

General pathology

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Master pathology

Lect.1

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Q. Define pathology

- **Pathology** is the branch of medical science that deals with the study of morphologic (structural) changes caused by disease in cells, tissues, organs, body fluids or whole body.

Q. What are the four aspects of a disease that form the core of pathology?

- 1- Cause (Aetiology)
- 2- Mechanism of development (Pathogenesis)
- 3- Structural alteration (morphological changes)
- 4- Functional consequences (clinical significance)

- Q. Define homeostasis.
- When a cell is able to handle the normal physiologic demands, maintaining a steady state, it is said to be in homeostasis.
- Q. Define cellular adaptation.
- Excessive physiologic stress or pathologic stimuli bring about reversible functional and morphologic changes, pushing a normal cell into an altered, but steady state called cellular adaptation
- Q. Define cell injury.
- When the cell cannot adapt anymore or when the limits of adaptive response to a stimulus are exceeded, a sequence of events labelled cell injury follows.

- **Q. Enumerate the various cellular responses to injury.**

Cellular responses to injury may manifest as

1. Cellular adaptations: Include atrophy, hypertrophy, hyperplasia and metaplasia.

2. Cell injury: Sublethal or chronic injurious stimuli can cause

(a) ‘reversible and irreversible injury’ (the latter may lead to cell death by necrosis or apoptosis) and

(b) ‘subcellular alterations’ (residual effects of cell injury).

3. Intracellular accumulations: Sublethal or chronic injurious stimuli as well as metabolic derangements can cause intracellular accumulation of normal cellular constituents, abnormal cellular constituents or pigments

4. Cell ageing: Represents progressive accumulation over the years of sublethal injury that manifests with either cell death or inadequate response of the cell to injury. Ageing is influenced by genetic factors, diet and social environment as well as diseases like atherosclerosis, diabetes and osteoarthritis

- Q. What are the different types of cell injuries?

Types of cell injuries:

1. **Reversible**: If the structural and functional changes, induced by an injurious stimulus, can revert to normal on removal of the stimulus, it is called reversible injury
2. **Irreversible**: If the structural and functional changes, induced by an injurious stimulus, cannot be reversed even after removal of the stimulus, it is called irreversible injury

- Q. Enumerate and describe in brief different types of cellular adaptations.

Adaptive response may be in the form of

1. Hyperplasia
2. Hypertrophy
3. Atrophy
4. Metaplasia

- **Hyperplasia**

Definition

Increase in number of cells in an organ or tissue leading to increased size/mass of the tissue or organ. Hyperplasia takes place in cells, which are capable of synthesizing DNA. In nondividing cells, only hypertrophy occurs.

Mechanism

- **Production of transcription factors** that induce genes encoding growth factors, receptors for growth factors and cell-cycle regulators.
- **In hormonal hyperplasia**, hormones themselves act as growth factors and trigger transcription of genes.
- In compensatory hyperplasia, there is proliferation of remaining cells and development of new cells from stem cells.

- Types

- 1. Physiologic hyperplasia:

- (a) Hormonal hyperplasia: Hormonal stimulation increases the functional capacity of the tissue when needed, eg, breast and uterus in puberty, pregnancy and lactation.

- (b) Compensatory hyperplasia: Increase in tissue mass after damage or partial resection, eg, regeneration of liver after partial hepatectomy.

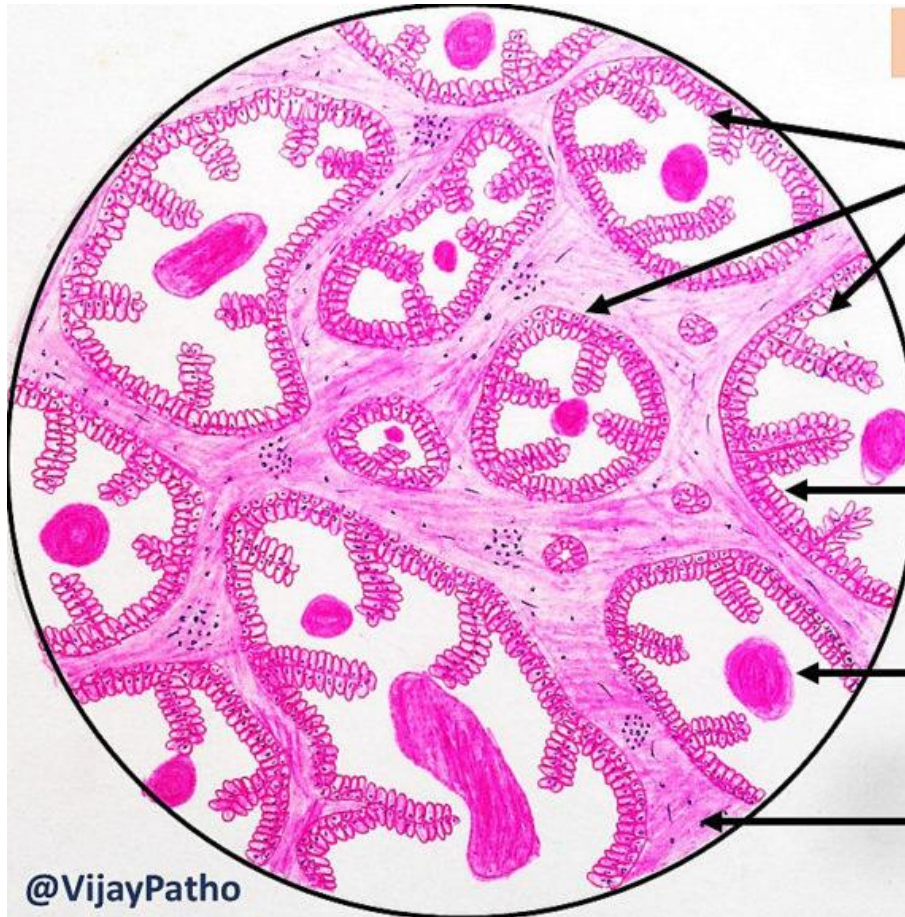
- 2. Pathologic hyperplasia: Hyperplasia due to excessive hormonal stimulation or excessive effects of growth factors on target cells, eg, endometrial hyperplasia (occurs when balance between progesterone and oestrogen is disturbed) and benign nodular prostatic hyperplasia or NHP (occurs due to androgen excess;

