

The background features abstract, overlapping geometric shapes in various shades of green, ranging from light lime to dark forest green. These shapes are primarily located on the left and right sides of the slide, framing the central text. The overall aesthetic is clean and modern.

Cellular responses to stress and toxic insults

Introduction to pathology

- ▶ Pathology is the study of the structural, biochemical, and functional changes in cells, tissues, and organs that underlie disease.
- ▶ The four aspects of a disease process are etiology, pathogenesis, morphologic changes and clinical manifestations.
- ▶ Virtually all diseases start with molecular or structural alterations in cells.
- ▶ This concept of the cellular basis of disease was first put forth in the nineteenth century by Rudolf Virchow, known as the father of modern pathology

Overview of cellular responses to stress and Noxious Stimuli

- ▶ Adaptations are reversible functional and structural responses to changes in physiologic states (e.g., pregnancy) and some pathologic stimuli, during which new but altered steady states are achieved.
- ▶ If the limits of adaptive responses are exceeded, a sequence of events follows that is termed cell injury.
- ▶ Cell injury is reversible up to a point, but if the injurious stimulus is persistent or severe, the cell suffers irreversible injury and ultimately undergoes cell death.

Overview of cellular responses to stress and Noxious Stimuli

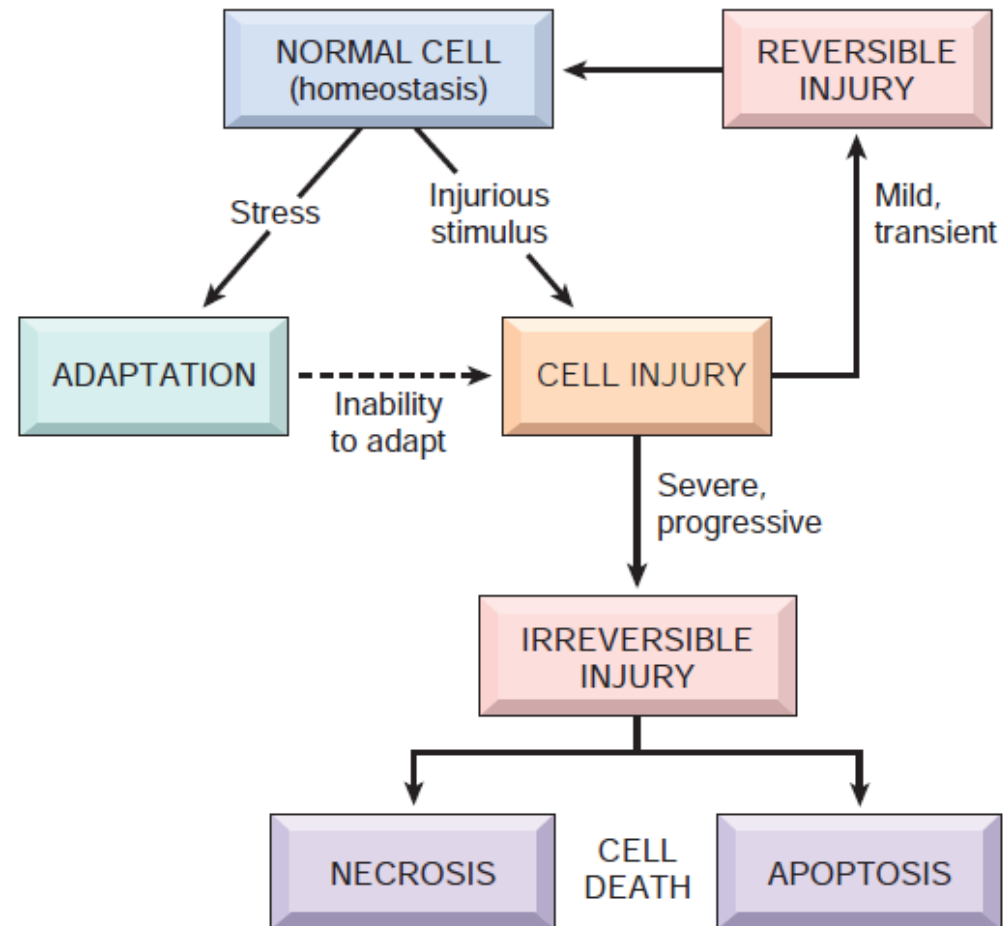
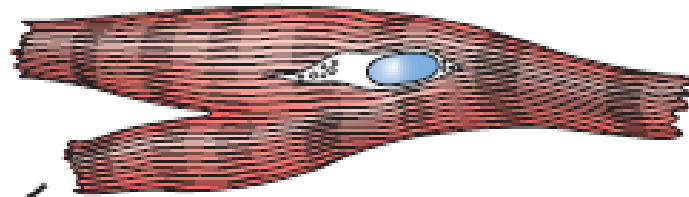


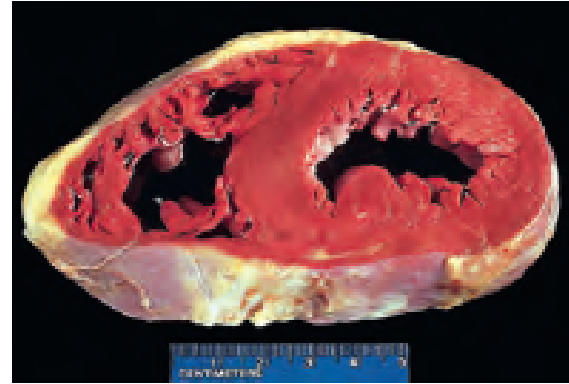
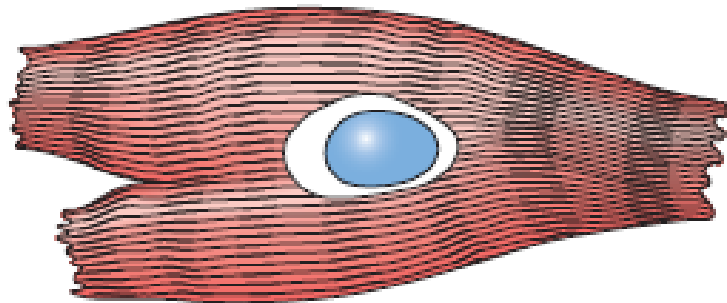
Figure 2.1 Stages of the cellular response to stress and injurious stimuli.

Normal myocyte



*Adaptation:
response to
increased
load*

Adapted myocyte
(hypertrophy)

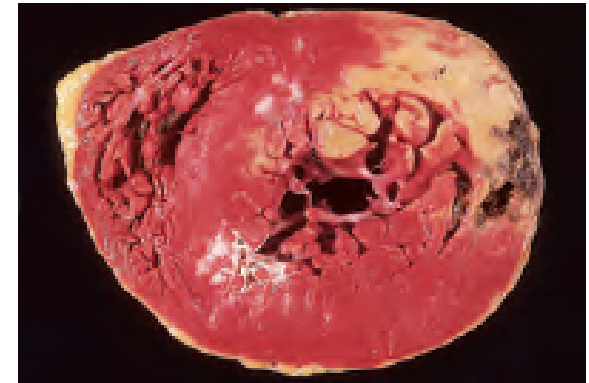
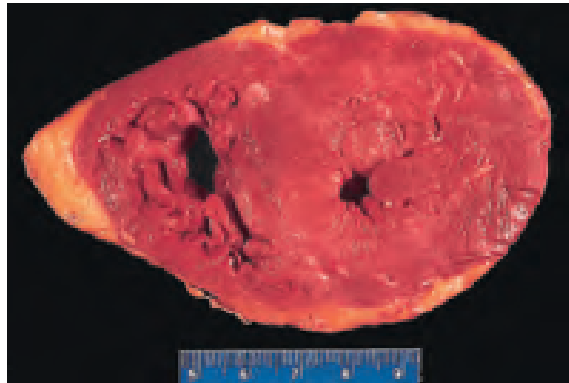


*Cell
injury*

Reversibly injured myocyte



Cell death

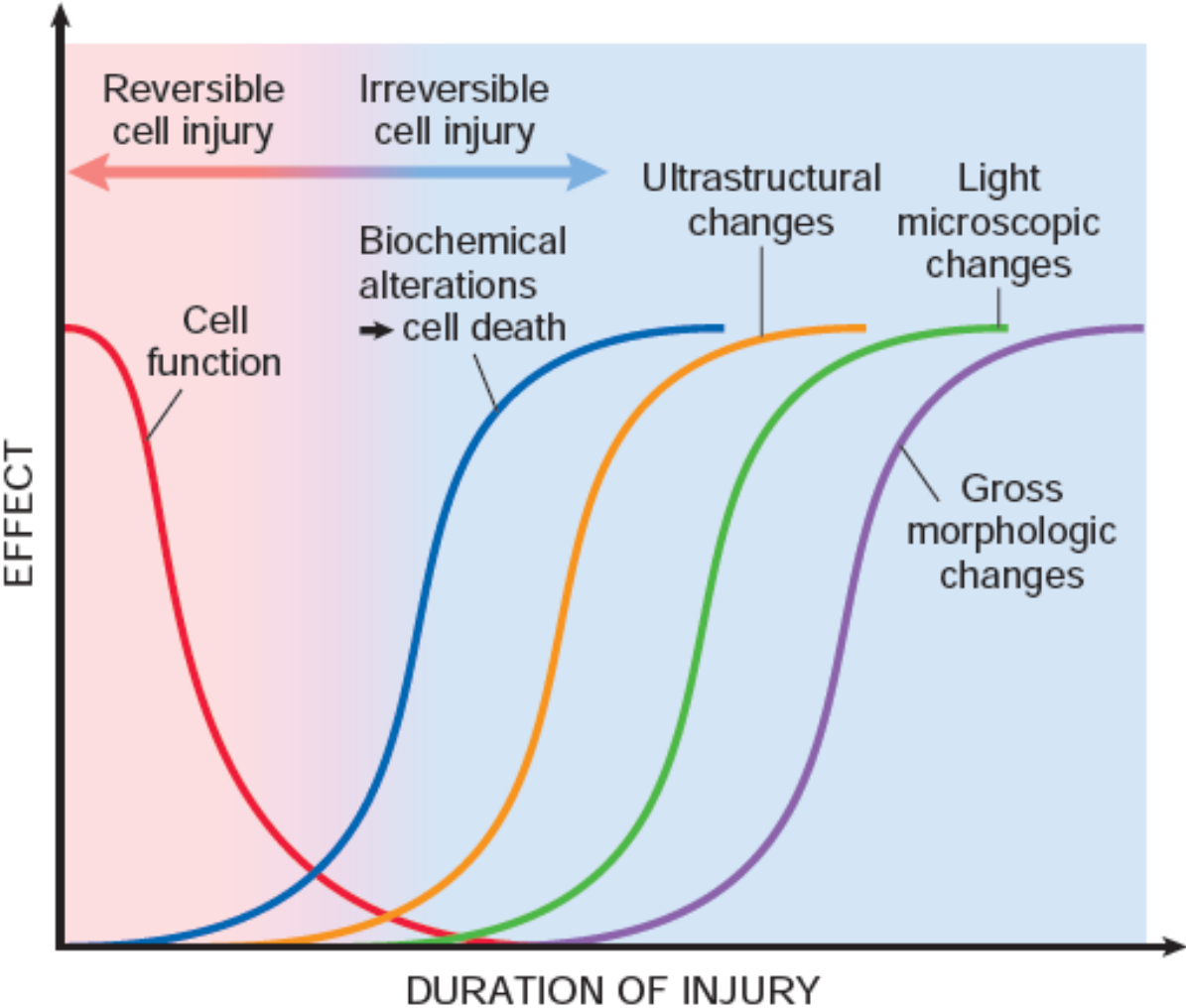


Causes of cell injury

- ▶ Physical Agents
- ▶ Chemical Agents and Drugs
- ▶ Oxygen deprivation
- ▶ Infectious Agents
- ▶ Immunologic Reactions
- ▶ Genetic Abnormalities
- ▶ Nutritional Imbalances

- ▶ All stresses and noxious influences exert their effects first at the molecular or biochemical level
- ▶ There is a time lag between the stress and the morphologic changes of cell injury or death; .
- ▶ With histochemical, ultrastructural, or biochemical techniques, changes may be seen in minutes to hours after injury, whereas changes visible by light microscopy or the naked eye may take considerably longer (hours to days) to appear.

