- Cell membranes
  - Plasma membrane
  - Organelle membranes
- DNA
- Proteins
  - Structural
  - Enzymes
- Mitochondria
  - oxidative phosphorylation



Pathogenesis of cell injury - general

- Reduced ATP synthesis/mitochondrial damage
- Loss of calcium homeostasis
- Disrupted membrane permeability
- Free radicals

Free radicals

- Highly reactive, unstable chemicals
- Associated with cell injury
- Chemicals/drugs, reperfusion injury, inflammation, irradiation, oxygen toxicity, carcinogenesis
- Uncharged atom or group of atoms with an unpaired electron
- Formed by radiation, redox reactions, chemicals
- Atom is unstable
- needs to gain or lose an electron
- can alter chemical bonds in proteins, lipids, carbohydrates and nucleic acids
- can cause chain reaction in cell

Free radicals

- Free radical generation occurs by….
  - Absorption of irradiation

    E.g. OH^- and H^-
  - Endogenous normal metabolic reactions

    E.g. O_2, and H_2O_2 that release O^ Nascent Oxygen (oxygen radical) monoatomic oxygen
  - Transition metals

    E.g. Fe^{+++}
  - nitrous oxide

    an important paracrine-t-ype mediator that helps regulate vascular pressure
  - Toxins

    e.g. carbon tetrachloride

Free radicals

- Free radicals are removed by….
  - Spontaneous decay
  - Anti-oxidants
    - E.g. Vitamin E, vitamin A, ascorbic acid, glutathione
  - Storage proteins
    - E.g. transferrin, ferritin, ceruloplasmin
  - Enzymes
    - Catalase, SOD (super oxide dimutase), glutathione peroxidase

Free radicals

- Injure cells by…..
  - Membrane lipid peroxidation
    - Autocatalytic chain reaction
  - Interaction with proteins
    - Protein fragmentation and protein-protein cross-linkage
  - DNA damage
    - Single strand breaks (genomic and mitochondrial)

CELL DEATH

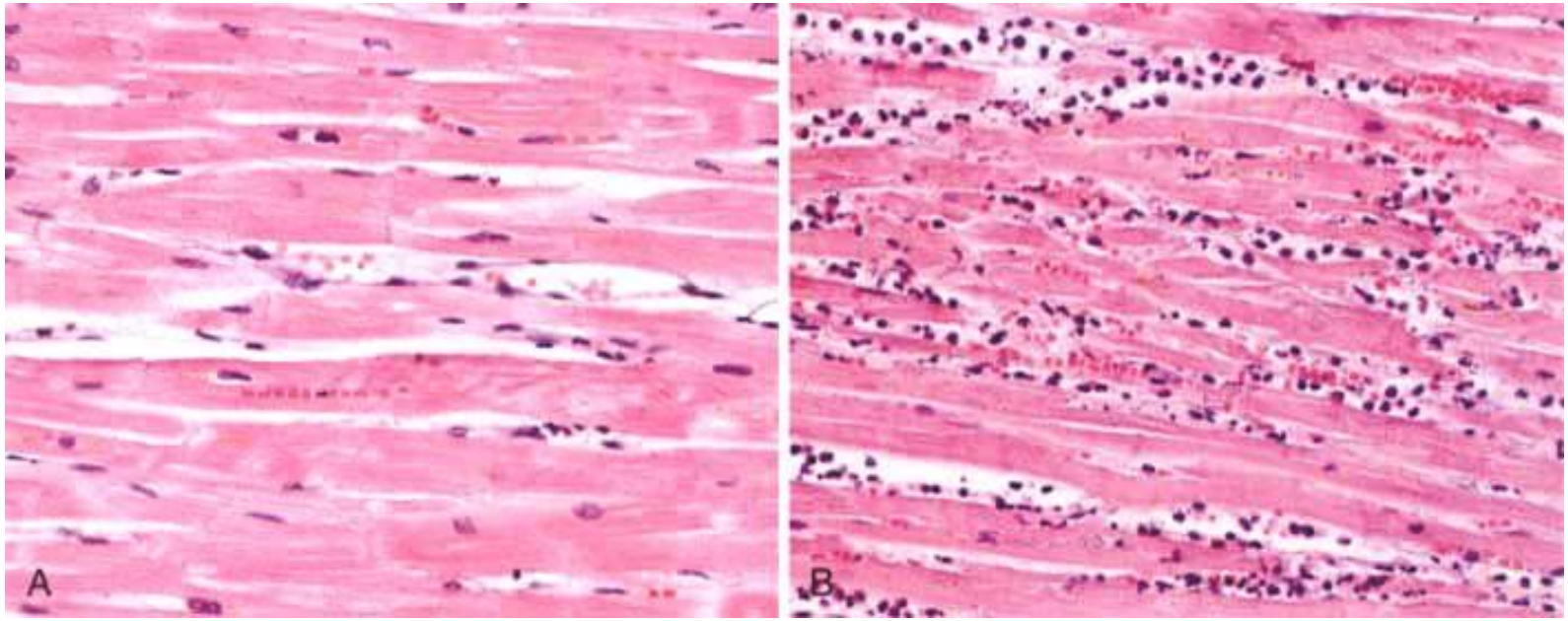
CELL DEATH

- APOPTOSIS vs. NECROSIS
- What is DEATH? (What is LIFE?)
  - DEATH is IRREVERSIBLE
- APOPTOSIS ("normal" death)
- NECROSIS ("premature" or "untimely" death due to "causes"

