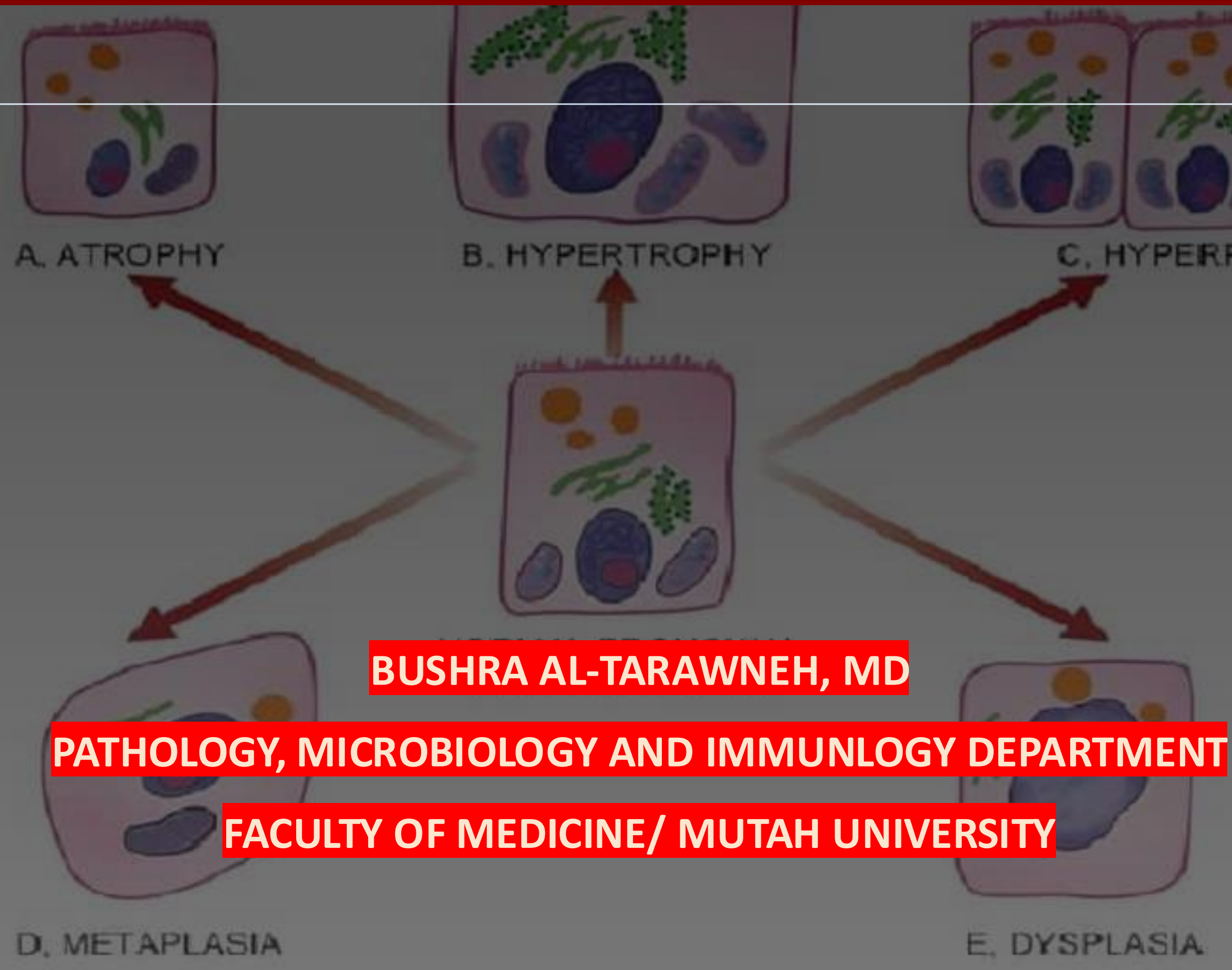
CELLULAR ADAPTATIONS TO STRESS



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Adaptations

- Adaptations are reversible changes in the number, size, phenotype, metabolic activity, or functions of cells in response to changes in their environment.
- **Physiologic adaptations** include the responses of cells to normal stimulation by hormones or endogenous chemical mediators, or to the demands of mechanical stress (in the case of bones and muscles).
- **Pathologic adaptations** are responses to stress that allow cells to modulate their structure and function and thus escape injury, but at the expense of normal function.