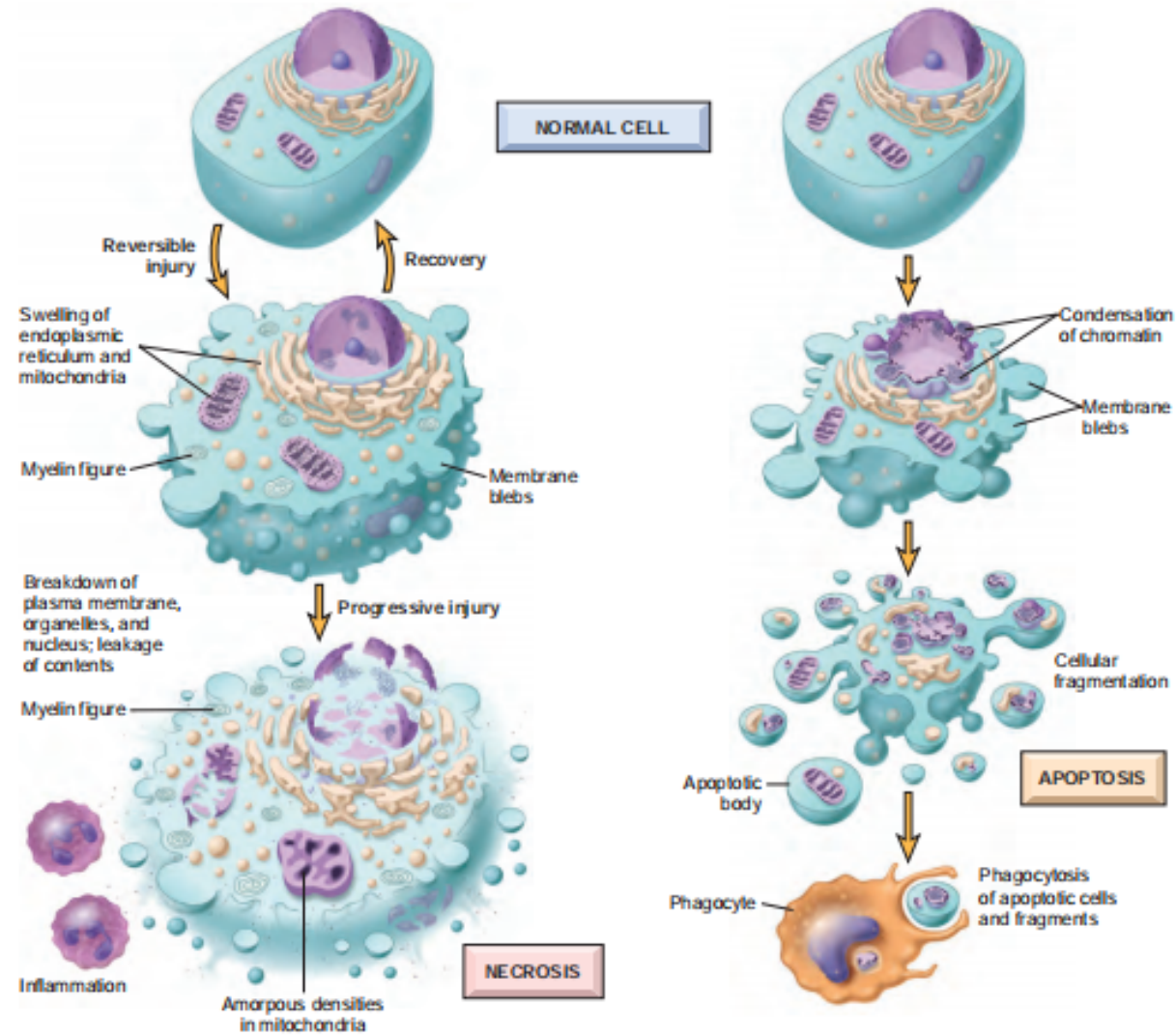
Progression of cell injury and death

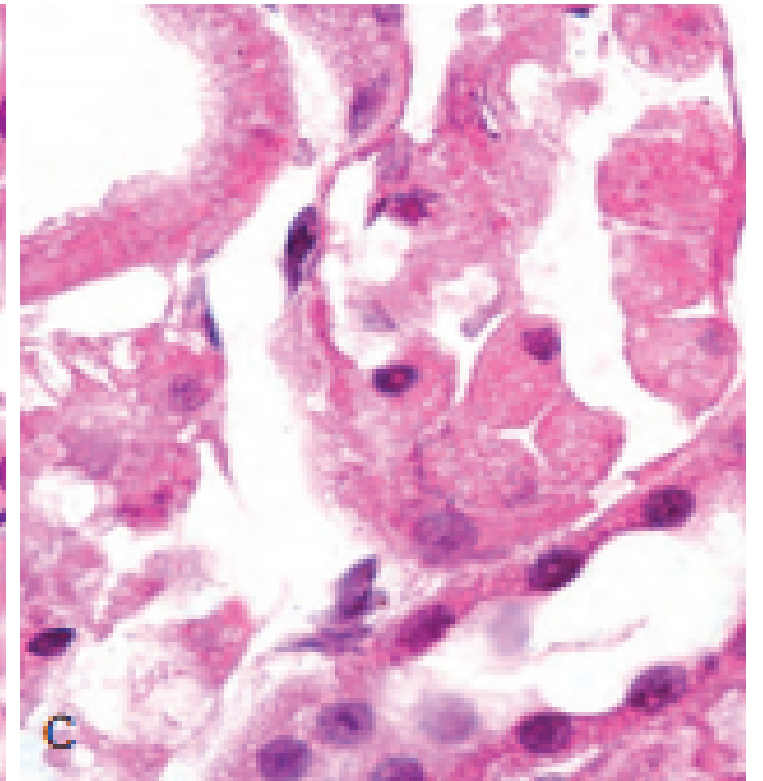
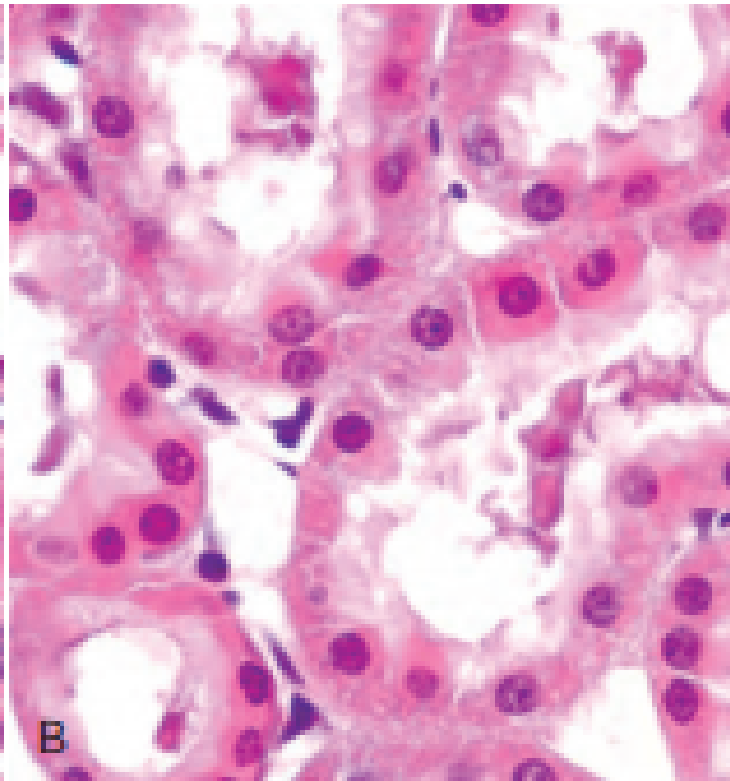
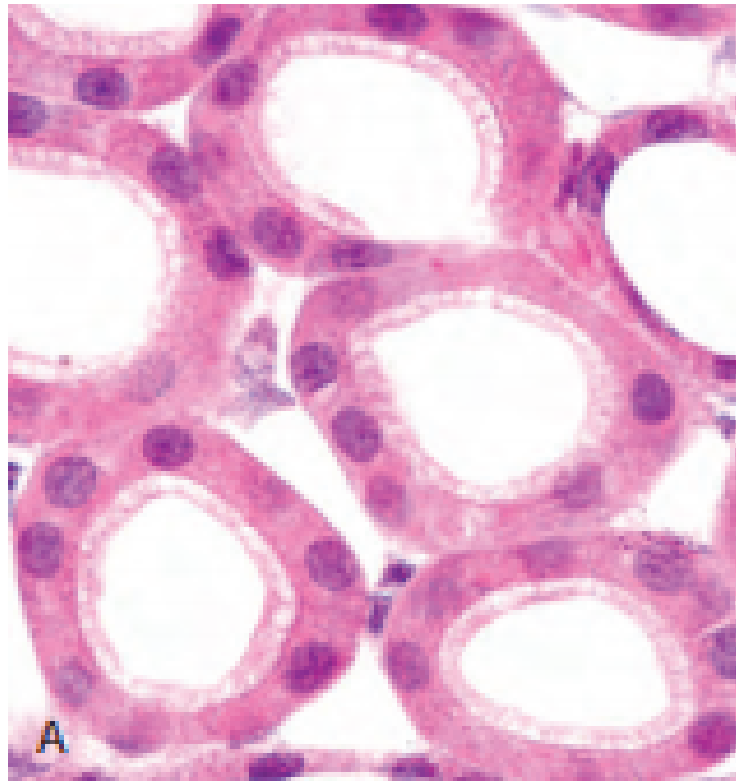


Reversible Cell Injury

- ▶ Reversible cell injury is characterized by functional and structural alterations in early stages or mild forms of injury, which are correctable if the damaging stimulus is removed
- ▶ Two features are consistently seen in reversibly injured cells: cellular swelling and fatty change

Cell Death





Patterns of cell Death

Table 2.1 Features of Necrosis and Apoptosis

Feature	Necrosis	Apoptosis
Cell size	Enlarged (swelling)	Reduced (shrinkage)
Nucleus	Pyknosis, karyorrhexis, karyolysis	Fragmentation into nucleosome-size fragments
Plasma membrane	Disrupted	Intact; altered structure, especially orientation of lipids
Cellular contents	Enzymatic digestion; may leak out of cell	Intact; may be released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Usually pathologic (culmination of irreversible cell injury)	Often physiologic, means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA damage

Patterns of necrosis

- ▶ **Coagulative necrosis:** is a form of necrosis in which the architecture of dead tissue is preserved for a span of at least some days.
- ▶ Ischemia caused by obstruction in a vessel may lead to coagulative necrosis of the supplied tissue in all organs except the brain

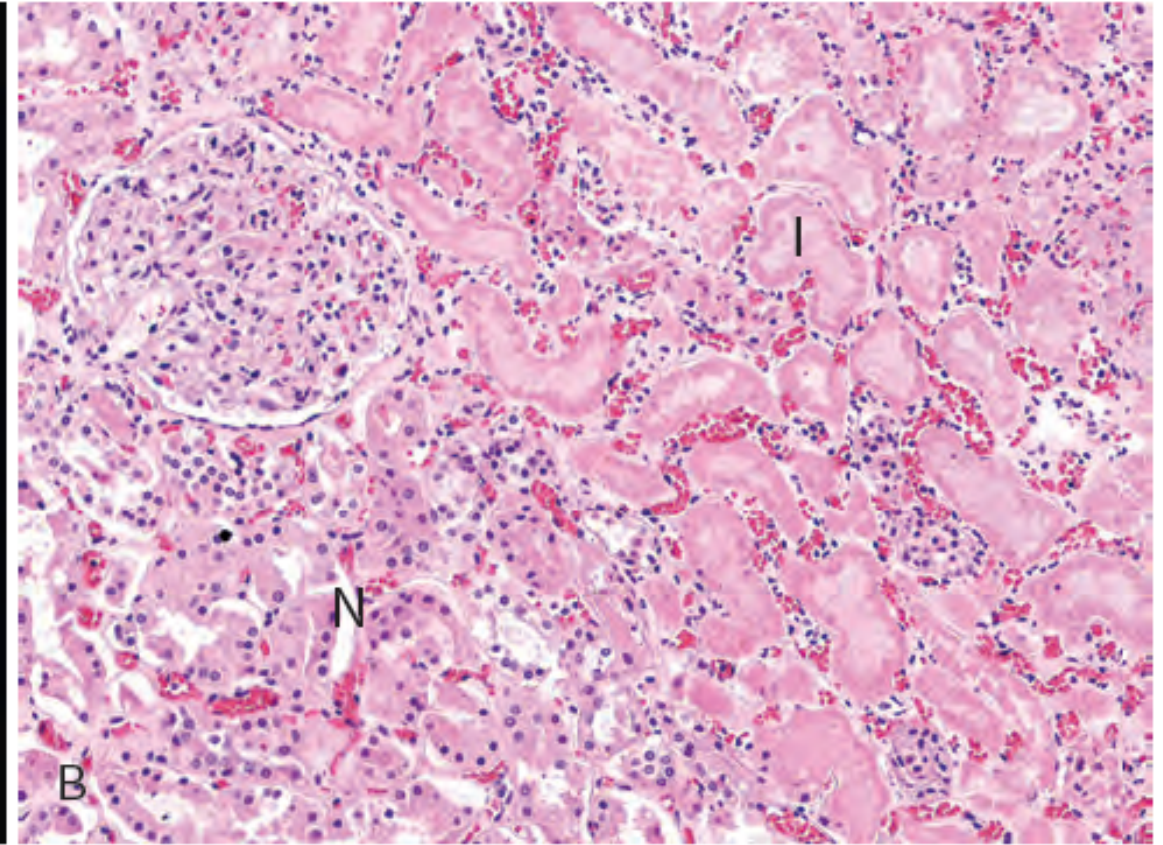
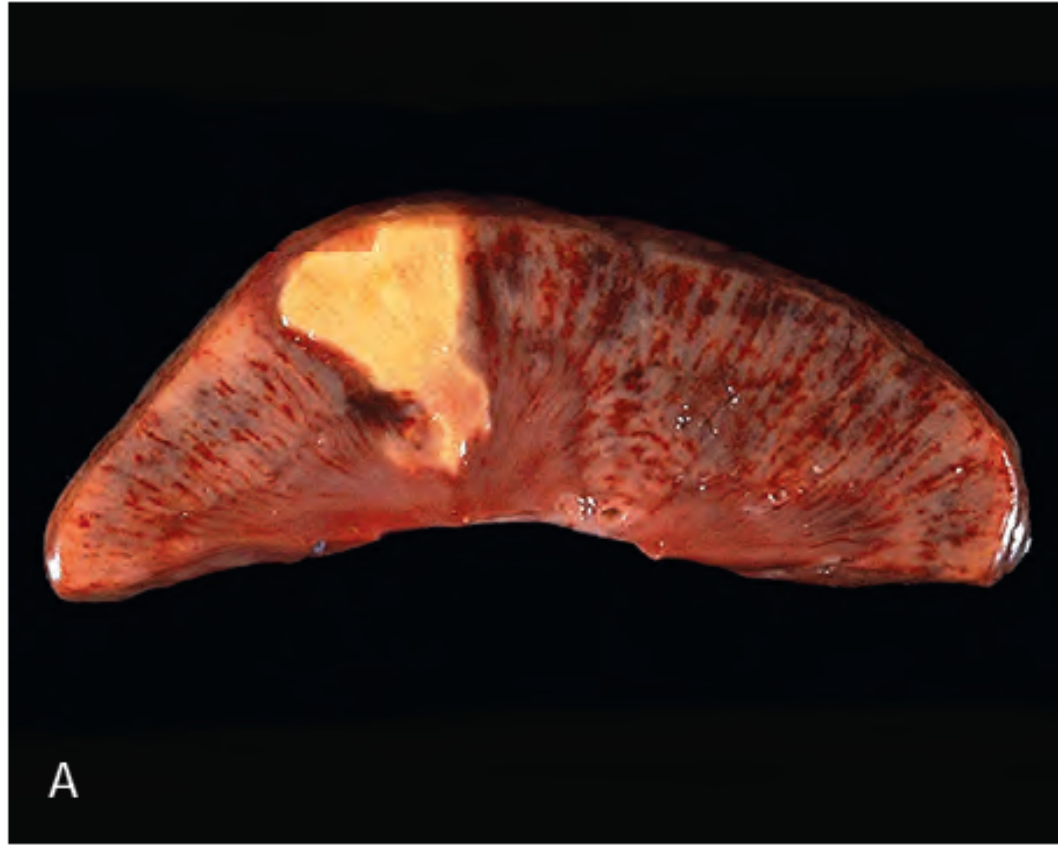


Figure 2.7 Coagulative necrosis. (A) A wedge-shaped kidney infarct (*yellow*). (B) Microscopic view of the edge of the infarct, with normal kidney (*N*) and necrotic cells in the infarct (*I*) showing preserved cellular outlines with loss of nuclei and an inflammatory infiltrate (seen as nuclei of inflammatory cells in between necrotic tubules).

- ▶ **Liquefactive necrosis:** Is characterized by digestion of the dead cells, resulting in transformation of the tissue into a viscous liquid.
- ▶ It is seen in focal bacterial or, occasionally, fungal infections, because microbes stimulate the accumulation of leukocytes and the liberation of enzymes from these cells.

