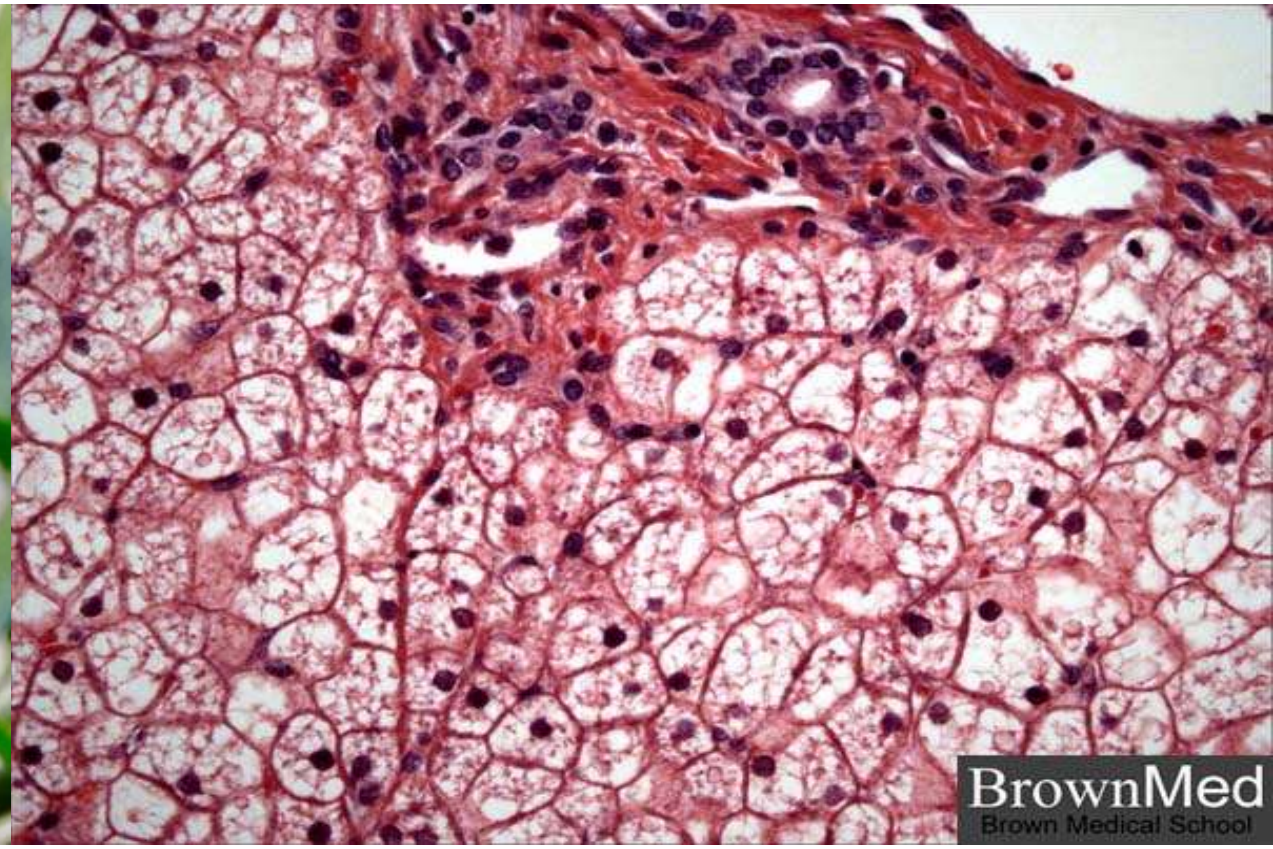
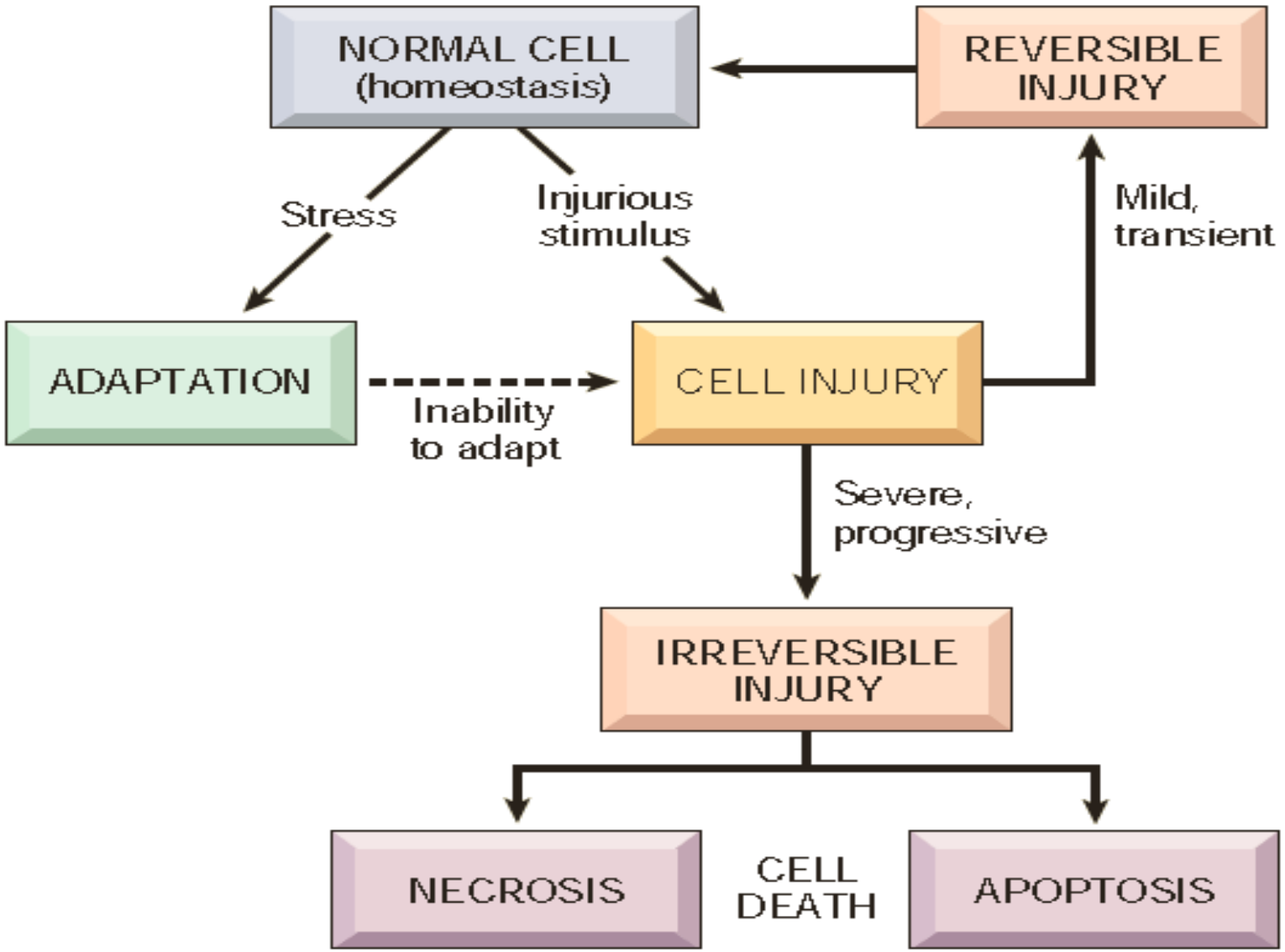


Cellular Adaptations and accumulations

Ghadeer Hayel, M.D.
Assistant Professor of Pathology
Consultant Hematopathologist
10/14/2024

