chapter 1

Cellular Reaction to Injury

I. ADAPTATION TO ENVIRONMENTAL STRESS

A. Hypertrophy

1. Hypertrophy is an **increase in the size of an organ or tissue due to an increase in the size of cells.**
2. Other characteristics include an increase in protein synthesis and an increase in the size or number of intracellular organelles.
3. A cellular adaptation to increased workload results in hypertrophy, as exemplified by the increase in skeletal muscle mass associated with exercise and the enlargement of the left ventricle in hypertensive heart disease.

B. Hyperplasia

1. Hyperplasia is an **increase in the size of an organ or tissue caused by an increase in the number of cells.**
2. It is exemplified by glandular proliferation in the breast during pregnancy.
3. In some cases, hyperplasia occurs together with hypertrophy. During pregnancy, uterine enlargement is caused by both hypertrophy and hyperplasia of the smooth muscle cells in the uterus.

C. Aplasia

1. Aplasia is a **failure of cell production.**
2. During fetal development, aplasia results in **agenesis,** or absence of an organ due to failure of production.
3. Later in life, it can be caused by permanent loss of precursor cells in proliferative tissues, such as the bone marrow.

D. Hypoplasia

1. Hypoplasia is a **decrease in cell production that is less extreme than in aplasia.**
2. It is seen in the partial lack of growth and maturation of gonadal structures in Turner syndrome and Klinefelter syndrome.

E. Atrophy

1. Atrophy is a **decrease in the size of an organ or tissue and results from a decrease in the mass of preexisting cells (Figure 1-1).**
2. Most often, causal factors are disuse, nutritional or oxygen deprivation, diminished endocrine stimulation, aging, and denervation (lack of nerve stimulation in peripheral muscles caused by injury to motor nerves).
3. Characteristic features often include the presence of **autophagic granules,** which are intracytoplasmic vacuoles containing debris from degraded organelles.

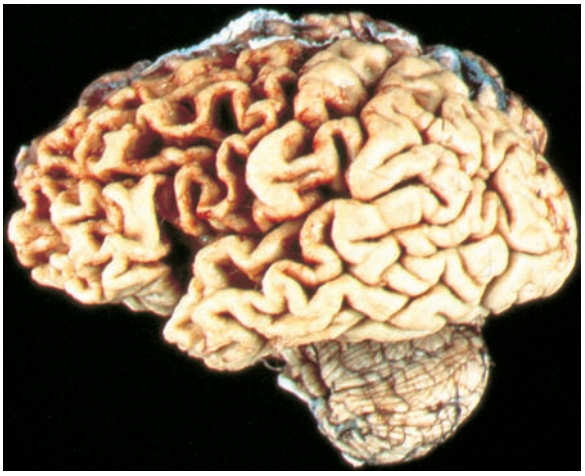


FIGURE 1-1 Marked atrophy of frontal cortex of brain. Note the thinning of the gyri and the widening of the sulci. (From Rubin R, Strayer D, et al., eds.: *Rubin's Pathology. Clinicopathologic Foundations of Medicine,* 5th ed. Baltimore, Lippincott Williams & Wilkins, 2008, p. 3. Original source: Okazaki H, Scheithauer BW: *Atlas of Neuropathology.* New York, Gower Medical Publishing, 1988. By permission of the author.)

4. In some instances, atrophy is thought to be mediated in part by the ubiquitin-proteosome pathway of protein degradation. In this pathway, ubiquitin-linked proteins are degraded within the proteosome, a large cytoplasmic protein complex.

F. Metaplasia is the **replacement of one differentiated tissue by another (Figure 1-2).**

1. **Squamous metaplasia**
   - **a.** Squamous metaplasia is exemplified by the replacement of columnar epithelium at the squamocolumnar junction of the cervix by squamous epithelium.
   - **b.** It can also occur in the respiratory epithelium of the bronchus, in the endometrium, and in the pancreatic ducts.
   - **c.** Associated conditions include chronic irritation (e.g., squamous metaplasia of the bronchi with long-term use of tobacco) and vitamin A deficiency.
   - **d.** This process is often reversible.
2. **Osseous metaplasia**
   - **a.** Osseous metaplasia is the formation of new bone at sites of tissue injury.
   - **b.** Cartilaginous metaplasia may also occur.
3. **Myeloid metaplasia** (extramedullary hematopoiesis) is proliferation of hematopoietic tissue at sites other than the bone marrow, such as the liver or spleen.

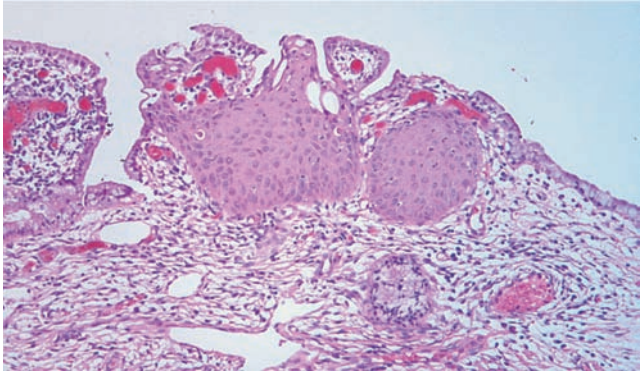


FIGURE 1-2 Squamous metaplasia in the uterine cervix. The columnar epithelium is partially replaced with squamous epithelium. Although this is a benign process, it can become a focus of dysplasia, which can lead to malignant change. (Reprinted with permission from Rubin R, Strayer D, et al., eds.: *Rubin's Pathology. Clinicopathologic Foundations of Medicine*, 5th ed. Baltimore, Lippincott Williams & Wilkins, 2008, p. 7.)

