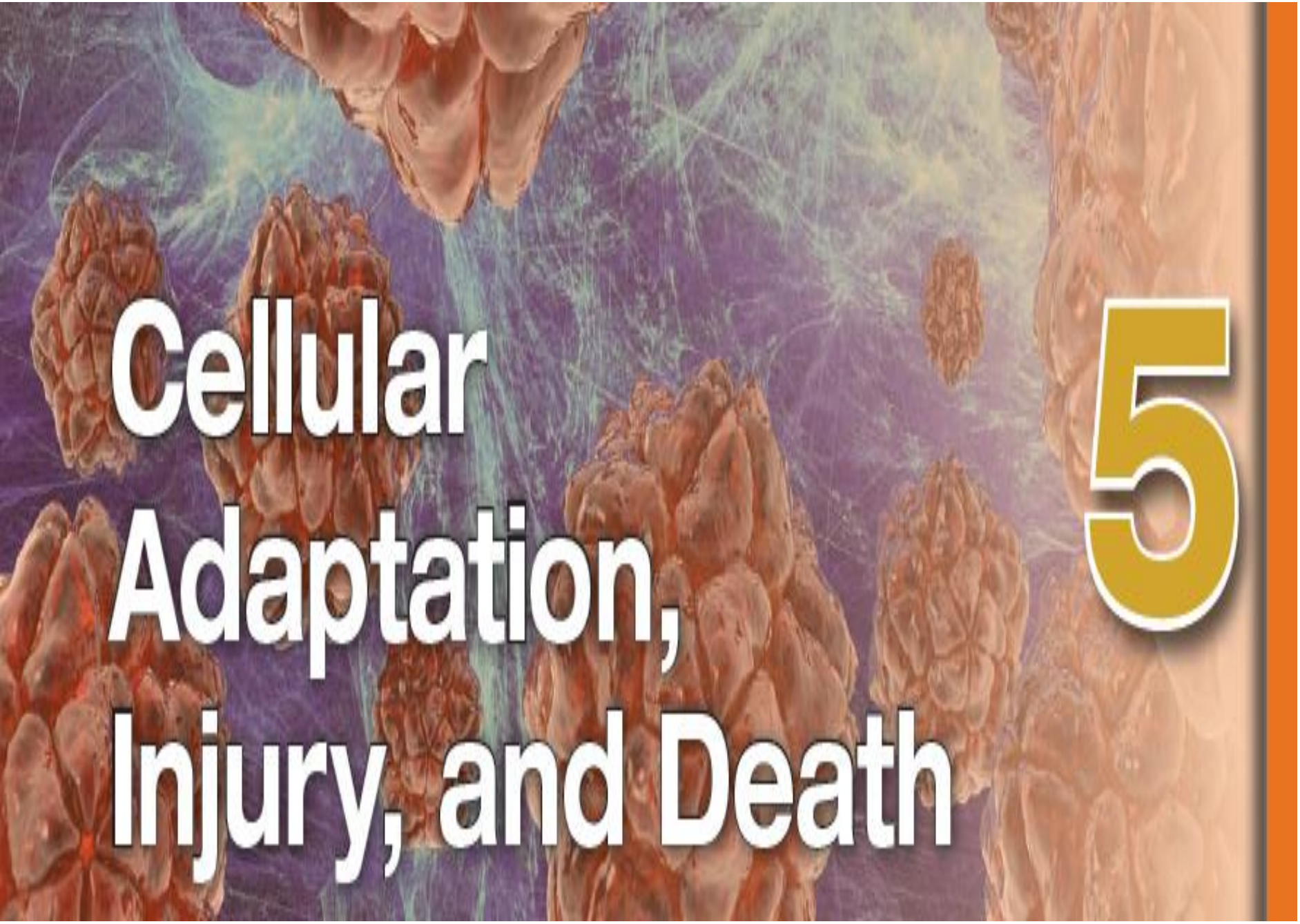

Cellular
Adaptation,
Injury, and Death
5

CELLULAR ADAPTATION

CELL INJURY AND DEATH

Causes of Cell Injury

Mechanisms of Cell Injury

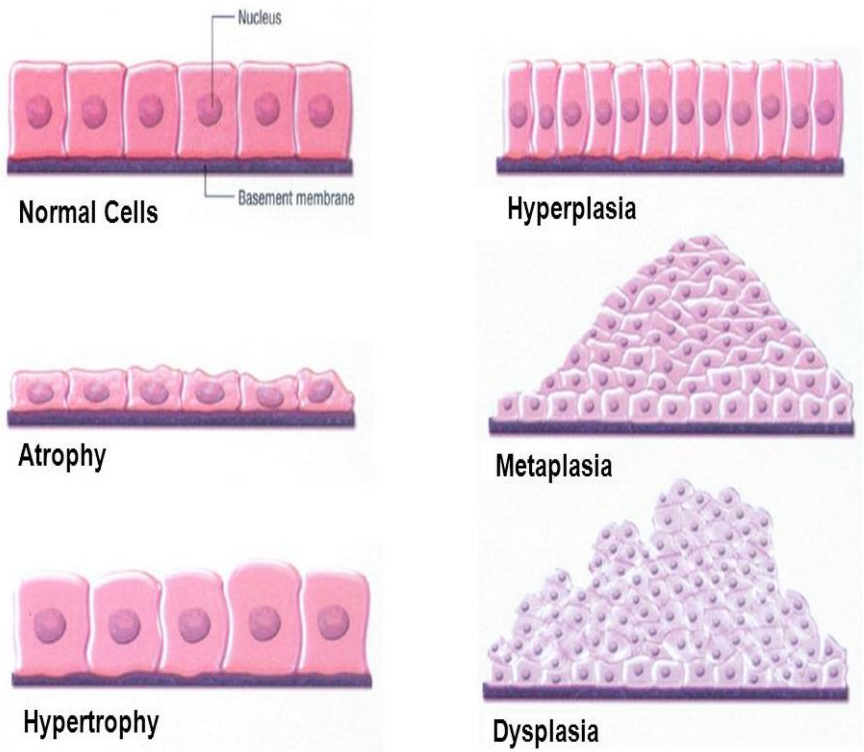
Reversible Cell Injury and Cell Death

Necrosis

Cellular Aging

OVERVIEW OF CELLULAR RESPONSES TO STRESS

- Cells normally maintain a steady state called homeostasis.
- As cells encounter physiologic stresses or pathologic stimuli, they can undergo adaptive changes that permit survival and maintenance of function.
- Cells are able to adapt to increased work demands or threats to survival by changing their size (atrophy and hypertrophy), number (hyperplasia),and form (metaplasia).