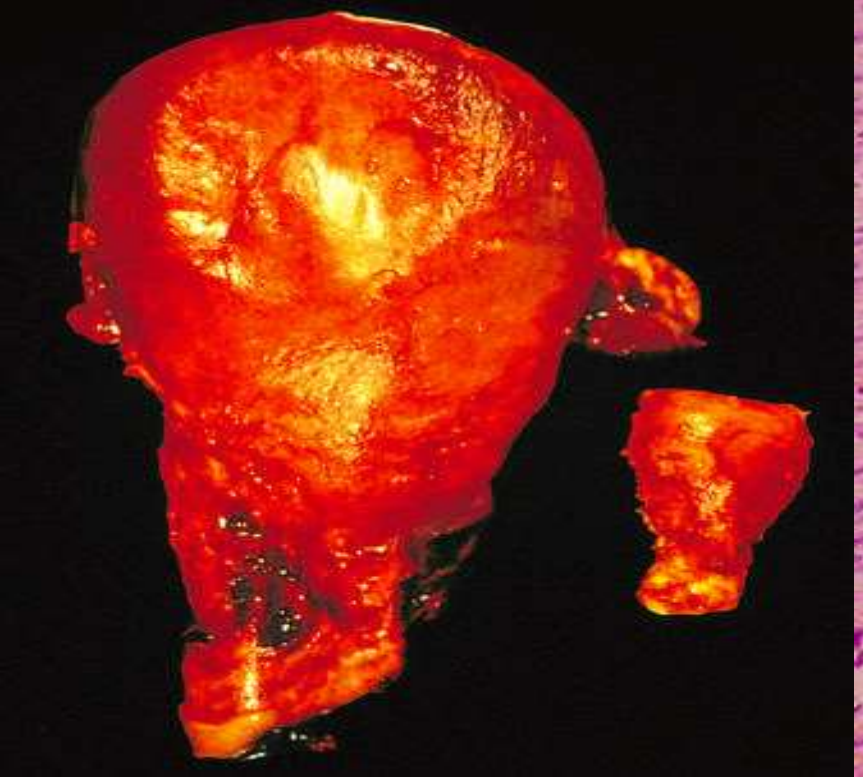
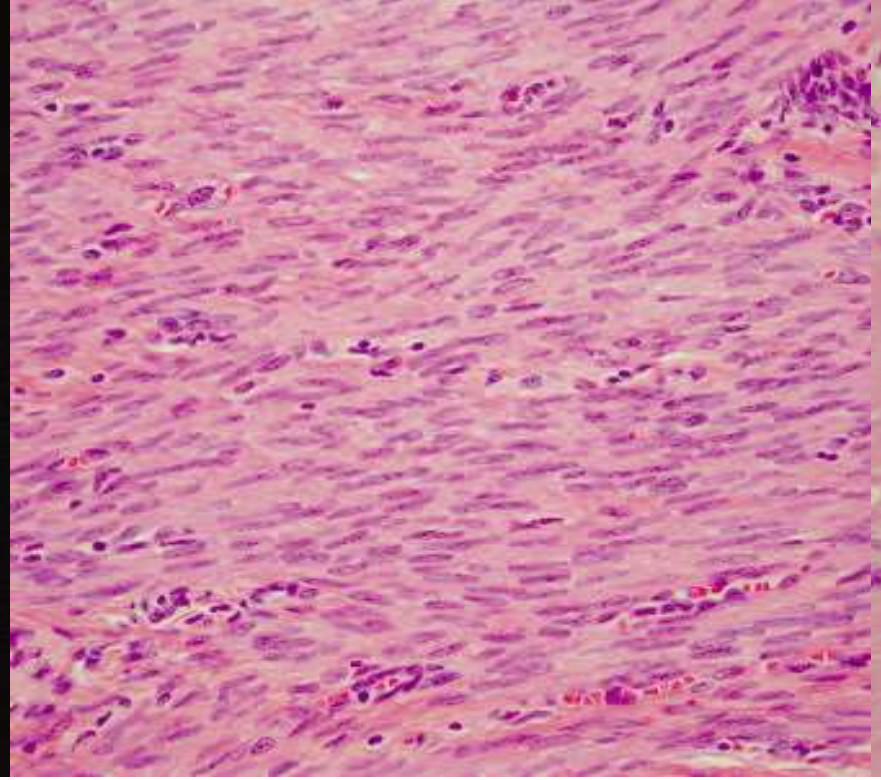
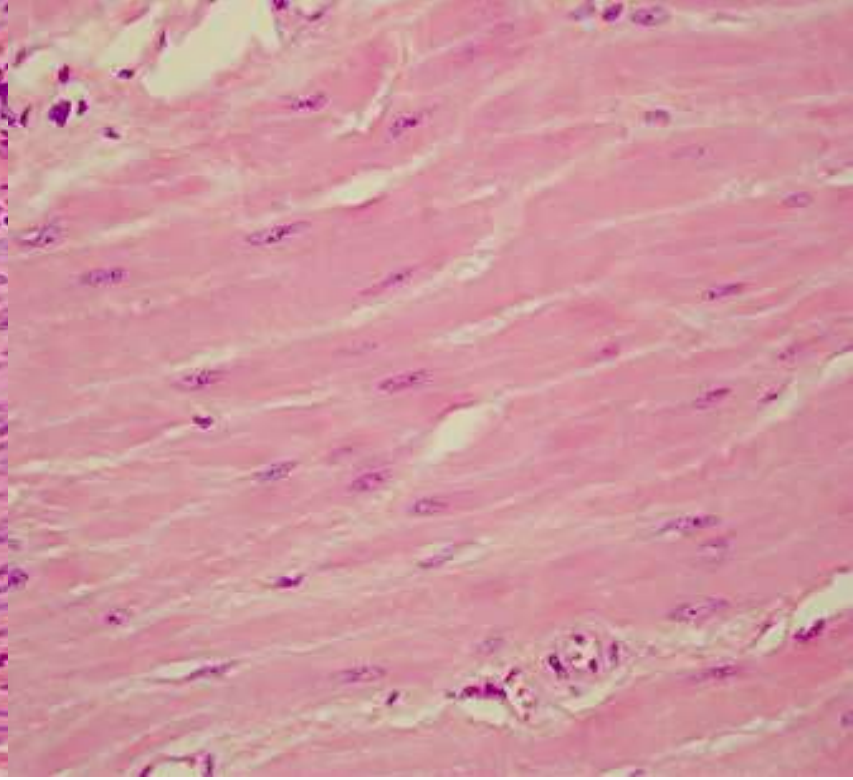

NORMAL CELL
(homeostasis)
REVERSIBLE
INJURY
Stress
Injurious
stimulus
Mild,
transient
ADAPTATION
Inability
to adapt
CELL INJURY
Severe,
progressive
IRREVERSIBLE
INJURY
NECROSIS
CELL
DEATH
APOPTOSIS

Adaptations

- Reversible changes in the number, size, phenotype, metabolic activity, or functions of cells in response to changes in their environment.
- Can be physiologic or pathologic.
- **Physiologic:** responses of cells to normal (1) stimulation by hormones or endogenous chemical mediators. (Breast & uterus during pregnancy) or to the (2) demands of mechanical stress (bones and muscles).
- **Pathologic:** responses to stress that allow cells to modulate their structure &function, thus escape injury, but at the expense of normal function. (squamous metaplasia of bronchial epithelium in smokers)

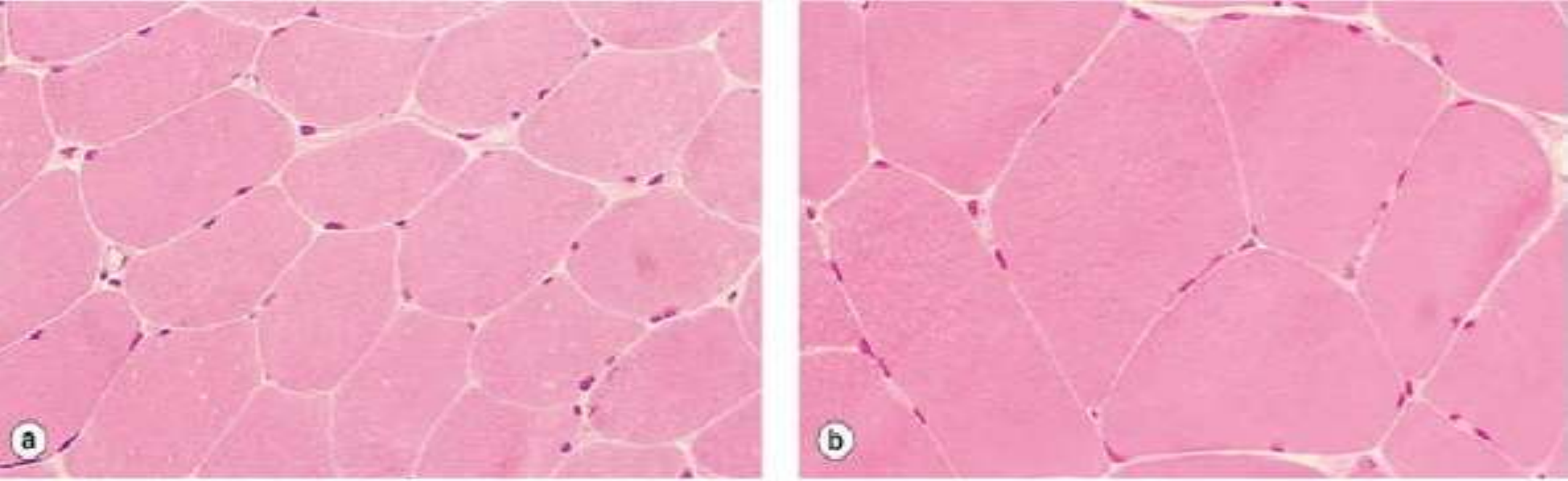
1. Hypertrophy

- **Hypertrophy is an increase in the size of cells resulting in an increase in the size of the organ.**
- Hypertrophy & hyperplasia also can occur together.
- Hyperplasia happens in cells capable of replication, whereas hypertrophy occurs when cells have a limited capacity to divide.
- In pure hypertrophy there are no new cells, just bigger cells with increased amounts of structural proteins & organelles.
- **Hypertrophy can be physiologic or pathologic**

Hypertrophy - physiologic - stimulation

The massive enlargement of the uterus during pregnancy → a consequence of estrogen stimulated smooth muscle hypertrophy & smooth muscle hyperplasia.