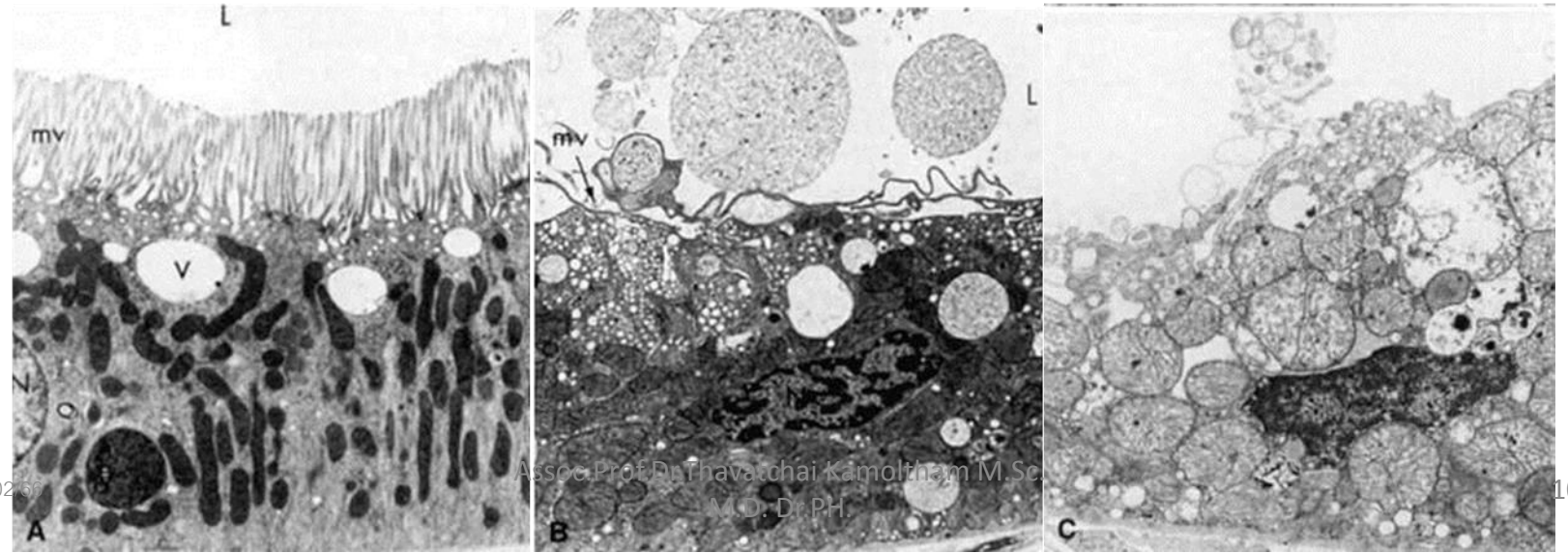
Reversible-Irreversible VS Life-Death

INJURY CAUSES (REVERSIBLE)	INJURY MECHANISMS (REVERSIBLE)	IRREVERSIBLE = DEATH
Hypoxia, (decreased O2)	• ATP Depletion • Cellular swelling • Reduce Oxidative Phosphorylation	SOME INJURIES CAN LEAD TO DEATH IF PROLONGED and/or SEVERE enough
PHYSICAL Agents	MITOCHONDRIAL DAMAGE	• IRREVERSIBLE MITOCHONDRIAL DYSFUNCTION
CHEMICAL Agents	INCREASED INTRACELLULAR CALCIUM	
INFECTIOUS Agents	INCREASED FREE RADICALS	
Immunologic	INCREASED CELL MEMBRANE PERMEABILITY	PROFOUND MEMBRANE DISTURBANCES, IRREVERSIBLE MEMBRANE DEFECTS
Genetic		
Nutritional		