II. HYPOXIC CELL INJURY

A. Causes. Hypoxic cell injury results from cellular **anoxia** or **hypoxia,** which in turn results from various mechanisms, including:

1. **Ischemia** (obstruction of arterial blood flow), which is the most common cause
2. **Anemia,** which is a reduction in the number of oxygen-carrying red blood cells
3. **Carbon monoxide poisoning,** which results in diminution in the oxygen-carrying capacity of red blood cells by chemical alteration of hemoglobin
4. **Decreased perfusion of tissues by oxygen-carrying blood,** which occurs in cardiac failure, hypotension, and shock
5. **Poor oxygenation of blood** secondary to pulmonary disease

B. Early stage. Hypoxic cell injury first affects the mitochondria, with resultant decreased oxidative phosphorylation and adenosine triphosphate (ATP) synthesis. Consequences of **decreased ATP availability** include:

1. **Failure of the cell membrane pump** (ouabain-sensitive Na^+-K^+-ATPase) results in increased intracellular Na^+ and water and decreased intracellular K^+. This process causes cellular swelling and swelling of organelles.
   - **a.** Cellular swelling, or **hydropic change,** is characterized by the presence of large vacuoles in the cytoplasm.
   - **b. Swelling of the endoplasmic reticulum** is one of the first ultrastructural changes evident in reversible injury.
   - **c. Swelling of the mitochondria** progresses from reversible, low-amplitude swelling to irreversible, high-amplitude swelling, which is characterized by marked dilation of the inner mitochondrial space.
2. **Disaggregation of ribosomes leads to failure of protein synthesis.** Ribosomal disaggregation is also promoted by membrane damage.
3. **Stimulation of phosphofructokinase activity** results in increased glycolysis, accumulation of lactate, and decreased intracellular pH. Acidification causes reversible clumping of nuclear chromatin.

C. Late stage

1. Hypoxic cell injury eventually results in **membrane damage** to plasma and to lysosomal and other organelle membranes, with loss of membrane phospholipids.
2. Reversible morphologic signs of damage include the formation of:
   - **a. Myelin figures,** whorl-like structures probably originating from damaged membranes
   - **b. Cell blebs,** a cell surface deformity most likely caused by disorderly function of the cellular cytoskeleton

D. Cell death. Finally, **cell death** is caused by severe or prolonged injury.

1. The **point of no return** is marked by **irreversible damage to cell membranes,** leading to **massive calcium influx, extensive calcification of the mitochondria,** and cell death.
2. **Intracellular enzymes and various other proteins are released** from necrotic cells into the circulation as a consequence of the loss of integrity of cell membranes. This phenomenon is the basis of a number of useful laboratory determinations as indicators of necrosis.
   - **a. Myocardial enzymes in serum.** These are discussed in more depth in Chapter 10.
     - **(1)** Enzymes that have been useful in the diagnosis of myocardial infarction ("heart attack," see Chapters 3 and 10) include the following:
       - **(a) Aspartate aminotransferase (AST,** previously known as **SGOT)**
       - **(b) Lactate dehydrogenase (LDH)**
       - **(c) Creatine kinase (CK,** also known as **CPK)**
     - **(2)** These markers of myocardial necrosis vary in specificity for heart damage, as well as in the time period after the necrotic event in which elevations in the serum appear and persist. The delineation of isoenzyme forms of LDH and CK has been a useful adjunct in adding specificity to these measures.

(3) The foregoing enzymes are beginning to be replaced by other myocardial proteins in serum as indicators of myocardial necrosis. Important examples include the **troponins** (troponin I [TnI] and troponin T [TnT]) and **myoglobin.**

b. Liver enzymes in serum. These enzymes are discussed in more detail in Chapter 16. Enzymes of special interest include the transaminases **(AST** and **alanine aminotransferase [ALT]), alkaline phosphatase,** and **γ-glutamyltransferase (GGT).**

3. The **vulnerability of cells to hypoxic injury varies** with the tissue or cell type. Hypoxic injury becomes irreversible after:

a. 3–5 minutes for neurons. Purkinje cells of the cerebellum and neurons of the hippocampus are more susceptible to hypoxic injury than are other neurons.

b. 1–2 hours for myocardial cells and hepatocytes

c. Many hours for skeletal muscle cells

III. FREE RADICAL INJURY

A. Free radicals

1. These molecules have a single unpaired electron in the outer orbital.
2. Examples include the activated products of oxygen reduction, such as the superoxide ($O_2^{-\cdot}$) and the hydroxyl ($OH\cdot$) radicals.

B. Mechanisms that generate free radicals

1. **Normal metabolism**
2. **Oxygen toxicity,** such as in the alveolar damage that can cause adult respiratory distress syndrome or as in retrolental fibroplasia (retinopathy of prematurity), an ocular disorder of premature infants that leads to blindness
3. **Ionizing radiation**
4. **Ultraviolet light**
5. **Drugs and chemicals,** many of which promote both proliferation of the smooth endoplasmic reticulum (SER) and induction of the P-450 system of mixed function oxidases of the SER. Proliferation and hypertrophy of the SER of the hepatocyte are classic ultrastructural markers of barbiturate intoxication.
6. **Reperfusion after ischemic injury**

C. Mechanisms that degrade free radicals

1. **Intracellular enzymes,** such as glutathione peroxidase, catalase, or superoxide dismutase
2. **Exogenous and endogenous antioxidants,** such as vitamin A, vitamin C, vitamin E, cysteine, glutathione, selenium, ceruloplasmin, or transferrin
3. **Spontaneous decay**

IV. CHEMICAL CELL INJURY

Chemical cell injury is illustrated by **the model of liver cell membrane damage induced by carbon tetrachloride** (CCl_4).