Stevens et al: Core Pathology, 3rd Edition.
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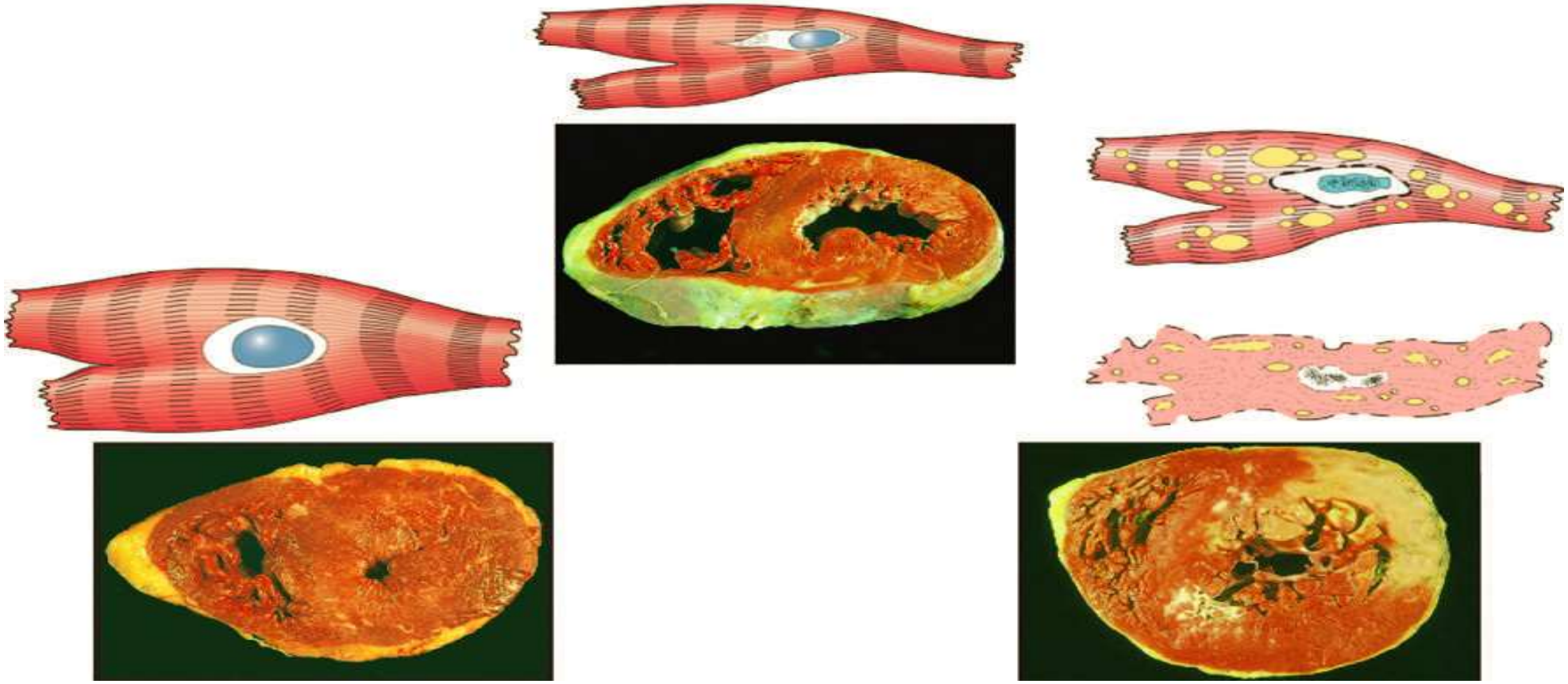
Hypertrophy - physiologic - ↑ demand

In response to increased workload the striated muscle cell undergo hypertrophy. **Adult muscle cells have a limited capacity to divide →** chiseled physique of weightlifter **stems only from the hypertrophy**



Hypertrophy - pathologic - ↑ demand

In response to increased workload (hypertension or aortic valve disease) myocardial hypertrophy (lower left → to generate the required higher contractile force → heart undergo **only hypertrophy** because cardiac muscles have a limited capacity to divide.

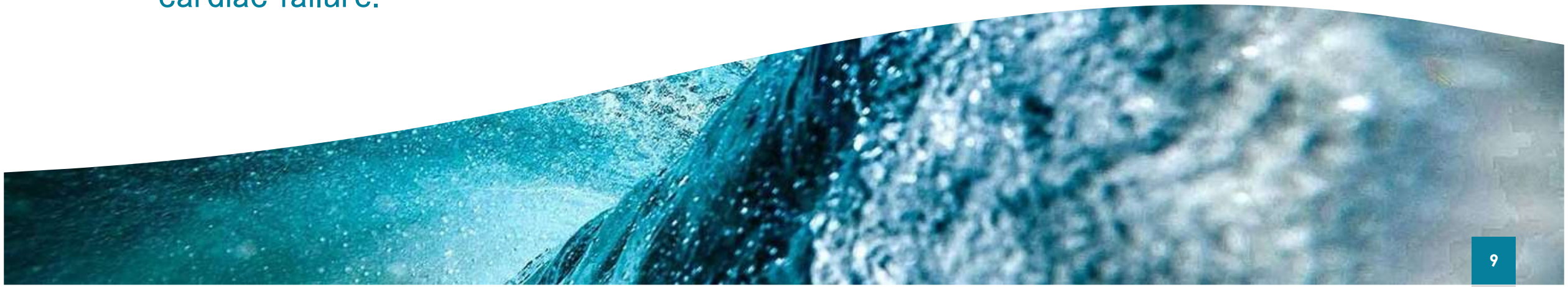
- **The mechanisms driving cardiac hypertrophy involve two types of signals:**

(1) mechanical triggers (e.g. stretch)
(2) soluble mediators that stimulate cell growth (growth factors & adrenergic hormones).

- stimuli →signal transduction pathways →the induction of a number of genes → stimulate synthesis of many cellular proteins (growth factors & structural proteins).
- The result is synthesis of more proteins & myofilaments per cell, which increases the force generated with each contraction, enabling the cell to meet increased work demands.
- Switch of contractile proteins from adult to fetal or neonatal forms. (α-myosin heavy chain is replaced by the fetal β-myosin heavy chain; which produces slower, more energetically economical contraction)

An important point..

- An adaptation to stress such as hypertrophy can progress to functionally significant cell injury if the stress is not relieved:
- A limit is reached beyond which the enlargement of muscle mass can no longer compensate for the increased burden.
- In the heart, several degenerative changes occur in the myocardial fibers, the most important are fragmentation & loss of myofibrillar contractile elements, ultimately cardiac failure.



2. Hyperplasia

- **Hyperplasia is an increase in the number of cells in an organ that stems from increased proliferation, either of differentiated cells or, in some instances, less differentiated progenitor cells.**
- Hyperplasia takes place if the tissue contains cell populations capable of replication.
- may occur concurrently with hypertrophy
- **Hyperplasia can be physiologic or pathologic; in both situations, cellular proliferation is stimulated by growth factors that are produced by a variety of cell types.**

The two types of physiologic hyperplasia are

(1) Hormonal hyperplasia: the proliferation of the glandular epithelium of the female breast at puberty & during pregnancy.

(2) Compensatory hyperplasia: residual tissue grows after damage or resection of part of an organ. (part of a liver is resected → mitotic activity in the remaining cells begins as early as 12 hours later, eventually restoring the liver to its normal size.

- The stimuli here is polypeptide growth factors produced by uninjured hepatocytes and other nonparenchymal cells in the live.
- After restoration of the liver mass, various growth inhibitors turn off cell proliferation.


Christian Griepenkerl (1839-1916): Die Strafe. Photo © Maicar Förlag - GML

Pathologic hyperplasia

- Caused by **excessive** hormonal or growth factor stimulation.
- E.g. **Normally**, after a normal menstrual period there is a burst of uterine epithelial proliferation (tightly regulated by the stimulatory effects of pituitary hormones and ovarian estrogen and the inhibitory effects of progesterone)

A **disturbance** in this balance → increased estrogenic stimulation → endometrial hyperplasia, (a common cause of abnormal menstrual bleeding).

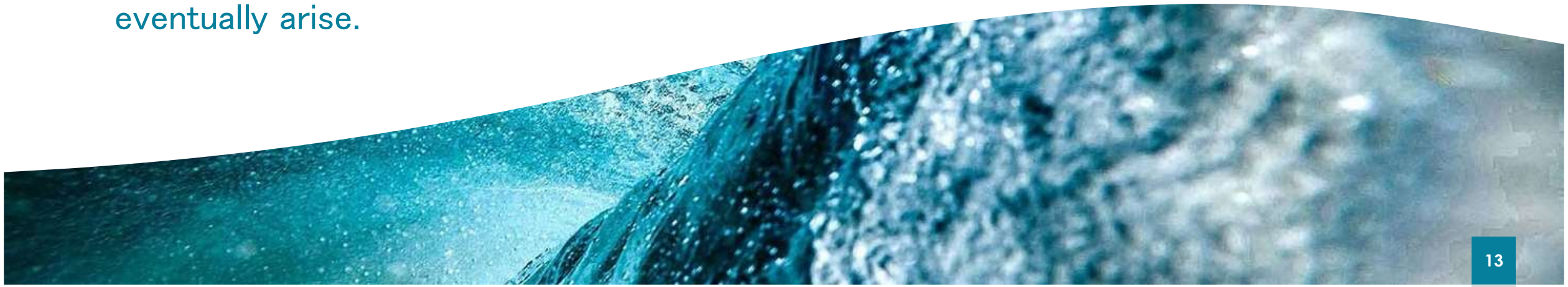
- Benign prostatic hyperplasia is (hormonal stimulation by androgens)
- Certain viral infections (papillomaviruses cause skin warts & mucosal lesions - masses of hyperplastic epithelium)

An important point

The hyperplastic process remains controlled; if the signals that initiate it abate, the hyperplasia disappears.

It is this responsiveness to normal regulatory control mechanisms that distinguishes pathologic hyperplasias from cancer (growth control mechanisms become permanently dysregulated or ineffective)

In many cases, pathologic hyperplasia constitutes a fertile soil in which cancers may eventually arise.