DEATH:LIGHT MICROSCOPY

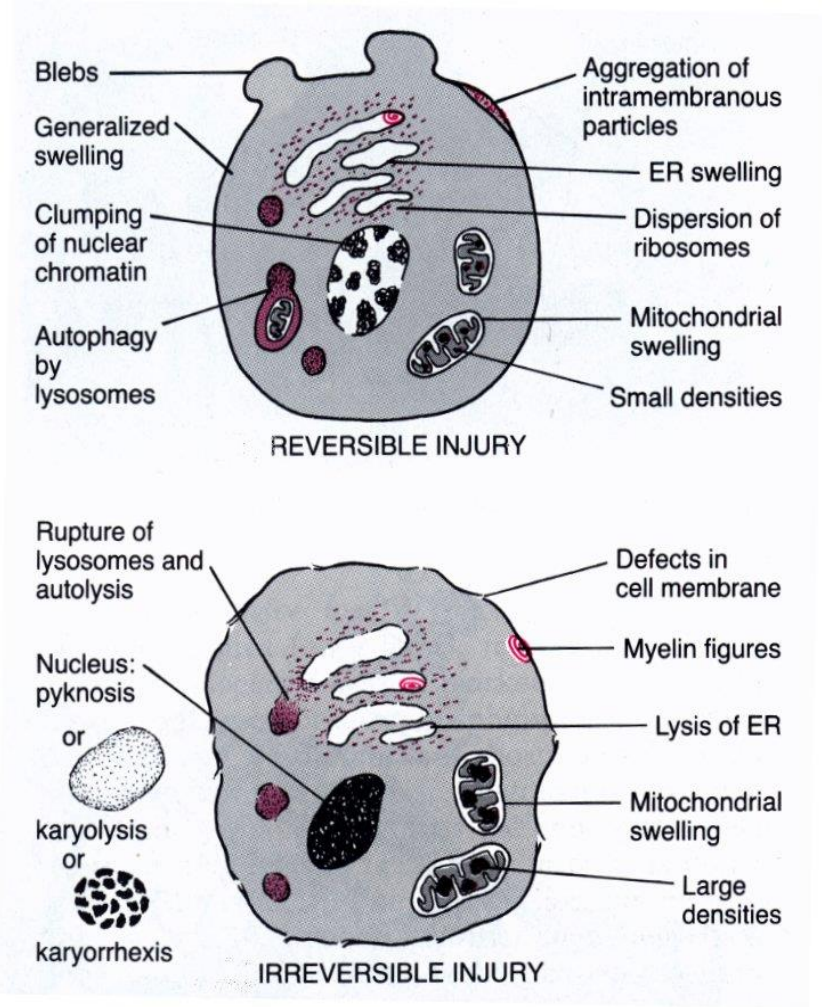


DEATH:ELECTRON MICROSCOPY



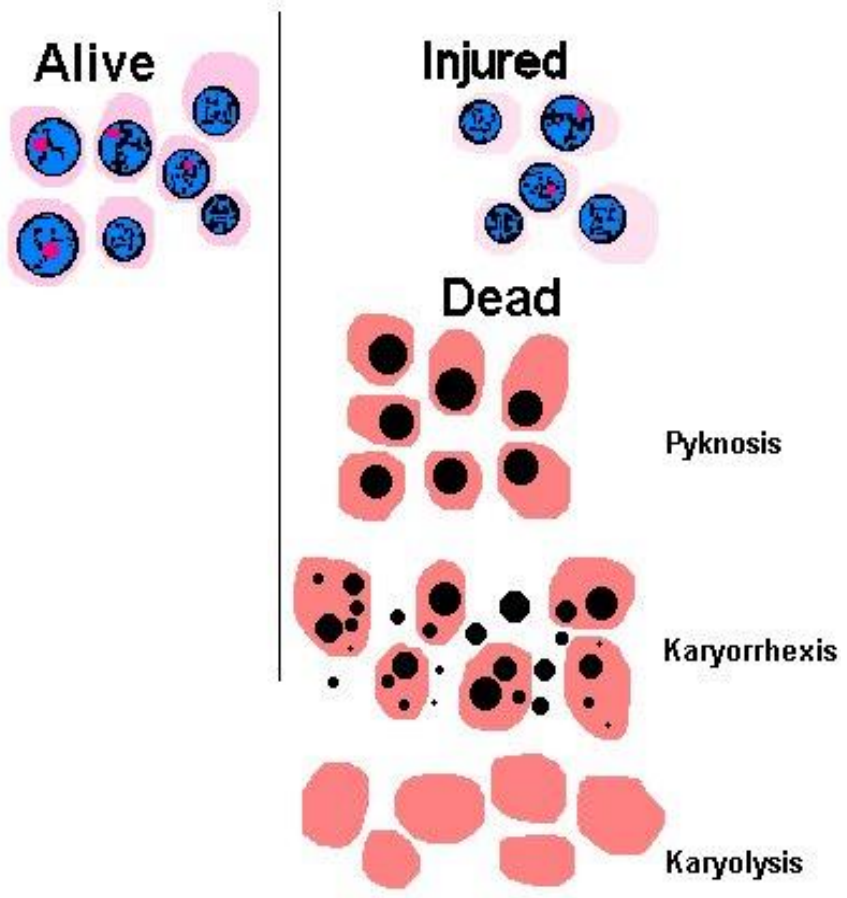
Cell injury - morphology

- Reversible
- Irreversible



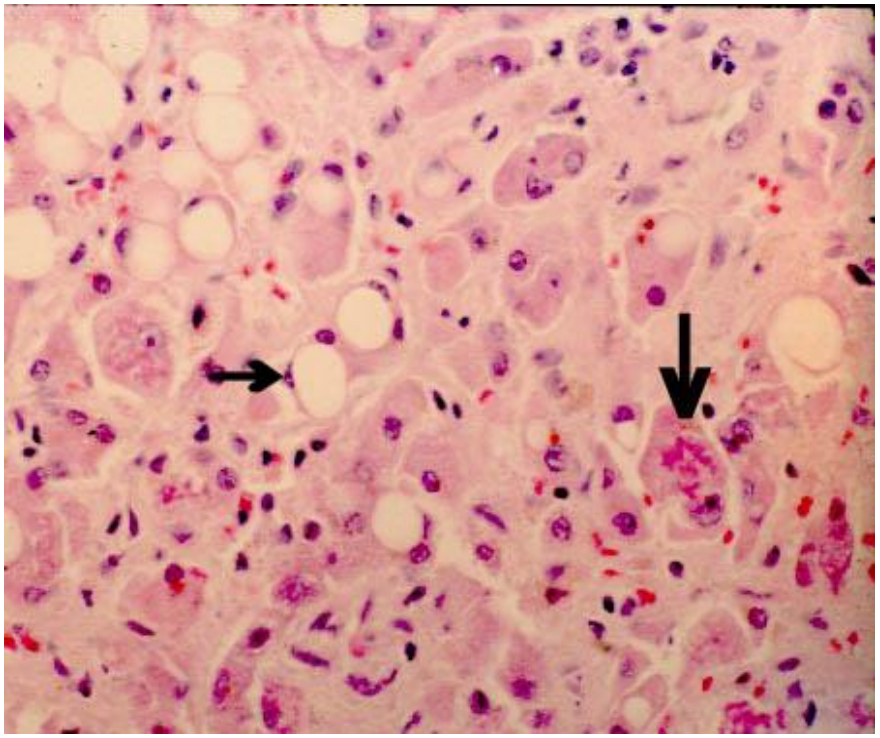
Cell injury - morphology

- Light microscopy
  - Cytoplasmic changes
  - Nuclear changes



Cell injury - morphology

- Abnormal accumulations
  - Lipid
  - Protein



1. Necrosis

- Definition
  - Death of groups of contiguous cells in tissue or organ
- Patterns
  - Coagulative
  - Liquefactive
  - Caseous
  - Fat necrosis
  - (gangrene)
  - (Infarct)
    - Red/haemorrhagic
    - White

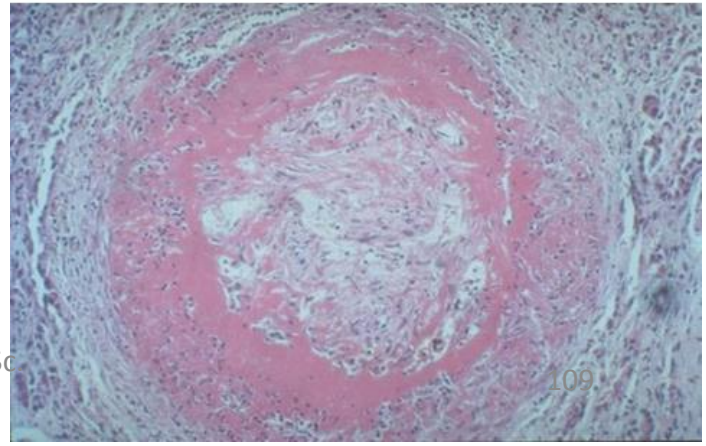
NECROSIS

- Liquefactive necrosis (Brain)
- Gangrenous necrosis (Extremities, Bowel, non-specific)
  - WET
  - DRY
- Fibrinoid necrosis (Rheumatoid, non-specific)
- Caseous necrosis (cheese) (Tuberculosis)
- Fat necrosis (Breast, any fat)
- Ischemic necrosis (non-specific)
- Avascular necrosis (aseptic), radiation, organ specific, papillary