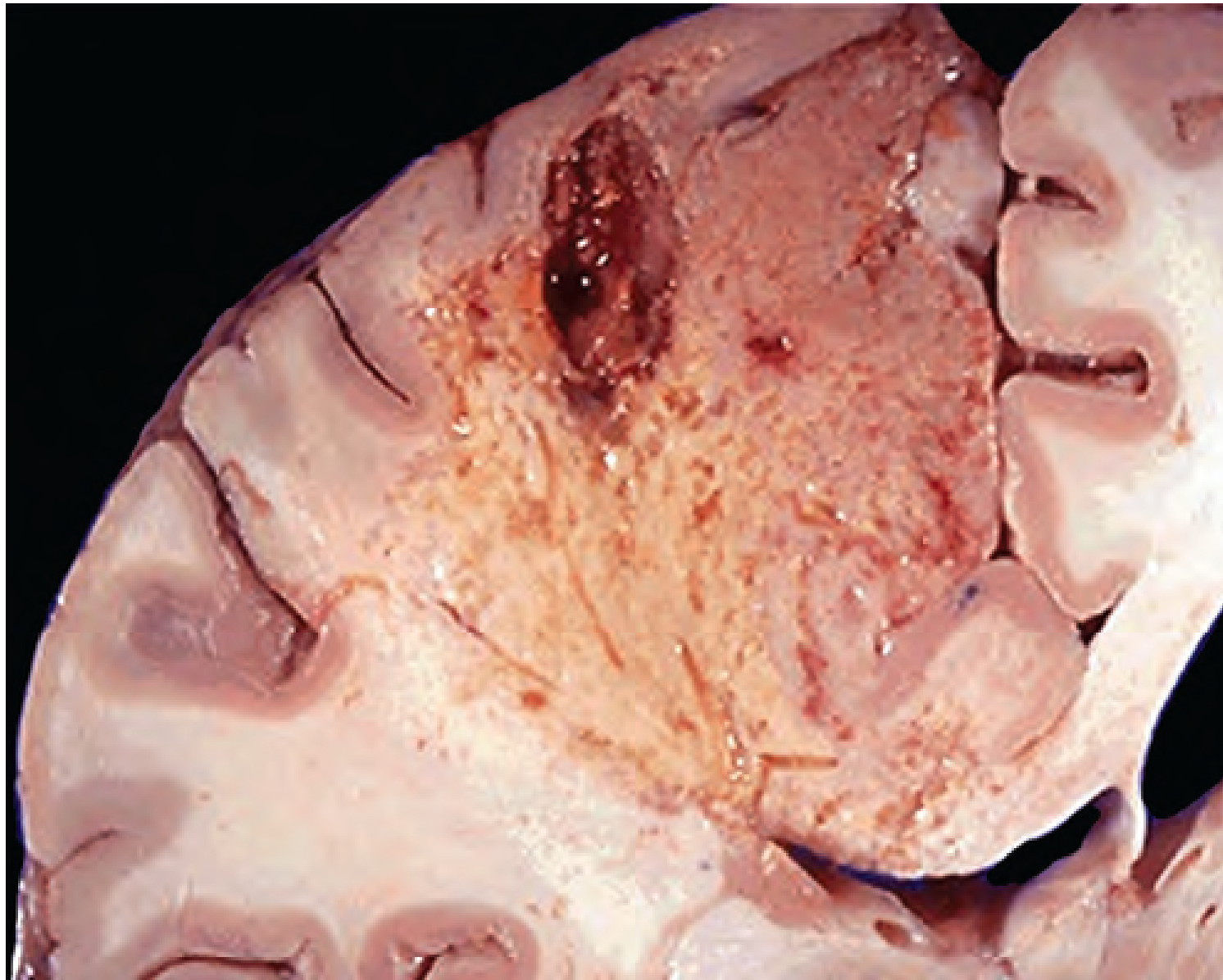


Figure 2.8 Liquefactive necrosis. An infarct in the brain, showing dissolution of the tissue.

- ▶ **Gangrenous necrosis:** is not a specific pattern of cell death, but the term is commonly used in clinical practice. It is usually applied to a limb, generally the lower leg, that has lost its blood supply and has undergone necrosis
- ▶ When bacterial infection is superimposed, there is more liquefactive necrosis because of the actions of degradative enzymes in the bacteria and the attracted leukocytes (giving rise to so-called **wet gangrene**)

- ▶ **Caseous necrosis** is encountered most often in foci of tuberculous infection. The term *caseous* (cheeselike) is derived from the friable white appearance of the area of necrosis
- ▶ On microscopic examination, the necrotic area appears as a structureless collection of fragmented or lysed cells and amorphous granular debris enclosed within a distinctive inflammatory border; this appearance is characteristic of a focus of inflammation known as a **granuloma**

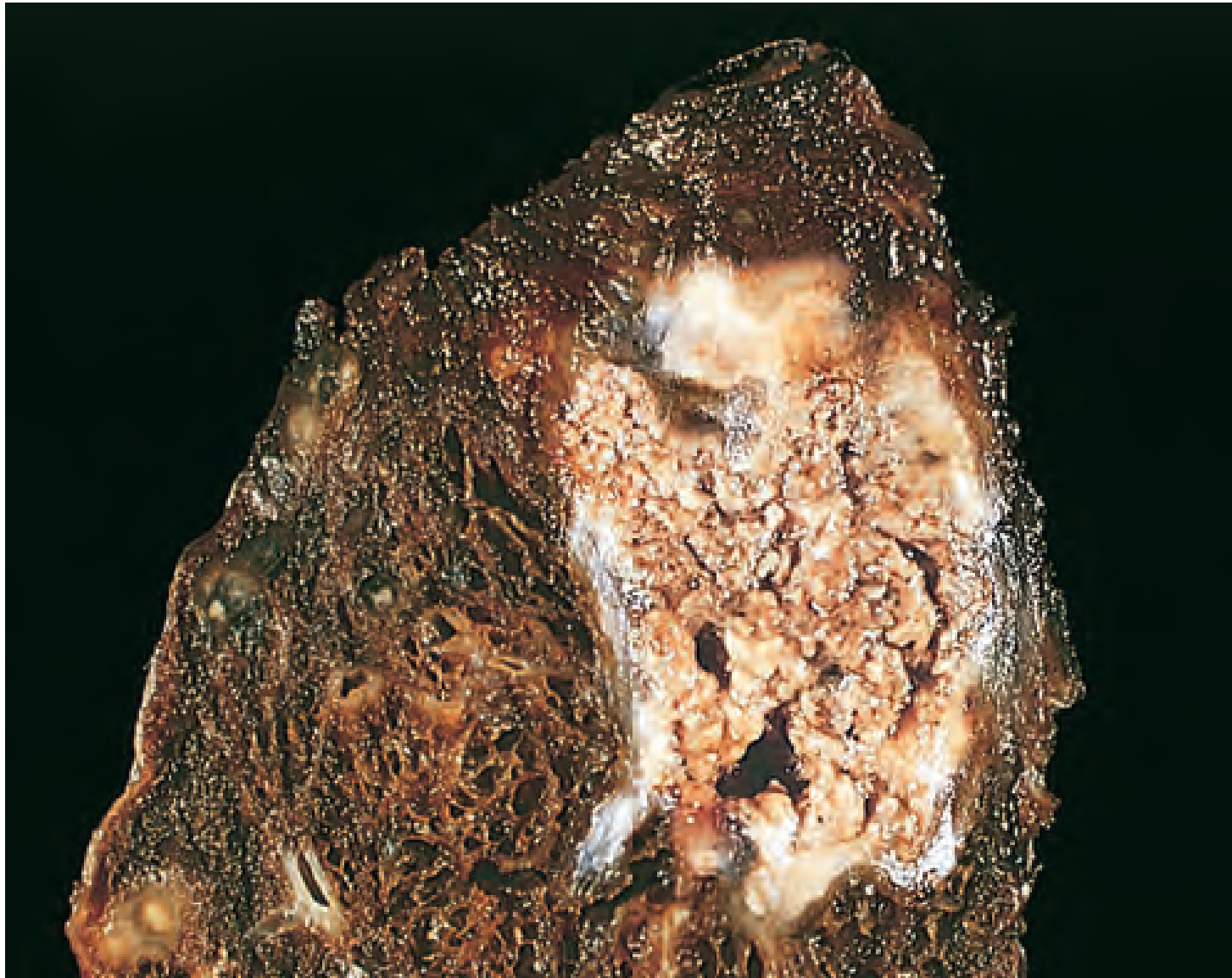


Figure 2.9 Caseous necrosis. Tuberculosis of the lung, with a large area of caseous necrosis containing yellow-white and “cheesy” appearing debris.

- ▶ **Fat necrosis** refers to focal areas of fat destruction, typically resulting from release of activated pancreatic lipases into the substance of the pancreas and the peritoneal cavity. This occurs in the calamitous abdominal emergency known as acute pancreatitis

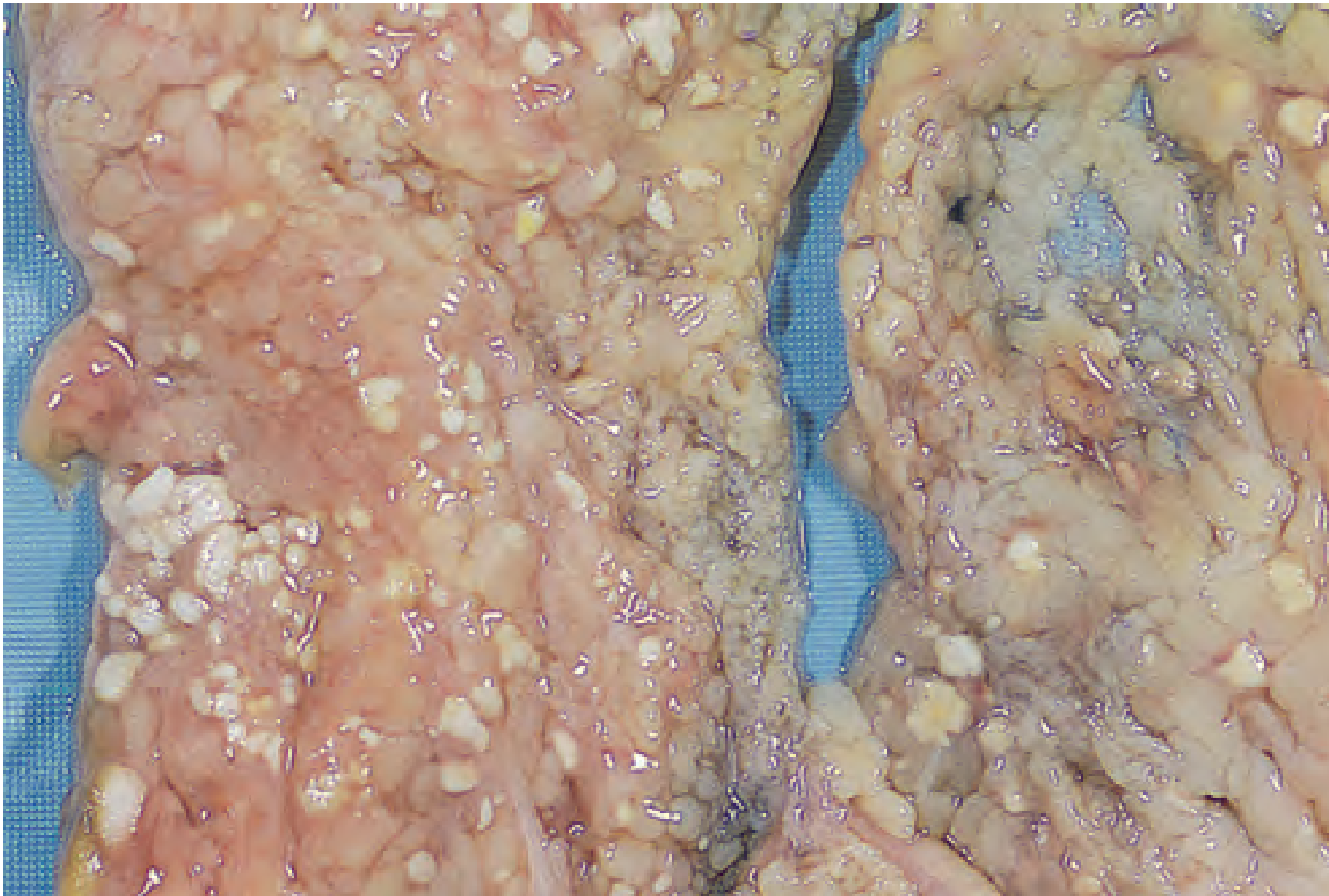


Figure 2.10 Fat necrosis. The areas of white chalky deposits represent foci of fat necrosis with calcium soap formation (saponification) at sites of lipid breakdown in the mesentery.

- ▶ **Fibrinoid necrosis** is a special form of vascular damage usually seen in immune reactions involving blood vessels. It typically occurs when complexes of antigens and antibodies are deposited in the walls of arteries.
- ▶ Deposits of these immune complexes, together with plasma proteins that has leaked out of vessels, result in a bright pink and amorphous appearance in H&E stains called “fibrinoid” (fibrin-like) by pathologists