3. Atrophy

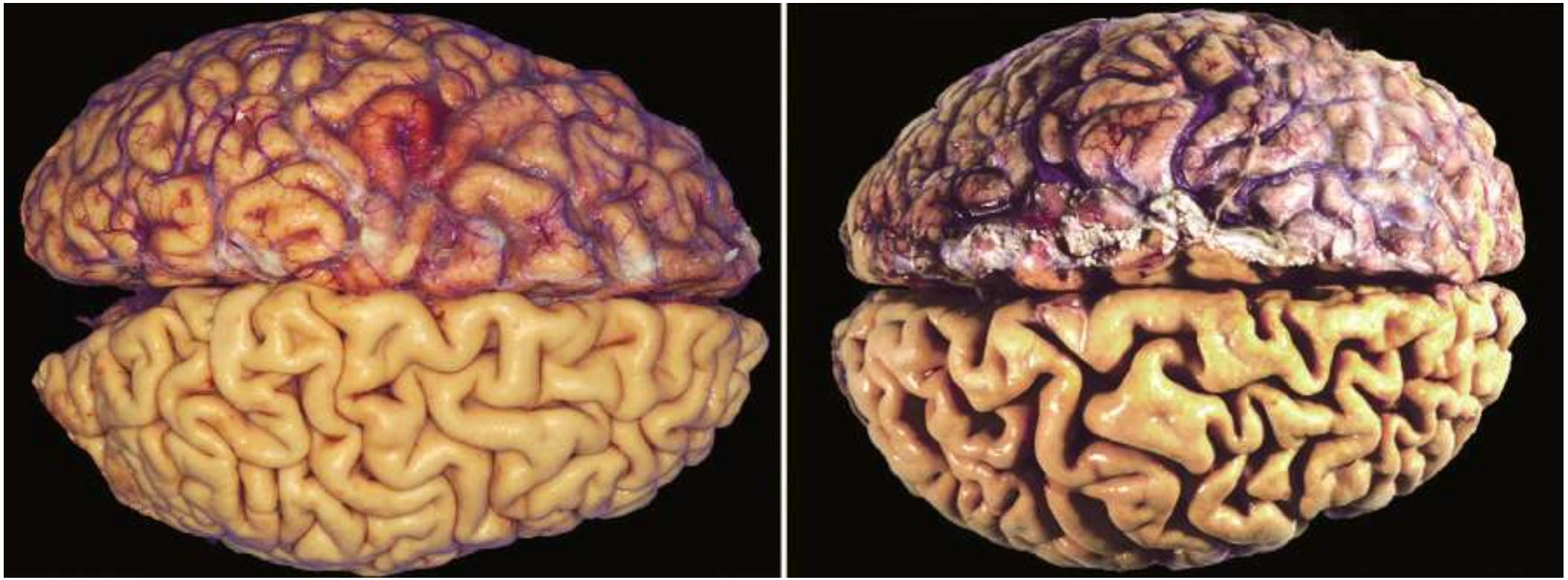
- **Atrophy is shrinkage in the size of cells by the loss of cell substance**, at **which survival is still possible**
- If a sufficient number of cells are involved, the entire tissue or organ is reduced in size (atrophic).
- Atrophic cells may have diminished function, **they are not dead.**
- Causes of atrophy include a decreased workload (immobilization of a limb to permit healing of a fracture),loss of innervation, diminished blood supply, inadequate nutrition, loss of endocrine stimulation, & aging (senile atrophy).
- Some of these stimuli are physiologic (the loss of hormone stimulation in menopause) & others are pathologic (denervation), but the fundamental cellular changes are similar.

- **The process of cellular atrophy results from a combination of:**

(1) decreased protein synthesis: reduced metabolic activity.

(2) increased protein degradation: occurs mainly by the ubiquitin-proteasome pathway:

- Nutrient deficiency and disuse may activate ubiquitin ligases, which attach multiple copies of the small peptide ubiquitin to cellular proteins and target them for degradation in proteasomes.
- In many situations, atrophy also is associated with autophagy.



Atrophy - pathologic - ↓ blood supply

82-year-old man with atherosclerotic disease. Atrophy of the brain is caused by aging & reduced blood supply. Note that loss of brain substance **narrows the gyri & widens the sulci.** The meninges have been stripped from the bottom half of each specimen to show the surface of the brain.

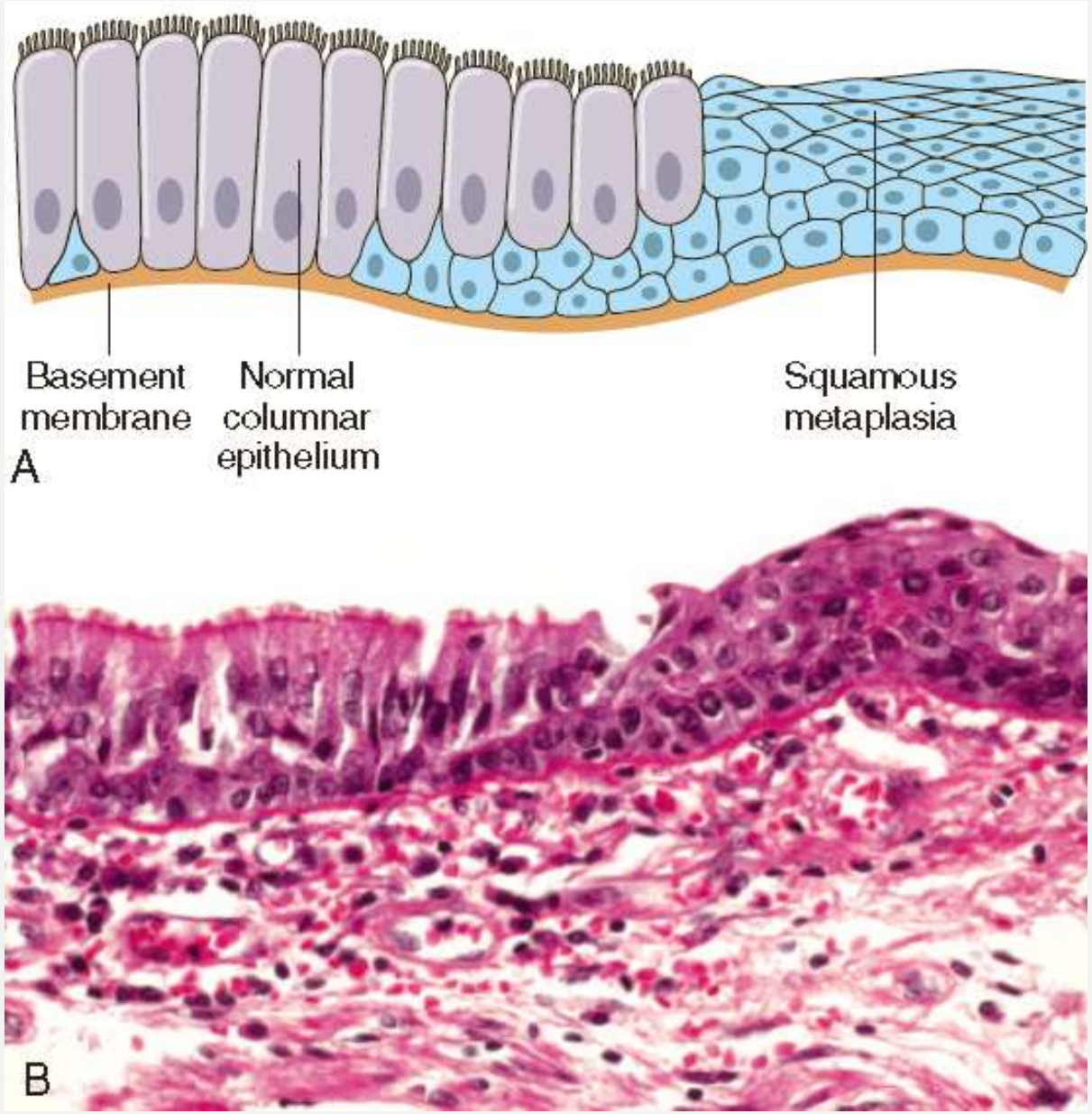
4. Metaplasia

- **In Metaplasia; one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type.**

- Here a cell type is sensitive to a particular stress is replaced by another cell type better able to withstand the adverse environment.

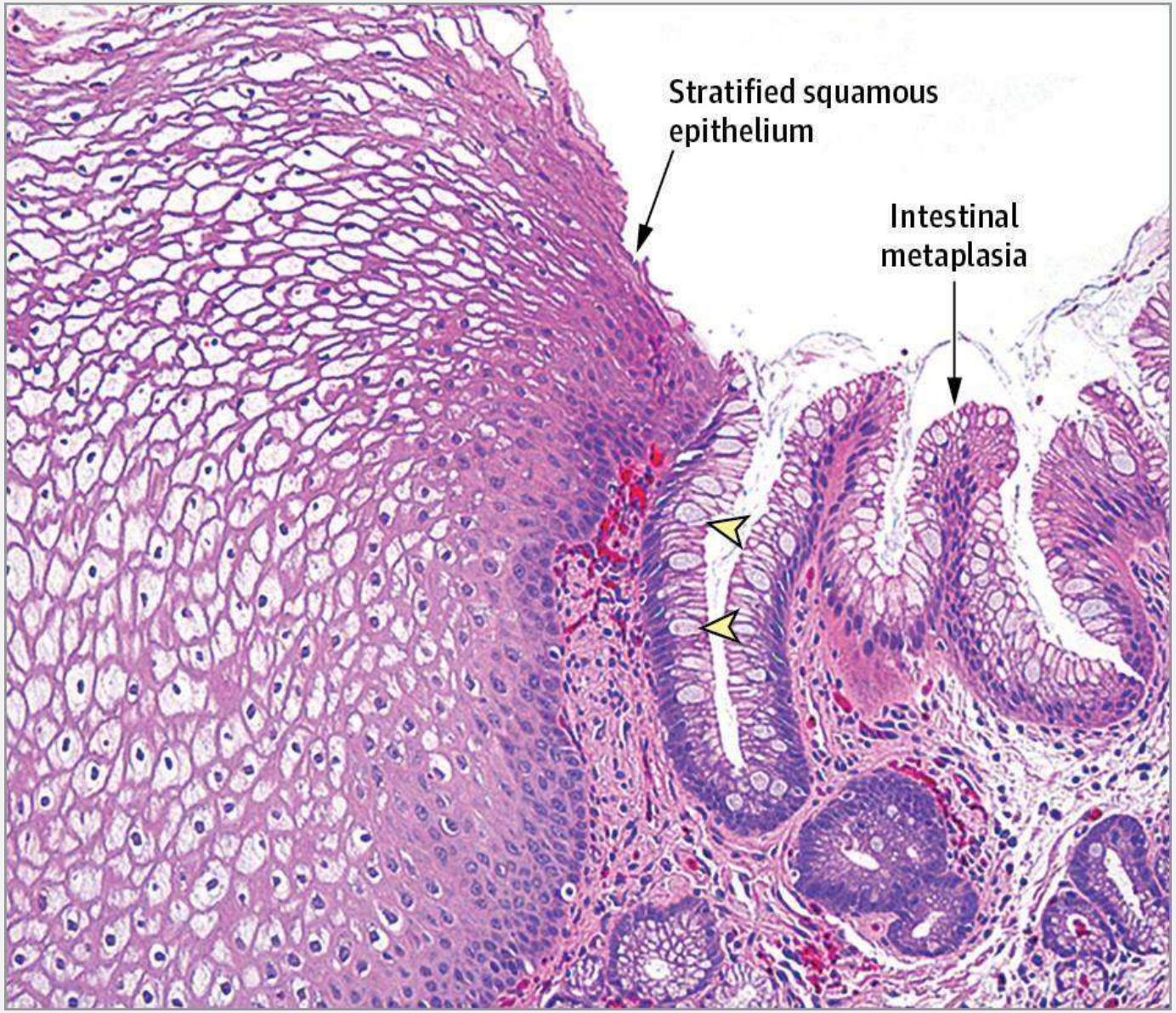
- It arise by the **reprogramming of stem cells** to differentiate along a new pathway & **not** by a phenotypic change (transdifferentiation) of already differentiated cells.