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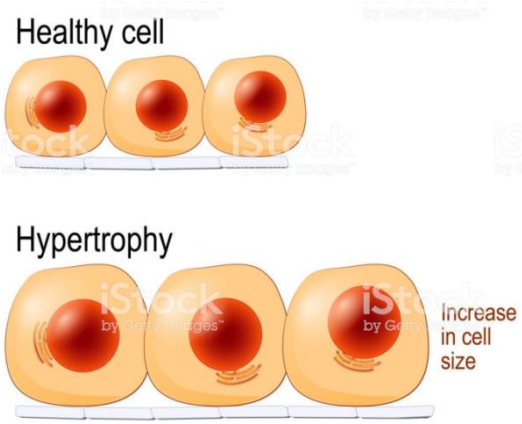
1) *Physiologic adaptations include* responses of cells to normal stimulation by hormones or endogenous chemical mediators (e.g., the hormone-induced enlargement of the breast and uterus during pregnancy).
2) *Pathologic adaptations are* responses to stress that allow cells to modulate their structure and function and thus escape injury.

Adaptation forms

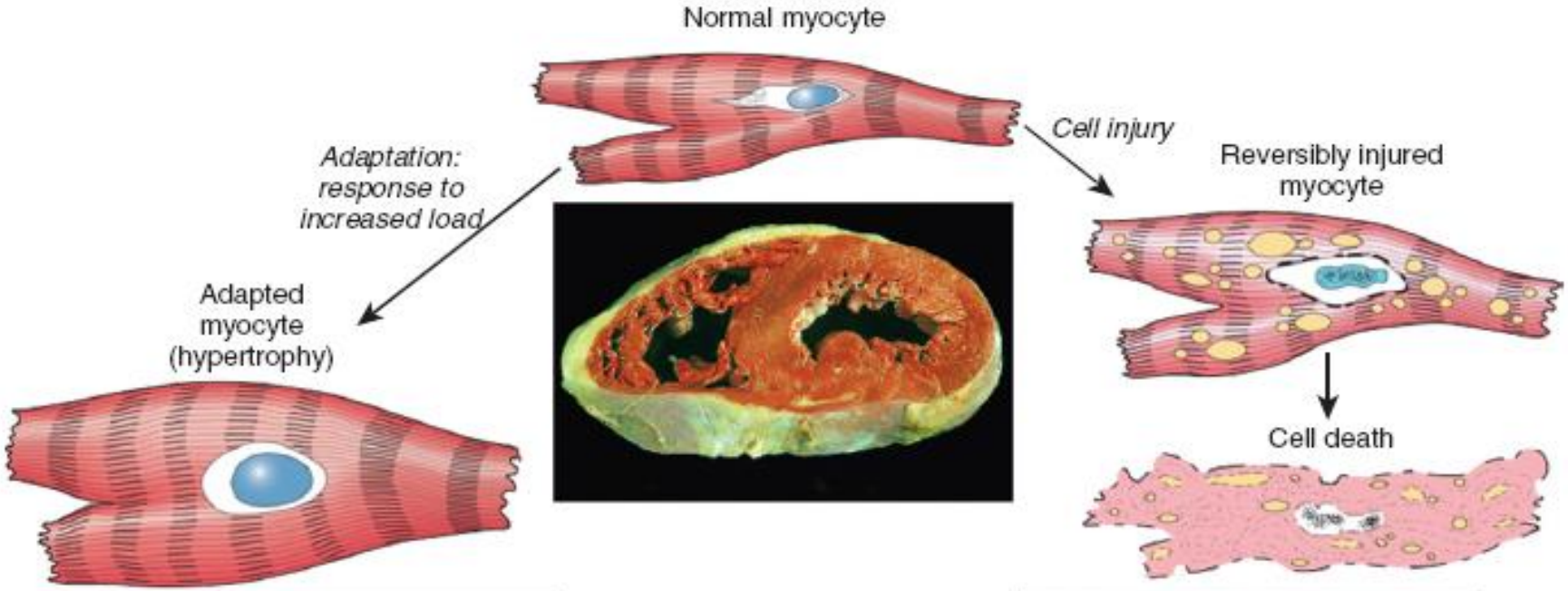
1) Hypertrophy: is an increase in the size (not number) of cells resulting in increase in the size of the organ.

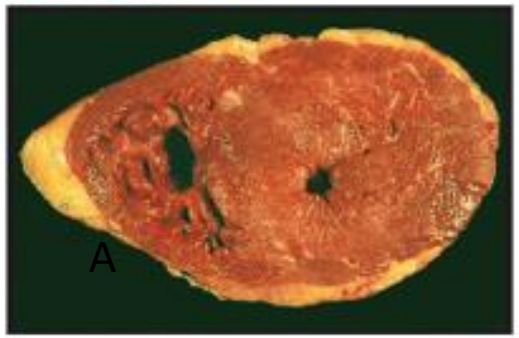


- *It* occurs in the cells which have a limited capacity to divide like skeletal muscle and cardiac muscle.
- *It* can be physiologic (e.g., uterus during pregnancy and skeletal muscle as a result of increasing the workload (weightlifter)) or pathologic that occurs as a result of disease condition.
- Types of pathologic hypertrophy are: 1. Adaptive (e.g., myocardial hypertrophy due to HTN). 2. Compensatory (e.g., nephrectomy (kidney removal).

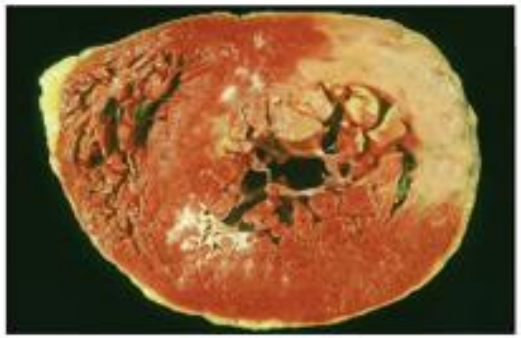
- *It is caused* by increased functional demand or by growth factor or hormonal stimulation.