- Hypertrophy

Definition

Increase in size of the cell due to increased synthesis of structural components and not due to cellular swelling is known as hypertrophy. Nondividing cells, eg, myocardial fibers, undergo hypertrophy only. Dividing cells (stable cells, quiescent cells) undergo both hyperplasia and hypertrophy.

BENIGN PROSTATIC HYPERPLASIA



Hyperplastic glands
Variably sized glands with
papillary infoldings

Glands lined by double
layered epithelium. Inner
columnar and outer cuboidal

Corpora Amylacea

Fibromuscular stroma

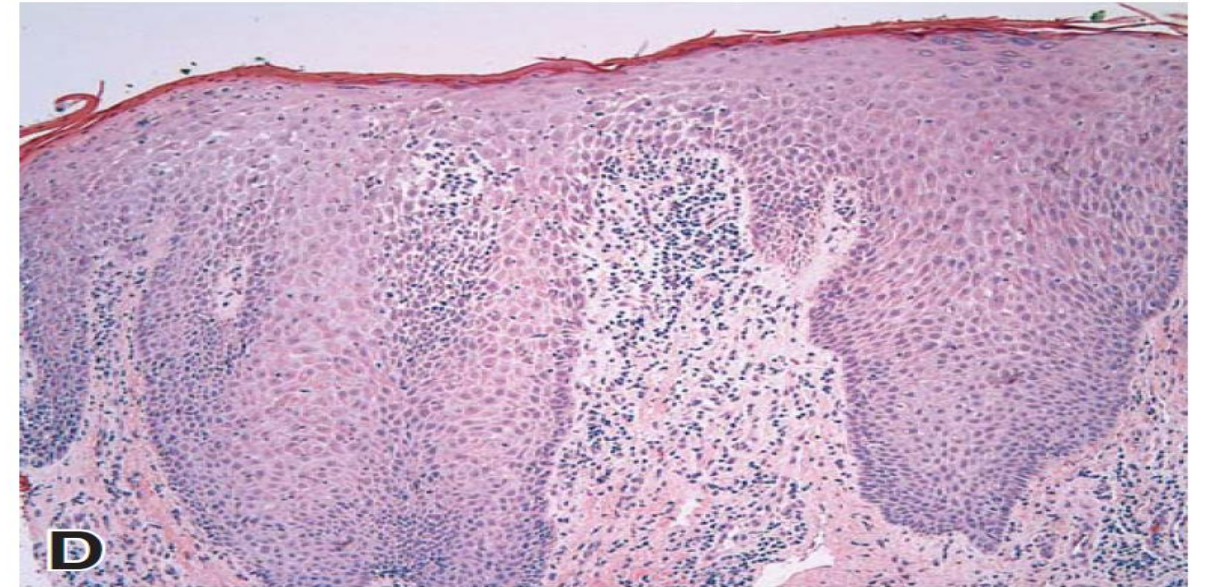
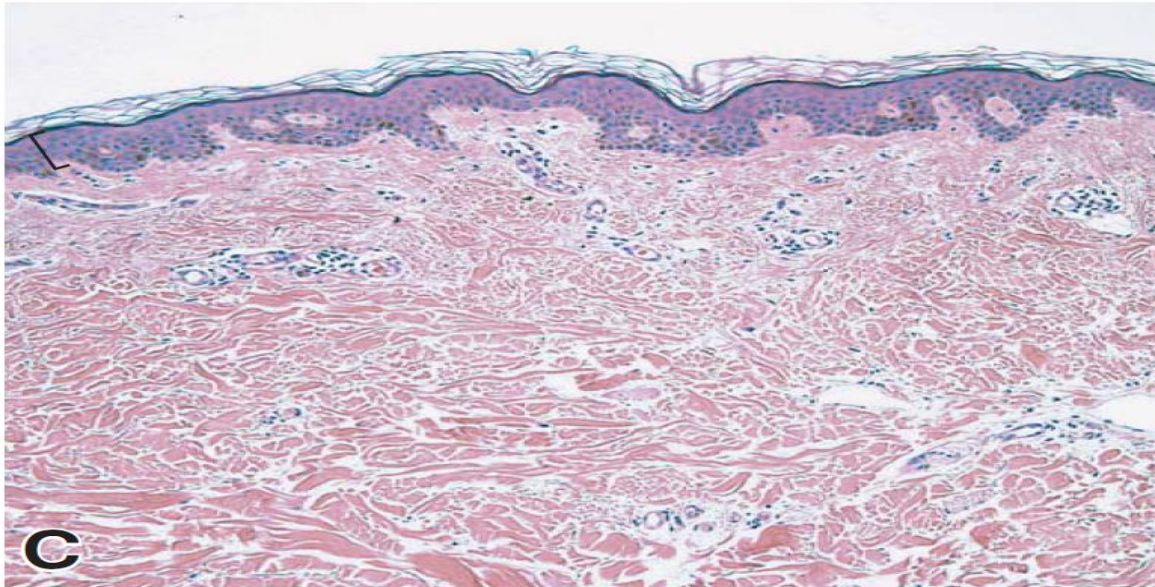
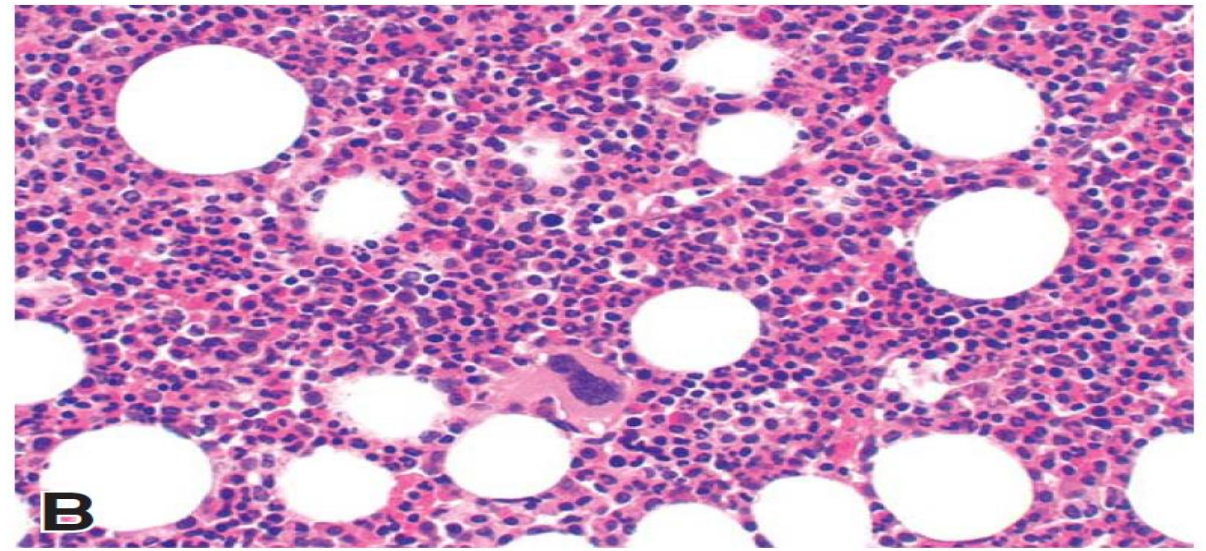
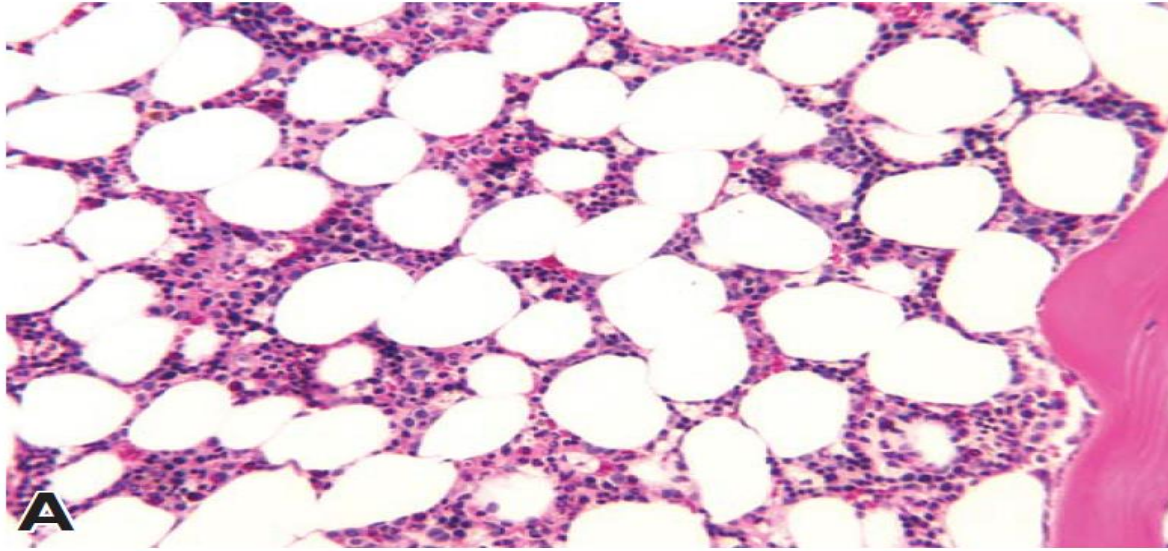