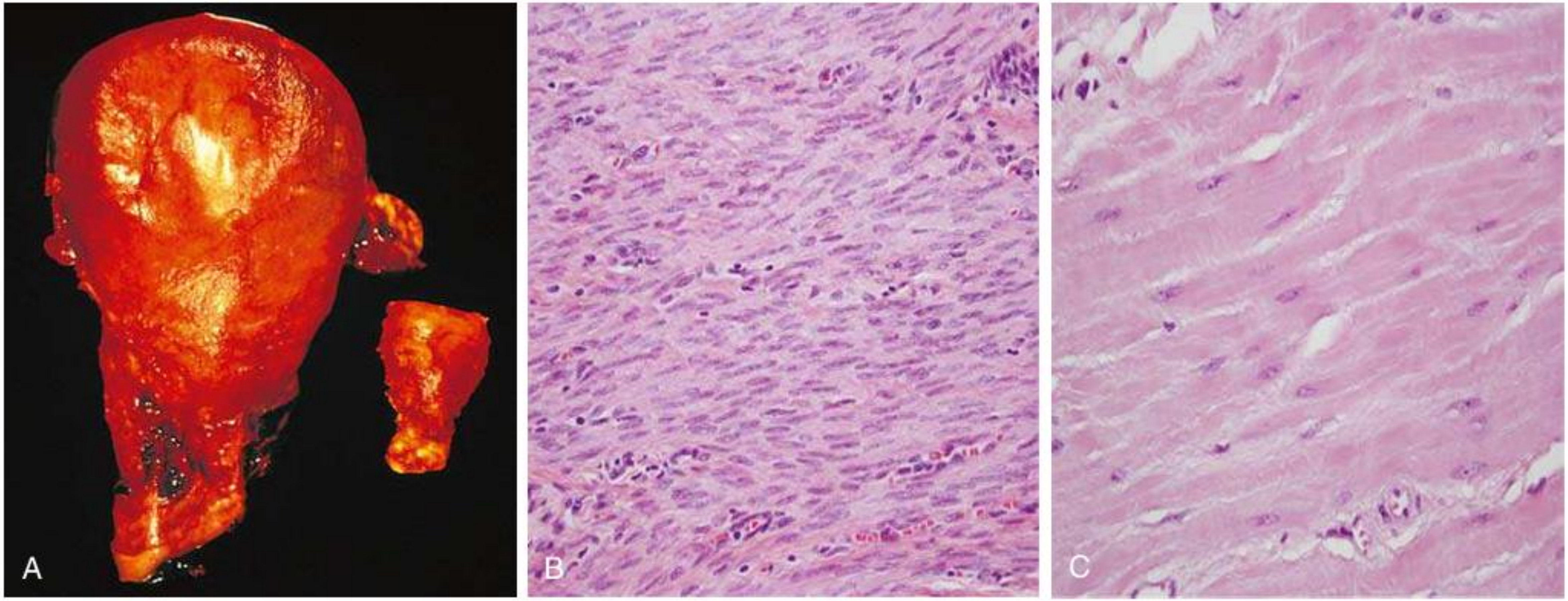
1-Hypertrophy

- Hypertrophy refers to an enlargement of cells that results in increase in the size of the organ. By contrast, **hyperplasia** (discussed next) is an increase in cell number.
- In pure hypertrophy, there are no new cells, just larger cells containing increased amounts of structural proteins and organelles. Pure hypertrophy is largely confined to cell types with a limited capacity to divide.
- In other tissues, hypertrophy and hyperplasia may occur together and combine to produce an enlarged (hypertrophic) organ.