A. In this model, CCl_4 is processed by the P-450 system of mixed function oxidases within the SER, producing the **highly reactive free radical $CCl_3\cdot$.**

B. $CCl_3\cdot$ diffuses throughout the cell, initiating **lipid peroxidation of intracellular membranes.** Widespread injury results, including:

1. **Disaggregation of ribosomes,** resulting in **decreased protein synthesis.** Failure of the cell to synthesize the apoprotein moiety of lipoproteins causes an accumulation of intracellular lipids **(fatty change).**

2. **Plasma membrane damage,** caused by products of lipid peroxidation in the smooth endoplasmic reticulum, resulting in **cellular swelling** and **massive influx of calcium,** with resultant mitochondrial damage, denaturation of cell proteins, and cell death

V. NECROSIS (TABLE 1-1)

A. General considerations

1. **Necrosis** is one of two contrasting morphologic patterns of tissue death. The other is apoptosis (see VI).
2. **Necrosis** is the sum of the degradative and inflammatory reactions occurring after tissue death caused by injury (e.g., hypoxia, exposure to toxic chemicals); it **occurs within living organisms.** In pathologic specimens, fixed cells with well-preserved morphology are dead but not necrotic.
3. **Autolysis** refers to degradative reactions in cells caused by intracellular enzymes indigenous to the cell. **Postmortem autolysis** occurs after the death of the entire organism and is not necrosis.
4. **Heterolysis** refers to cellular degradation by enzymes derived from sources extrinsic to the cell (e.g., bacteria, leukocytes).

B. Types of necrosis

1. **Coagulative necrosis**
   a. Coagulative necrosis results most often from a sudden cutoff of blood supply to an organ (ischemia), particularly the heart and kidney.
   b. General **preservation of tissue architecture** is characteristic in the early stages.
   c. **Increased cytoplasmic eosinophilia** occurs because of protein denaturation and loss of cytoplasmic RNA.

table 1-1 Types of Necrosis

Type	Mechanism	Pathologic Changes
Coagulative necrosis	Most often results from interruption of blood supply, resulting in denaturation of proteins; best seen in organs supplied by end arteries with limited collateral circulation, such as the heart and kidney	General architecture well preserved, except for nuclear changes; increased cytoplasmic binding of acidophilic dyes
Liquefactive necrosis	Enzymatic liquefaction of necrotic tissue, most often in the CNS, where it is caused by interruption of blood supply; also occurs in areas of bacterial infection	Necrotic tissue soft and liquefied
Caseous necrosis	Shares features of both coagulation and liquefaction necrosis; most commonly seen in tuberculous granulomas	Architecture not preserved but tissue not liquefied; gross appearance is soft and cheese-like; histologic appearance is amorphous, with increased affinity for acidophilic dyes
Gangrenous necrosis	Most often results from interruption of blood supply to a lower extremity or the bowel	Changes depend on tissue involved and whether gangrene is dry or wet
Fibrinoid necrosis	Characterized by deposition of fibrin-like proteinaceous material in walls of arteries; often observed as part of immune-mediated vasculitis	Smudgy pink appearance in vascular walls; actual necrosis may or may not be present
Fat necrosis	Liberation of pancreatic enzymes with autodigestion of pancreatic parenchyma; trauma to fat cells	Necrotic fat cells, acute inflammation, hemorrhage, calcium soap formation, clustering of lipid-laden macrophages (in the pancreas)

d. Nuclear changes, the morphologic hallmark of irreversible cell injury and necrosis, are characteristic. These include:

(1) Pyknosis, chromatin clumping and shrinking with increased basophilia

(2) Karyorrhexis, fragmentation of chromatin

(3) Karyolysis, fading of chromatin material

(4) Disappearance of stainable nuclei

2. Liquefactive necrosis

a. Ischemic injury to the central nervous system (CNS) characteristically results in liquefactive necrosis. After the death of CNS cells, liquefaction is caused by autolysis.

b. Digestion, softening, and liquefaction of tissue are characteristic.

c. Suppurative infections characterized by the formation of pus (liquefied tissue debris and neutrophils) by heterolytic mechanisms involve liquefactive necrosis.

3. Caseous necrosis

a. This type of necrosis occurs as **part of granulomatous inflammation** and is a manifestation of partial immunity caused by the interaction of T lymphocytes (CD4+, CD8+, and CD4-CD8-), macrophages, and probably cytokines, such as interferon-γ, derived from these cells.

b. Tuberculosis is the leading cause of caseous necrosis.

c. Caseous necrosis combines features of both coagulative necrosis and liquefactive necrosis.

d. On gross examination, caseous necrosis has a cheese-like (caseous) consistency.

e. On histologic examination, caseous necrosis has an **amorphous eosinophilic appearance.**

4. Gangrenous necrosis

a. This type of necrosis most often affects the lower extremities or bowel and is secondary to vascular occlusion.

b. When complicated by infective heterolysis and consequent liquefactive necrosis, gangrenous necrosis is called **wet gangrene.**

c. When characterized primarily by coagulative necrosis without liquefaction, gangrenous necrosis is called **dry gangrene.**

5. Fibrinoid necrosis

a. This **deposition of fibrin-like proteinaceous material in the arterial walls** appears smudgy and acidophilic.

b. Fibrinoid necrosis is often associated with immune-mediated vascular damage.

6. Fat necrosis occurs in two forms.

a. Traumatic fat necrosis, which occurs after a severe injury to tissue with high fat content, such as the breast

b. Enzymatic fat necrosis, which is a complication of **acute hemorrhagic pancreatitis,** a severe inflammatory disorder of the pancreas

(1) Proteolytic and lipolytic pancreatic enzymes diffuse into inflamed tissue and literally digest the parenchyma.

(2) Fatty acids liberated by the digestion of fat form calcium salts (saponification, or **soap formation**).

(3) Vessels are eroded, with resultant hemorrhage.

VI. APOPTOSIS (TABLE 1-2)

A. General considerations

1. Apoptosis is a second morphologic pattern of tissue death. (The other is necrosis; see V.) It is often referred to as programmed cell death.