The relationship among normal, adapted, reversibly injured, and dead myocardial cells.



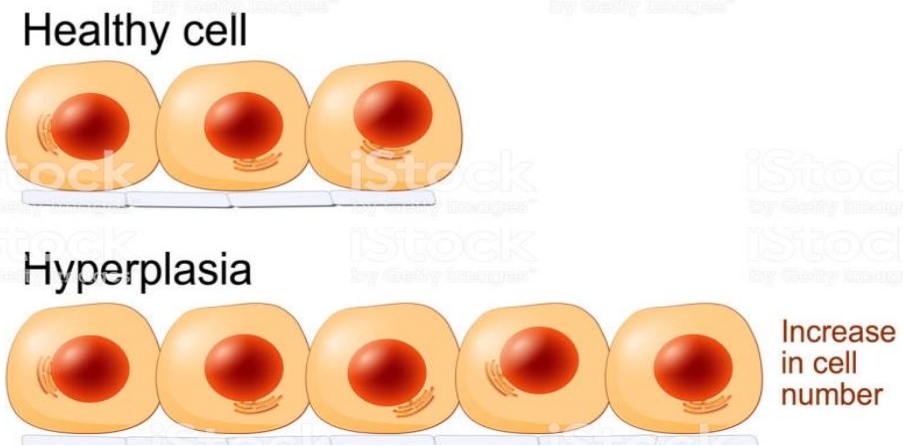


Cross section of the heart with left ventricular hypertrophy.



Adaptation or injury (reversible or irreversible changes) are not dependent only on the nature and severity of stress but also on other variables including: 1. Blood supply. 2. Cellular metabolism. 3. Nutritional status.

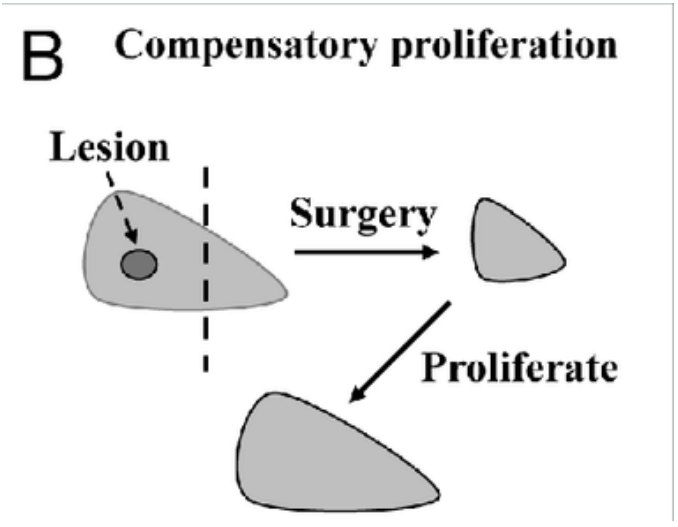
- **2) *Hyperplasia:*** refers to an increase in the number of cells in an organ or tissue. It occurs in tissues with cells that are capable of mitotic division, such as the epidermis, intestinal epithelium, and glandular tissue.
  - *It* may occur concurrently with hypertrophy and often in response to the same stimuli.
  - *It can be physiologic or pathologic.*



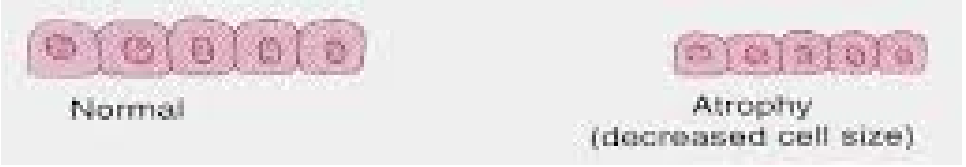
– Two types of *physiologic hyperplasia*

1. *Hormonal hyperplasia (e.g.,* proliferation of glandular epithelium of the female breast at puberty and during pregnancy, and uterine enlargements during pregnancy that results from estrogen stimulation.
2. *Compensatory hyperplasia, in* which residual tissue grows after removal or loss of part of an organ (e.g Liver).

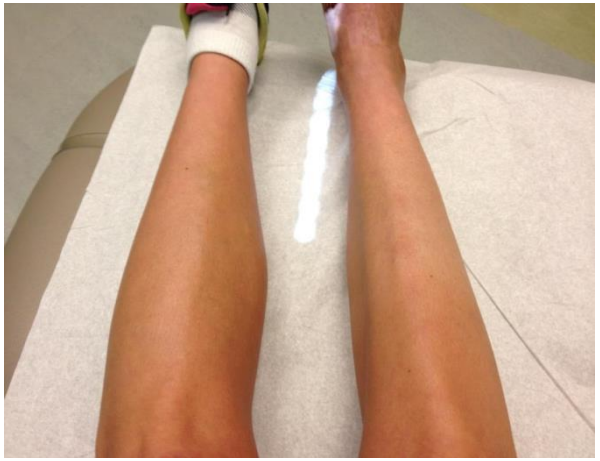
- Most forms of *pathologic hyperplasia are caused by excessive* hormonal or growth factor stimulation (e.g: endometrial hyperplasia causing abnormal menstrual bleeding, fibroblast proliferation aid for wound healing, papilloma viruses caused skin warts and mucosal lesions.
- *The hyperplastic process remains **controlled process** (differs from cancer); if the signals that initiate it stop, the hyperplasia disappears.*



3) Atrophy: is the shrinkage in the size of the cell by the loss of cell substance.



- The organ size is decreased
- Atrophied cells may have diminished function but they are <u>not dead</u>
- Causes of atrophy include:
  - Decreased workload (e.g., immobilisation of limbs).
  - Loss of innervation (e.g., paralysed limbs).
  - Diminished blood supply (ischemia).
  - Inadequate nutrition (malnutrition).
  - Loss of endocrine stimulation (e.g. menopause)
  - Aging



- *The mechanisms of atrophy consist of a combination of <u>decreased protein synthesis and increased protein degradation</u> (by activation of ubiquitin-proteasome pathway) in cells in addition to <u>stimulation of a</u>*utophagy (<u>“self-eating”) process.</u>

4) *Metaplasia:* is a reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type that have better ability to withstand the adverse environment.