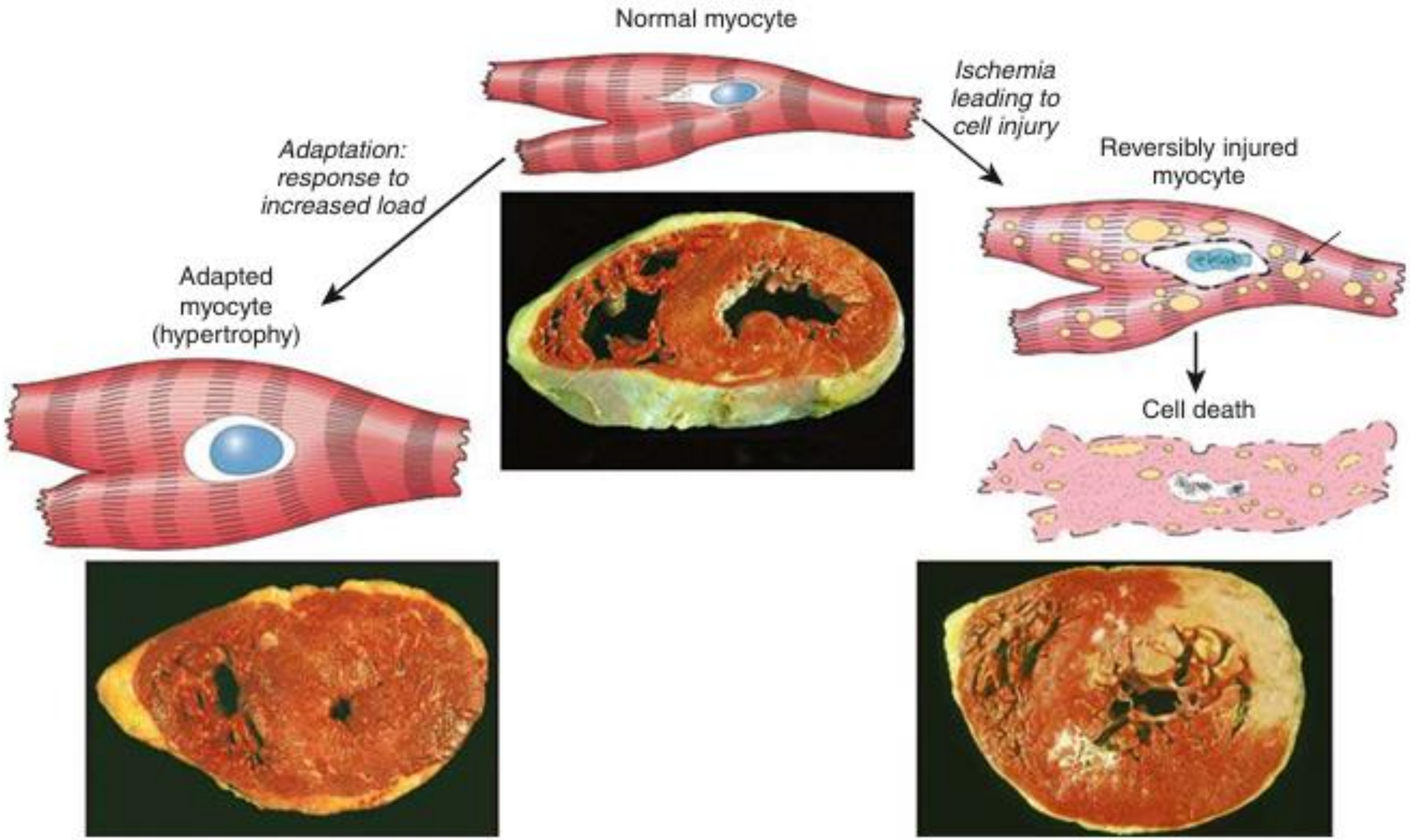
Hypertrophy can be physiologic or pathologic and is caused either by increased functional demand or by growth factor or hormonal stimulation.

- Physiologic enlargement of the uterus during pregnancy occurs as a consequence of estrogen-stimulated smooth muscle hypertrophy and hyperplasia.

By contrast, in response to increased workload the striated muscle cells in both the skeletal muscle and the heart undergo only hypertrophy, as these cell types have a limited capacity to divide.



Physiologic hypertrophy of the uterus during pregnancy. (A) Gross appearance of a nongravid uterus *(right)* and a gravid uterus *(left)* that was removed for postpartum bleeding. (B) Small spindle-shaped uterine smooth muscle cells from a nongravid uterus. (C) Large, plump hypertrophied smooth muscle cells from a gravid uterus; compare with B. (B and C, Same magnification.)



Pathologic hypertrophy of the heart occurs with hypertension and other disorders that increase intracardiac pressures, such as narrowing of the aortic valve (stenosis). In these situations, myocardial cells are subjected to a persistently increased workload and adapt by enlarging to generate the required higher contractile force.

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, progenitor cells.

As discussed earlier, hyperplasia happens if the tissue contains cell populations capable of replication; it may occur concurrently with hypertrophy and often in response to the same stimuli.

Hyperplasia can be physiologic or pathologic; in both situations, cellular proliferation is stimulated by hormones or growth factors.

Physiologic Hyperplasia

- The two types of physiologic hyperplasia are

(1) Hormonal hyperplasia, exemplified by the proliferation of the glandular epithelium of the female breast at puberty and during pregnancy.

(2) Compensatory hyperplasia, in which residual tissue grows after removal or loss of part of an organ.

For example, when part of a liver is resected, mitotic activity in the remaining hepatocytes be gins as early as 12 hours later, eventually restoring the liver to its normal weight. The stimuli for hyperplasia in this setting are polypeptide growth factors produced by uninjured hepatocytes as well as nonparenchymal cells in the liver After the liver returns to its normal size, cell proliferation is turned off by various growth inhibitors.

Pathologic hyperplasia

- Hormonal imbalances can lead to pathologic hyperplasia.