2. This is an important mechanism for the removal of cells. An example is apoptotic removal of cells with irreparable DNA damage (from free radicals, viruses, cytotoxic immune mechanisms), protecting against neoplastic transformation.

table 1-2 Comparison of Necrosis and Apoptosis

Characteristics	Necrosis	Apoptosis
Etiology	Gross irreversible cellular injury	Subtle cellular damage, physiologic programmed cell removal
Morphologic changes	Involves many contiguous cells Increased cytoplasmic eosinophilia due to denaturation of proteins Progressive nuclear condensation and fragmentation with eventual disappearance of nuclei Preservation of tissue architecture in early stages of coagulative necrosis	Involves single cells or small clusters of cells Cytoplasmic shrinking and increased eosinophilic staining Chromatin condensation and fragmentation Fragmentation into membrane-bound apoptotic bodies
Biochemical changes	Passive form of cell death not requiring gene involvement or new protein synthesis DNA fragmentation is haphazard rather than regular, resulting in an electrophoretic smudge pattern	Active form of cell death requiring gene expression, protein synthesis, and energy consumption DNA fragmentation is regular at nucleosomal boundaries, resulting in an electrophoretic "laddered" pattern
Inflammatory reaction	Marked inflammatory reaction, liberation of lysosomal enzymes, digestion of cell membranes, and disruption of cells Influx of macrophages due to release of chemotactic factors Removal of debris by phagocytic macrophages	No inflammatory reaction Apoptotic bodies engulfed by neighboring macrophages and epithelial cells

3. In addition, apoptosis is an important mechanism for physiologic cell removal during embryogenesis and in programmed cell cycling (e.g., endometrial cells during menstruation).
4. This involutional process is similar to the physiologic loss of leaves from a tree; *apoptosis* is a Greek term for "falling away from."

B. Morphologic features

1. A tendency to involve single isolated cells or small clusters of cells within a tissue
2. Progression through a series of changes marked by a lack of inflammatory response
   a. Blebbing of plasma membrane, cytoplasmic shrinkage, chromatin condensation
   b. Budding of cell and separation of apoptotic bodies (membrane-bound segments)
   c. Phagocytosis of apoptotic bodies
3. **Involution and shrinkage** of affected cells and cell fragments, resulting in small round eosinophilic masses often containing chromatin remnants, exemplified by Councilman bodies in viral hepatitis

C. Biochemical events

1. Diverse injurious stimuli (e.g., free radicals, radiation, toxic substances, withdrawal of growth factors or hormones) trigger a variety of stimuli, including cell surface receptors such as FAS, mitochondrial response to stress, and cytotoxic T cells.
2. The **extrinsic pathway of initiation** is mediated by cell surface receptors exemplified by FAS, a member of the tumor necrosis factor receptor family of proteins. This pathway is initiated by signaling by molecules such as the FAS ligand, which in turn signals a series of events that involve activation of caspases. Caspases are aspartate-specific cysteine proteases that have been referred to as "major executioners" or "molecular guillotines." The death signals are conveyed in a proteolytic cascade, through activation of a chain of caspases and other targets. The initial activating caspases are caspase-8 and caspase-9, and the terminal caspases (executioners) include caspase-3 and caspase-6 (among other proteases).

3. The **intrinsic, or mitochondrial, pathway,** which is initiated by the loss of stimulation by growth factors and other adverse stimuli, results in the inactivation and loss of bcl-2 and other antiapoptotic proteins from the inner mitochondrial membrane. This loss results in increased mitochondrial permeability, the release of cytochrome c, and the stimulation of proapoptotic proteins such as bax and bak. Cytochrome c interacts with Apaf-1 causing self-cleavage and activation of caspase-9. Downstream caspases are activated by upstream proteases and act themselves to cleave cellular targets.
4. **Cytotoxic T-cell activation** is characterized by direct activation of caspases by granzyme B, a cytotoxic T-cell protease that perhaps directly activates the caspase cascade. The entry of granzyme B into target cells is mediated by perforin, a cytotoxic T-cell protein.
5. Degradation of DNA by endonucleases into nucleosomal chromatin fragments that are multiples of 180–200 base pairs results in the typical **"laddering"** appearance of DNA on electrophoresis. This phenomenon is characteristic of, but not entirely specific for, apoptosis.
6. Activation of **transglutaminases** crosslinks apoptotic cytoplasmic proteins.
7. The caspases consist of a group of aspartic acid-specific cysteine proteases that are activated during apoptosis.
8. Newer methods such as the TUNEL assay (Terminal Transferase dUTP Nick End Labeling) are ways to quantitate cleaving of nucleosomes and, thus, apoptosis. Similarly, caspase assays are coming into use as apoptotic markers. Surely more will follow.

D. Regulation of apoptosis is mediated by a number of genes and their products. Important genes include bcl-2 (gene product inhibits apoptosis), bax (gene product facilitates apoptosis), and p53 (gene product decreases transcription of bcl-2 and increases transcription of bax, thus facilitating apoptosis).

E. Additionally, complex signaling pathways involving multiple genes and gene products are the subject of vigorous scientific investigation. Since many pathologic processes are related to either stimulation or inhibition of apoptosis (e.g., many forms of cancer), this area of inquiry promises to yield major understanding that will surely lead to important therapeutic applications.

VII. REVERSIBLE CELLULAR CHANGES AND ACCUMULATIONS

A. Fatty change (fatty metamorphosis, steatosis)

1. **General considerations**
   a. Fatty change is characterized by the **accumulation of intracellular parenchymal triglycerides** and is observed most frequently in the **liver, heart,** and **kidney.** For example, in the liver, fatty change may be secondary to alcoholism, diabetes mellitus, malnutrition, obesity, or poisonings.
2. **Imbalance among the uptake, utilization, and secretion of fat** is the cause of fatty change, and this can result from any of the following mechanisms:
   a. **Increased transport of triglycerides or fatty acids** to affected cells
   b. **Decreased mobilization of fat from cells,** most often mediated by decreased production of apoproteins required for fat transport. Fatty change is thus linked to the disaggregation of ribosomes and consequent decreased protein synthesis caused by failure of ATP production in CCl_4-injured cells.
   c. **Decreased use of fat by cells**
   d. **Overproduction of fat in cells**

B. Hyaline change

1. This term denotes a characteristic (homogeneous, glassy, eosinophilic) appearance in hematoxylin and eosin sections.
2. It is caused most often by nonspecific accumulations of proteinaceous material.