FIGURE 1-14. Hyperplasia. A. Normal adult bone marrow. Normocellular bone marrow shows the usual ratio of fat to hematopoietic cells. **B. Hyperplasia** of the bone marrow. Cellularity is increased; fat is relatively decreased. **C. Normal epidermis.** Epidermal thickness is modest (*bracket*) compared to the dermis (below). **D. Epidermal hyperplasia** in psoriasis is shown at the same magnification as in C. The epidermis is thickened owing to an increase in the number of squamous cells.

- Mechanism

Induction of genes stimulates synthesis of cellular proteins, eg, genes encoding transcription factors, growth factors and vasoactive agents. In the heart, increased workload (mechanical stretch), growth factors (transforming growth factor-beta and Insulin-like growth factor-1) and a-adrenergic hormones activate signal transduction pathways (phosphoinositide-3-kinase/AKT pathway and downstream signalling of G-protein coupled receptors), which in turn activate transcription factors like GATA4 (critical transcription factor for proper mammalian cardiac development and essential for survival of the embryo), NFAT (nuclear factor of activated T cells) and MEF 2 (myocyte enhancer 2).

They work together to increase synthesis of proteins responsible for cardiac hypertrophy

- Types

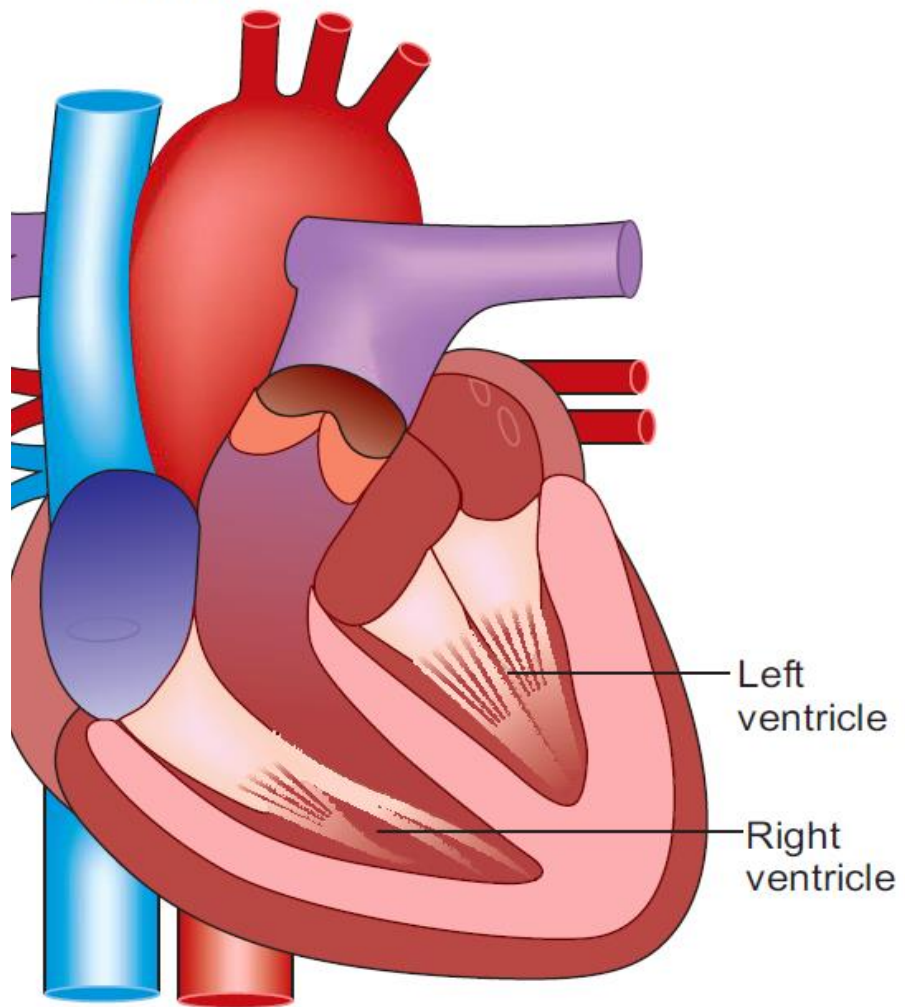
1. Physiological hypertrophy: This occurs due to increased functional demand and stimulation by growth factors and hormones, eg, uterine enlargement in pregnancy and breast hypertrophy during lactation.