For example, after a menstrual period there is a burst of uterine epithelial proliferation that is normally tightly regulated by the stimulatory effects of pituitary hormones and ovarian estrogen and the inhibitory effects of progesterone. A disturbance in this balance leading to increased estrogenic stimulation causes endometrial hyperplasia, a common cause of abnormal menstrual bleeding.

Benign prostatic hyperplasia is another common example of pathologic hyperplasia induced by responses to hormonal stimulation, in this case by androgens and estrogens.

An important point is that in all these situations, the hyperplastic process remains controlled; if the signals that initiate it abate, the hyperplasia ceases.

It is this responsiveness to normal regulatory control mechanisms that distinguishes pathologic hyperplasia from cancer, in which growth control mechanisms become permanently dysregulatedor ineffective.

Nevertheless, in many cases, pathologic hyperplasia constitutes a fertile soil in which cancers may eventually arise. For example, patients with hyperplasia of the endometrium are at increased risk of developing endometrial cancer.

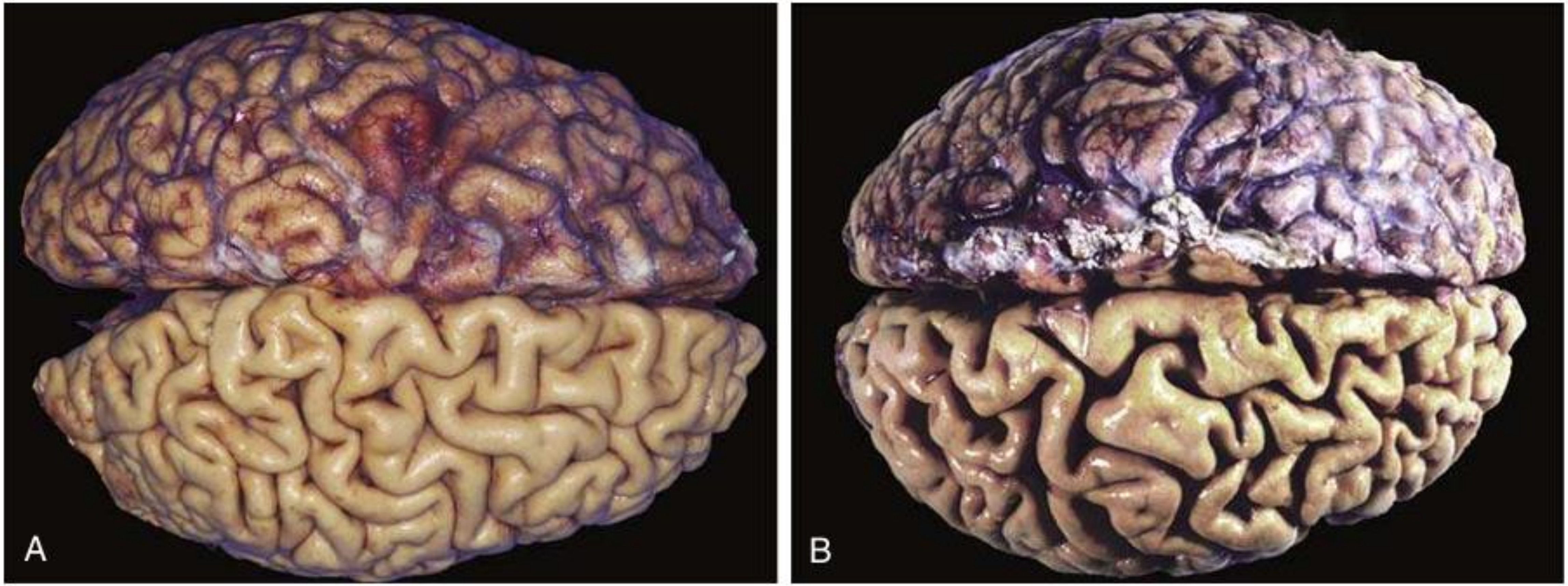
3- Atrophy

- **Atrophy is reduced size of an organ or tissue caused by reduction in the size and number of cells.**
- **Causes of atrophy include:**
  - **Decreased workload (e.g., 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).**

Although some of these causes are a physiologic part of life (e.g., the loss of hormone stimulation in menopause) and others are pathologic (e.g., denervation), the fundamental cellular changes are similar.

Atrophy results from a combination of decreased protein synthesis and increased protein degradation

- Protein synthesis decreases because of reduced metabolic activity.
- The degradation of cellular proteins 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 the proteasome.
- Atrophy is also accompanied by increased autophagy, with resulting increases in the number of autophagic vacuoles.