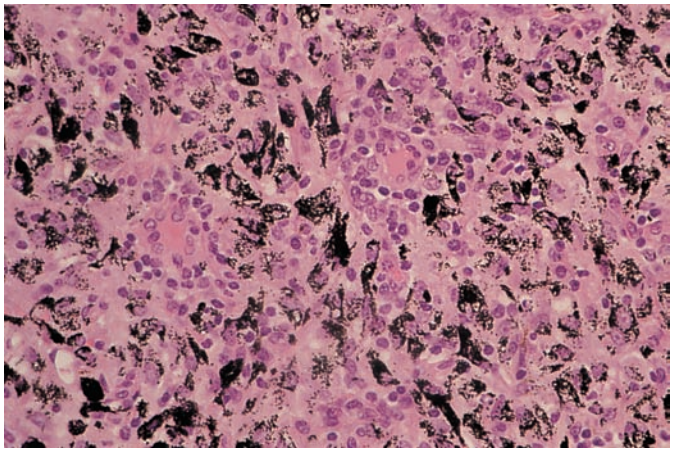


FIGURE 1-3 Anthracotic deposition. Note the accumulation of black carbonaceous pigment in this mediastinal lymph node. (Reprinted with permission from Rubin R, Strayer D, et al., eds.: *Rubin's Pathology. Clinicopathologic Foundations of Medicine*, 5th ed. Baltimore, Lippincott Williams & Wilkins, 2008, p. 19.)

C. Accumulations of exogenous pigments

1. **Pulmonary accumulations of carbon (anthracotic pigment), silica, and iron dust**
2. **Plumbism** (lead poisoning)
3. **Argyria** (silver poisoning), which may cause a permanent gray discoloration of the skin and conjunctivae (Figure 1-3)

D. Accumulations of endogenous pigments

1. **Melanin**
   - **a.** This pigment is formed from tyrosine by the action of tyrosinase, synthesized in melanosomes of melanocytes within the epidermis, and transferred by melanocytes to adjacent clusters of keratinocytes and also to macrophages (melanophores) in the subjacent dermis.
   - **b.** **Increased melanin pigmentation** is associated with suntanning and with a wide variety of disease conditions.
   - **c.** **Decreased melanin pigmentation** is observed in albinism and vitiligo.
2. **Bilirubin**
   - **a.** This pigment is a catabolic product of the heme moiety of hemoglobin and, to a minor extent, myoglobin.
   - **b.** In various pathologic conditions, bilirubin accumulates and stains the blood, sclerae, mucosae, and internal organs, producing a yellowish discoloration called jaundice.
     - **(1)** **Hemolytic jaundice,** which is associated with the destruction of red cells, is discussed in more depth in Chapter 11.
     - **(2)** **Hepatocellular jaundice,** which is associated with parenchymal liver damage, and **obstructive jaundice,** which is associated with intra- or extrahepatic obstruction of the biliary tract, are discussed more fully in Chapter 16.
3. **Hemosiderin**
   - **a.** This **iron-containing pigment** consists of aggregates of ferritin. It appears in tissues as golden brown amorphous aggregates and can be positively identified by its staining reaction (blue color) with Prussian blue dye. It exists normally in small amounts as physiologic iron stores within tissue macrophages of the bone marrow, liver, and spleen.
   - **b.** It accumulates pathologically in tissues in excess amounts (sometimes massive) **(Table 1-3).**
     - **(1)** **Hemosiderosis** is defined by accumulation of hemosiderin, primarily within tissue macrophages, without associated tissue or organ damage.
     - **(2)** **Hemochromatosis** is more extensive accumulation of hemosiderin, often within parenchymal cells, with accompanying tissue damage, scarring, and organ dysfunction. This condition occurs in both hereditary (primary) and secondary forms.

table 1-3 Abnormal Deposition of Hemosiderin

Type	Pathologic Features	Mechanisms
Local hemosiderosis	Local deposition of hemosiderin	Most often results from hemorrhage into tissue; hemosiderin derived from breakdown of hemoglobin
Systemic hemosiderosis	Generalized hemosiderin deposition without tissue or organ damage	May result from hemorrhage, multiple blood transfusions, hemolysis, and excessive dietary intake of iron, often accompanied by alcohol consumption
Hemochromatosis	Damage to many tissues and organs; scarring and organ dysfunction manifested as hepatic cirrhosis and fibrosis of pancreas, leading to diabetes mellitus; increased melanin pigmentation in skin	More extensive accumulation than hemosiderosis; can result from any of the causes of systemic hemosiderosis; most often a hereditary disorder characterized by increased iron absorption (hereditary hemochromatosis)

(a) Hereditary hemochromatosis is most often caused by a mutation in the *Hfe* gene on chromosome 6.

(i) Hemosiderin deposition and organ damage in the liver, pancreas, myocardium, and multiple endocrine glands is characteristic, as well as melanin deposition in the skin.

(ii) This results in the triad of **micronodular cirrhosis, diabetes mellitus,** and **skin pigmentation.** This set of findings is referred to as **"bronze diabetes."** Laboratory abnormalities of note include marked elevation of the serum transferrin saturation because of the combination of **increased serum iron** and **decreased total iron-binding capacity (TIBC).**

(b) Secondary hemochromatosis is most often caused by **multiple blood transfusions** administered to subjects with hereditary hemolytic anemias such as β-thalassemia major (Figure 1-4).