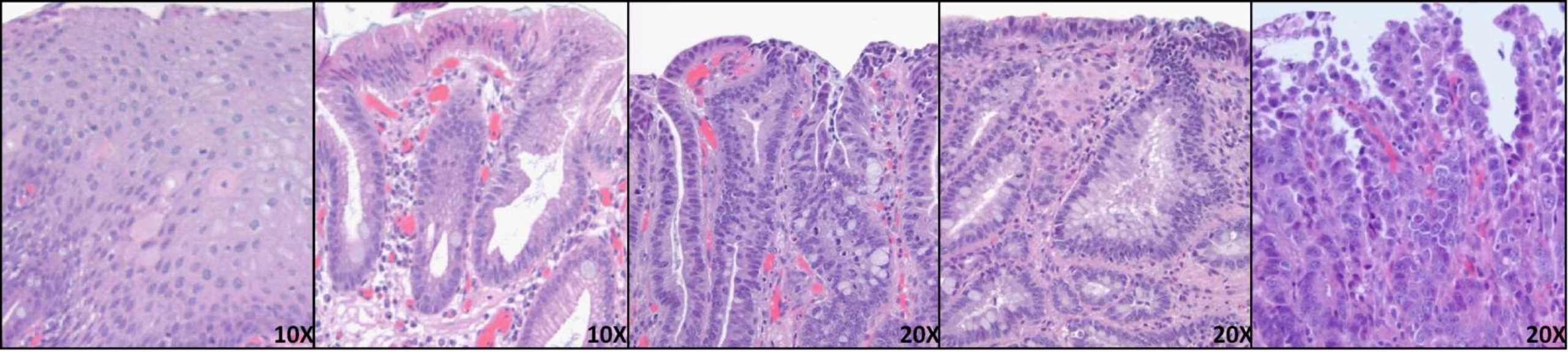
- In the respiratory epithelium of habitual cigarette smokers the normal ciliated columnar epithelial cells of the trachea and bronchi → metaplasia → stratified squamous epithelial cells.
- The rugged stratified squamous epithelium can survive the noxious chemicals in cigarette smoke that columnar epithelium would not tolerate.
- Metaplasia here has survival advantages, but important protective mechanisms are lost, such as mucus secretion and ciliary clearance.



- In chronic gastric reflux; the normal stratified squamous epithelium of the lower esophagus → metaplasia→ gastric or intestinal-type columnar epithelium.

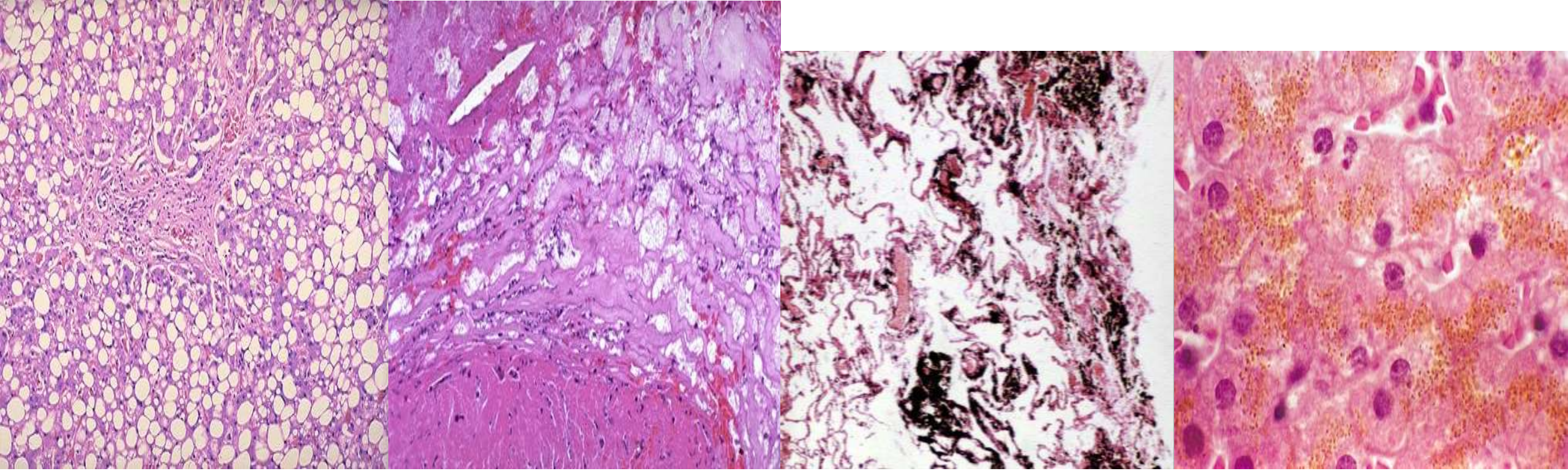
- Metaplasia also occur in mesenchymal cells, where it is generally a reaction to some pathologic alteration (bone is occasionally formed in soft tissues, particularly in foci of injury.





Squamous | Metaplasia | LGD | HGD | ACA

- **The influences that induce metaplastic change in an epithelium, <u>if persistent</u>, may predispose to malignant transformation.**
- Squamous cell metaplasia of the respiratory epithelium often coexists with lung cancers composed of malignant squamous cells.
- And columnar epithelium in the esophagus can coexist also with esophageal cancer of adenocarcinoma type.



Intracellular Accumulations

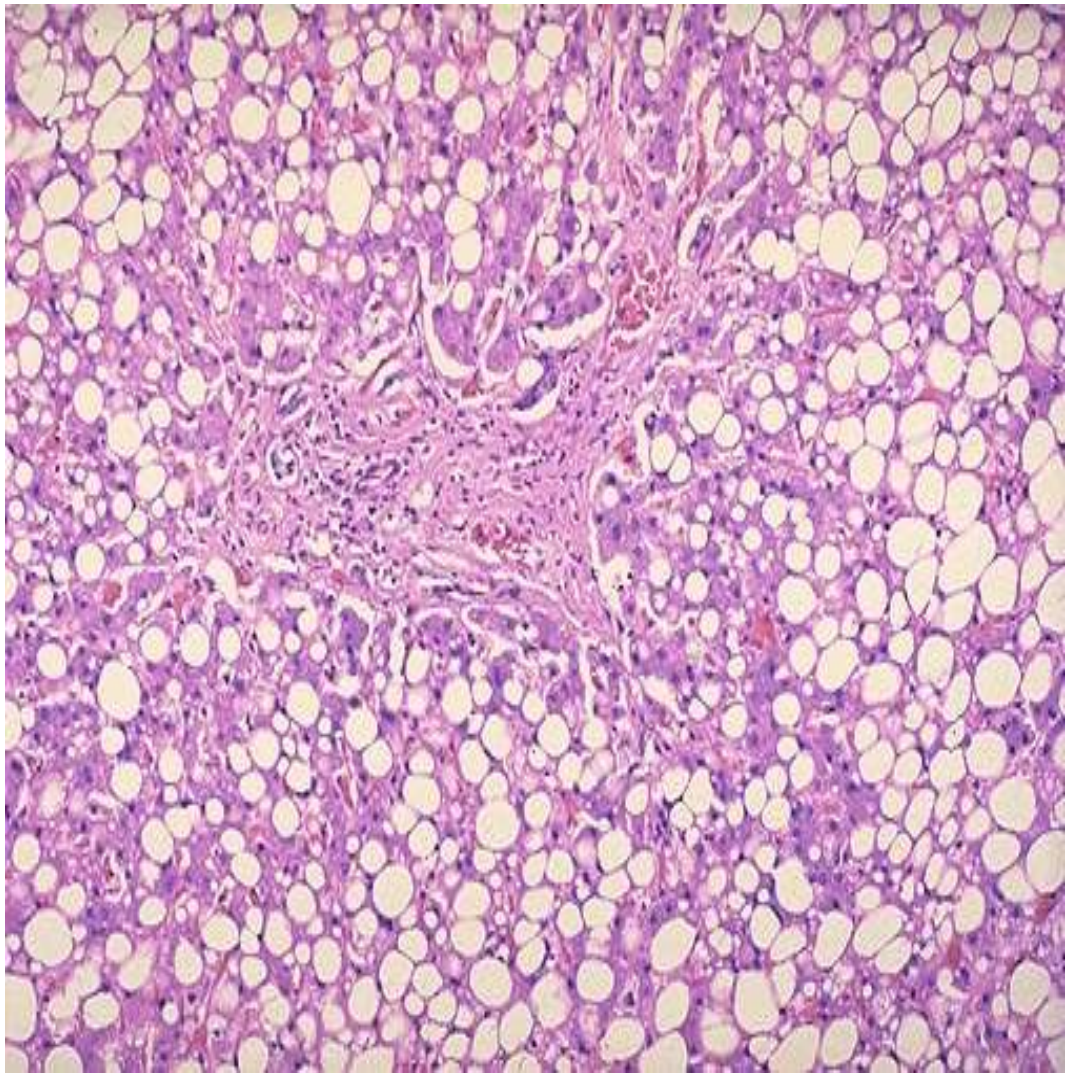
Intracellular accumulations

- Cells may accumulate abnormal amounts of various substances under some circumstances, **can be harmless or cause varying degrees of injury**.
- The substance may be located in the **cytoplasm**, within **organelles** (lysosomes), or in the **nucleus**.
- Synthesized by the affected cells or it may be produced elsewhere.
- The main pathways of abnormal intracellular accumulations are

(1) inadequate removal and degradation.
(2) excessive production of an endogenous substance.
(3) deposition of an abnormal exogenous material.