EXAMPLES of Cell INJURY/NECROSIS

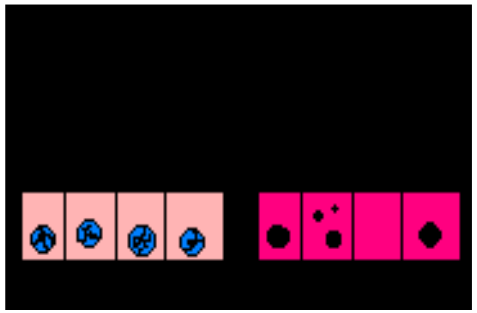
- Ischemic (Hypoxic) - DEATH (INFARCT)
- Ischemia/Reperfusion- Damage
- Initiates inflammation
- Gangrene – large mass of tissue undergoes necrosis

FIBRINOID NECROSIS

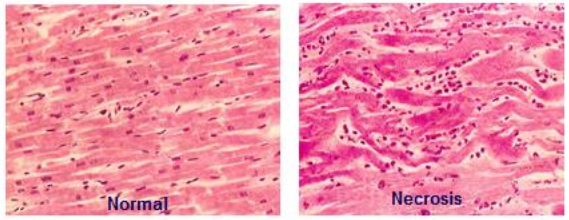


Coagulative necrosis

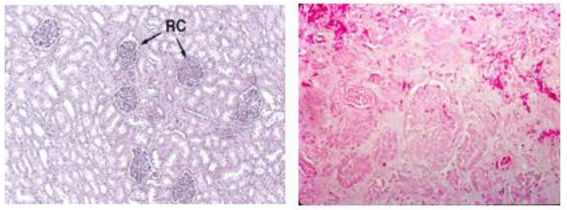
- Cells have died but the basic shape and architecture of the tissue endures
- Most common manifestation of ischaemic necrosis in tissues.
- Affected tissue maintains solid consistency.
- In most cases the necrotic cells are ultimately removed by inflammatory cells.
- The dead cells may be replaced by regeneration from neighboring cells, or by scar (fibrosis).



Coagulative necrosis

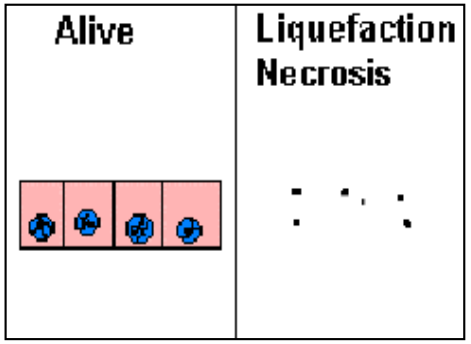


Coagulative necrosis

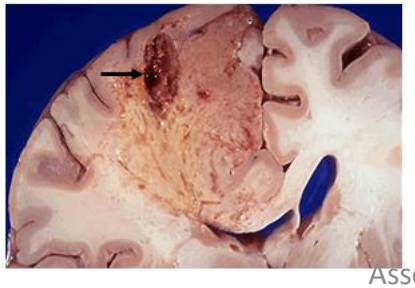


Liquefactive necrosis

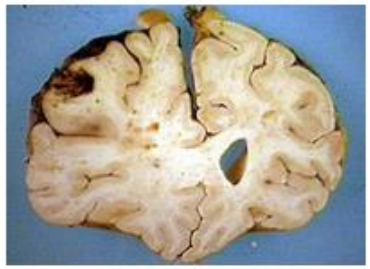
- Complete dissolution of necrotic tissue.
- Most commonly due to massive infiltration by neutrophils (abscess formation).
  - Release of reactive oxygen species and proteases
- Liquefaction is also characteristic of ischaemic necrosis in the brain.

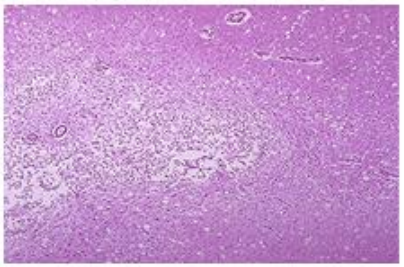


Liquefactive necrosis



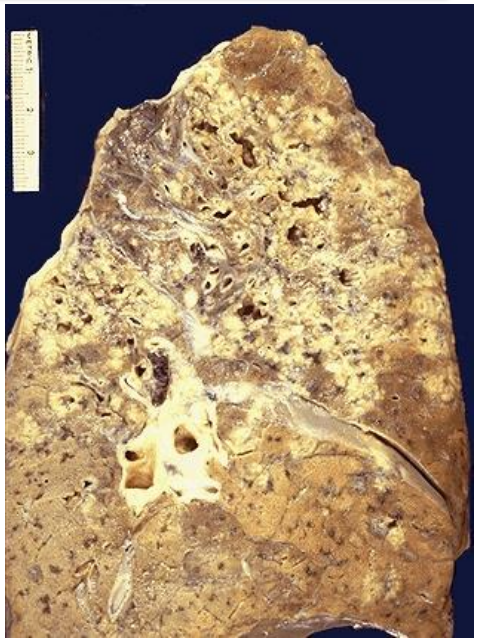
LIQUEFACTIVE NECROSIS, BRAIN

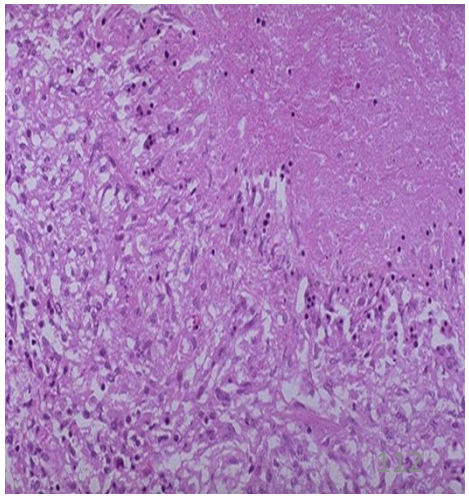




Caseous necrosis

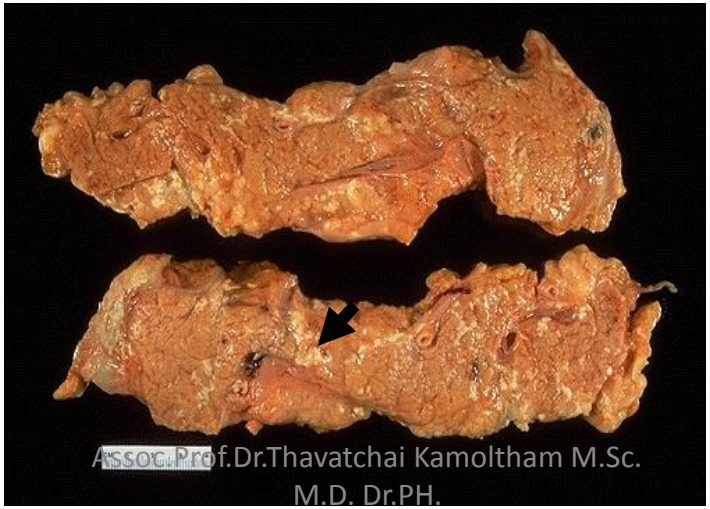
- Accumulation of amorphous (no structure) debris within an area of necrosis.
- Tissue architecture is abolished and viable cells are no longer recognizable.
- Characteristically associated with the granulomatous inflammation of tuberculosis. Also seen in some fungal infections.