4. Lipofuscin

a. This yellowish, fat-soluble pigment is an end product of membrane lipid peroxidation.

b. It is sometimes referred to as "wear-and-tear" pigment.

c. It commonly accumulates in elderly patients, in whom the pigment is found most often within hepatocytes and at the poles of nuclei of myocardial cells. The combination of lipofuscin accumulation and atrophy of organs is referred to as **brown atrophy.**

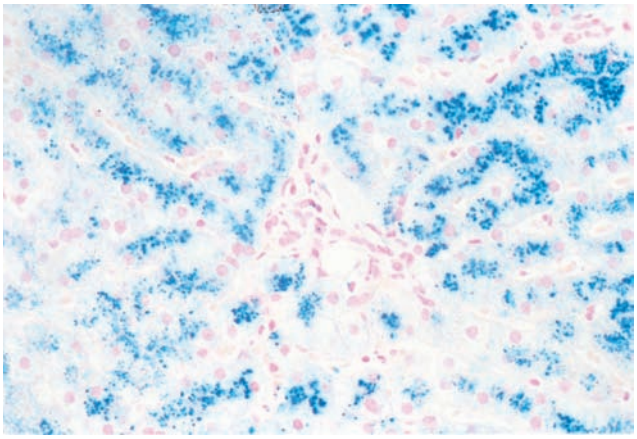


FIGURE 1-4 Hereditary hemochromatosis. Prussian blue staining marks the intraparenchymal deposition of hemosiderin. (Reprinted with permission from Rubin R, Strayer D, et al., eds.: *Rubin's Pathology. Clinicopathologic Foundations of Medicine*, 5th ed. Baltimore, Lippincott Williams & Wilkins, 2008, p. 19.)

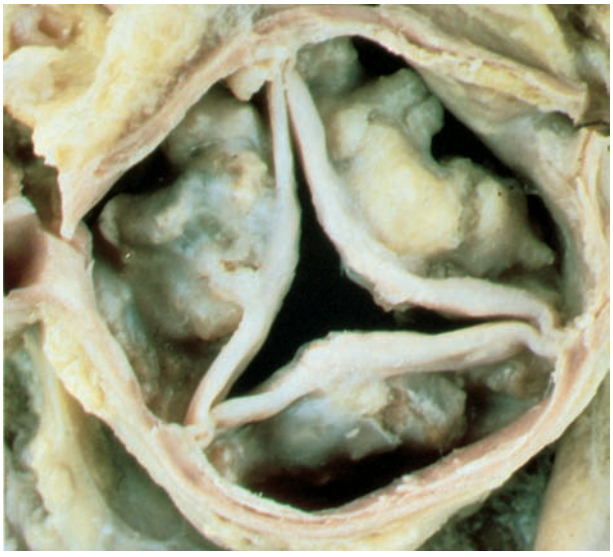


FIGURE 1-5 Calcific aortic stenosis. This is an example of dystrophic calcification, *i.e.*, calcification of a previously damaged structure. (Reprinted with permission from Rubin R, Strayer D, et al., eds.: *Rubin's Pathology. Clinicopathologic Foundations of Medicine*, 5th ed. Baltimore, Lippincott Williams & Wilkins, 2008, p. 8.)

E. Pathologic calcifications

1. **Metastatic calcification**
   - **a. The cause of metastatic calcification is hypercalcemia.**
   - **b.** Hypercalcemia most often results from any of the following causes:
     - **(a)** Hyperparathyroidism
     - **(b)** Osteolytic tumors with resultant mobilization of calcium and phosphorus
     - **(c)** Hypervitaminosis D
     - **(d)** Excess calcium intake, such as in the milk-alkali syndrome (nephrocalcinosis and renal stones caused by milk and antacid self-therapy)
2. **Dystrophic calcification**
   - **a.** Dystrophic calcification is **defined as calcification in previously damaged tissue,** such as areas of old trauma, tuberculosis lesions, scarred heart valves, and atherosclerotic lesions.
   - **b.** The cause is not hypercalcemia; typically, the serum calcium concentration is normal (Figure 1-5).

VIII. DISORDERS CHARACTERIZED BY ABNORMALITIES OF PROTEIN FOLDING

A. These disorders involve failure of protein structural stabilization or degradation by specialized proteins known as chaperones. Important chaperones include heat shock proteins induced by stress, one of which is ubiquitin, which marks abnormal proteins for degradation.

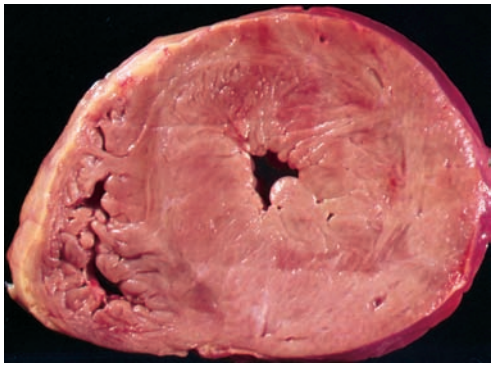
B. Two known pathogenetic mechanisms include:

1. **Abnormal protein aggregation,** which is characteristic of amyloidosis; a number of neurodegenerative diseases, such as Alzheimer disease, Huntington disease, and Parkinson disease; and perhaps prion diseases, such as "mad cow" disease
2. **Abnormal protein transport and secretion,** which is characteristic of cystic fibrosis and α_1-antitrypsin deficiency

Review Test

Directions: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of the statement. Select the **one** lettered answer or completion that is best in each case.

1. The illustration shows a section of the heart from a 45-year-old African-American man with long-standing hypertension who died of a "stroke." Which of the following adaptive changes is exemplified in the illustration?



(Reprinted with permission from Rubin R, Strayer D, et al., eds.: *Rubin's Pathology. Clinicopathologic Foundations of Medicine*, 5th ed. Baltimore, Lippincott Williams & Wilkins, 2008, p. 5.)

(A) Aplasia
(B) Atrophy
(C) Hyperplasia
(D) Hypertrophy
(E) Hypoplasia

2. A 16-year-old girl undergoes radiologic imaging of her abdomen and is found to have only one kidney. She had been entirely unaware of this problem. Which of the following terms is most descriptive of this finding?

(A) Agenesis
(B) Atrophy
(C) Hyperplasia
(D) Hypoplasia
(E) Metaplasia

3. An impending myocardial infarction was successfully averted by thrombolytic (clot-dissolving) therapy in a 55-year-old man. Which of the following biochemical events most likely occurred during the period of hypoxia?