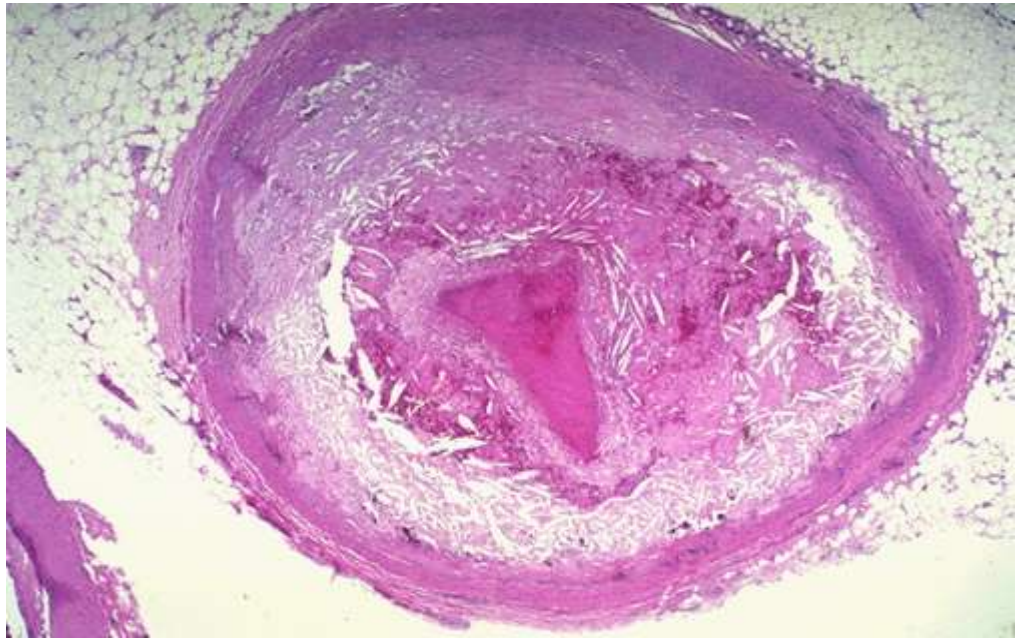
Fatty Change

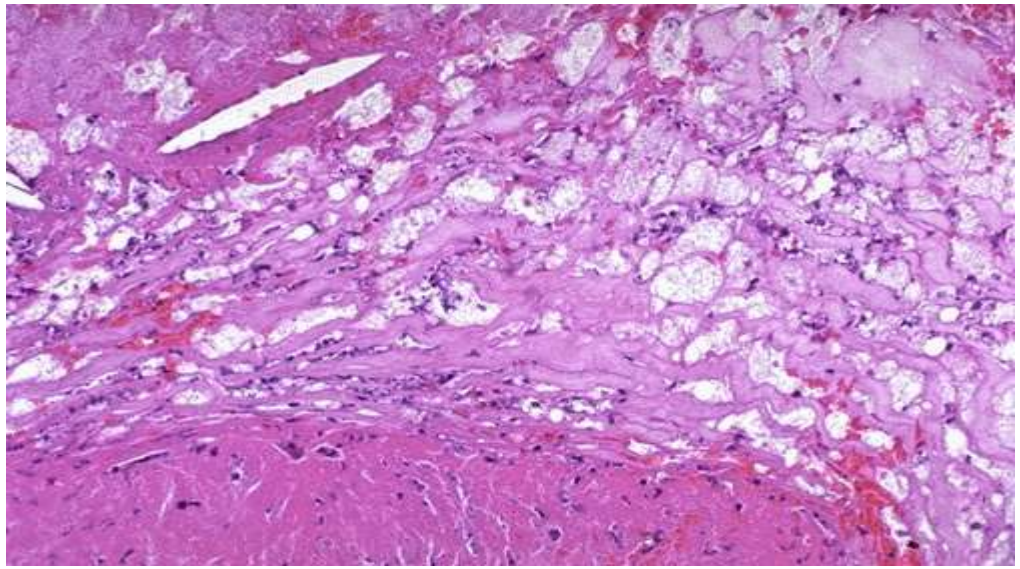
- Fatty change, called steatosis.
- Any accumulation of triglycerides within parenchymal cells.
- Mostly seen in the **liver**, (the major organ involved in fat metabolism) , also occur in heart, skeletal muscle, kidney, and other organs.
- Caused by toxins, protein malnutrition, diabetes mellitus, obesity, or anoxia.
- Alcohol abuse and diabetes associated with obesity are the most common causes of fatty change in the liver.



Cholesterol and Cholesteryl Esters

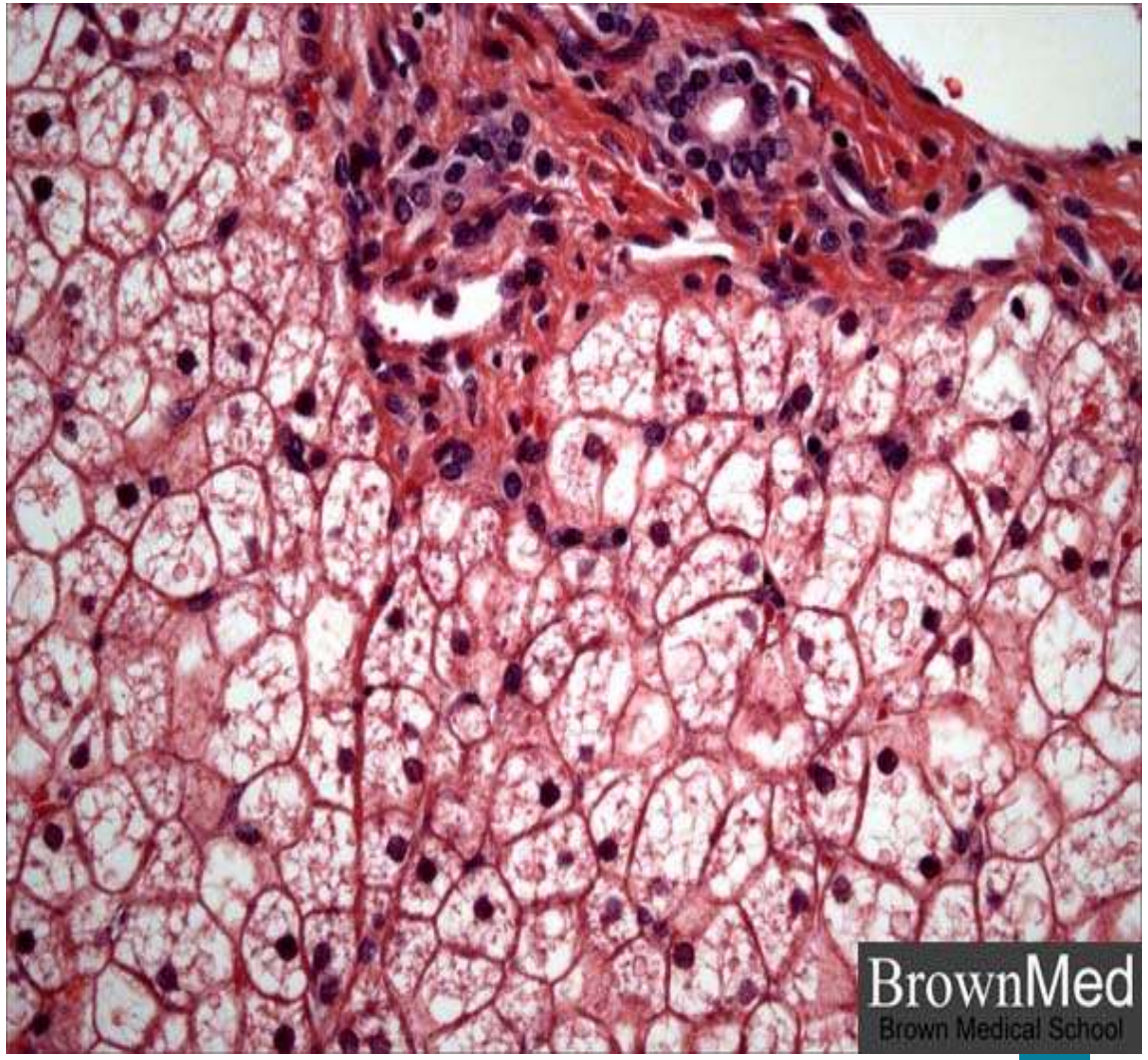
- Cellular cholesterol metabolism is tightly regulated to ensure normal generation of cell membranes (in which cholesterol is a key component) without accumulation.
- Phagocytic cells may become overloaded in different pathologic processes, mostly **increased intake** or decreased catabolism of lipids.
- **Atherosclerosis** is the most important.