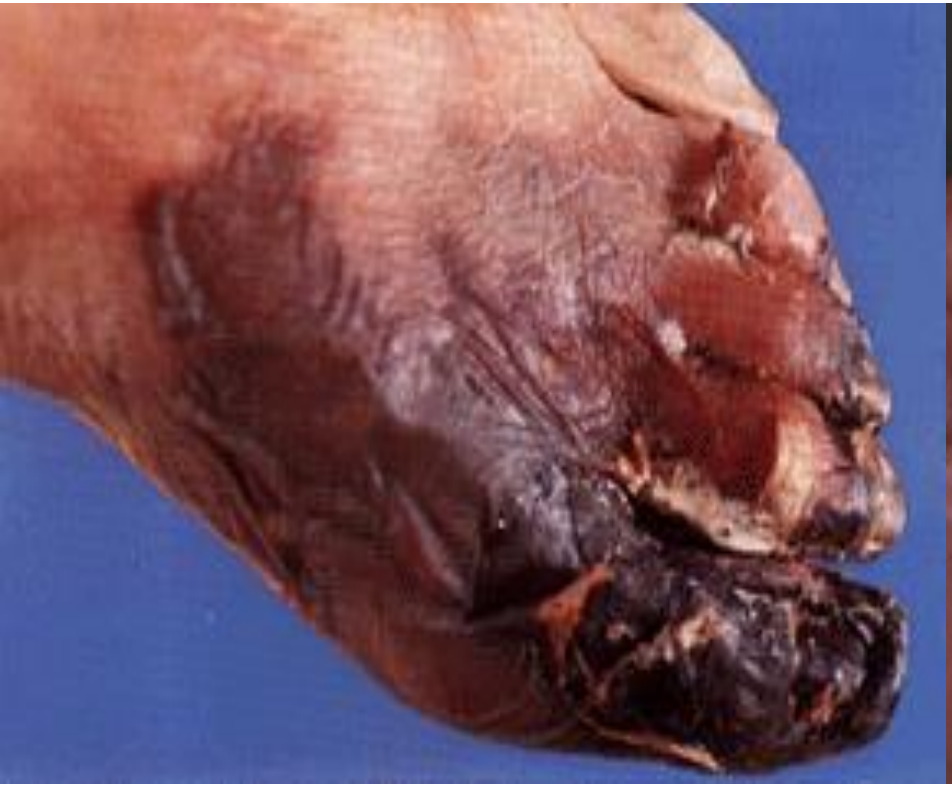


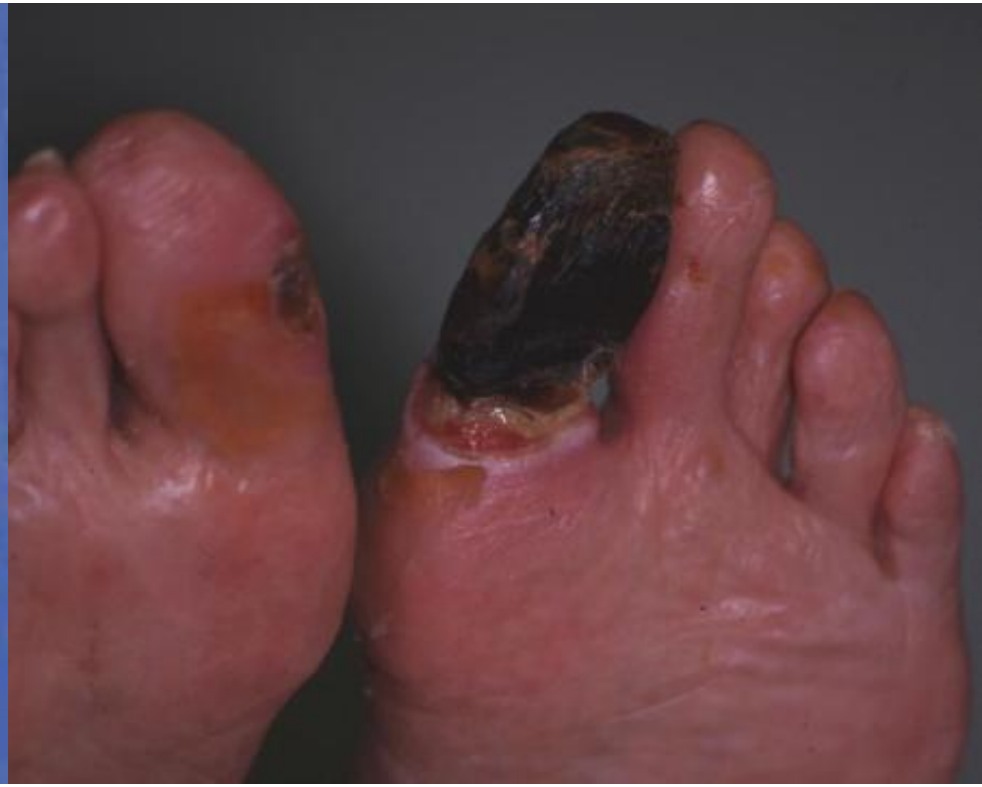
Fat necrosis

- Results from the action of lipases released into adipose tissue.
  - pancreatitis, trauma.
- Free fatty acids accumulate and precipitate as calcium soaps (saponification).
  - These precipitates are grossly visible as pale yellow/white nodules
- Microscopically, the digested fat loses its cellular outlines. There is often local inflammation