- Metaplasia is thought to arise by reprogramming of stem cells to differentiate along a new pathway to produce the new more resistant type of cells.
- It occurs in response to chronic irritation and inflammation.
- Exp: Smokers' trachae and bronchi are lined by stratified squamous epithelial cells in place of normal columnar epithelial cells in order to survive under these harsh circumstances.
- Metaplastic cells *have survival advantages, but they lack some specialized functions of the normal cells.*
- *Under prolonged effects of the stressful agent the metaplastic cells may be transformed to cancer cells*

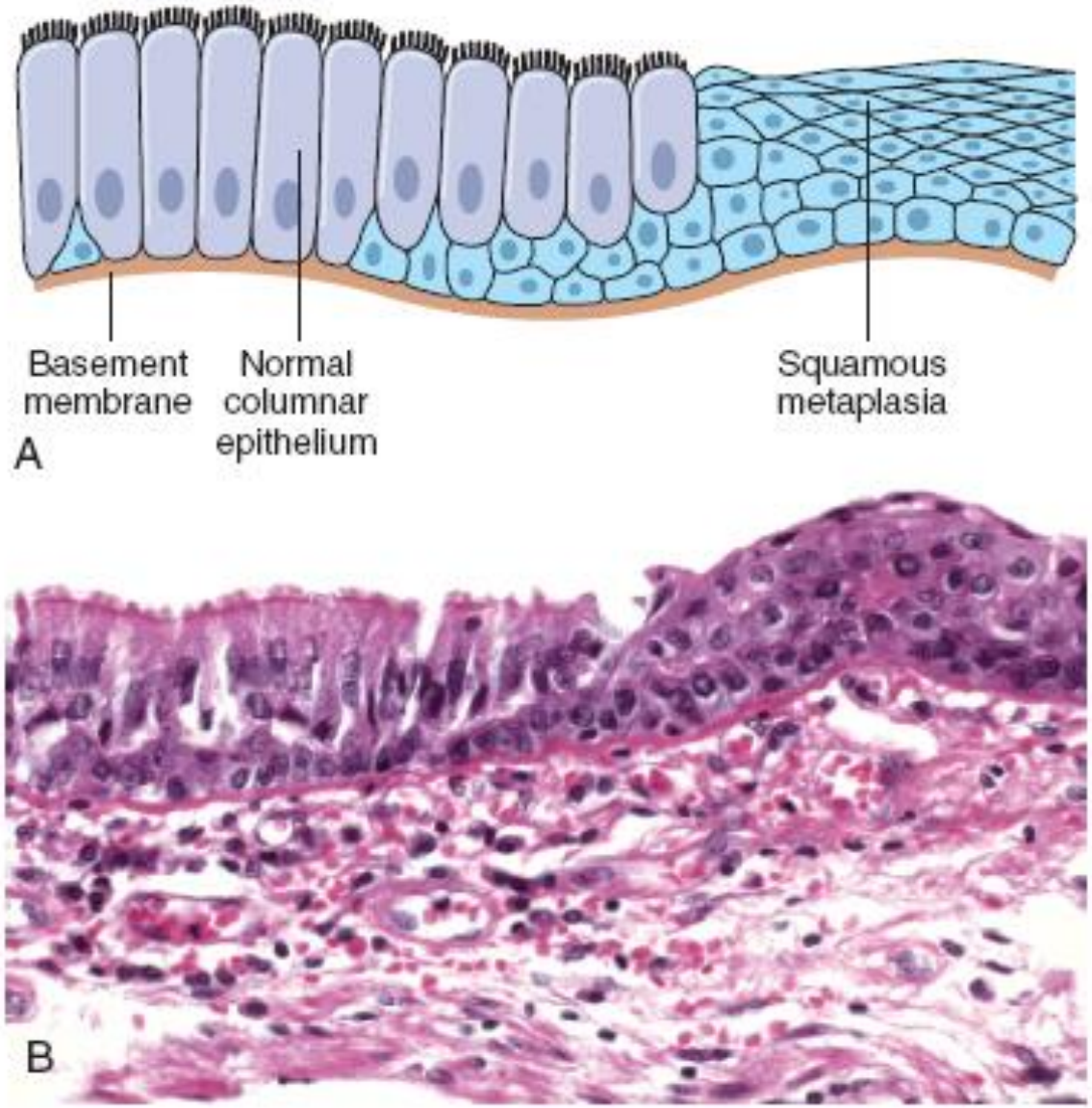


Figure 1–5 Metaplasia of normal columnar (*left*) to squamous epithelium (*right*) in a bronchus, shown schematically (**A**) and histologically (**B**).