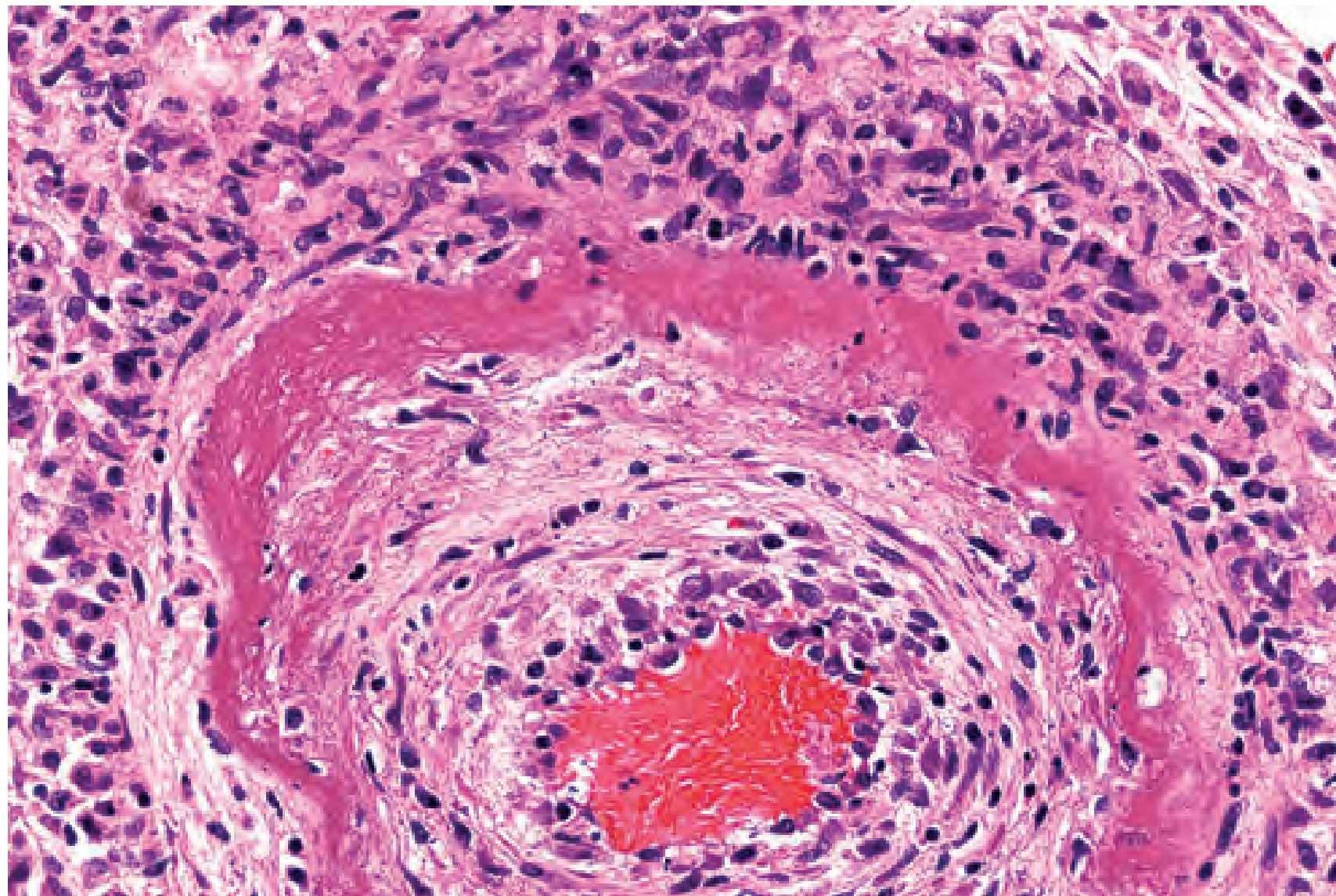


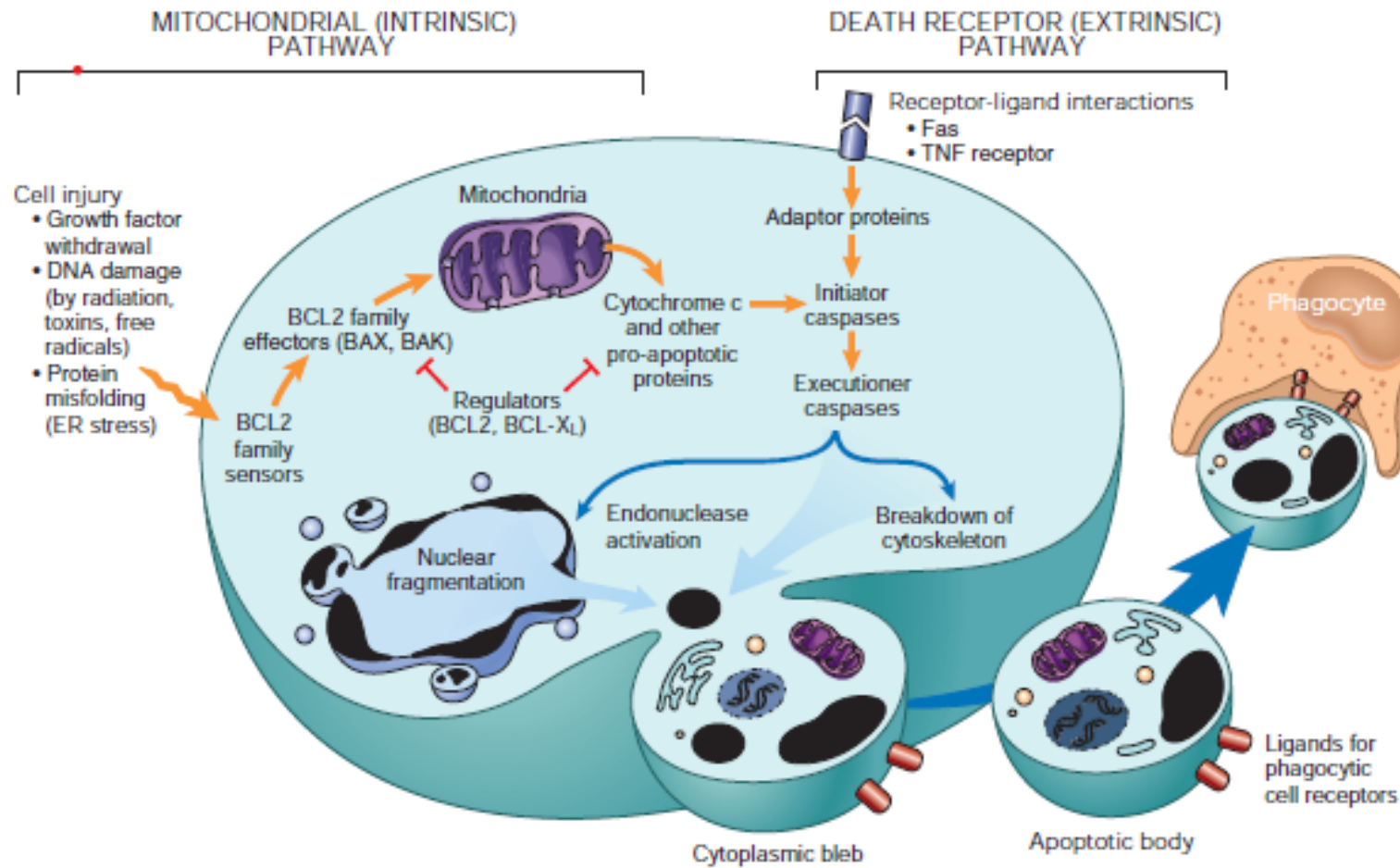
Figure 2.11 Fibrinoid necrosis in an artery. The wall of the artery shows a circumferential bright pink area of necrosis with inflammation (neutrophils with dark nuclei).

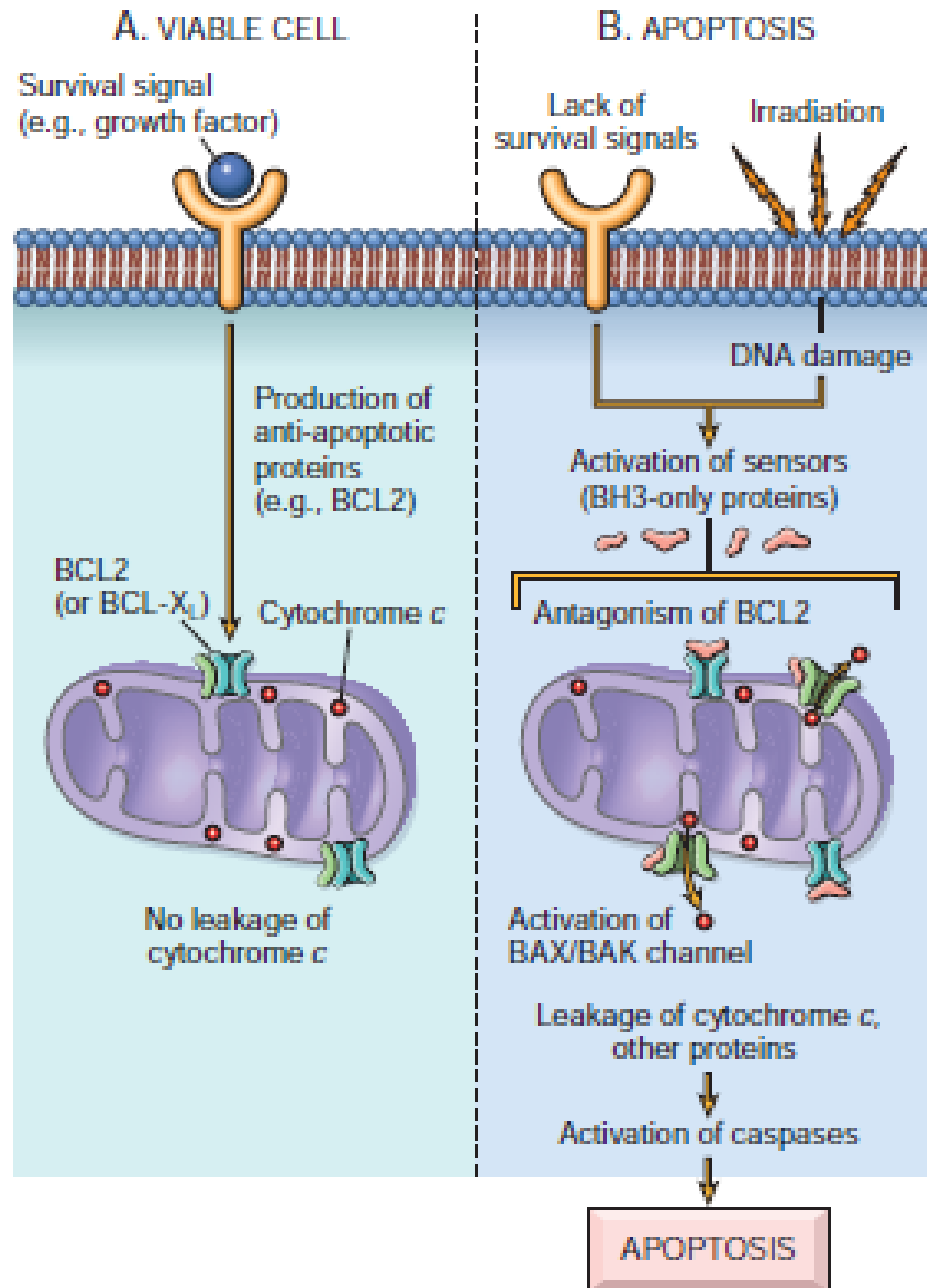
Apoptosis

- ▶ Apoptosis is a type of cell death that is induced by a tightly regulated suicide program in which cells destined to die activate intrinsic enzymes that degrade the cells' genomic DNA and nuclear and cytoplasmic proteins.
- ▶ Apoptotic cells break up into plasma membrane-bound fragments, called *apoptotic bodies*, which contain portions of the cytoplasm and nucleus.
- ▶ the dead cell and its fragments are rapidly devoured, before the contents leak out, and therefore apoptosis does not elicit an inflammatory reaction

Physiological	Pathological
Removal of supernummary cells during development	DNA Damage
Involution of hormone dependent tissue on hormone withdrawal(menstrual cycle)	Accumulation of misfolded proteins
Cell turnover in proliferating cell populations such as immature lymphocytes, epithelial cells in intestinal crypts	Apoptosis can be induced during certain infections, particularly viral infections
Elimination of potentially harmful self reacting lymphocytes	Apoptosis may also contribute to pathologic atrophy in parenchymal organs after duct obstruction, such as occurs in the pancreas, parotid gland, and kidney
Death of host cells that have served their useful purpose like neutrophils in an acute inflammatory response or lymphocytes at the end of an immune response	

Mechanisms of Apoptosis

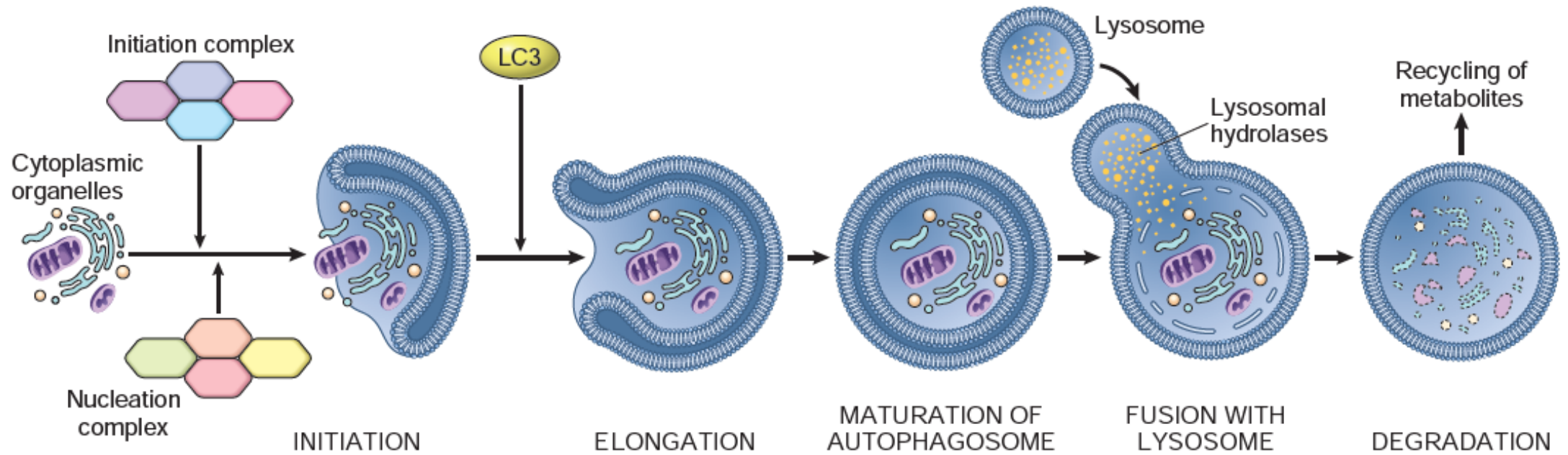




Other Mechanisms of Cell Death

- ▶ Although necrosis and apoptosis are the best-defined mechanisms of cell death, several other ways by which cells die have been described. These include the following:
- ▶ **Necroptosis.** As the name indicates, this form of cell death is a hybrid that shares aspects of both necrosis and apoptosis.
- ▶ **Pyroptosis** is a form of apoptosis that is accompanied by the release of the fever-inducing cytokine IL-1 (*pyro* refers to fever).
- ▶ **Ferroptosis.** Only discovered in 2012, ferroptosis is a distinct form of cell death that is triggered when excessive intracellular levels of iron or reactive oxygen species overwhelm the glutathione-dependent antioxidant defenses to cause unchecked membrane lipid peroxidation.

Autophagy



Role of autophagy in human disease

- ▶ **Cancer:** Autophagy can both promote cancer growth and act as a defense against cancers
- ▶ **Neurodegenerative disorders:** Many neurodegenerative disorders are associated with dysregulation of autophagy
- ▶ **Infectious diseases:** Many pathogens are degraded by autophagy;
- ▶ **Inflammatory bowel diseases:** Genome-wide association studies have linked both Crohn disease and ulcerative colitis to single-nucleotide polymorphisms (SNPs) in the autophagy-related gene ATG16L1

Mechanisms of cell injury

- ▶ The molecular alterations that lead to cell injury are complex, but several principles are relevant to most forms of cell injury
- ▶ The cellular response to injurious stimuli depends on the nature of the injury, its duration, and its severity.
- ▶ The consequences of cell injury depend on the type, state, and adaptability of the injured cell.
- ▶ Any injurious stimulus may simultaneously trigger multiple interconnected mechanisms that damage cells.

General mechanisms of cell injury and intracellular targets of injurious stimuli

- ▶ Cell injury results from abnormalities in one or more essential cellular components
- ▶ Principal targets of injurious stimuli are mitochondria, cell membranes, the machinery of protein synthesis and secretion, and DNA
- ▶ The consequences of injury of each of these cellular components are distinct but overlapping.

Mitochondrial damage

- ▶ Mitochondria are critical players in all pathways leading to cell injury and death because of the critical role they play in ATP generation
- ▶ Mitochondria can be damaged by increases of cytosolic Ca^{2+} , ROS and oxygen deprivation, which makes them sensitive to virtually all types of injurious stimuli, including hypoxia and toxins
- ▶ Mutations in mitochondrial genes are the cause of some inherited diseases

Consequences of Mitochondrial Damage

- ▶ ATP depletion.
- ▶ The activity of the plasma membrane energy-dependent sodium pump (Na^+, K^+ -ATPase) is reduced
- ▶ Cellular energy metabolism is altered.
- ▶ reduction in protein synthesis
- ▶ Incomplete oxidative phosphorylation also leads to the formation of ROS, which have many deleterious effects
- ▶ leakage of mitochondrial proteins due to channel formation by pro-apoptotic proteins which is the initial step in apoptosis

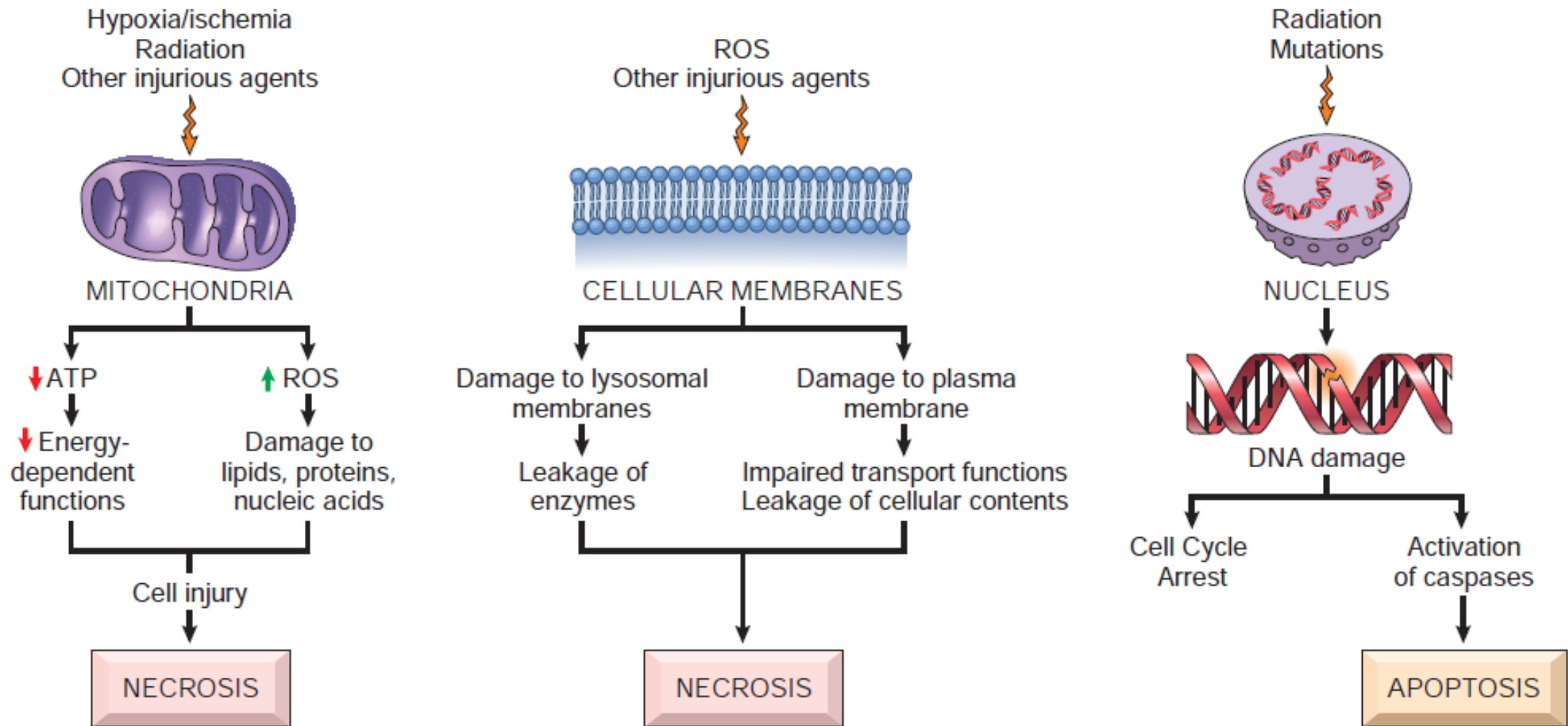


Figure 2.18 The principal forms and sites of damage in cell injury. *ATP*, Adenosine triphosphate; *ROS*, reactive oxygen species.