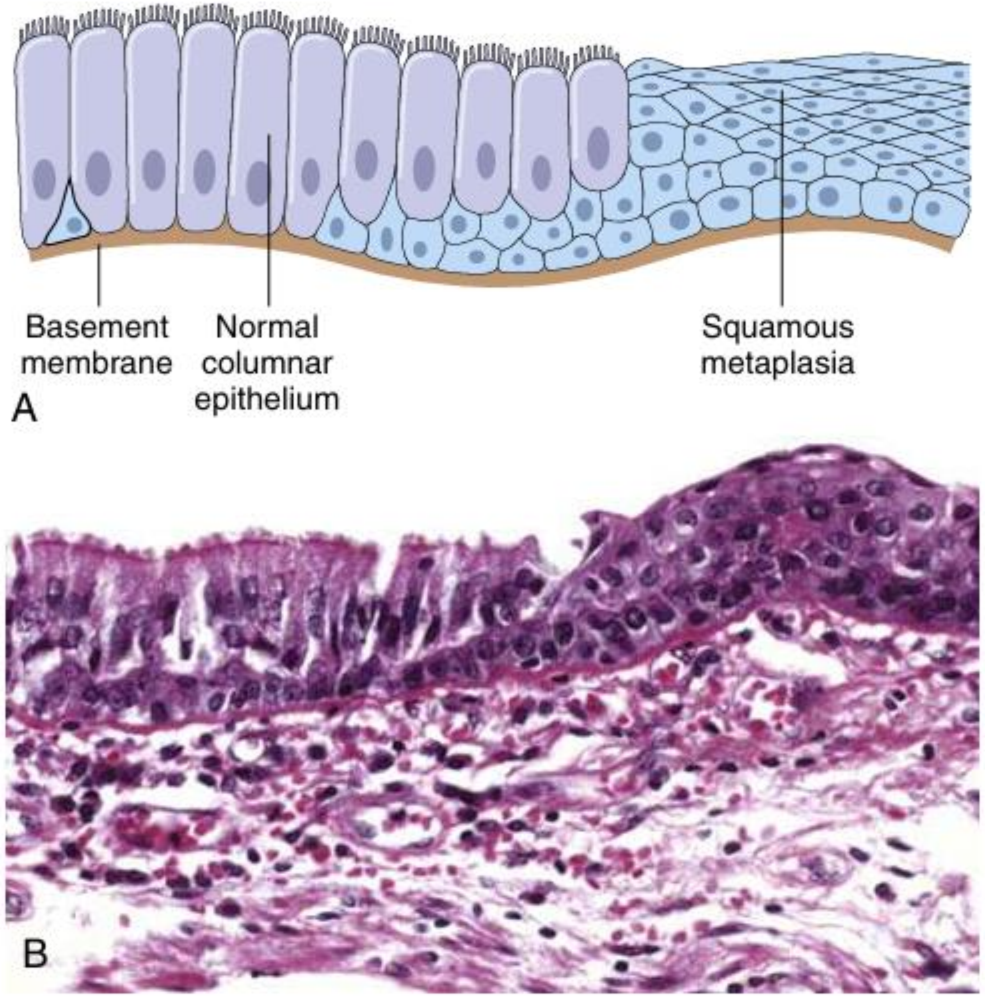


Atrophy of the brain. (A) Normal brain of a young adult. (B) Atrophy of the brain in an 81-year-old man with atherosclerotic cerebrovascular disease. Atrophy of the brain is due to aging and reduced blood supply. Note that loss of brain substance narrows the gyri and widens the sulci. The meninges have been stripped from the bottom half of each specimen to reveal the surface of the brain.

4- Metaplasia

- Metaplasia is a change in which one adult cell type is replaced by another adult cell type.
- In this type of cellular adaptation, a cell type sensitive to a particular stress is replaced by another cell type better able to withstand the adverse environment.
- Metaplasia is thought to usually arise by reprogramming of stem cells to differentiate along a new pathway rather than a phenotypic change of differentiated cells (transdifferentiation).
- e.g., in chronic gastric reflux, the normal stratified squamous epithelium of the lower esophagus may undergo metaplastic transformation to gastric or intestinal-type columnar epithelium.

Epithelial metaplasia is exemplified by the change in the respiratory epithelium that occurs with prolonged cigarette smoking. In this process, the normal, relatively delicate ciliated columnar epithelial cells of the trachea and bronchi are replaced by tough stratified squamous epithelial cells, which are better suited to withstand the noxious chemicals in cigarette smoke.



Metaplasia of normal columnar *(left)* to squamous epithelium *(right)* in a bronchus, shown schematically (A) and histologically (B).

PROGRESS

The influences that induce metaplastic change, if persistent, predispose to malignant transformation of the epithelium.