2. Pathological hypertrophy:

(a) Hypertrophy of cardiac muscle in systemic hypertension and aortic valve stenosis (chronic haemodynamic overload) leading to left ventricular hypertrophy

(b) Compensatory hypertrophy, which occurs when an organ or tissue is called upon to do additional work or to perform the work of destroyed tissue or of a paired organ.

Normal heart



Left ventricular hypertrophy

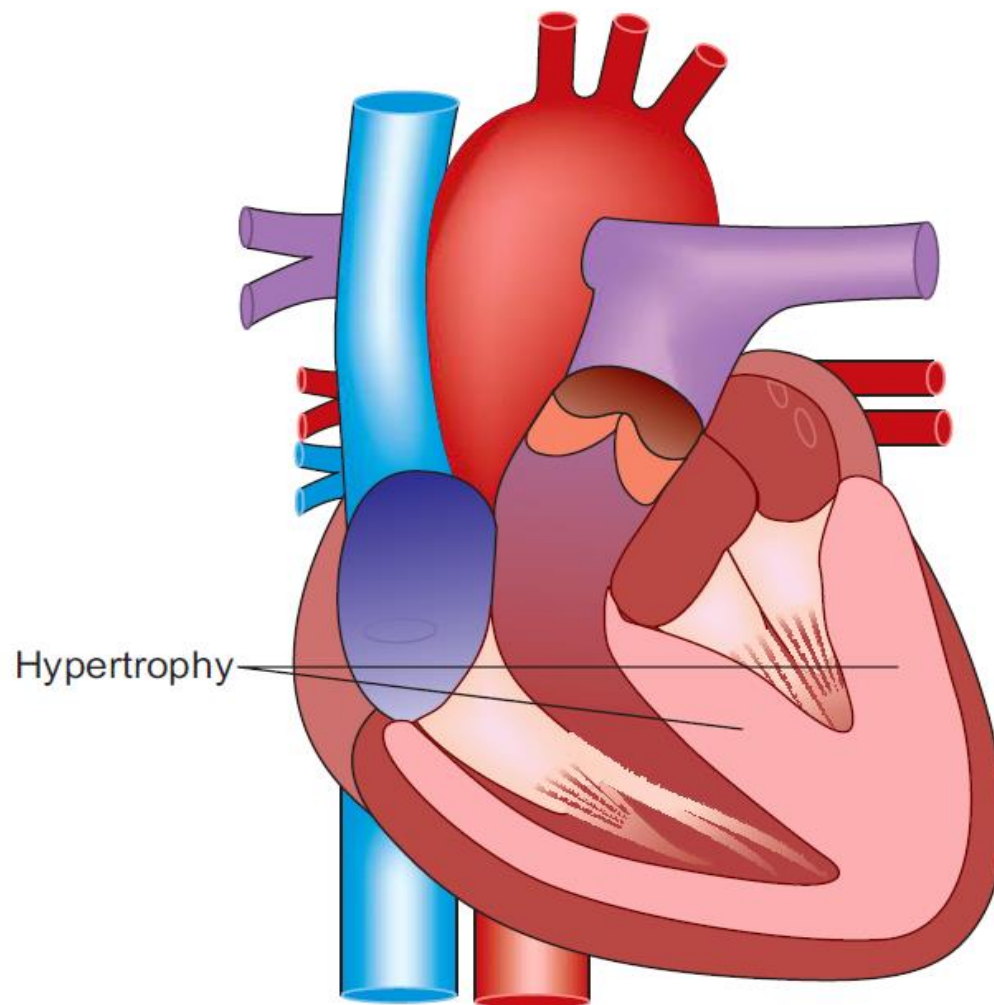


FIGURE 1.3. Pathological hypertrophy, left ventricle.