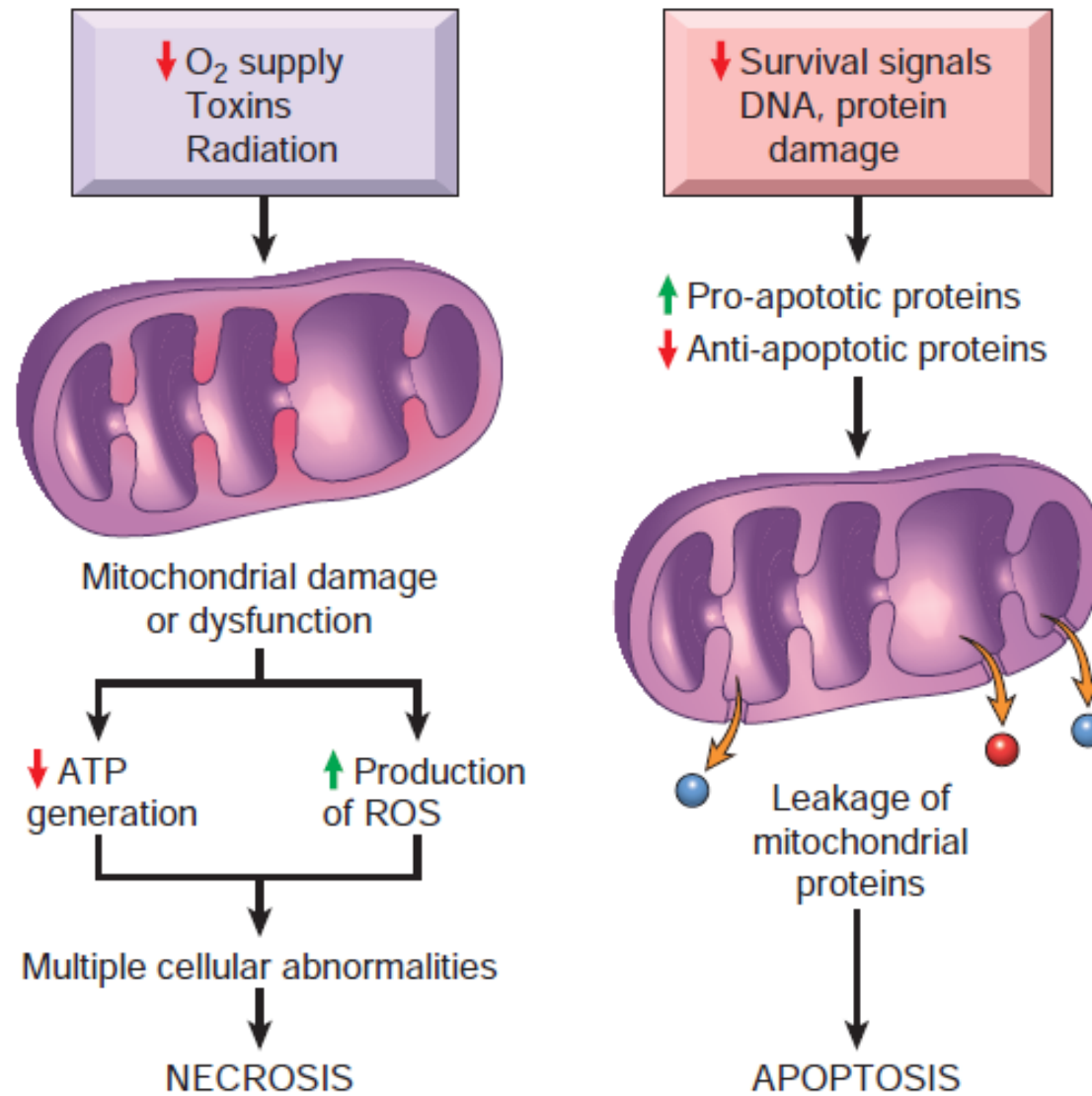
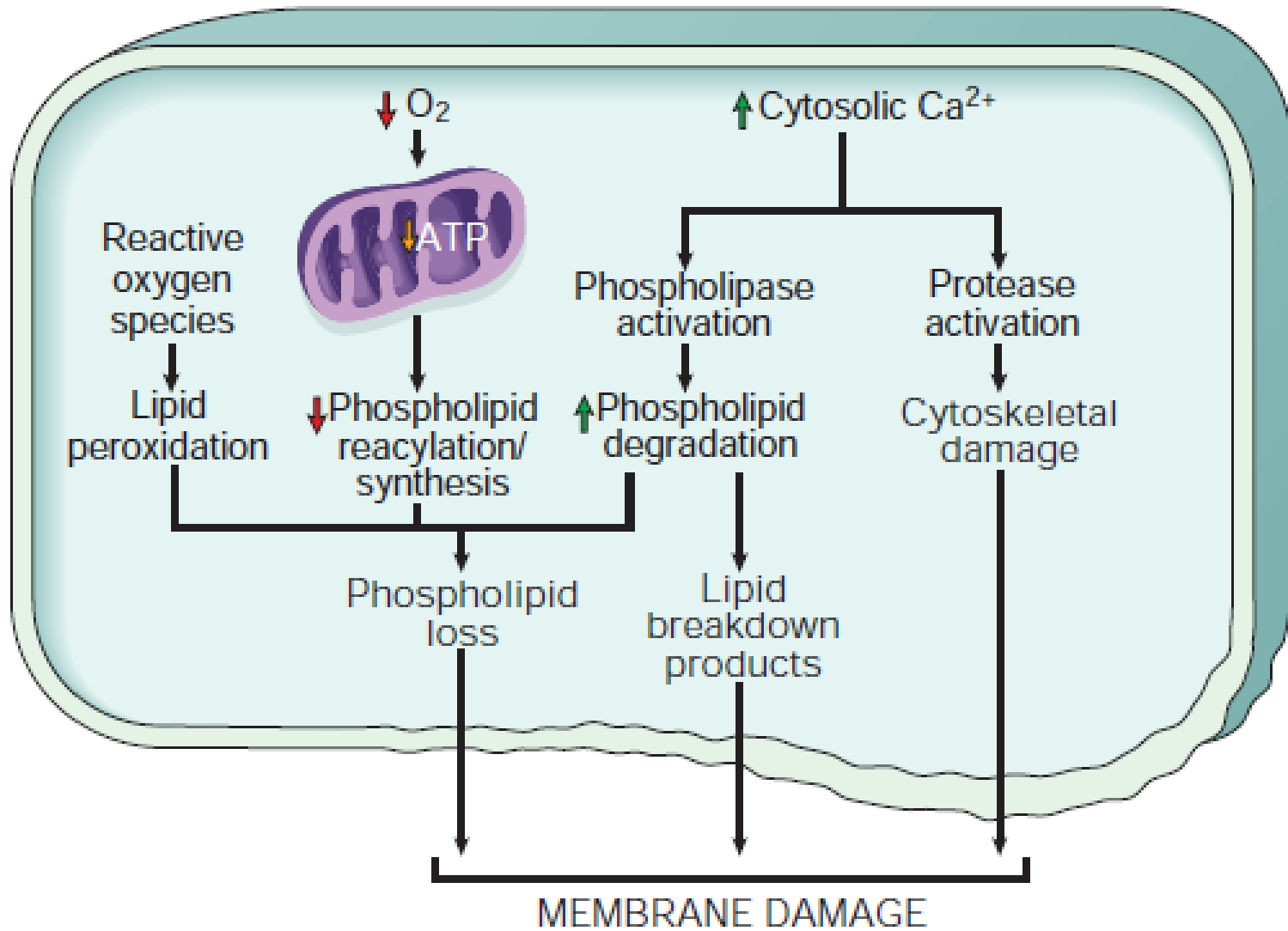


Figure 2.19 Role of mitochondria in cell injury and death. Mitochondria are affected by a variety of injurious stimuli, and their abnormalities lead to necrosis or apoptosis. *ATP*, Adenosine triphosphate; *ROS*, reactive oxygen species.

Membrane Damage

- ▶ Early loss of selective membrane permeability, leading ultimately to overt membrane damage, is a consistent feature of most forms of cell injury (except apoptosis)
- ▶ In ischemic cells, membrane defects may be the result of ATP depletion and calcium-mediated activation of phospholipases
- ▶ The plasma membrane can also be damaged directly by bacterial toxins, viral proteins, lytic complement components, and a variety of physical and chemical agents

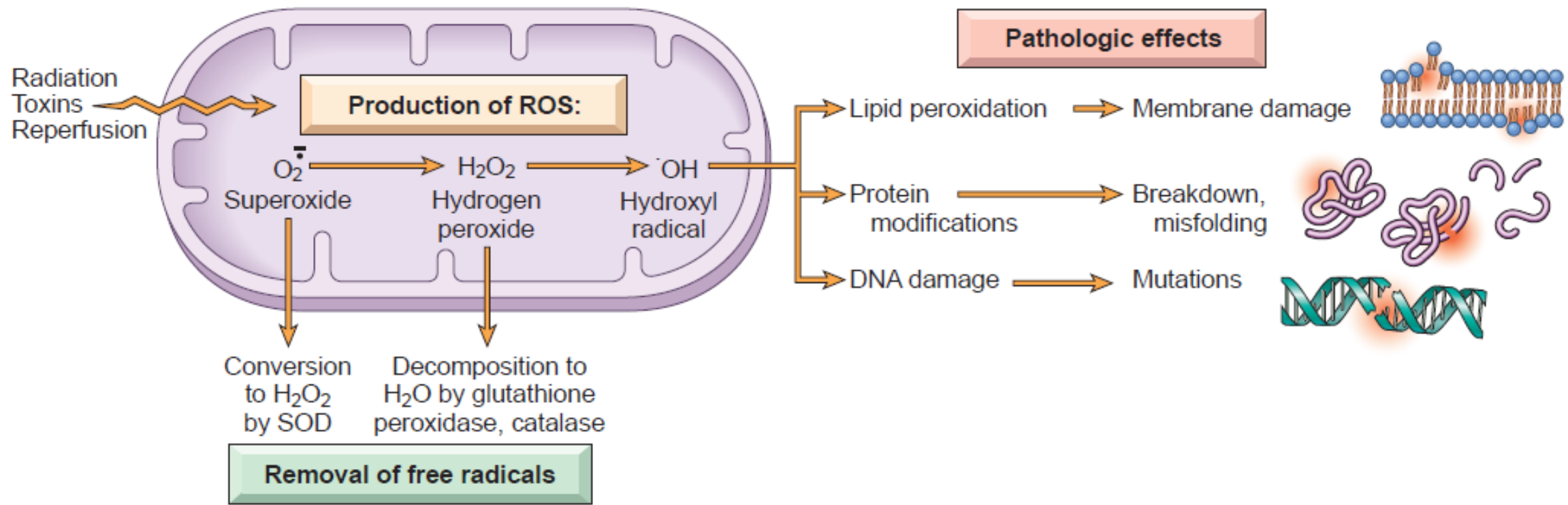


Damage to DNA

- ▶ Damage to nuclear DNA activates sensors that trigger p53-dependent pathways
- ▶ DNA damage may be caused by exposure to radiation, chemotherapeutic (anticancer) drugs, and ROS, or may occur spontaneously as a part of aging, due largely to deamination of cytosine residues to uracil residues
- ▶ DNA damage activates p53, which arrests cells in the G1 phase of the cell cycle and activates DNA repair mechanisms
- ▶ Predictably, mutations in p53 that interfere with its ability to arrest cell cycling or to induce apoptosis are associated with numerous cancers

Oxidative Stress

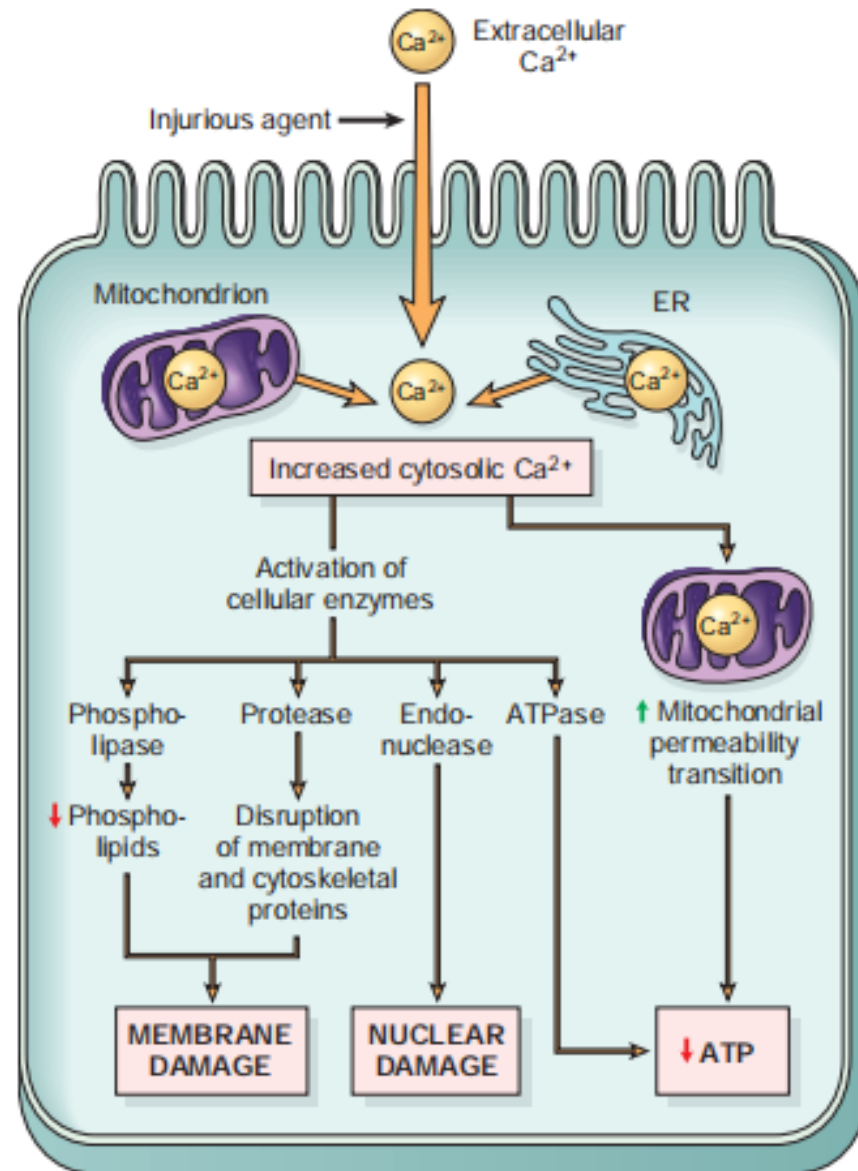
- ▶ Free radicals are chemical species that have a single unpaired electron in an outer orbit.
- ▶ ROS are produced normally in cells during mitochondrial respiration and energy generation, but they are degraded and removed by intracellular ROS scavengers.
- ▶ Increased production or decreased scavenging of ROS may lead to an excess of free radicals, a condition called *oxidative stress*
- ▶ Oxidative stress has been implicated in a wide variety of pathologic processes, including cell injury, cancer, aging, and some degenerative diseases, such as Alzheimer disease.