(A) Decreased hydrogen ion concentration
(B) Increase in oxidative phosphorylation
(C) Loss of intracellular Na^+ and water
(D) Stimulation of ATP synthesis
(E) Stimulation of anaerobic glycolysis and glycogenolysis

4. A 45-year-old man with a long history of alcoholism presents with severe epigastric pain, nausea, vomiting, fever, and an increase in serum amylase. During a previous hospitalization for a similar episode, computed tomography scanning demonstrated calcifications in the pancreas. A diagnosis of acute pancreatitis superimposed on chronic pancreatitis was made. In this condition, which of the following types of necrosis is most characteristic?

(A) Caseous
(B) Coagulative
(C) Enzymatic
(D) Fibrinoid
(E) Liquefactive

5. A 29-year-old man hospitalized for acquired immunodeficiency syndrome (AIDS) is found to have pulmonary tuberculosis. Which type of necrosis is found in the granulomatous lesions (clusters of modified macrophages) characteristic of this increasingly frequent complication of AIDS?

(A) Caseous
(B) Coagulative
(C) Enzymatic
(D) Fibrinoid
(E) Liquefactive

6. A 45-year-old woman is investigated for hypertension and is found to have enlargement of the left kidney. The right kidney is smaller than normal. Contrast studies reveal stenosis of the right renal artery. The size change in the right kidney is an example of which of the following adaptive changes?

(A) Aplasia
(B) Atrophy
(C) Hyperplasia
(D) Hypertrophy
(E) Metaplasia

7. A 56-year-old man recovered from a myocardial infarction after his myocardium was entirely "saved" by immediate thrombolytic therapy. If it had been possible to examine microscopic sections of his heart during his ischemic episode, which of the following would be the most likely cellular change to be found?

(A) Karyolysis
(B) Karyorrhexis
(C) Pyknosis
(D) Swelling of the endoplasmic reticulum

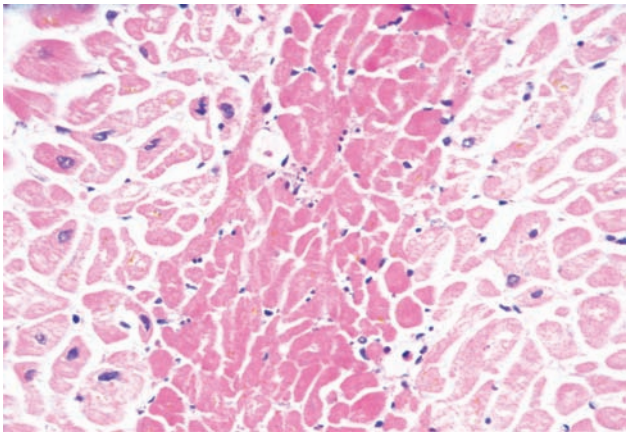
8. A 64-year-old woman presents with fever, chills, headache, neck stiffness, vomiting, and confusion. The Kernig sign (passive knee extension eliciting neck pain) and Brudzinski sign (passive neck flexion eliciting bilateral hip flexion) are both positive. Examination of the cerebrospinal fluid reveals changes consistent with bacterial meningitis, and brain imaging demonstrates a localized abscess. Which of the following types of necrosis is most characteristic of abscess formation?

(A) Caseous
(B) Coagulative
(C) Enzymatic
(D) Fibrinoid
(E) Liquefactive

9. A 20-year-old man presents with yellowing of the sclerae, skin, and oral mucosa. Which of the following accumulations underlies these findings?

(A) Bilirubin
(B) Hemosiderin
(C) Lead
(D) Melanin
(E) Silver

10. This figure illustrates the microscopic appearance of the heart of a 56-year-old man who died after a 24-hour hospitalization for severe "crushing" chest pain complicated by hypotension and pulmonary edema. The type of necrosis shown is best described as



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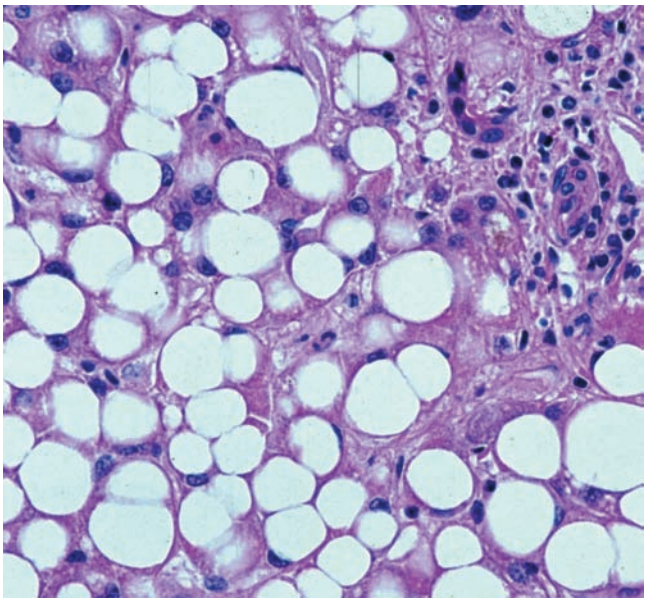
(A) caseous.
(B) coagulative.
(C) fibrinoid.
(D) gangrenous.
(E) liquefactive.

11. The illustration is from a liver biopsy of a 34-year-old woman with a long history of alcoholism. Which of the following is the best explanation for the changes shown here?



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(A) Accumulation of triglycerides within hepatocytes
(B) Apoptosis with replacement of damaged cells by lipid-laden macrophages
(C) Bilirubin accumulation with mobilization of fat by bile salts
(D) Enzymatic fat necrosis with digestion of liver parenchyma by released enzymes
(E) Irreversible damage to mitochondria

12. A 45-year-old man is referred because of a recent diagnosis of hereditary hemochromatosis. Which of the following is a correct statement about this disorder?