OVERVIEW OF CELLULAR RESPONSES TO STRESS AND NOXIOUS STIMULI

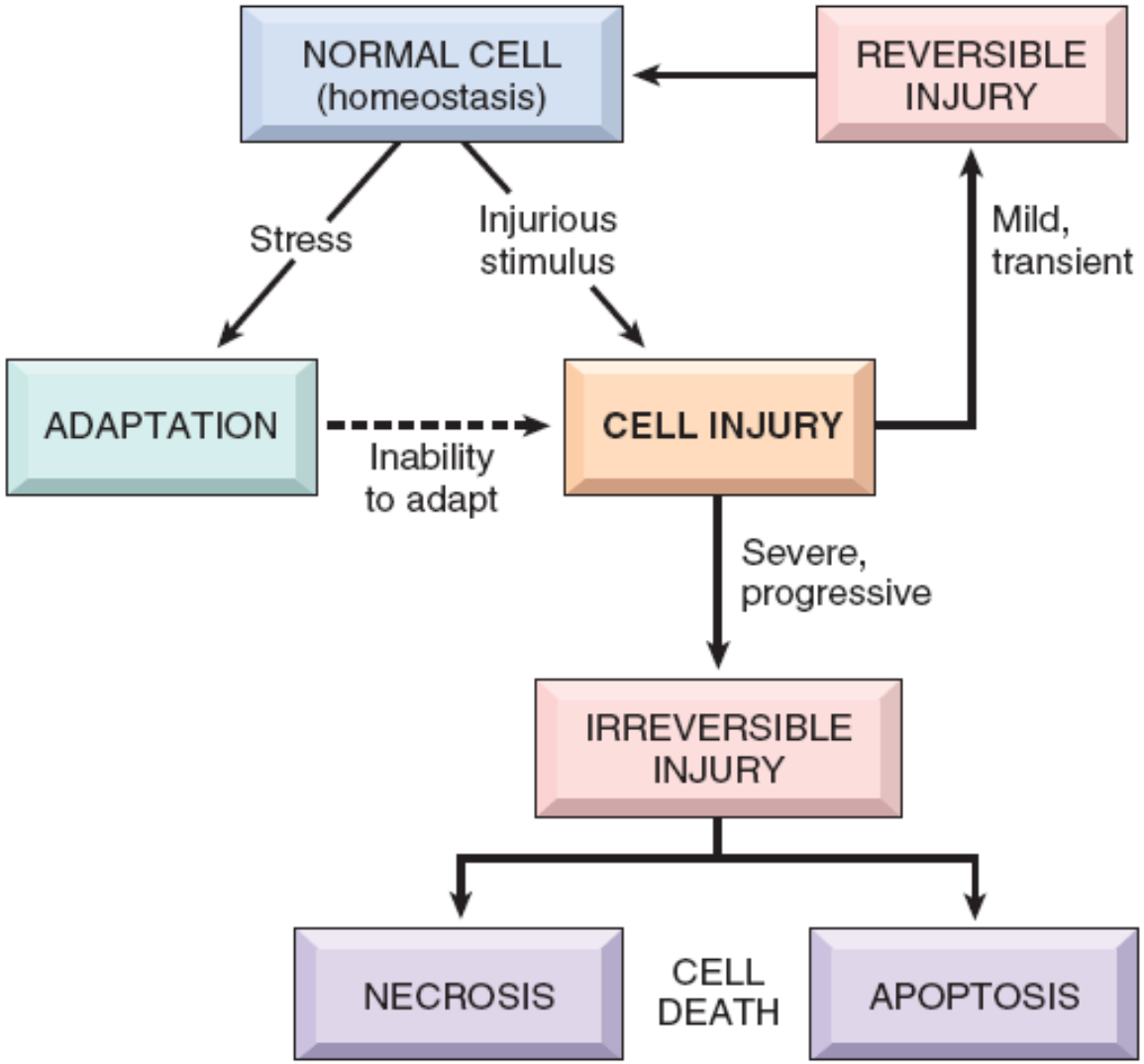


Figure 1–1 Stages in the cellular response to stress and injurious stimuli.

Cell Injury and Death

(a) Causes of cell injury

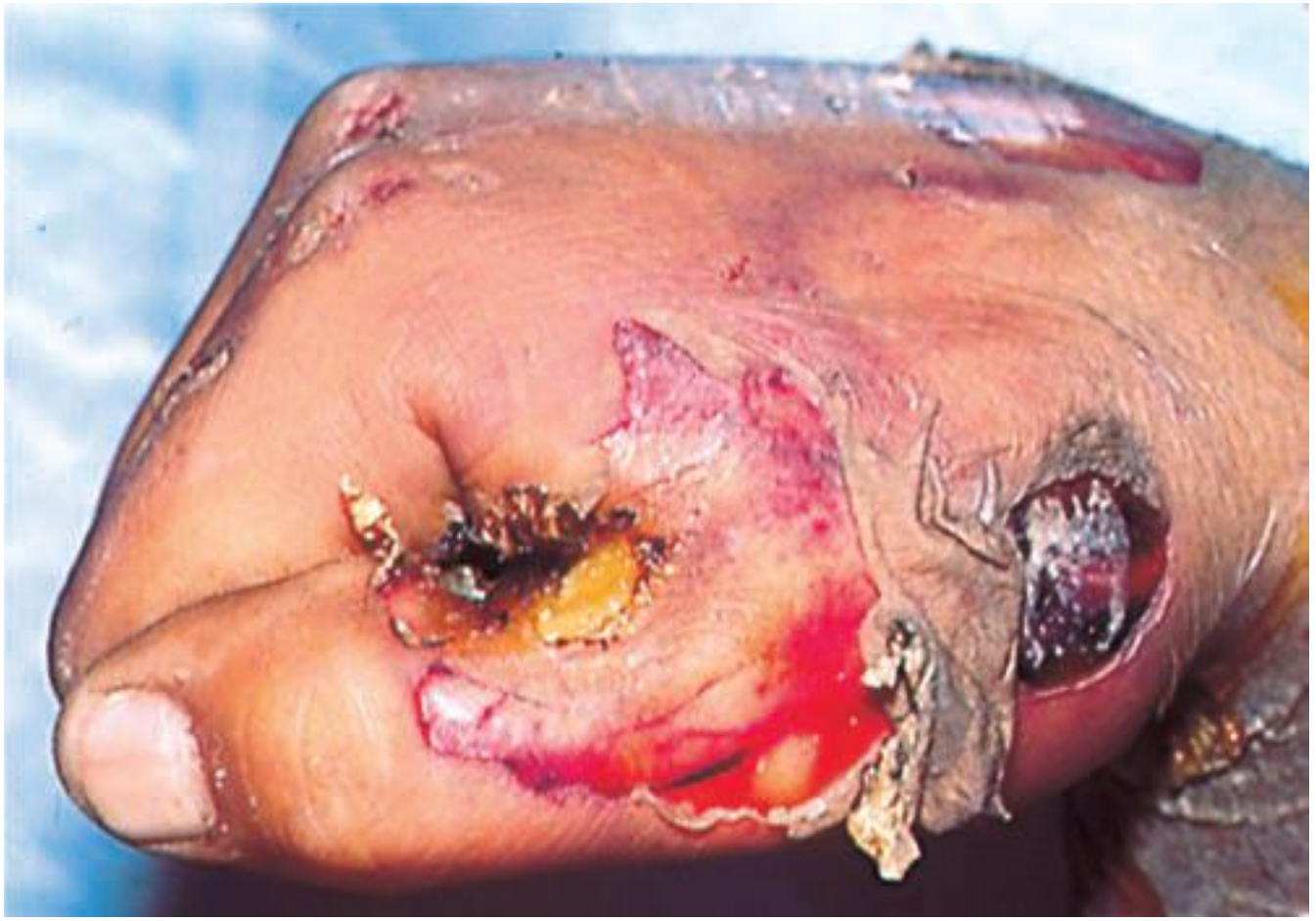
- Cell damage can occur in many ways. For purposes of discussion, the ways by which cells are injured have been grouped into five categories:

1. Injury from physical agents
2. Radiation injury
3. Chemical injury
4. Injury from biologic agents
5. Injury from nutritional imbalances

Physical injury

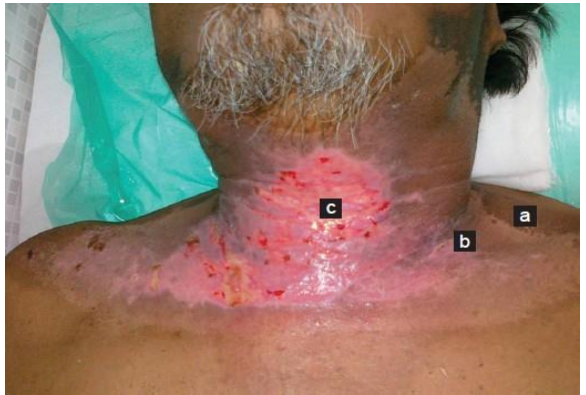
- **Mechanical Forces:** Injury or trauma due to mechanical forces occurs as the result of body impact with another object.
- **Temperature Extreme:** Extremes of heat and cold cause damage to the cell, its organelles, and its enzyme systems.
- **Electrical Forces:** Electrical forces can affect the body through extensive tissue injury caused by heat production>>burning and disruption of neural and cardiac impulses.

Electrical burn of the skin



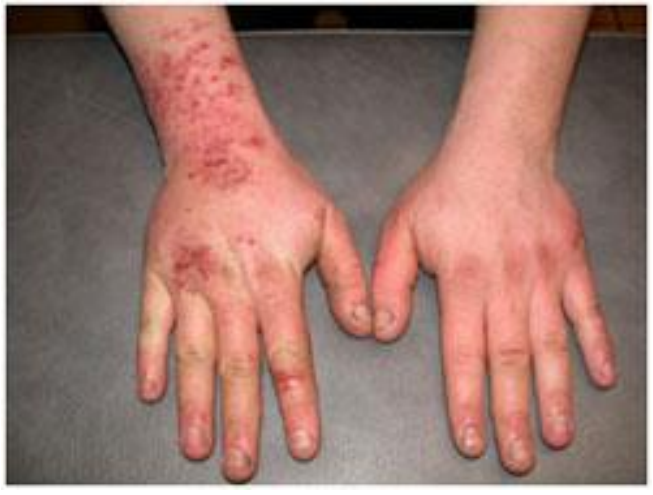
Radiation Injury

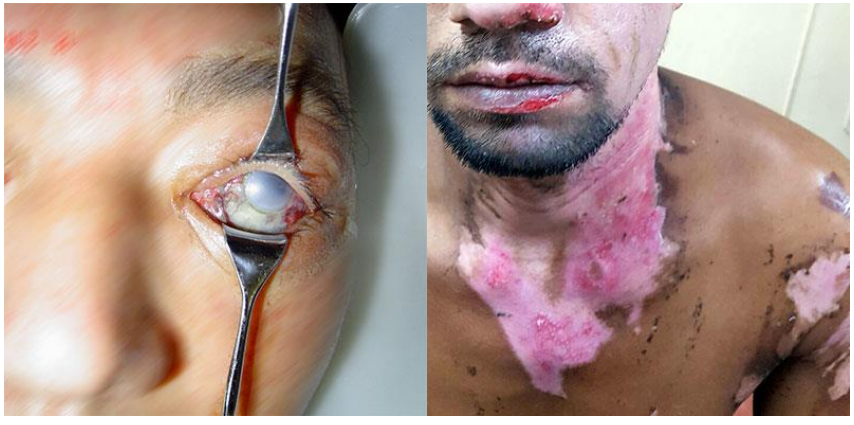
- Radiation energy above the ultraviolet (UV) range is called *ionizing radiation, while below those of visible light is called nonionizing radiation.*
- Ionizing radiation impacts cells by causing ionization of molecules and atoms in the cell and consequently the production of free radicals that destroy the vital molecules in the cells.
- Nonionizing radiation includes infrared light, ultrasound, microwaves, and laser energy. They exert their effect by causing vibration and rotation of atoms>>>thermal energy.
- Ultraviolet radiation causes sun-burn and increases the risk of skin cancers (by damaging DNA, damaging to melanin-producing process in the skin cells and producing ROS).



Chemical injury (chemical burns)

- Chemical agents can injure the cell membrane and other cell structures, block enzymatic pathways, coagulate cell proteins, and disrupt the osmotic and ionic balance of the cell.
- Some of the most damaging chemicals exist in our **environment**, including gases such as carbon monoxide, insecticides, and trace metals such as lead.
- Irritant or corrosive chemical product





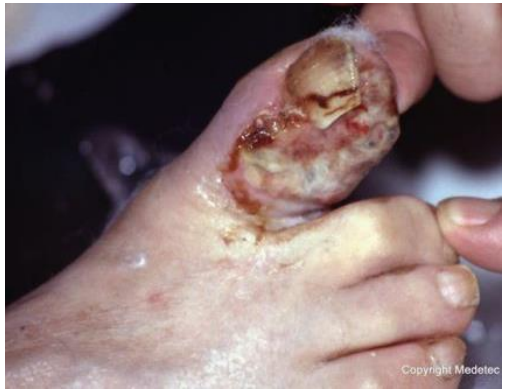
Chemical injury

- **Drugs**: many drugs—alcohol, prescription drugs, over the-counter drugs, and street drugs—are capable of directly or indirectly damaging tissues. Ethyl alcohol can harm the gastric mucosa, liver, developing fetus, and other organs.
- **Lead Toxicity**: The toxicity of lead is related to its multiple biochemical effects. It has the ability to 1) inactivate enzymes required for hemoglobin synthesis and that leads to RBC hemolysis, 2) compete with calcium for incorporation into bone, 3) and interfere with nerve transmission and brain development. The major targets of lead toxicity are the red blood cells, the gastrointestinal tract, the kidneys, and the nervous system.