Pathologic Effects of free radicals

- ▶ Lipid peroxidation in membranes.
- ▶ Oxidative modification of protein
- ▶ Lesions in DNA

Disturbance in calcium hemostasis



Endoplasmic Reticulum Stress

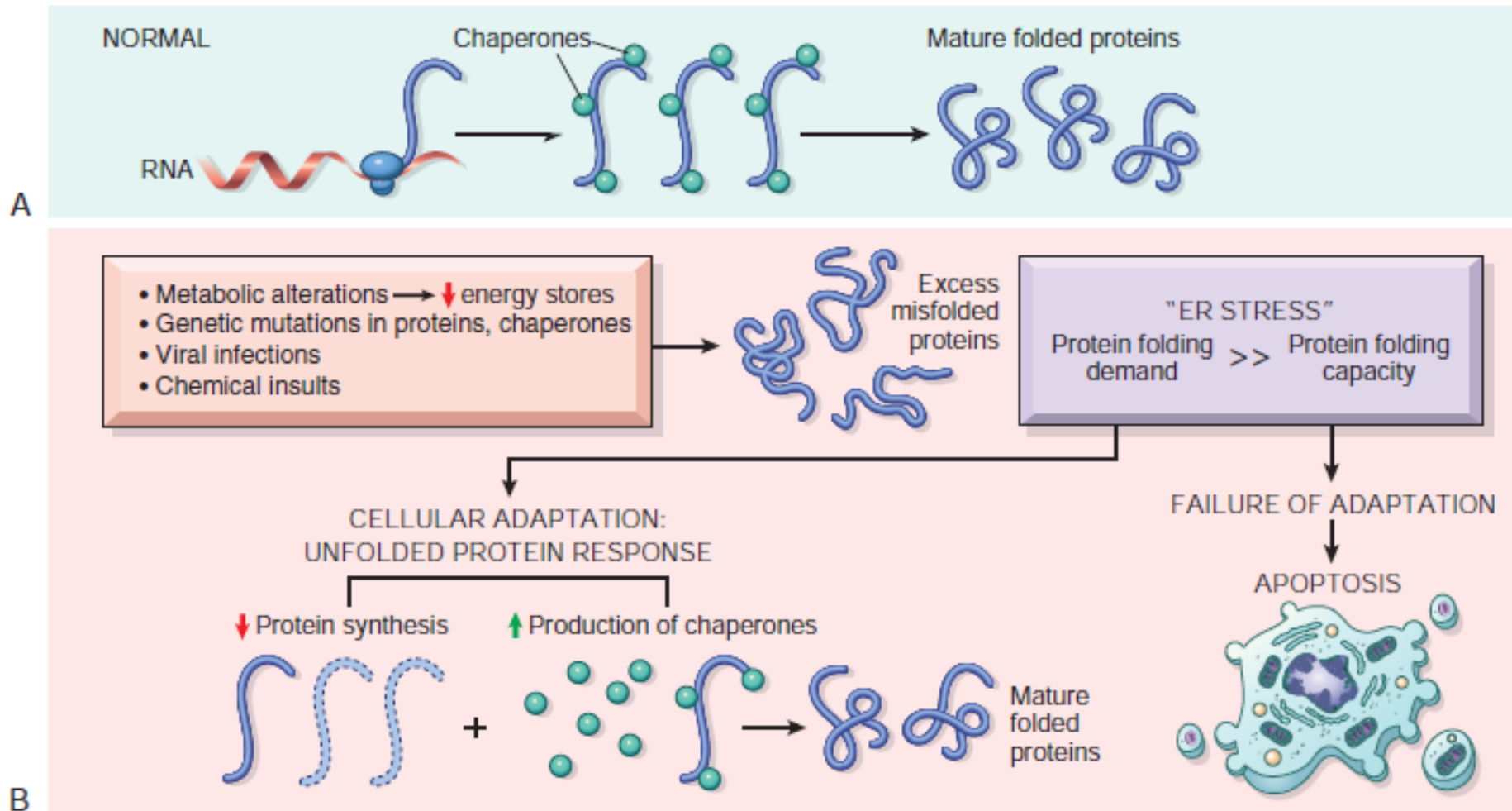


Table 2.3 Selected Examples of Diseases Caused by Misfolding of Proteins

Disease	Affected Protein	Pathogenesis
Cystic fibrosis	Cystic fibrosis transmembrane conductance regulator (CFTR)	Loss of CFTR leads to defects in chloride transport
Familial hypercholesterolemia	LDL receptor	Loss of LDL receptor leads to hypercholesterolemia
Tay-Sachs disease	Hexosaminidase β subunit	Lack of the lysosomal enzyme leads to storage of GM ₂ gangliosides in neurons
α_1 -antitrypsin deficiency	α_1 -antitrypsin	Storage of nonfunctional protein in hepatocytes causes apoptosis; absence of enzymatic activity in lungs causes destruction of elastic tissue giving rise to emphysema
Creutzfeldt-Jacob disease	Prions	Abnormal folding of PrP ^{sc} causes neuronal cell death
Alzheimer disease	A β peptide	Abnormal folding of A β peptides causes aggregation within neurons and apoptosis

Clinicopathological correlations: selected examples of cell injury and death

- ▶ **Hypoxia and Ischemia:** Ischemia, the most common cause of cell injury in clinical medicine, results from hypoxia induced by reduced blood flow, most often due to a mechanical arterial obstruction

Mechanism of injury

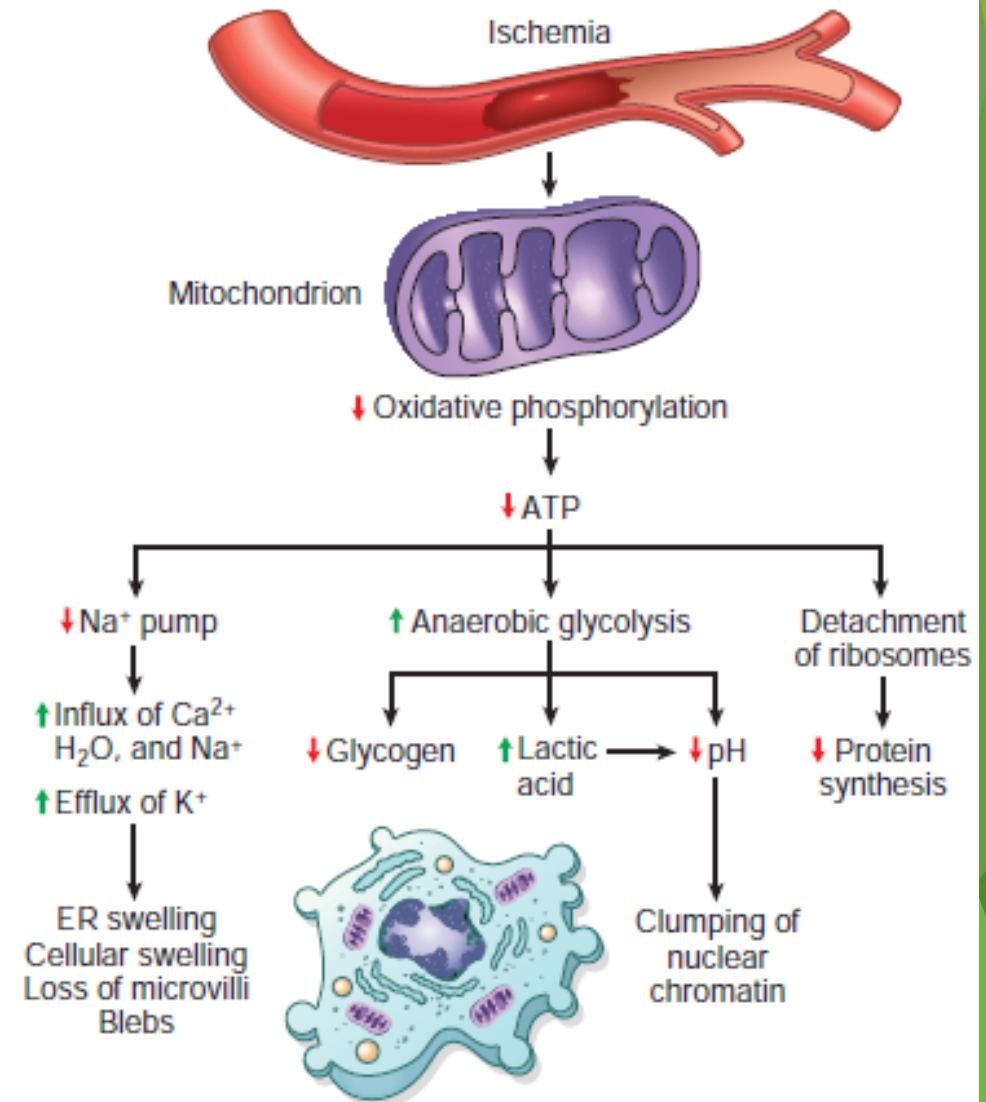


Figure 2.24 Functional and morphologic consequences of decreased intracellular adenosine triphosphate (ATP) in ischemic cell injury. The morphologic changes shown here are indicative of reversible cell injury. Further depletion of ATP results in cell death, typically by necrosis. ER, Endoplasmic reticulum.

Ischaemic reperfusion Injury

- ▶ Restoration of blood flow to ischemic tissues can promote recovery of cells if they are reversibly injured but can also paradoxically exacerbate cell injury and cause cell death.
- ▶ As a consequence, reperfused tissues may sustain loss of viable cells in addition to those that are irreversibly damaged by the ischemia.
- ▶ new damaging processes are set in motion during reperfusion, causing the death of cells that might have recovered otherwise.

Mechanism of injury

- ▶ Oxidative stress
- ▶ Intracellular calcium overload.
- ▶ Inflammation.
- ▶ Activation of the complement system

Chemical/toxic injury

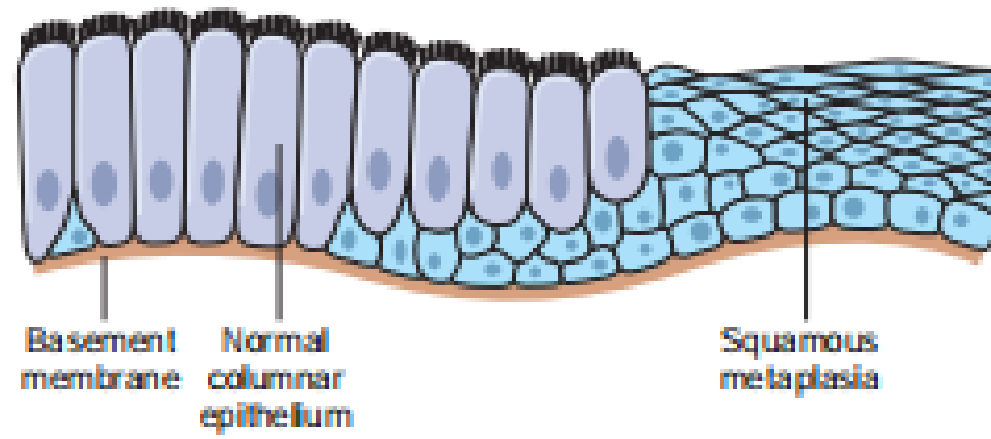
- ▶ Chemical injury remains a frequent problem in clinical medicine and is a major limitation to drug therapy.

Chemicals induce cell injury by one of two general mechanisms:

- ▶ *Direct toxicity.* Some chemicals injure cells directly by combining with critical molecular components
- ▶ *Conversion to toxic metabolites.* Most toxic chemicals are not biologically active in their native form but must be converted to reactive toxic metabolites
- ▶ This modification is usually accomplished by the cytochrome P-450 mixed-function oxidases in the smooth ER of the liver and other organs