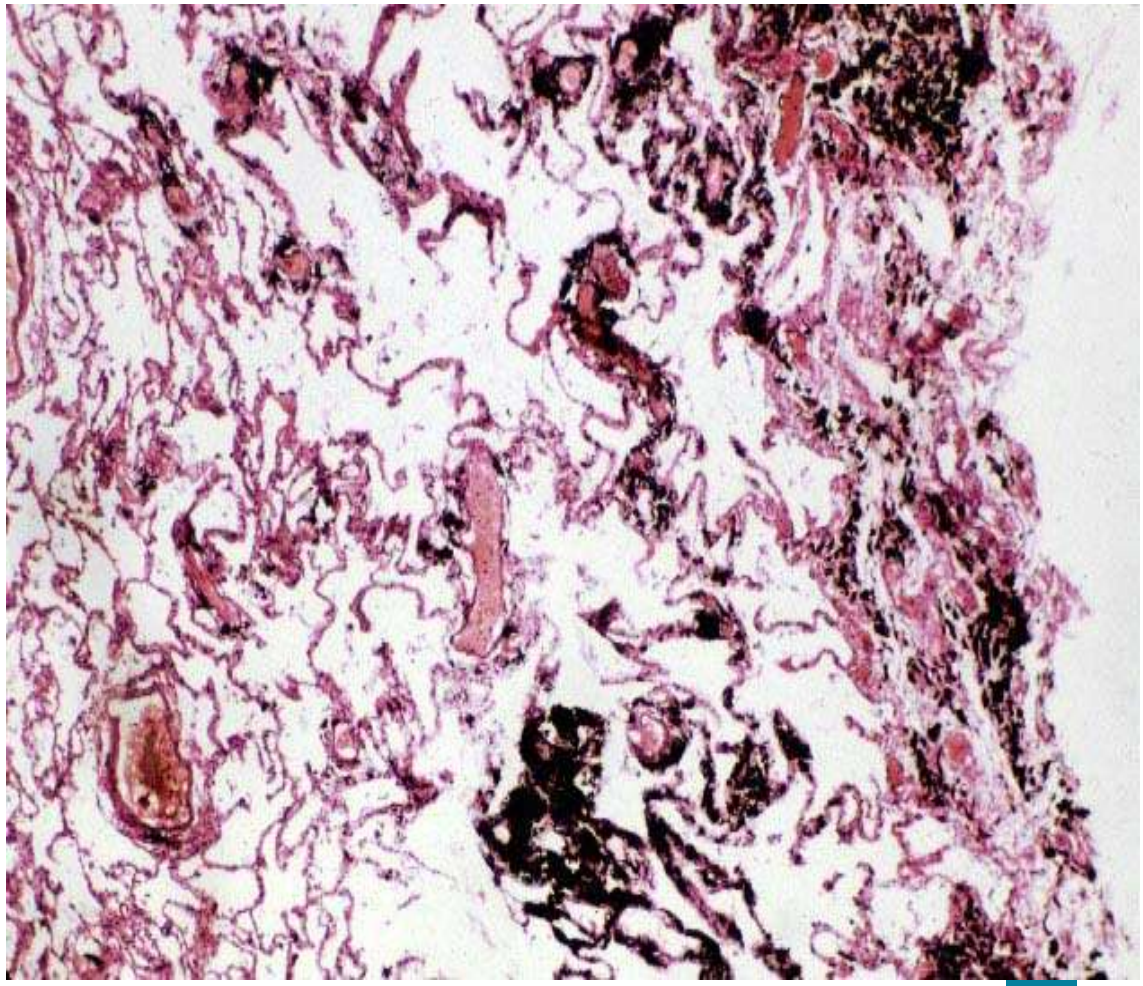
Glycogen.

- Excessive intracellular accumulation of glycogen are associated with abnormalities in the metabolism of glucose or glycogen.
- In poorly controlled diabetes mellitus, the prime example of abnormal glucose metabolism, glycogen accumulates in renal tubular epithelium, cardiac myocytes, and β cells of the islets of Langerhans.
- Glycogen also accumulates within cells in a group of related genetic disorders collectively referred to as **glycogen storage diseases**.



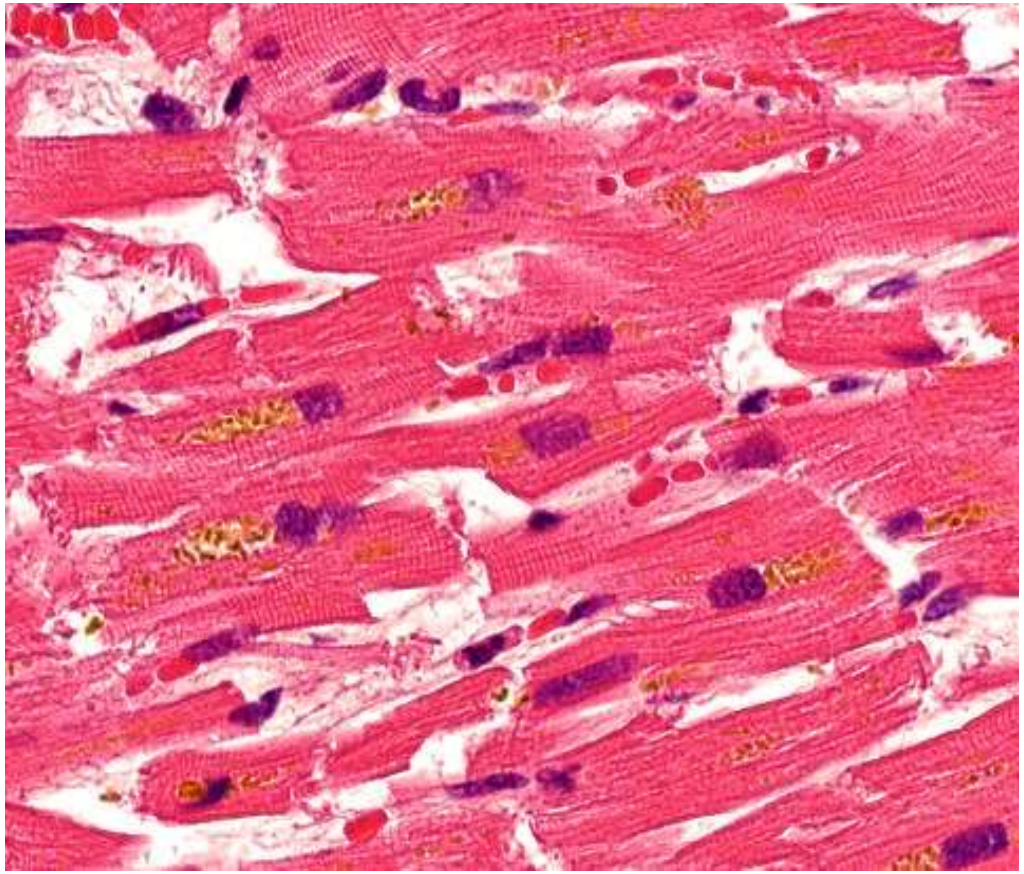
Pigments – Carbon

- Pigments are colored substances :
- + exogenous (from outside the body) such as carbon,
- + endogenous (synthesized within the body) itself, such as lipofuscin, melanin, and certain derivatives of hemoglobin.
- The most common exogenous pigment is **carbon**, a ubiquitous air pollutant of urban life.
- When inhaled → phagocytosed by alveolar macrophages → transported by lymphatic channels to regional lymph nodes.
- Aggregates of the pigment blacken the draining lymph nodes and pulmonary parenchyma (called **anthracosis**)



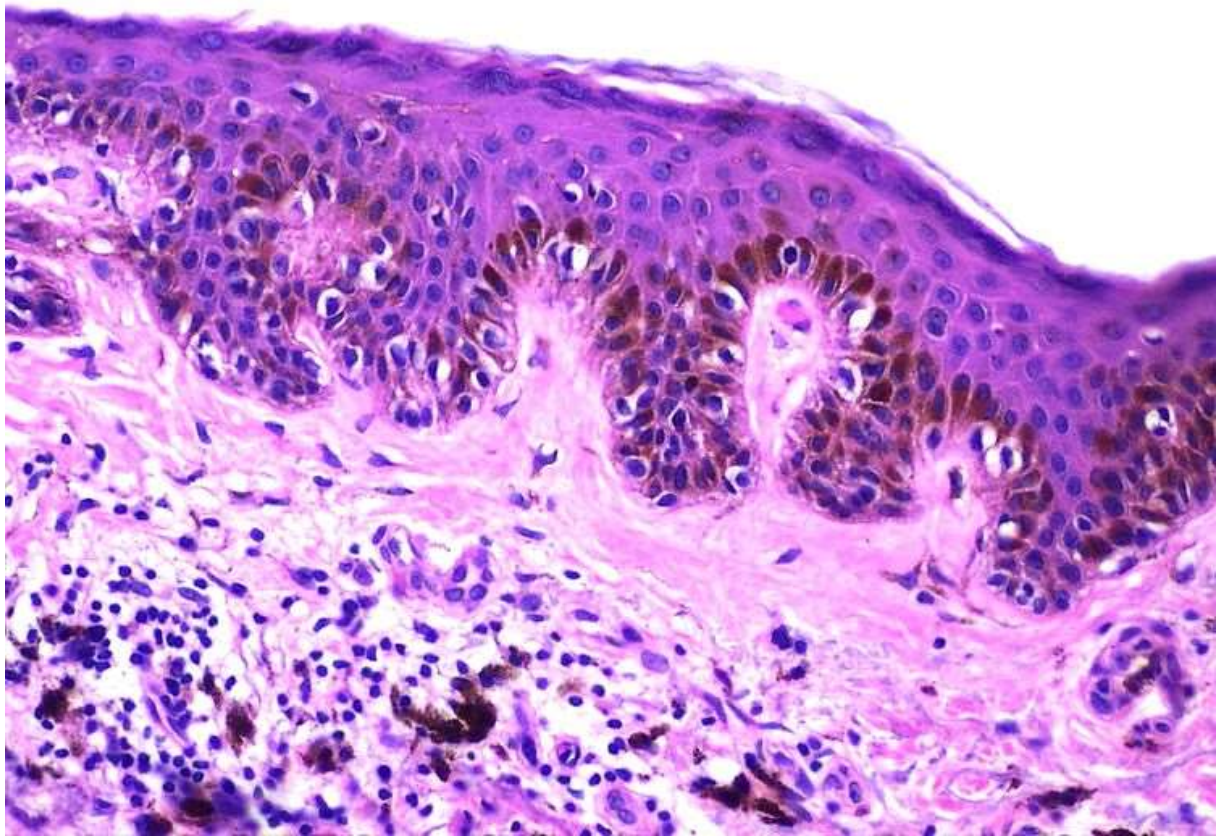
Pigments-Lipofuscin "wear-and-tear pigment"