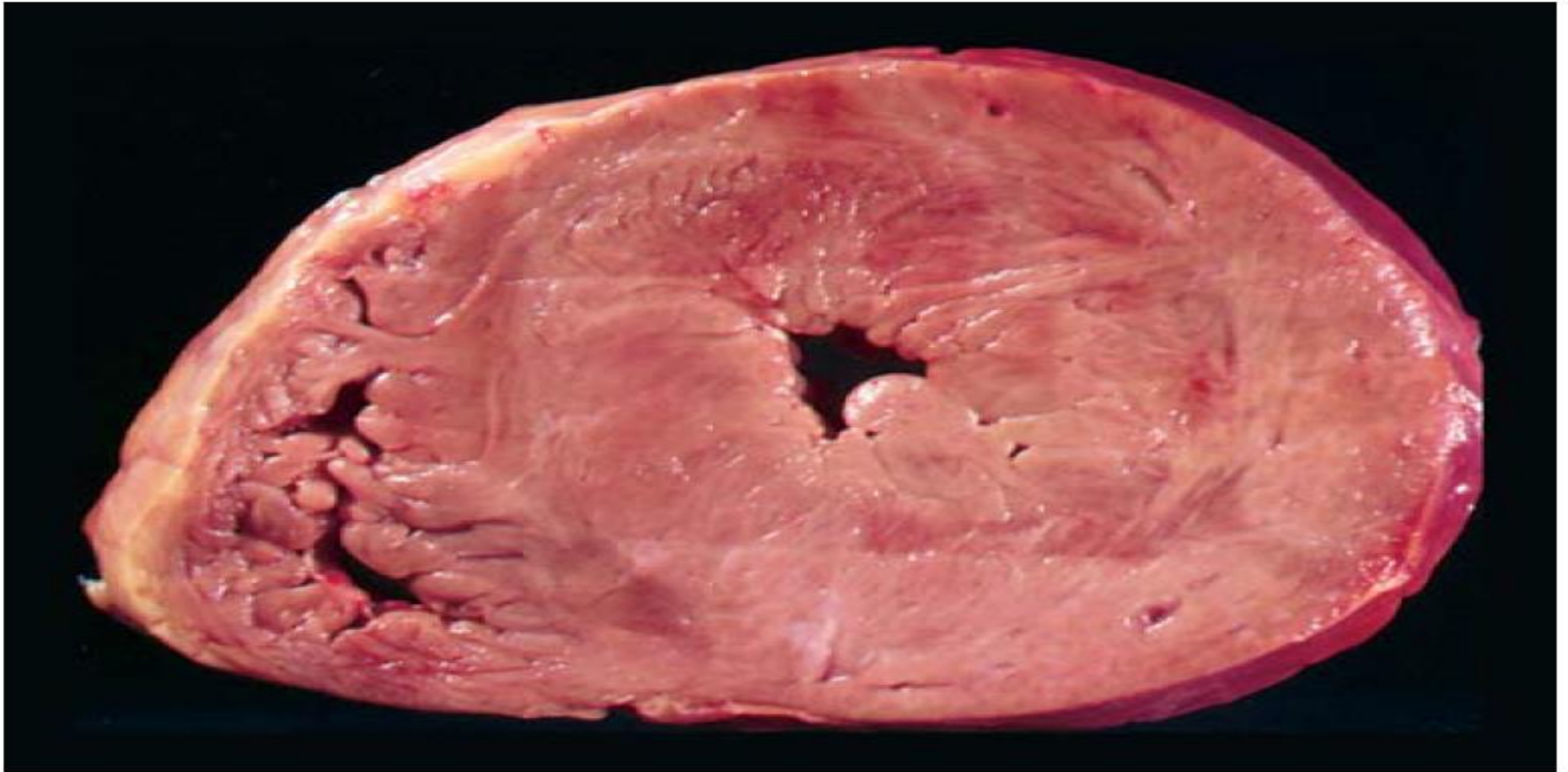


FIGURE 1-18. Myocardial hypertrophy. Cross-section of the heart of a patient with long-standing hypertension shows pronounced, concentric left ventricular hypertrophy.

- Atrophy

Definition

A decrease in size of a body organ, tissue or cell along with decreased function, owing to disease, injury or lack of use.

Mechanism

Atrophy is the result of decreased protein synthesis or increased protein degradation.

Protein degradation is mediated by

- Lysosomal acid hydrolases, which degrade endocytosed proteins (taken up from extracellular environment, cell surface as well as some cellular components).
- Ubiquitin-proteasome pathway, which causes degradation of many cytosolic and nuclear proteins.

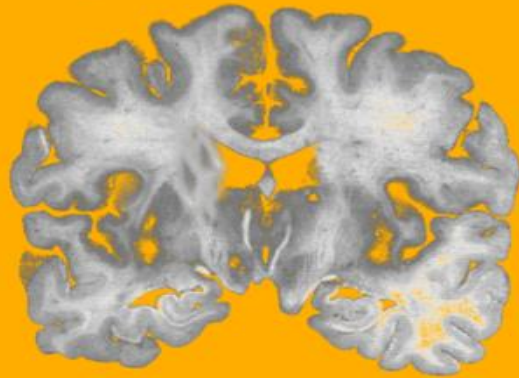
- Types

1. Physiological atrophy: Common during early development, eg, atrophy of notochord or thyroglossal duct during fetal development and uterus after parturition.