Adaptations of cellular Growth and differentiation

- ▶ Hypertrophy
- ▶ Hyperplasia
- ▶ Atrophy
- ▶ metaplasia



A

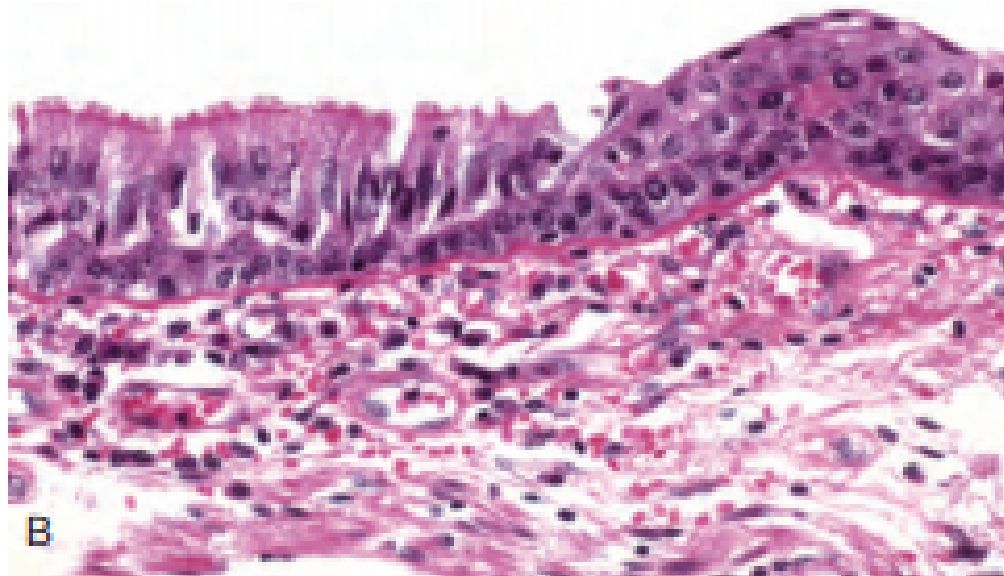
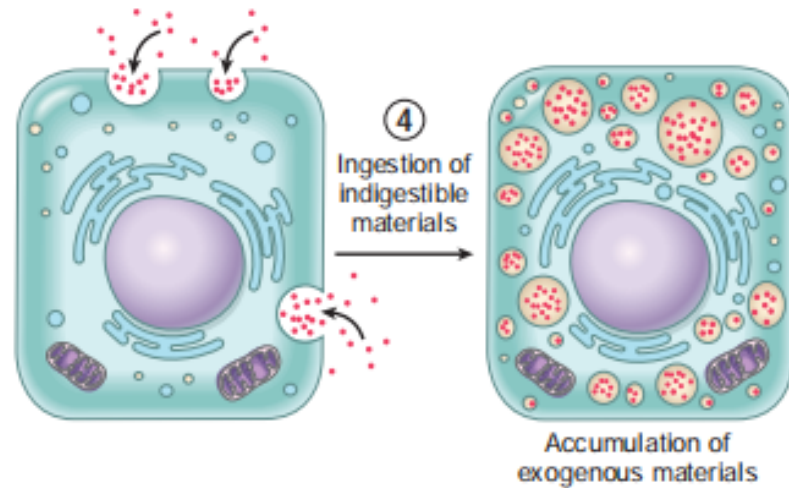
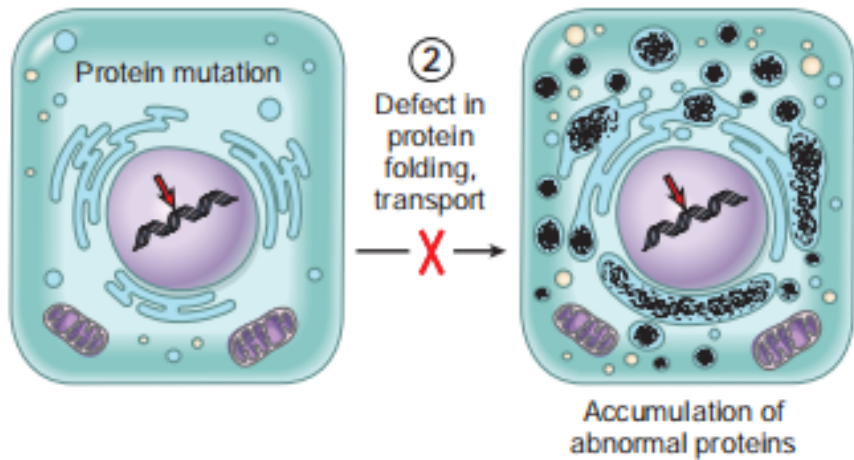
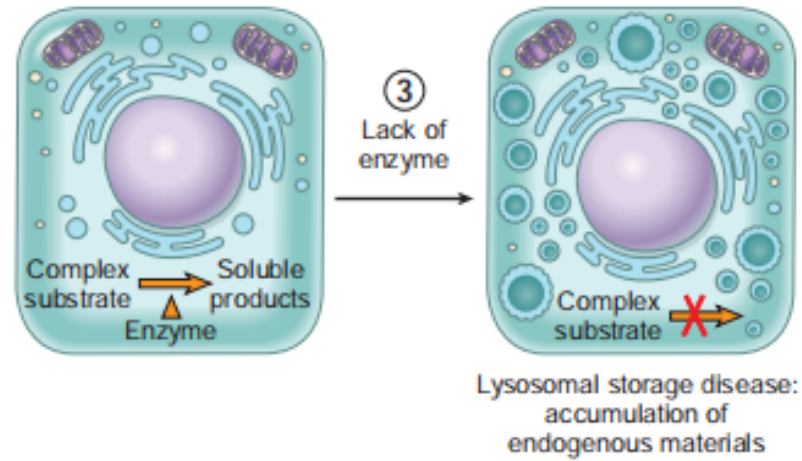
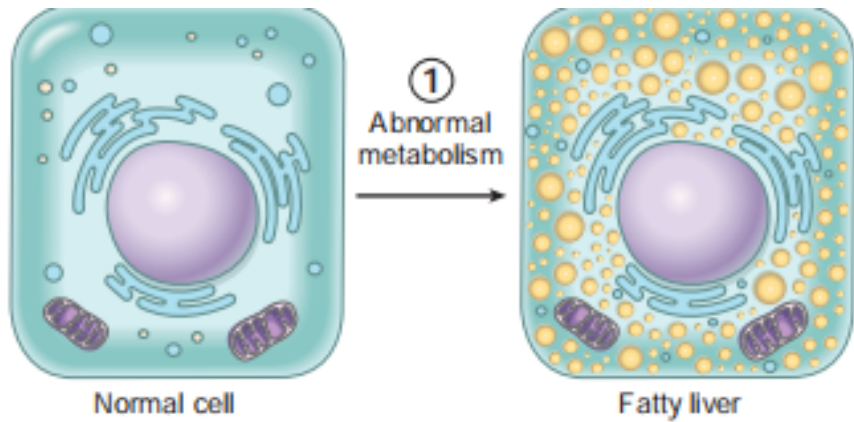


Figure 2.28 Metaplasia of columnar to squamous epithelium. (A) Schematic diagram. (B) Metaplasia of columnar epithelium (left) to squamous epithelium (right) in a bronchus (as often occurs with smoking).

Intracellular accumulations



Examples

- ▶ lipids
- ▶ proteins
- ▶ glycogen
- ▶ pigments

Lipids

- ▶ ***Steatosis (Fatty Change)***: The terms *steatosis* and *fatty change* describe abnormal accumulations of triglycerides within parenchymal cells.
- ▶ The causes of steatosis include toxins, protein malnutrition, diabetes mellitus, obesity, and anoxia.
- ▶ In higher-income nations, the most common causes of significant fatty change in the liver (fatty liver) are alcohol abuse and nonalcoholic fatty liver disease

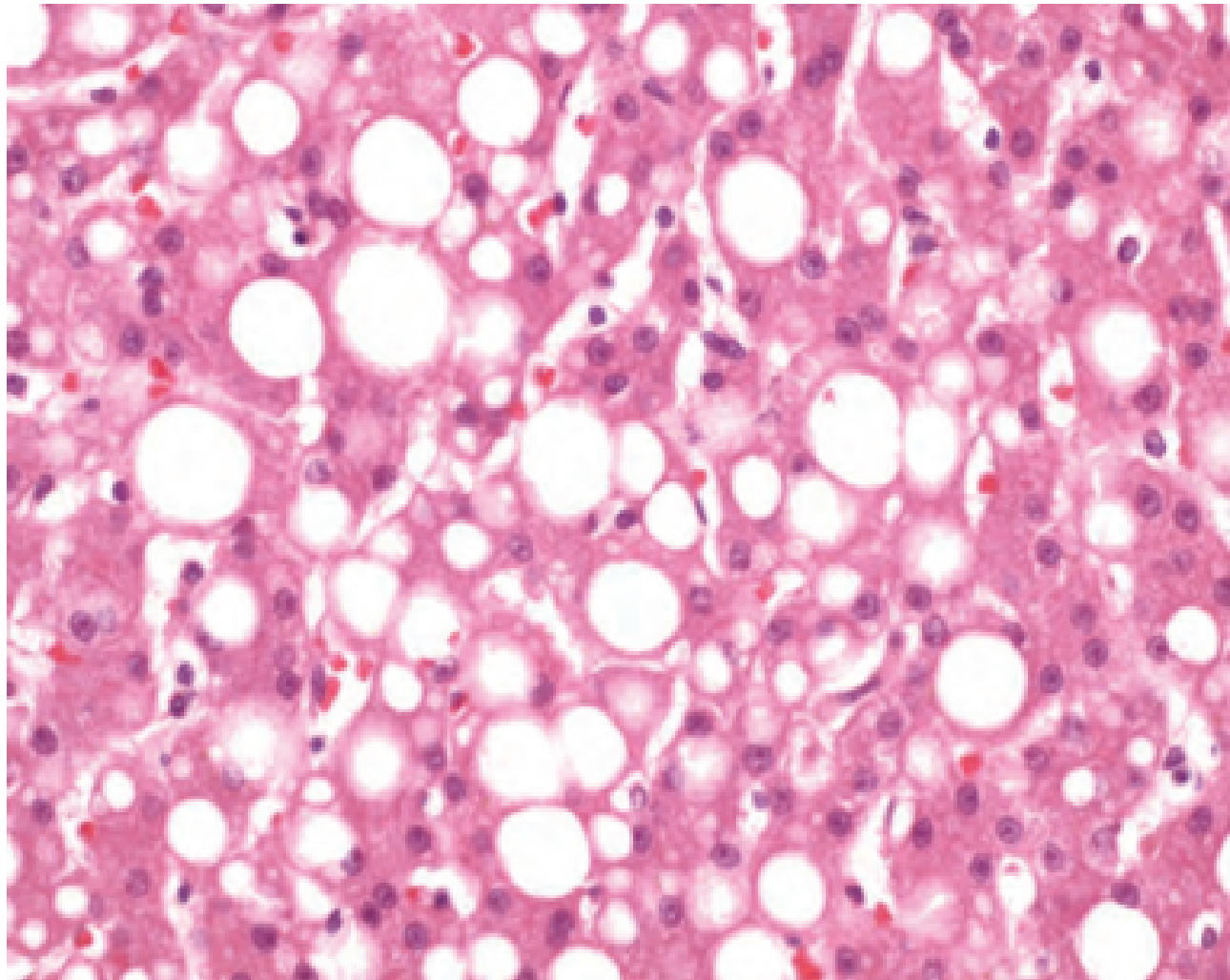


Figure 2.30 Fatty liver. High-power detail of fatty change of the liver. In most cells, the well-preserved nucleus is squeezed into the displaced rim of cytoplasm about the fat vacuole. (Courtesy Dr. James Crawford, Department of Pathology, Hofstra Northwell School of Medicine, NY)

Cholesterol and its Esters

- ▶ Accumulations manifested histologically by intracellular vacuoles are seen in several pathologic processes.
- ▶ ***Atherosclerosis***. In atherosclerotic plaques, smooth muscle cells and macrophages within the intimal layer of the aorta and large arteries are filled with lipid vacuoles, most of which contain cholesterol and cholesterol esters
- ▶ ***Xanthomas***. Intracellular accumulation of cholesterol within macrophages is also characteristic of acquired and hereditary hyperlipidemic states
- ▶ ***Cholesterolosis***. This refers to the focal accumulations of cholesterol-laden macrophages in the lamina propria of the gallbladder
- ▶ ***Niemann-Pick disease, type C***. This lysosomal storage disease is caused by mutations affecting an enzyme involved in cholesterol trafficking, resulting in cholesterol accumulation in multiple organs

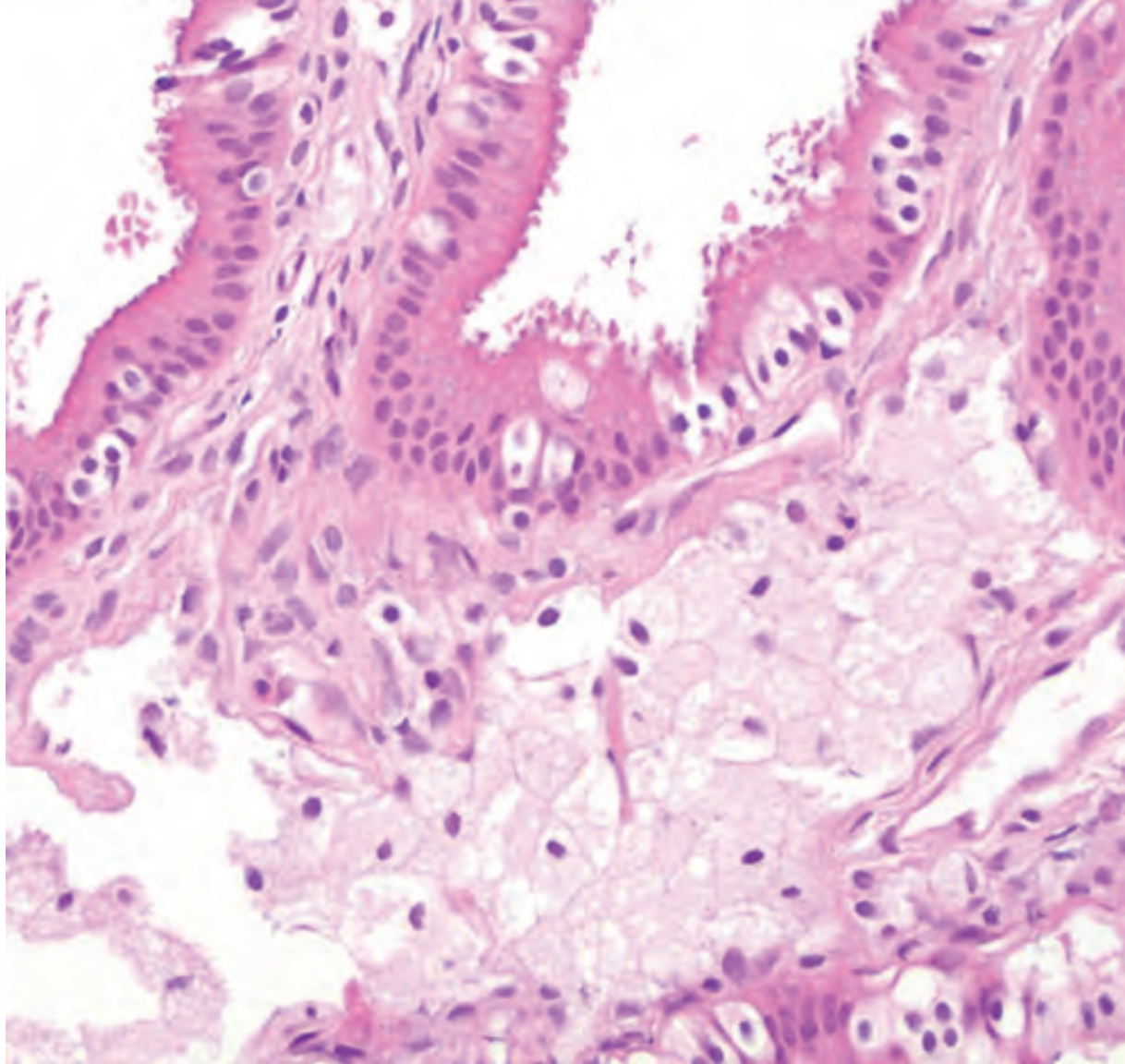


Figure 2.31 Cholesterolosis. Cholesterol-laden macrophages (foam cells, *arrow*) in a focus of gallbladder cholesterolosis. (Courtesy Dr. Matthew Yeh, Department of Pathology, University of Washington, Seattle, Wash.)

Proteins

- ▶ **Intracellular accumulations of proteins usually appear as rounded, eosinophilic droplets, vacuoles, or aggregates in the cytoplasm**
- ▶ Excesses of proteins within the cells sufficient to cause morphologically visible accumulation have diverse causes:
- ▶ *Reabsorption droplets in proximal renal tubules* are seen in renal diseases associated with protein loss in the urine (proteinuria).
- ▶ **In disorders with heavy protein leakage across the glomerular filter**, there is increased reabsorption of the protein into vesicles, and the protein appears as pink hyaline droplets within the cytoplasm of the tubular cell
- ▶ **The proteins that accumulate may be normal secreted proteins** that are produced in excessive amounts and accumulate within the ER, as occurs in certain plasma cells engaged in active synthesis of immunoglobulins.