- An insoluble **brownish-yellow granular** intracellular material that accumulates in a variety of tissues (heart, liver, and brain) with **aging or atrophy**.
- Lipofuscin represents complexes of lipid & protein that are produced by the free radical–catalyzed peroxidation of polyunsaturated lipids of subcellular membranes.
- It is not injurious to the cell but is a marker of past free radical injury.
- When present in large amounts, imparts an appearance to the tissue that is called **brown atrophy.**



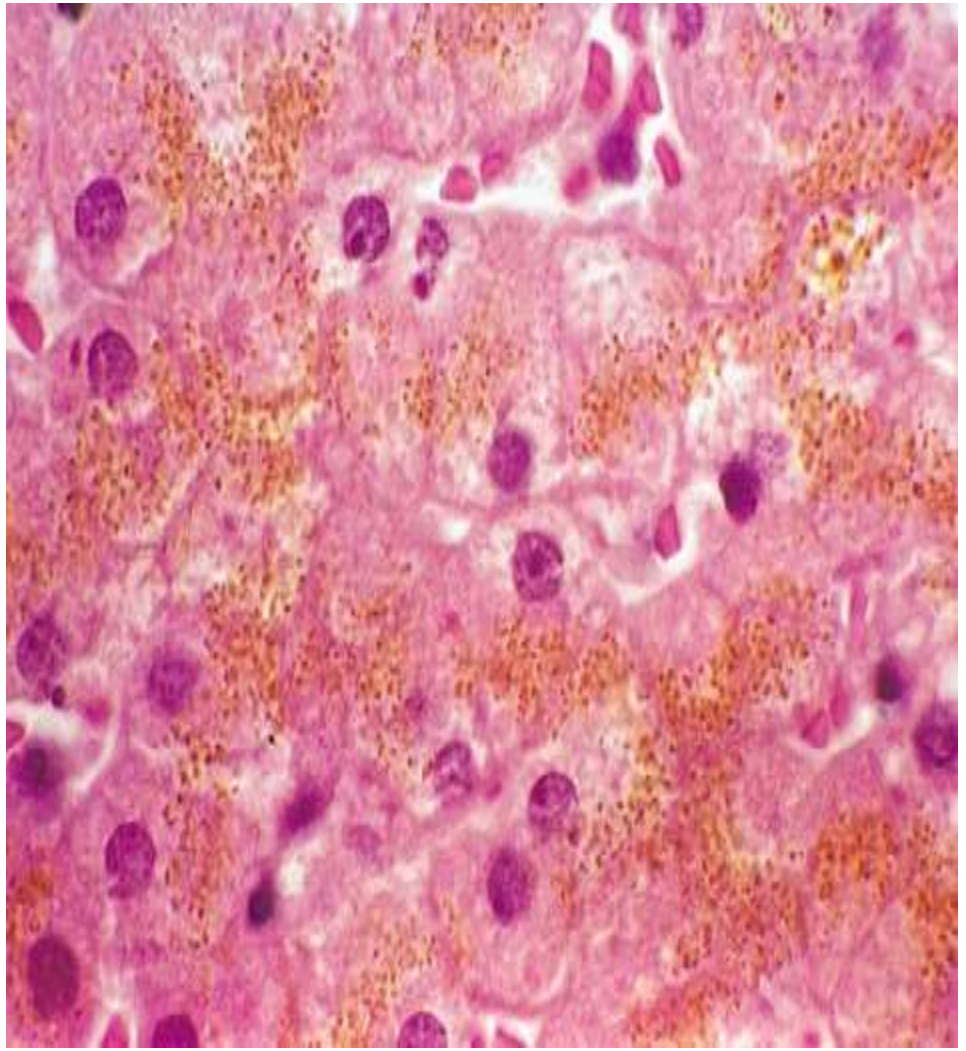
Pigments - Melanin.

- An endogenous, brown-black pigment that is synthesized by **melanocytes** located in the epidermis.
- Acts as a screen against harmful UV radiation.
- Although melanocytes are the only source of melanin, adjacent basal keratinocytes in the skin can accumulate the pigment (e.g., in freckles), as can dermal macrophages.



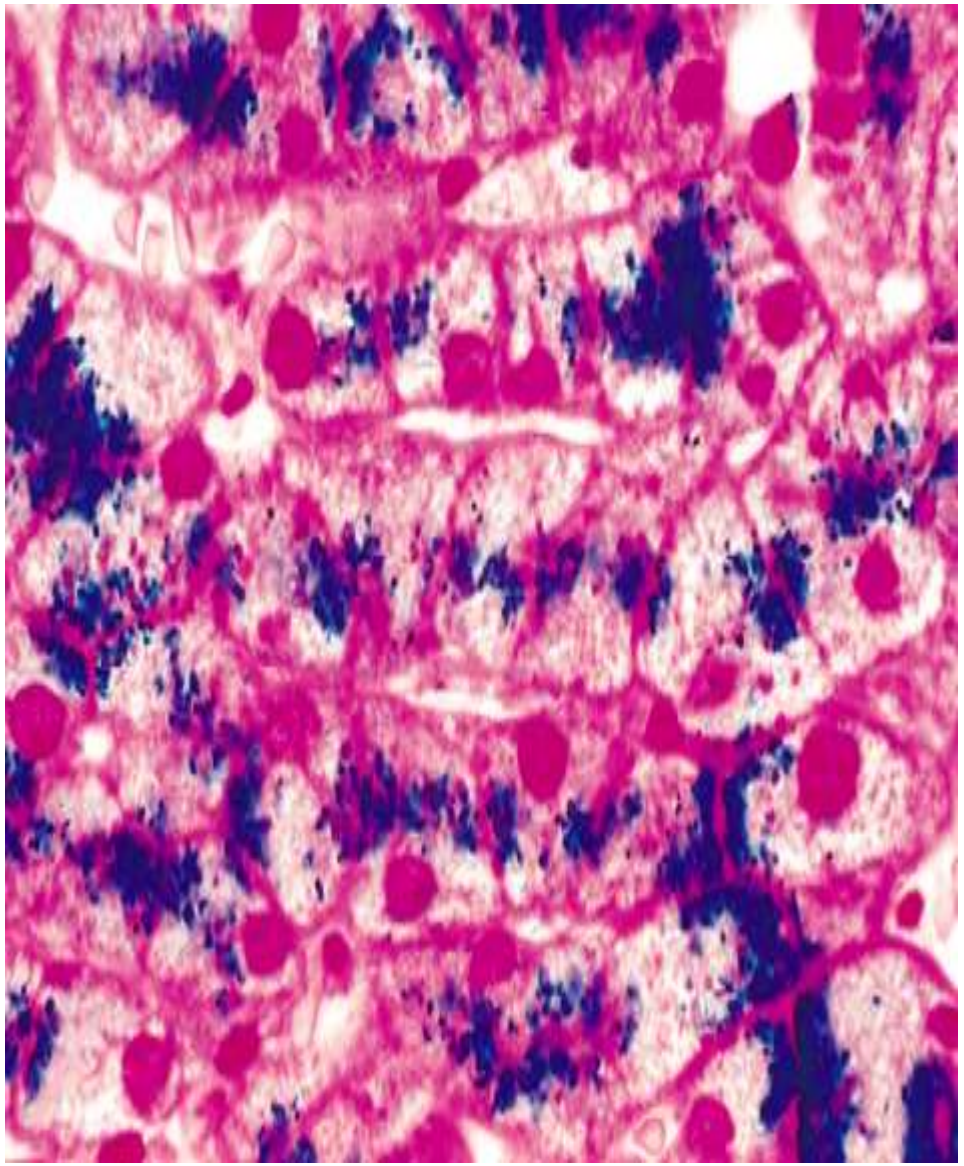
Pigments - Hemosiderin.

- A hemoglobin-derived granular pigment that is **golden yellow to brown.**
- Accumulates in tissues when there is a local or systemic excess of iron.
- Iron is normally stored within cells in association with the protein **apoferritin**, forming ferritin **micelles**.
- Hemosiderin pigment represents large aggregates of these ferritin micelles, readily visualized by light and electron microscopy.



… Pigments - Hemosiderin.

- the iron can be unambiguously identified by the Prussian blue histochemical reaction
- Small amounts of this pigment are normal in the mononuclear phagocytes of the bone marrow, spleen, and liver, where aging red cells are normally degraded.
- Excessive deposition of hemosiderin, called hemosiderosis.
- more extensive accumulations of iron seen in hereditary hemochromatosis



THANK YOU & GOOD LUCK ☺