Biological injury

- Biologic agents differ from other injurious agents in that they are able to replicate and can continue to produce their injurious effects. The most common infection-causing bacteria is ***Staphylococcus aureus*** and other types of staphylococci >> bacterial colonization

- Pathogenicity of microorganism depends on:
  - Invasion and destruction of cells.
  - Production of toxins.
  - Production of hypersensitivity reactions.

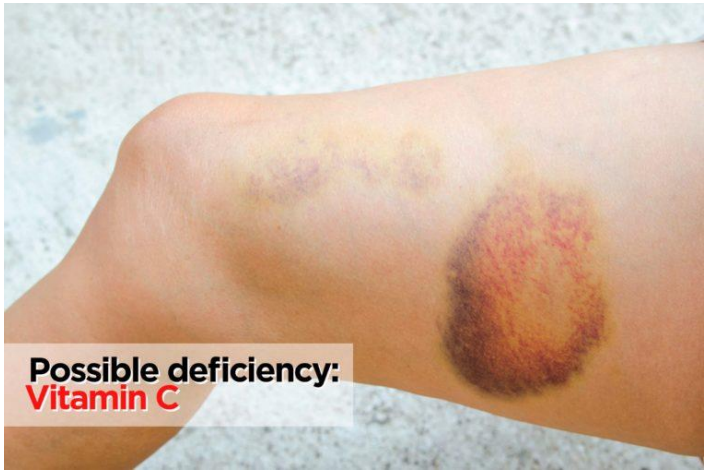


- Injury occurs by diverse mechanisms:

1. Enter host cells and become incorporated into DNA synthetic machinery.
2. Elaborate exotoxin that interferes with ATP production.
3. Elaborate endotoxin that causes cell injury and increase capillary permeability.

Nutritional imbalance

- Vitamin deficiency (as a result of starvation or stomach acid) and hypervitaminosis (as a result of excess nutrition).
- Diets rich in animal fat are strongly implicated in the development of obesity and consequently atherosclerosis.



Cellular features of necrosis and apoptosis

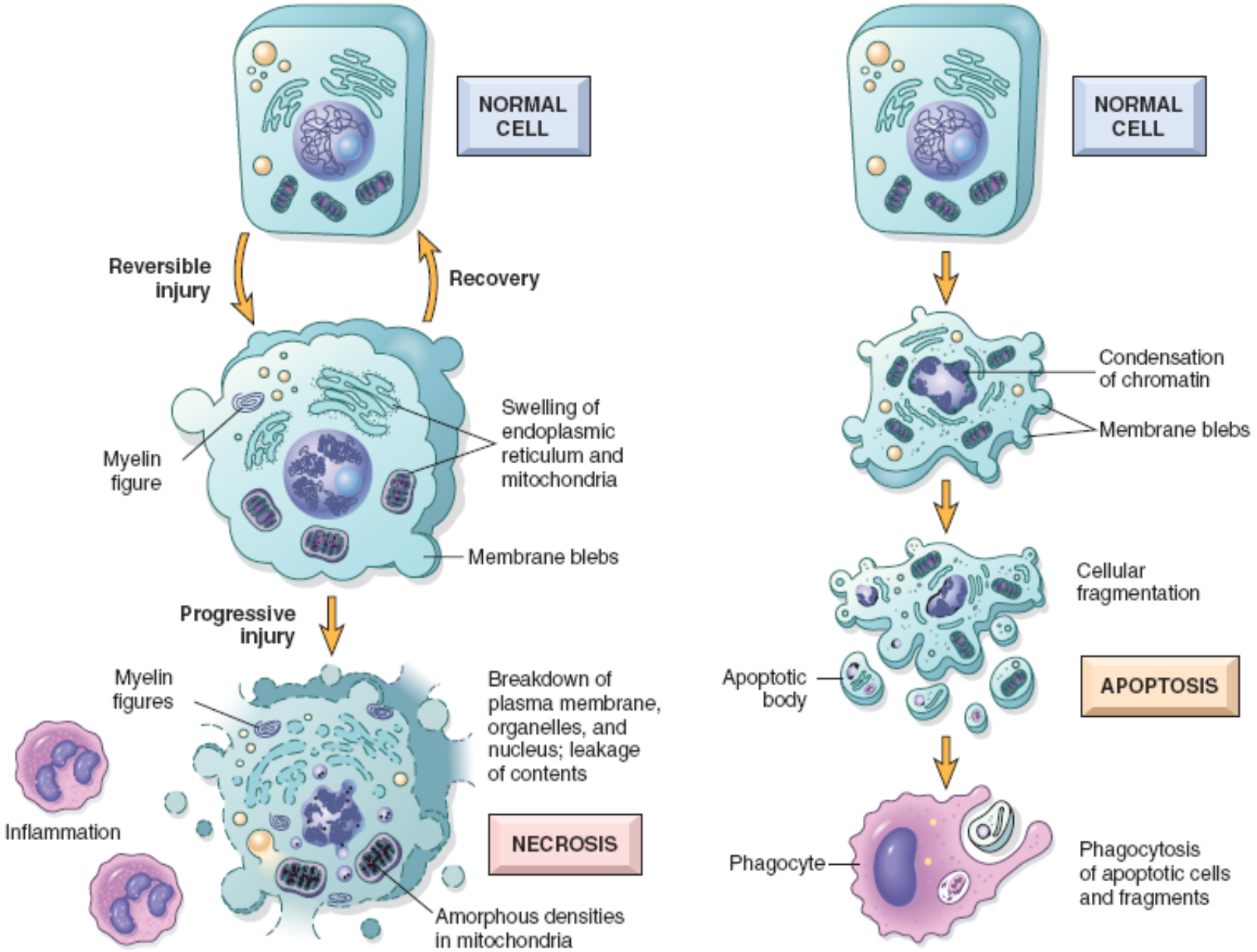


Figure 1–6 Cellular features of necrosis (*left*) and apoptosis (*right*).

Necrosis Vs. Apoptosis

Table 1–1 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	Invariably pathologic (culmination of irreversible cell injury)	Often physiologic; means of eliminating unwanted cells; may be pathologic after some forms of cell injury, especially DNA and protein damage

DNA, deoxyribonucleic acid.

Pyknosis>>> nuclear shrinkage due to DNA condenses into shrinking mass.
Karyorrhexis>>>nuclear fragmentation.
Karyolysis>>>nuclear fading or chromatin dissolution due to action of DNase and RNase.