(A) Damage to organs results from abnormal deposition of lead.
(B) It can progress to liver cirrhosis, diabetes mellitus, and skin pigmentation.
(C) Most cases are due to spontaneous mutations.
(D) Skin hyperpigmentation is due to bilirubin accumulation.
(E) The total iron-binding capacity (TIBC) is characteristically increased.

13. A 60-year-old woman with breast cancer and widespread bony metastases is found to have calcification of multiple organs. The calcifications are best described as

(A) dystrophic with decreased serum calcium.
(B) dystrophic with increased serum calcium.
(C) metastatic with decreased serum calcium.
(D) metastatic with increased serum calcium.

14. A 56-year-old man dies 24 hours after the onset of substernal chest pain radiating down his left arm to the ulnar aspect of his fingertips. Which of the following morphologic myocardial findings is an indicator of irreversible injury?

(A) Cell blebs
(B) Depletion of glycogen
(C) Mitochondrial swelling
(D) Myelin figures
(E) Pyknotic nuclei

Answers and Explanations

1. **The answer is D.** The illustration shows marked hypertrophy of the left ventricle. Hypertrophy of this extent, often seen in hypertensive heart disease, is caused by increased workload from increased ventricular pressure. This organ enlargement is the result of an increase in size of the individual muscle cells.

2. **The answer is A.** The patient has renal agenesis, absence of the kidney due to failure of organ development. The congenital lack of one kidney differs from atrophy, in which a decrease in the size of an organ results from a decrease in the mass of pre-existing cells. Unilateral renal agenesis is usually a harmless malformation, and the opposite kidney is often enlarged due to compensatory hypertrophy. Bilateral renal agenesis is incompatible with life and is of special interest since it can lead to the Potter progression (see Chapter 17).

3. **The answer is E.** The sequence of events in hypoxic cell damage is as follows: Hypoxia results in failure of oxidative phosphorylation, with resultant depletion of ATP and increase in AMP and ADP. Anaerobic glycolysis and glycogenolysis are stimulated (*not* inhibited) through increased phosphofructokinase and phosphorylase activities, respectively. This results in an accumulation of cell lactate, with a decrease in intracellular pH and depletion of cellular glycogen stores. Decreased availability of ATP also results in failure of the Na^+K^+-ATPase pump, which then leads to increased cell Na^+ and water and decreased cell K^+.

4. **The answer is C.** Pancreatic enzymatic fat necrosis represents autodigestion by proteolytic and lipolytic enzymes released from damaged parenchymal cells of the pancreas. Fatty acids liberated by the digestion of fat form calcium soaps, a process referred to as saponification. The precipitated calcium in the soaps can be visualized by radiologic imaging.

5. **The answer is A.** Caseous necrosis occurs as part of granulomatous inflammation, typified by the lesions of tuberculosis.

6. **The answer is B.** The decreased size is due to restriction of the blood supply, one of the causes of atrophy. The increase in size of the opposite kidney is referred to as compensatory hypertrophy. Unilateral renal artery stenosis is a well-known cause of secondary hypertension. In this setting, increased renin excretion and stimulation of the renin-angiotensin system results in a form of hypertension that is potentially curable by surgical correction of the underlying vascular abnormality.

7. **The answer is D.** If infarction is averted by immediate thrombolytic therapy, indicators of necrosis, such as karyorrhexis, pyknosis, and karyolysis, which represent irreversible changes, would not be expected. Swelling of the endoplasmic reticulum from increased cell water, one of the earliest ultrastructural changes observed in injured cells, is reversible and would be expected.

8. **The answer is E.** Liquefactive necrosis is characteristic of ischemic injury in the central nervous system and suppurative infections that cause abscess formation (see Chapter 2). The changes in the cerebrospinal spinal fluid characteristic of bacterial meningitis are detailed in Chapter 3.

9. **The answer is A.** Yellowing of the sclerae, skin, and oral mucosa are all characteristic of jaundice, the accumulation of bilirubin, the catabolic product of the heme moiety of hemoglobin. Jaundice can occur by diverse mechanisms: hemolytic (see Chapter 11), hepatocellular (see Chapter 16), or obstructive (see Chapter 16).

10. The answer is B. The figure illustrates general preservation of myocardial architecture with some fragmentation, more intense cytoplasmic staining corresponding to increased cellular eosinophilia, and loss of nuclei, all of which are characteristic of coagulative necrosis.

11. The answer is A. The figure illustrates fatty change of the liver, which is characterized by the accumulation of intracellular parenchymal triglycerides. It is seen most frequently in the liver, heart, and kidney and commonly is secondary to alcoholism. Fatty change results from an imbalance between the uptake, utilization, and mobilization of fat from liver cells. Alcoholic fatty liver may be reversible with complete abstinence from alcohol.

12. The answer is B. In advanced form, primary (hereditary) hemochromatosis is characterized by the triad of cirrhosis, diabetes, and hyperpigmentation, or so-called "bronze diabetes." The disease is most often caused by a mutation in the *Hfe* gene on chromosome 6 and is characteristically familial rather than sporadic. The manifestations of the disorder are the result of iron overload and deposition of hemosiderin in tissues such as the liver, pancreas, skin, joints, and pituitary. Laboratory abnormalities of note include increased serum iron and decreased total iron-binding capacity (TIBC). The skin hyperpigmentation is due largely to increases in melanin and to lesser accumulations of hemosiderin.

13. The answer is D. Metastatic calcification, or deposition of calcium in previously normal tissue, is caused by hypercalcemia. In this patient, tumor metastases to bone with increased osteolytic activity caused mobilization of calcium and phosphate, resulting in hypercalcemia. Metastatic calcification should be contrasted with dystrophic calcification, in which the serum calcium concentration is normal and previously damaged tissues are the sites of deposition.

14. The answer is E. Myelin figures, cell blebs, mitochondrial swelling, and glycogen depletion are all signs of reversible injury. Nuclear changes such as pyknosis, karyorrhexis, and karyolysis are signs of cell death and are, of course, irreversible.