- ▶ ***Defective intracellular transport and secretion of critical proteins.*** In α 1-antitrypsin deficiency, mutations in the protein significantly slow folding, resulting in the buildup of partially folded intermediates, which aggregate in the ER of the hepatocyte and are not secreted
- ▶ ***Accumulation of cytoskeletal proteins.*** There are several types of cytoskeletal proteins, including microtubules, thin actin filaments, thick myosin filaments, and intermediate filaments. Accumulation of each type is associated with certain types of cell injury
- ▶ ***Aggregation of abnormal proteins.*** Abnormal or misfolded proteins may deposit in tissues and interfere with normal functions. The deposits can be intracellular, extracellular, or both, and the aggregates may either directly or indirectly cause the pathologic changes. Certain forms of *amyloidosis*

Hyaline Change

- ▶ **The term *hyaline* usually refers to an alteration within cells or in the extracellular space that gives a homogeneous, glassy, pink appearance in routine histologic sections stained with H&E.**
- ▶ It is widely used as a descriptive histologic term rather than a specific marker for cell injury.
- ▶ *Intracellular hyaline* accumulations of protein include reabsorption droplets, Russell bodies, and alcoholic hyalin
- ▶ *Extracellular hyaline* has been more difficult to analyze. Collagenous fibers in old scars may appear hyalinized, but the biochemical basis of this change is not clear.

Glycogen

- ▶ **Excessive intracellular deposits of glycogen are seen in patients with an abnormality in either glucose or glycogen metabolism**
- ▶ it is most readily identified when tissues are fixed in absolute alcohol. Staining with Best carmine or the PAS reaction imparts a rose-to-violet color to the glycogen, but can also stain protein-bound carbohydrates
- ▶ Diabetes mellitus is the prime example of a disorder of glucose metabolism. In this disease, glycogen is found in renal tubular epithelial cells, as well as within liver cells
- ▶ Glycogen accumulates within select cells in a group of related genetic disorders that are collectively referred to as the *glycogen storage diseases*, or *glycogenoses*

pigments

- ▶ Pigments are colored substances, some of which are normal constituents of cells (e. g., melanin)
- ▶ ***Exogenous Pigments:*** The most common exogenous pigment is carbon. When inhaled, it is picked up by macrophages within the alveoli and then transported through lymphatic channels to lymph nodes in the tracheobronchial region.
- ▶ In coal miners, the aggregates of carbon dust may induce a fibroblastic reaction or even emphysema, and thus cause a serious lung disease known as *coal worker's pneumoconiosis*
- ▶ ***Endogenous Pigments:*** e.g Lipofuscin is an insoluble pigment, also known as lipochrome or wear-and-tear pigment.

- ▶ **Melanin:** Melanin, derived from the Greek (*melas*, black), is an endogenous, brown-black, pigment formed when the enzyme tyrosinase catalyzes the oxidation of tyrosine to dihydroxyphenylalanine in melanocytes.
- ▶ For practical purposes, melanin is the *only endogenous brown-black pigment*. The only other that could be considered in this category is homogentisic acid, a black pigment that occurs in patients with *alkaptonuria*, a rare metabolic disease.
- ▶ **Hemosiderin,** a hemoglobin-derived, golden yellow to-brown, granular, or crystalline pigment is one of the major storage forms of iron.
- ▶ Local or systemic excesses of iron cause hemosiderin to accumulate within cells. *Local excesses* result from hemorrhages in tissues.
- ▶ When there is *systemic iron overload*, hemosiderin may be deposited in many organs and tissues, a condition called *hemosiderosis*.

Pathologic Calcification

- ▶ Pathologic calcification is the abnormal tissue deposition of calcium salts, together with smaller amounts of iron, magnesium, and other mineral salts
- ▶ When the deposition occurs locally in dying tissues, it is known as *dystrophic calcification*; it occurs despite normal serum levels of calcium and in the absence of derangements in calcium metabolism
- ▶ In contrast, the deposition of calcium salts in otherwise normal tissues is known as *metastatic calcification*, and it almost always results from hypercalcemia secondary to some disturbance in calcium metabolism

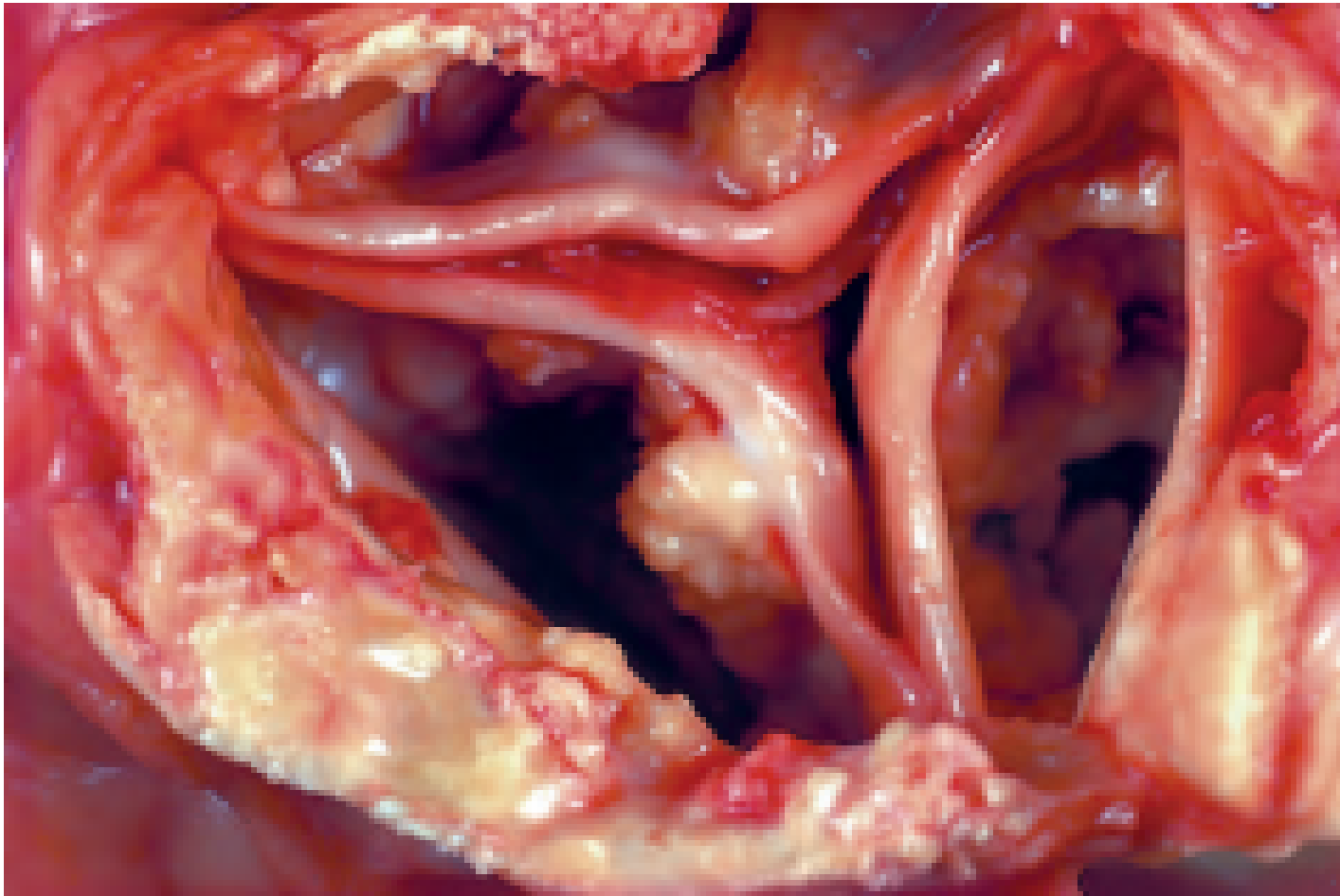


Figure 2.34 Dystrophic calcification of the aortic valve. View looking down onto the unopened aortic valve in a heart with calcific aortic stenosis. It is markedly narrowed (stenosis). The semilunar cusps are thickened and fibrotic, and behind each cusp are irregular masses of piled-up dystrophic calcification.

Cellular aging

- ▶ Individuals age because their cells age.
- ▶ aging has important health consequences, because age is one of the strongest independent risk factors for many chronic diseases, such as cancer, Alzheimer disease, and ischemic heart disease.
- ▶ Cellular aging is the result of a progressive decline in cellular function and viability caused by genetic abnormalities and the accumulation of cellular and molecular damage due to the effects of exposure to exogenous influences
- ▶ Several mechanisms, some cell intrinsic and others environmentally induced, are believed to play a role in aging. These include DNA Damage, cellular senescence, dysregulated nutrient sensing and defective protein homeostasis

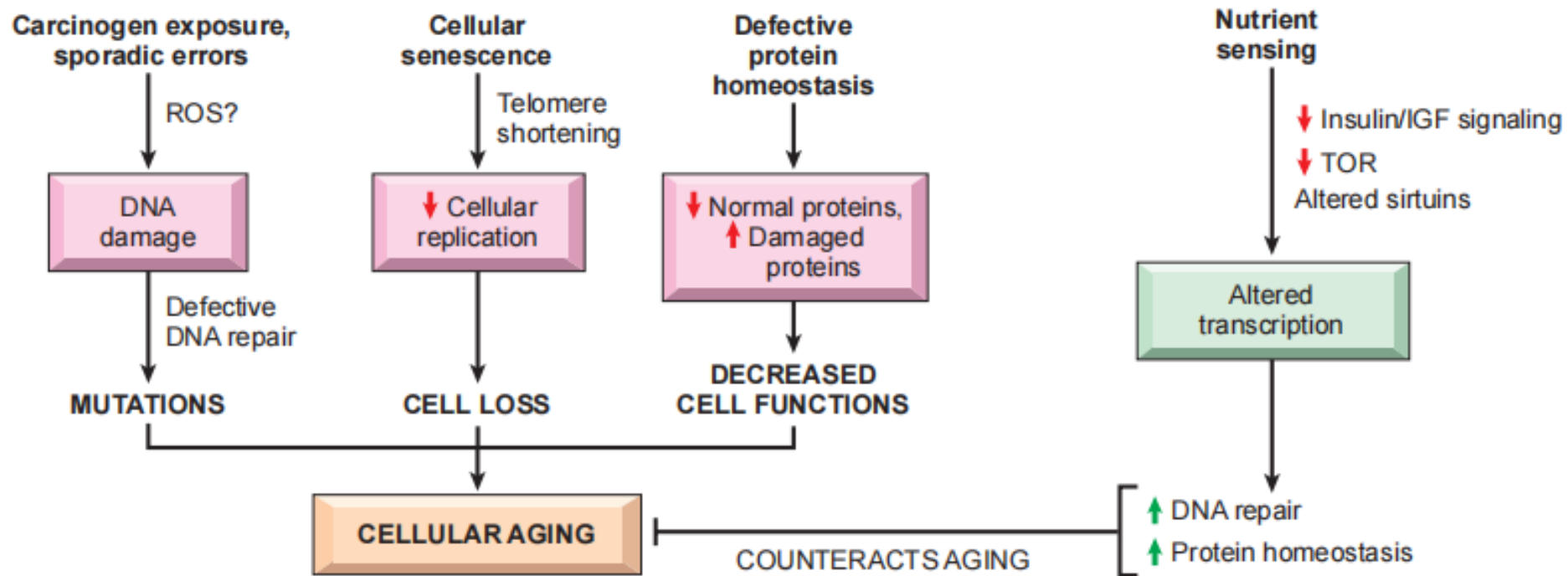
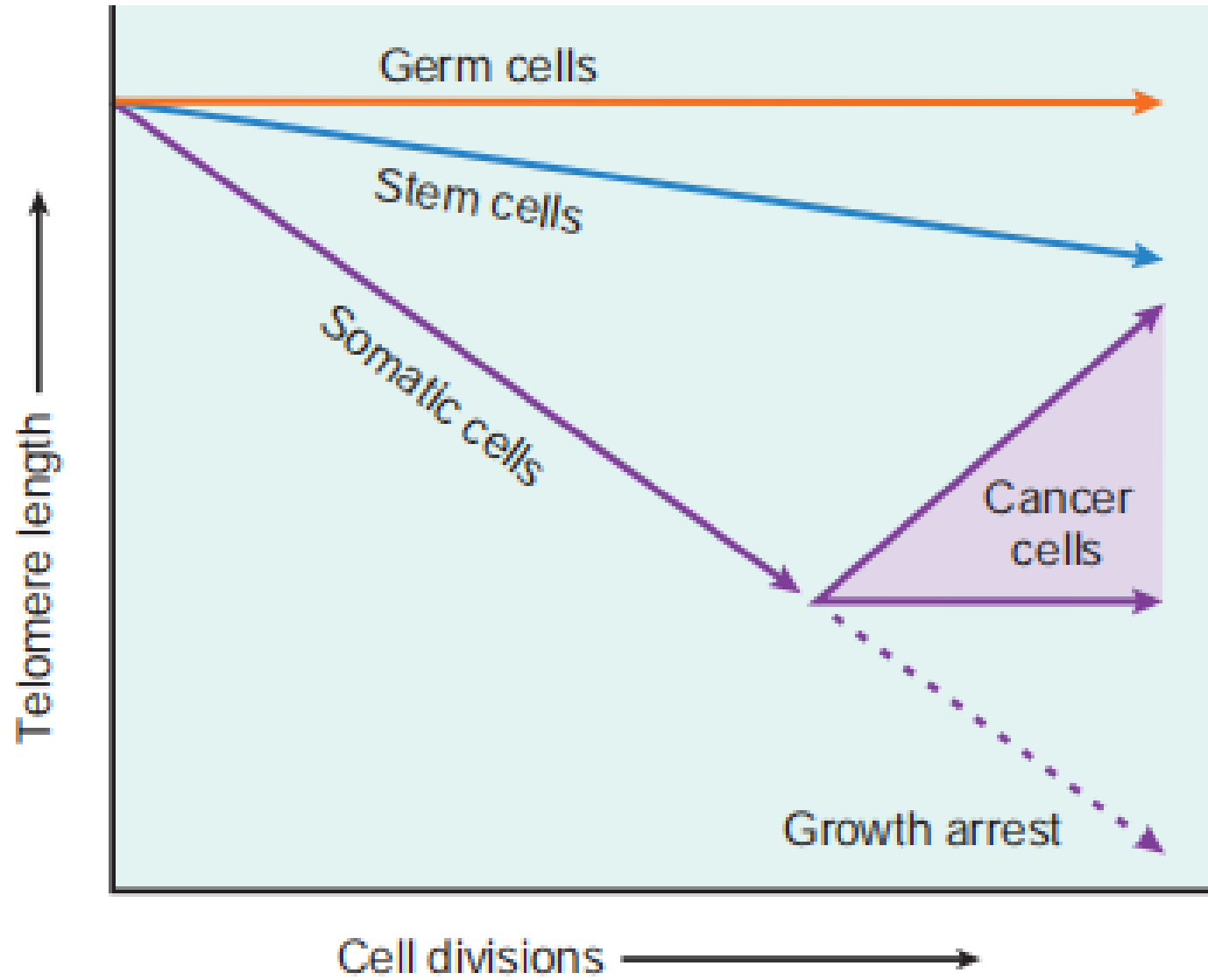


Figure 2.35 Mechanisms that cause and counteract cellular aging. DNA damage, replicative senescence, and decreased and misfolded proteins are among the best described mechanisms of cellular aging. Nutrient sensing, exemplified by caloric restriction, counteracts aging by activating various signaling pathways and transcription factors. *IGF*, Insulin-like growth factor; *ROS*, reactive oxygen species; *TOR*, target of rapamycin.



Thank you for your time!

The background features abstract, overlapping geometric shapes in various shades of green, ranging from light lime to dark forest green. These shapes are primarily located on the right side of the frame, with some extending towards the left. The overall aesthetic is clean and modern.