APOPTOSIS

Apoptosis in Physiological Conditions:

1) *The programmed destruction of cells during embryogenesis.*
2) *Involution of hormone-dependent tissues upon hormone deprivation (*regression of the lactating breast after weaning)
3) maintain a constant number of cell population in tissue.
4) *Elimination of cells that have served their useful purpose (*neutrophils after acute inflammatory response) or are deprived of necessarily survival signal.
5) *Elimination of potentially harmful self-reactive lymphocytes*
6) Defense mechanism against viruses and tumors

Apoptosis in Pathologic Conditions:

- *DNA damage (Radiation, cytotoxic anticancer drugs,* extremes of temperature, hypoxia)
- *Accumulation of misfolded proteins.*
- Viral infections
- *Duct Obstruction* (pancreas)

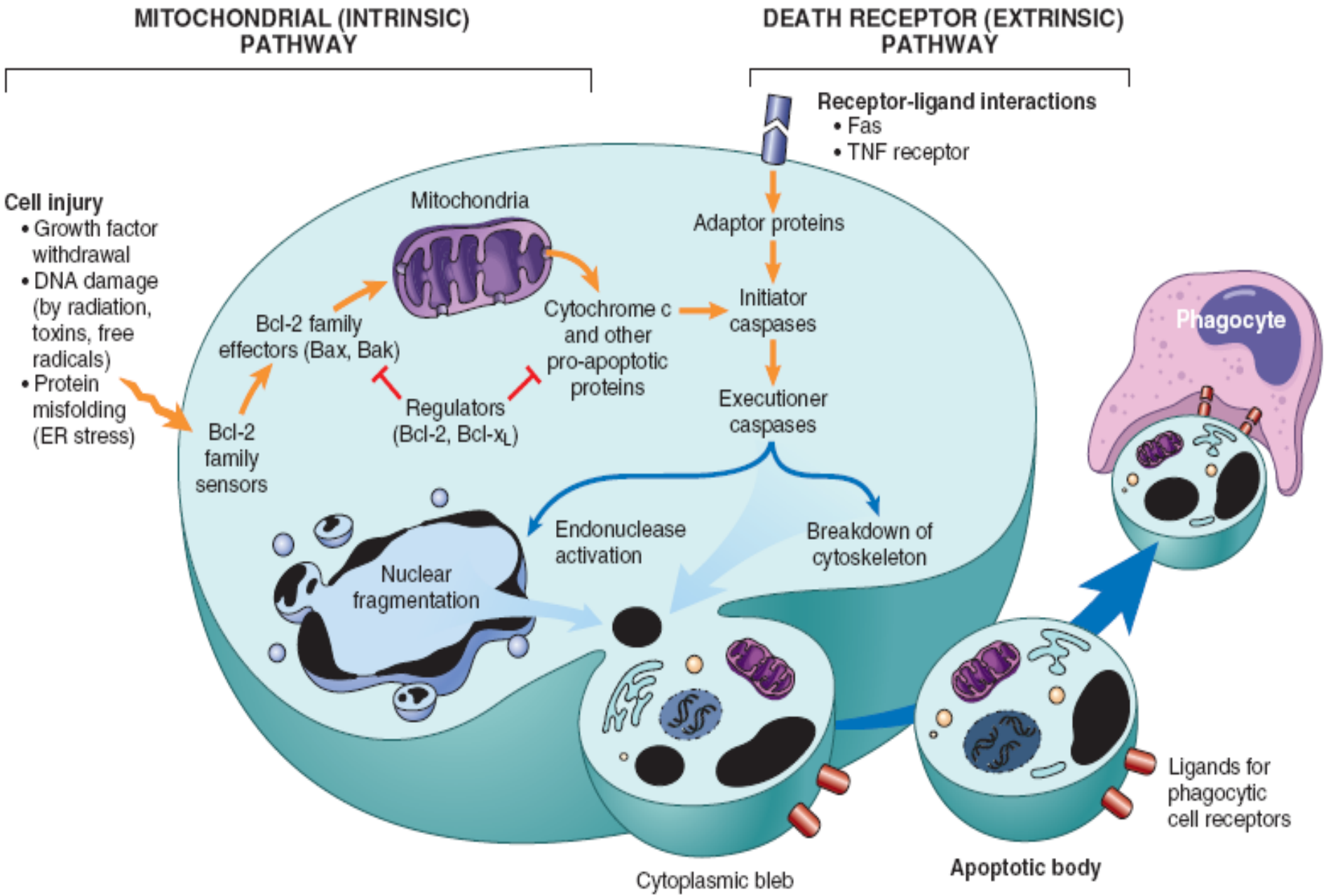
Mechanisms of Apoptosis

- Two basic pathways for apoptosis have been described.
- These are the extrinsic pathway, which is death receptor dependent, and the intrinsic pathway, which is death receptor independent. The execution phase of both pathways is carried out by proteolytic enzymes called *caspases*, which are present in the cell as *procaspases.*

The extrinsic pathway

- The *extrinsic pathway* involves the activation of receptors such as tumor necrosis factor (TNF) receptors and the Fas ligand (FasL) receptor.
- When T cells recognize Fas-expressing cell (target) binds to its receptor on the target cells, to form a death-initiating complex. The complex then converts procaspase-8 to caspase-8. Caspase-8 (initiator caspase), in turn, activates a cascade of executioner caspases that execute the process of apoptosis. (Initiator caspases initiate the apoptosis signal while the executioner caspases carry out the mass proteolysis that leads to apoptosis. Caspases will then cleave a range of substrates, including downstream caspases, nuclear proteins, plasma membrane proteins and mitochondrial proteins, ultimately leading to cell death.)
- The end result includes activation of endonucleases that cause fragmentation of DNA and cell death.

Mechanisms of Apoptosis



The intrinsic pathway

- The *intrinsic pathway*, or *mitochondrion-induced pathway*, It involves the opening of mitochondrial membrane permeability pores with release of cytochrome c from the mitochondria into the cytoplasm. Cytoplasmic cytochrome c activates caspases, including caspase-3 (executioner caspase).
- *Caspase-3 activation* is a common step to both the extrinsic and intrinsic pathways.
- The end result includes activation of endonucleases that cause fragmentation of DNA and cell death.

Mechanisms of Apoptosis