Many such examples exist. For example, the squamous metaplasia of the respiratory epithelium is a rich soil for the development of lung cancers composed of malignant squamous cells. Similarly, intestinal metaplasia of the stomach is associated with the development of gastric cancer.

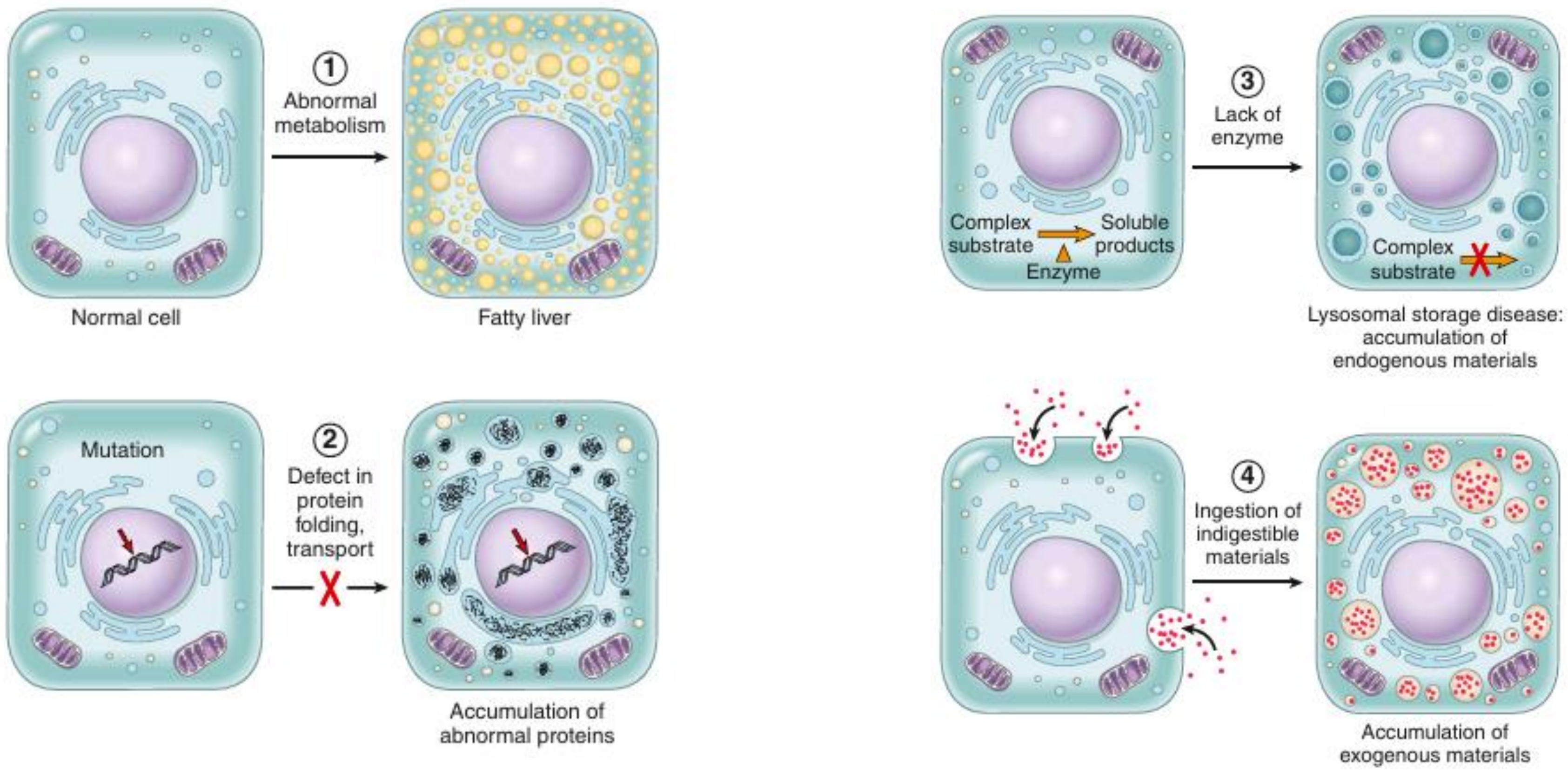
INTRACELLULAR AND EXTRACELLULAR DEPOSITIONS

INTRACELLULAR DEPOSITIONS

The main mechanisms of abnormal intracellular accumulations are inadequate removal and degradation or excessive production of an endogenous substance, or deposition of an abnormal exogenous material.