Gangrene=ตายเน่า





“WET” GANGRENE **“DRY” GANGRENE**

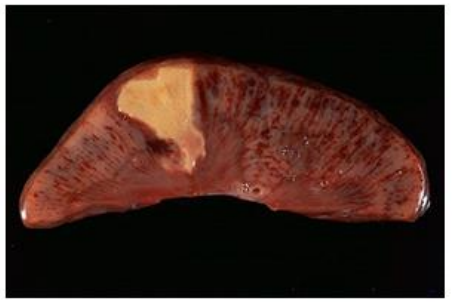
Gangrene ("gangrenous necrosis")

- Not a separate kind of necrosis at all, but a term for necrosis that is advanced and visible grossly.
  - If there's mostly coagulation necrosis, (i.e., the typical blackening, desiccating foot which dried up before the bacteria could overgrow), we call it dry gangrene.
  - If there's mostly liquefactive necrosis (i.e., the typical foul-smelling, oozing foot infected with several different kinds of bacteria), or if it's in a wet body cavity, we call it wet gangrene.

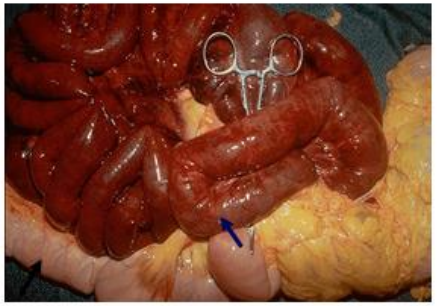
Infarction

- An area of ischaemic necrosis in a tissue or organ
  - White
    - Arterial occlusion in most solid tissues
  - Red/haemorrhagic
    - Venous occlusion
    - Loose tissues
    - Dual blood supply
    - Previously congested

White infarct



Red infarct



2. Apoptosis(Programmed Death)

- is a distinct reaction pattern which represents programmed single-cell suicide.
- Cells actually expend energy in order to die.
- Derived from Greek "falling off" (as for autumn leaves)
- Apoptosis is "the physiological way for a cell to die", seen in a variety of normal situations.

APOPTOSIS

NORMAL (preprogrammed)

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

PATHOLOGIC (associated with Necrosis)

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

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

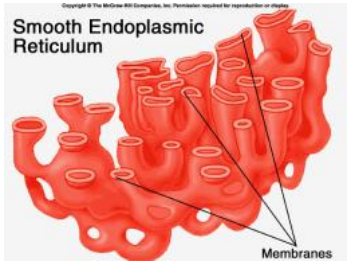
BIOCHEMISTRY

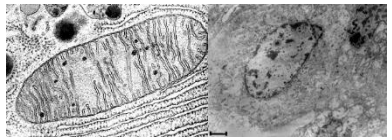
- Protein Digestion (Caspases)
- DNA breakdown
- Phagocytic Recognition

APOPTOSIS

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 (EX-ogenous, END-ogenous)**
- **Calcium**

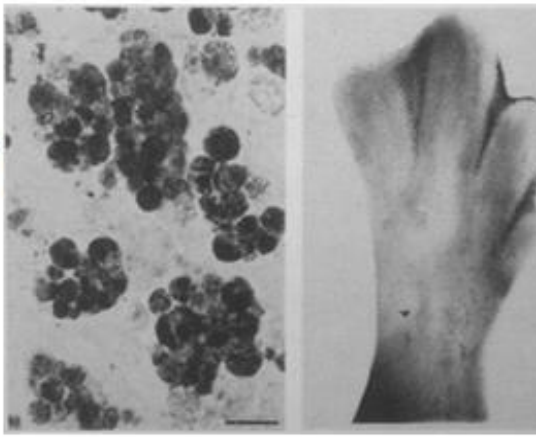
Apoptosis - morphology

- Necrosis:
  - pathological response to cellular injury.
  - Chromatin clumps, mitochondria swell and rupture, membrane lyses, cell contents spill, inflammatory response triggered
- Apoptosis
  - DNA cleaved at specific sites - 200 bp fragments.
  - Cytoplasm shrinks without membrane rupture
  - Blebbing of plasma and nuclear membranes
  - Cell contents in membrane bounded bodies, no inflammation

Apoptosis

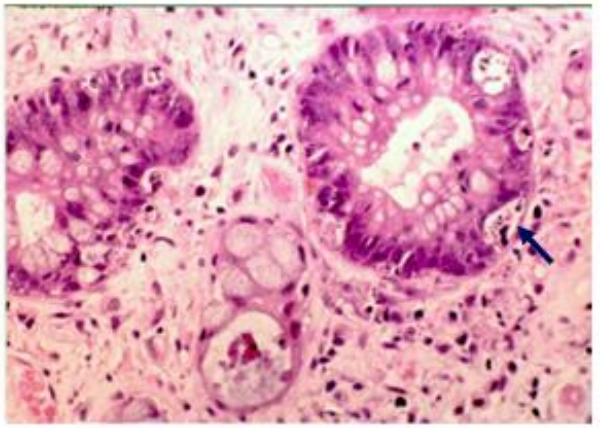
Apoptosis - normal

A stain for apoptotic cells in the developing paw of a foetal mouse.