- **Fatty Change (Steatosis):** refers to an abnormal accumulation of triglycerides within parenchymal cells.
- **Cholesterol and Cholesteryl Esters:** Cellular cholesterol metabolism is tightly regulated to ensure normal synthesis of cell membranes without significant intracellular accumulation. However, phagocytic cells may be come overloaded with lipids (triglycerides, cholesterol, and cholesteryl esters) in several pathologic processes characterized by increased intake or decreased catabolism of lipids. (atherosclerosis)
- **Proteins.** Morphologically, visible protein accumulations are less common than lipid accumulations; they may occur because of increased uptake or increased synthesis.
- **Glycogen**. Intracellular deposits of glycogen are associated with abnormalities in the metabolism of either glucose or glycogen. In poorly controlled diabetes, and a group of genetic disorders collectively called glycogen storage diseases.

Mechanisms of intracellular accumulations.



Pigments are colored substances that maybe exogenous, coming from outside the body, or endogenous, synthesized within the body.

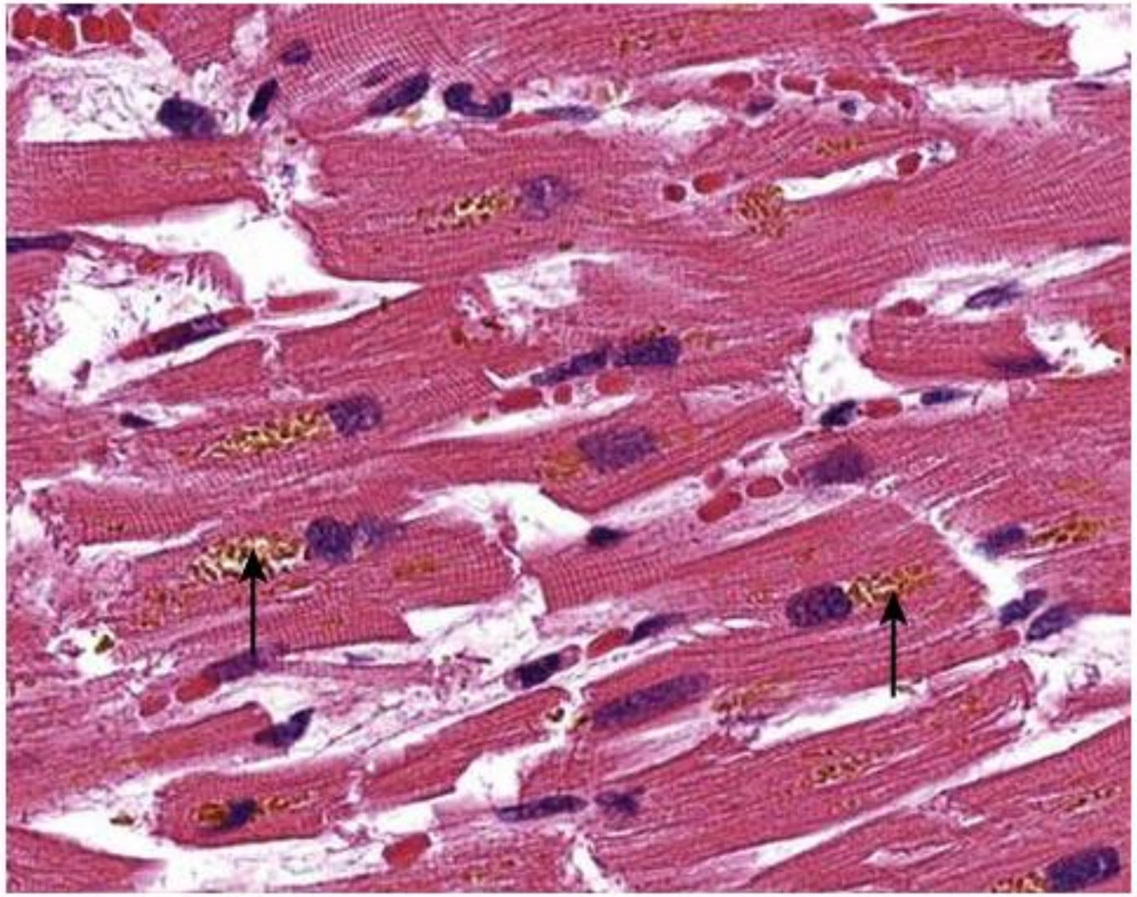
- **Carbon**, the most common exogenous pigment, is aubiquitous urban air pollutant. When inhaled, it is phagocytosed by alveolar macrophages and transported through lymphatic channels to the regional tracheobronchial lymph nodes. Aggregates of the pigment blacken the draining lymph nodes and pulmonary parenchyma (anthracosis))

- **Lipofuscin**,or“wear-and-tear pigment,” is an insoluble brownish yellow granular intracellular material that accumulates in a variety of tissues(particularly the heart, liver, and brain)as a function of age or atrophy. (brown atrophy)