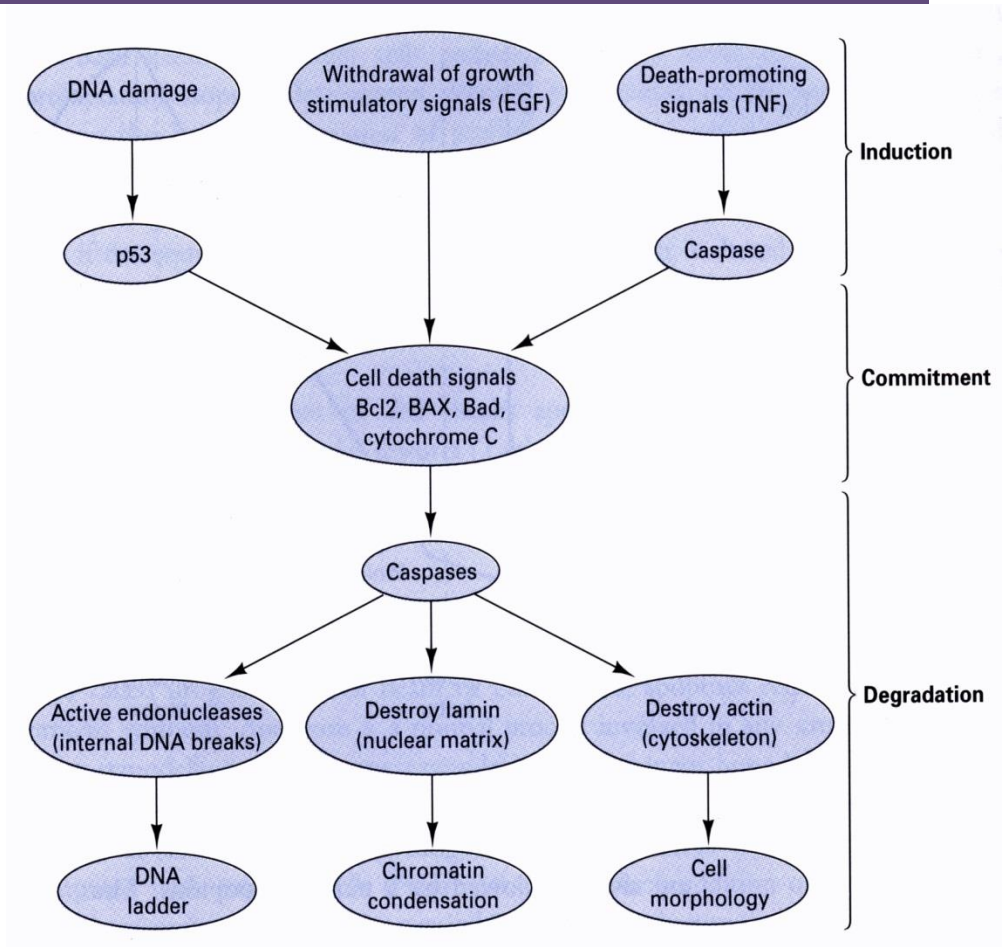
Apoptosis -pathological

Graft-versus-host disease in colonic mucosa

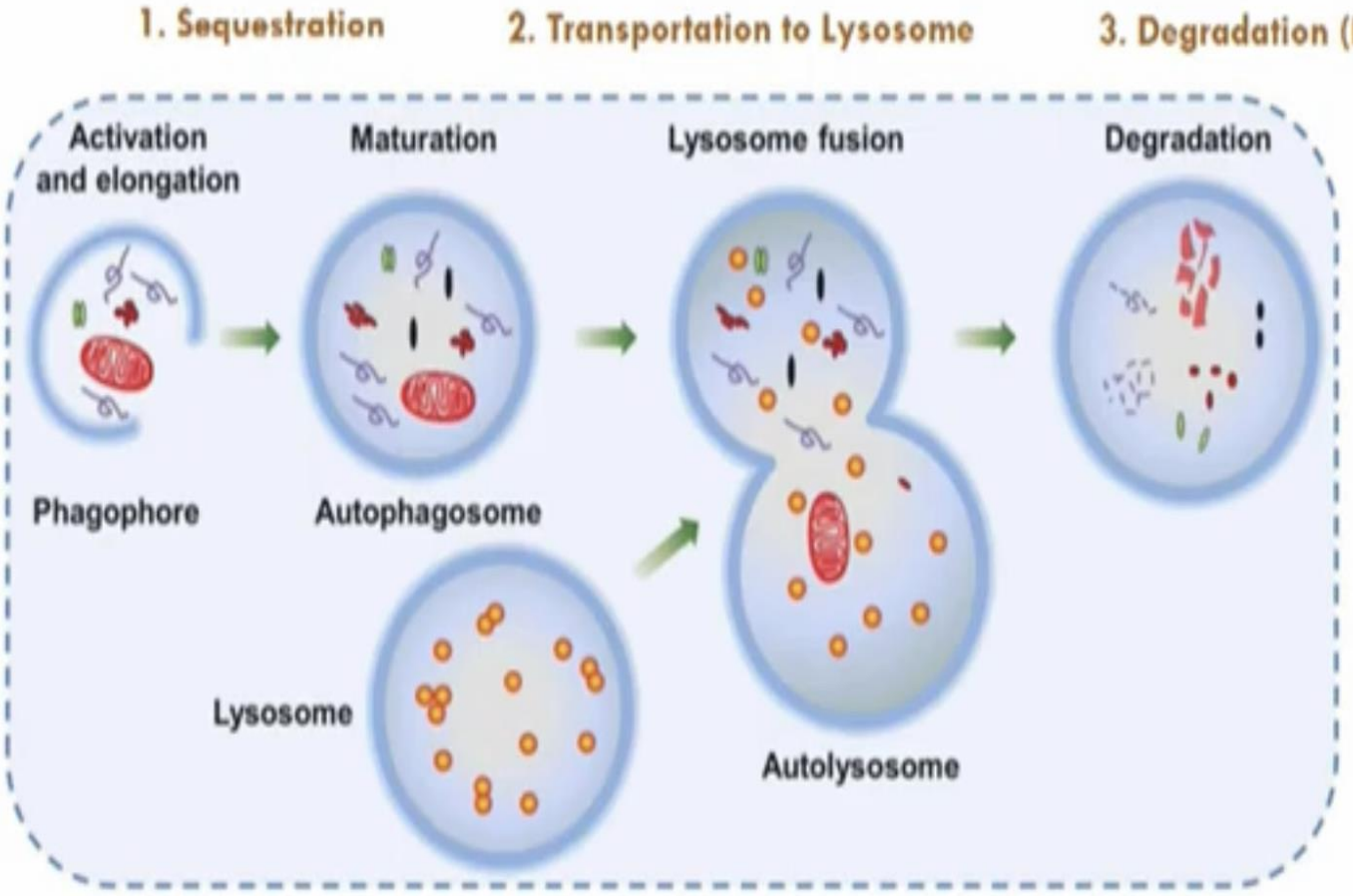


Apoptosis - mechanisms

- Extrinsic factors
  - E.g. by members of the TNF family
- Intrinsic mechanisms
  - E.g. hormone withdrawal



PROCESSES OF AUTOPHAGY



4. Reuse of Degradation products
- New protein synthesis
- ATP

EFFECTS OF AUTOPHAGY

Intracellular

- Decrease oxidative stress
- Increase genomic stability
- Increase bioenergetics metabolism
- Elimination of waste

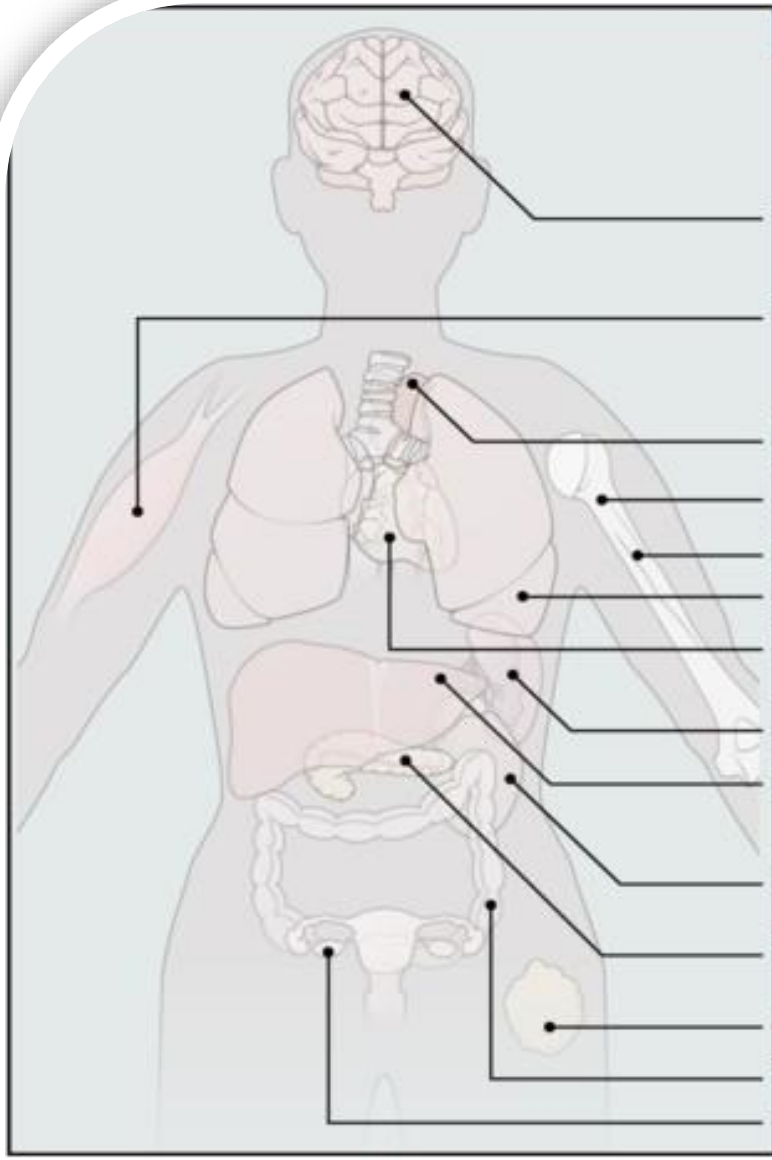
Extracellular

- Decrease inflammatory response
- Increase neuroendocrine homeostasis
- Increase immune system
- Increase elimination of aging cells

10 Natural Ways to Stimulate Autophagy

1. Caloric Restriction
2. Intracellular enzymatic reactions (co-factors from vitamins from plant based food)
3. Antioxidants (Resveratrol, Vitamin D, phytosubstances)
4. Avoid saturated fat/ dairy / sugar/ processed food (pro-imflammatory)
5. Exercise and Oxygenate
6. Restorative sleep
8. Protect your gene : electromagnetic radiation/ chemicals/ pollutants / toxins
9. Go outdoors = Sunlight
10. Relax & Release psychological trauma

Autophagy important for anti-ageing



Organ	Roles of Autophagy	Diseases
General function	Starvation-induced amino acid production; constitutive turnover of cytoplasmic contents; selective degradation of p62, damaged mitochondria, microbes, etc.; life-span extension/antiaging	Tumor suppression and progression
Brain	Prevention of aggregate formation; Parkin-dependent mitophagy; regulation of food intake and energy balance	Parkinson disease Alzheimer disease
Muscle	Maintenance of muscle mass	Myopathies : (Danon disease, XMEA, Bethlem myopathies, UCMD) Lysosomal storage diseases
Thymus	Negative selection	
Bone marrow / Hematopoiesis	Erythropoiesis; maintenance of hematopoietic stem cell	
Bone		Paget disease?
Lung	Regulation of airway responsiveness	Cystic fibrosis
Heart	Adaptation to hemodynamic stress; prevention of age-dependent dysfunction	Cardiac hypertrophy
Immune/ lymphoid system	Regulation of cytokine production; development of T cells and B cells	Infection
Liver	Prevention of hepatocellular degeneration; suppression of hepatic tumors; lipid droplet elimination; gluconeogenesis	α_1-antitrypsin deficiency Hepatocellular carcinoma?
Kidney	Maintenance of podocyte and tubular cell integrity	
Pancreas	β-cell adaptation to high-fat diet; prevention of trypsine autoactivation	Diabetes Acute pancreatitis
Adipose tissue	Adipogenesis	Obesity
Intestine	Maintenance of Paneth cell function	Crohn disease
Embryos	Preimplantation development	

https://www.cosmeticsdesign-asia.com/Article/2018/07/09/Why-autophagy-is-essential-for-cells-and-cosmetics-applications?utm_source=copyright&utm_medium=OnSite&utm_campaign=copyright

FOODS THAT MIGHT BE HELPFUL FOR AUTOPHAGY

- Cannabinoid (THC and CBD)

  ref: https://pubmed.ncbi.nim.gov/19425170/
- Cacao protective activity of liver cells by preventive apoptosis and including Autophagy
- Coffee: polyphenol in coffee increase autophagy in liver and muscle
- Curcumin: increase autophagy in pancreatic cells, inhibits proliferation of disease
- Olive oil
- Green tea, camellia seed oil, bergamot tea

Cell ageing

- CELL AGEING parallels ORGANISMAL AGING
- Programmed change theories
- PROGRAMMED THEORY (80%) vs. WEAR AND TEAR THEORY (20%)
- Telomerase

Final thought…

Our lives are filled with joys and strife,

And what is death but part of life?

Will come the day that we must die,

And leave behind those learning why.