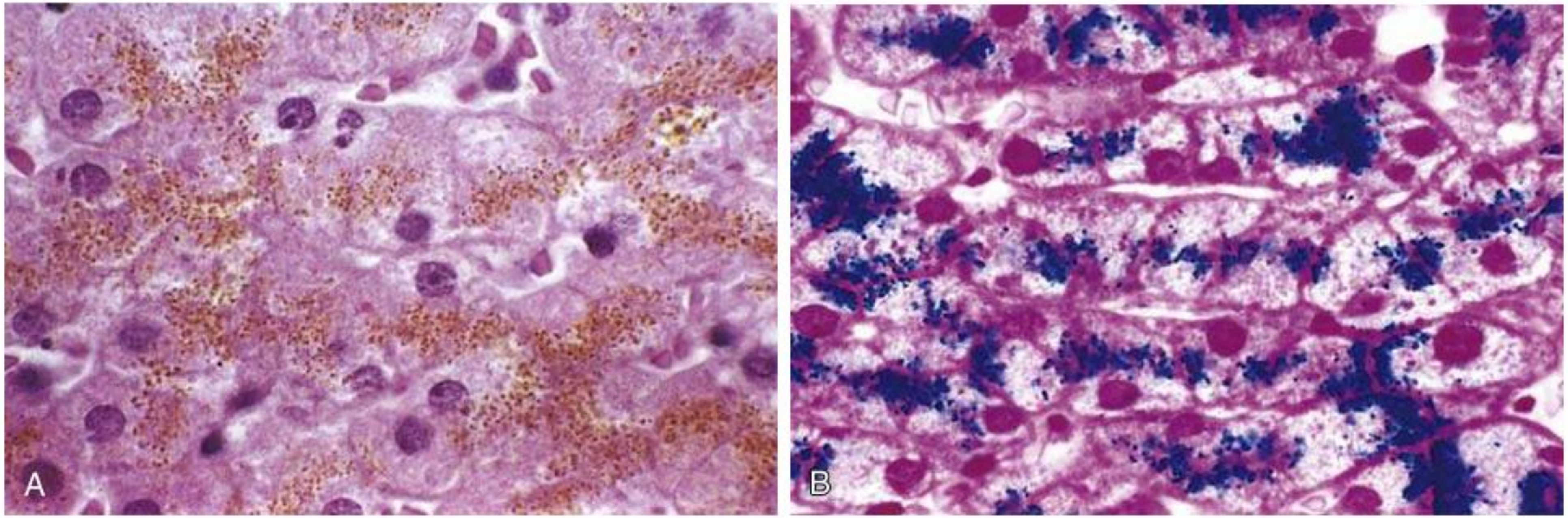
- **Melanin** is an endogenous, brown-black pigment that is synthesized by melanocytes located in the epidermis and acts as a screen against harmful ultraviolet radiation. Although melanocytes are the only source of melanin, adjacent basal keratinocytes in the skin can accumulate the pigment (e.g., in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

- **Hemosiderin** is a hemoglobin-derived golden yellow to brown, granular pigment that accumulates in tissues when there is a local or systemic excess of iron. (Excessive deposition of hemosiderin, called hemosiderosis, and more extensive accumulations of iron seen in hereditary hemochromatosis)

When present in large amounts, the brown pigment imparts an appearance to the atrophic tissue, particularly the heart, that is called brown atrophy.



Lipofuscin granules in cardiac myocytes (deposits indicated by *arrows*).



Hemosiderin granules in liver cells. (A) Hematoxylin-eosin—stained section showing golden-brown, finely granular pigment. (B) Iron deposits revealed by a special staining process called the Prussian blue reaction.

Extracellular Deposits: Pathologic Calcification

Dystrophic calcification. In this form, calcium metabolism is normal and the calcium deposits in injured or dead tissue, such as areas of necrosis of any type. It is virtually always seen in the arterial lesions of advanced atherosclerosis.

Metastatic calcification. This form is associated with hypercalcemia and can occur in otherwise normal tissues.

The major causes of hy percalcemia are:

(1) increased secretion of parathyroid hormone due to either primary parathyroid tumors or hyperplasia, or production of parathyroid hormone related protein by malignant tumors

(2) destruction of bone due to the effects of accelerated turnover (e.g., Paget disease), immobilization, or tumors (increased bone catabolism associated with multiple myeloma, leukemia, or diffuse skeletal metastases)

(3) vitamin D related disorders including vitamin D intoxication and sarcoidosis (in which macrophages activate a vitamin D precursor)

(4) renal failure