2. Pathological atrophy:

- (a) Decreased workload due to immobilization and prolonged functional inactivity leads to disuse atrophy.
- (b) In denervation atrophy, there is loss of innervation of muscle which induces its wasting, as in polio and motor neuron disease.
- (c) Atherosclerosis can cause ischaemic atrophy.
- (d) Nutritional deficiency, eg, marasmus and cancer cachexia are associated with the use of skeletal muscle as a source of energy and lead to nutritional atrophy.
- (e) Loss of endocrine stimulation after menopause induces atrophy of reproductive organs.
- (f) Senile atrophy is an ageing-associated cell loss which is typically seen in tissues containing permanent cells, eg, brain and heart or testes

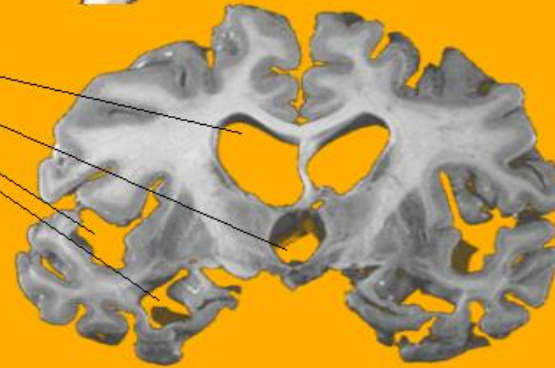
Normal



Atrophy



Brain Shrinkage



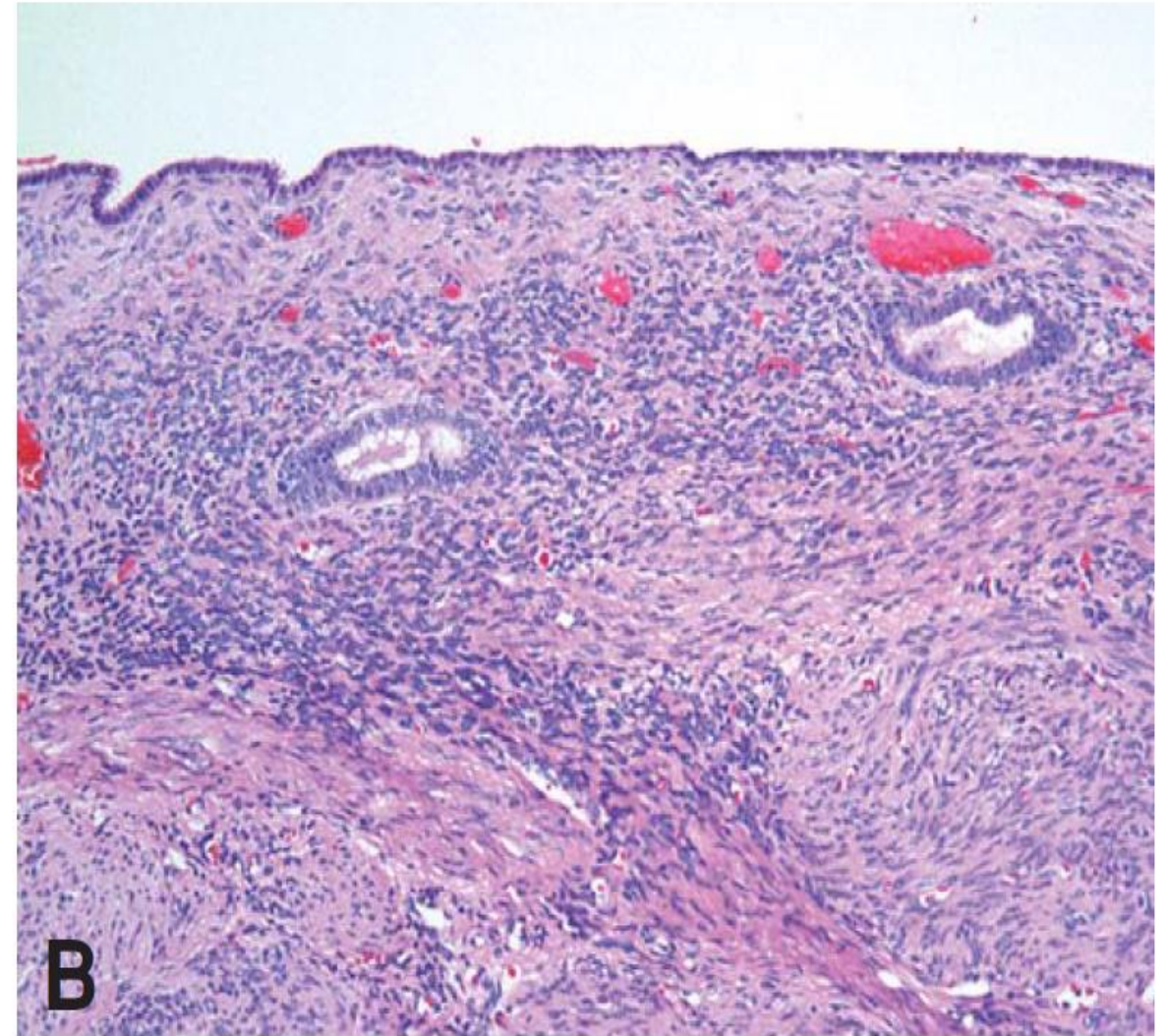
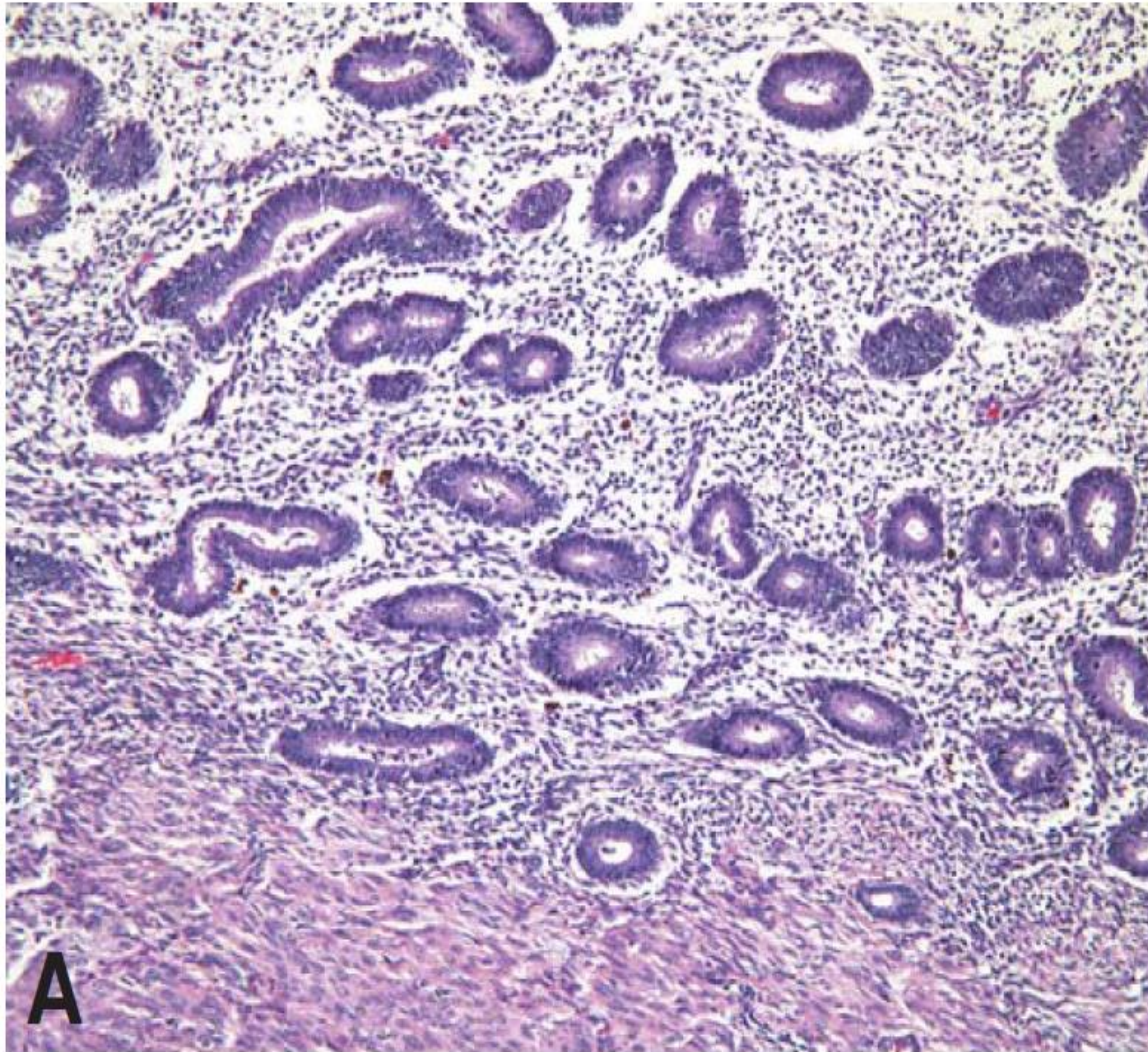


FIGURE 1-19. Atrophy of the endometrium. **A.** A section of the normal uterus from a woman of reproductive age reveals a thick endometrium composed of proliferative glands in an abundant stroma. **B.** The endometrium of a 75-year-old woman (shown at the same magnification) is thin and contains only a few atrophic and cystic glands.

- **Metaplasia**

- **Definition**

Reversible change in which there is replacement of one adult/differentiated cell type (epithelial or mesenchymal) by another adult/differentiated cell type.

Mechanism

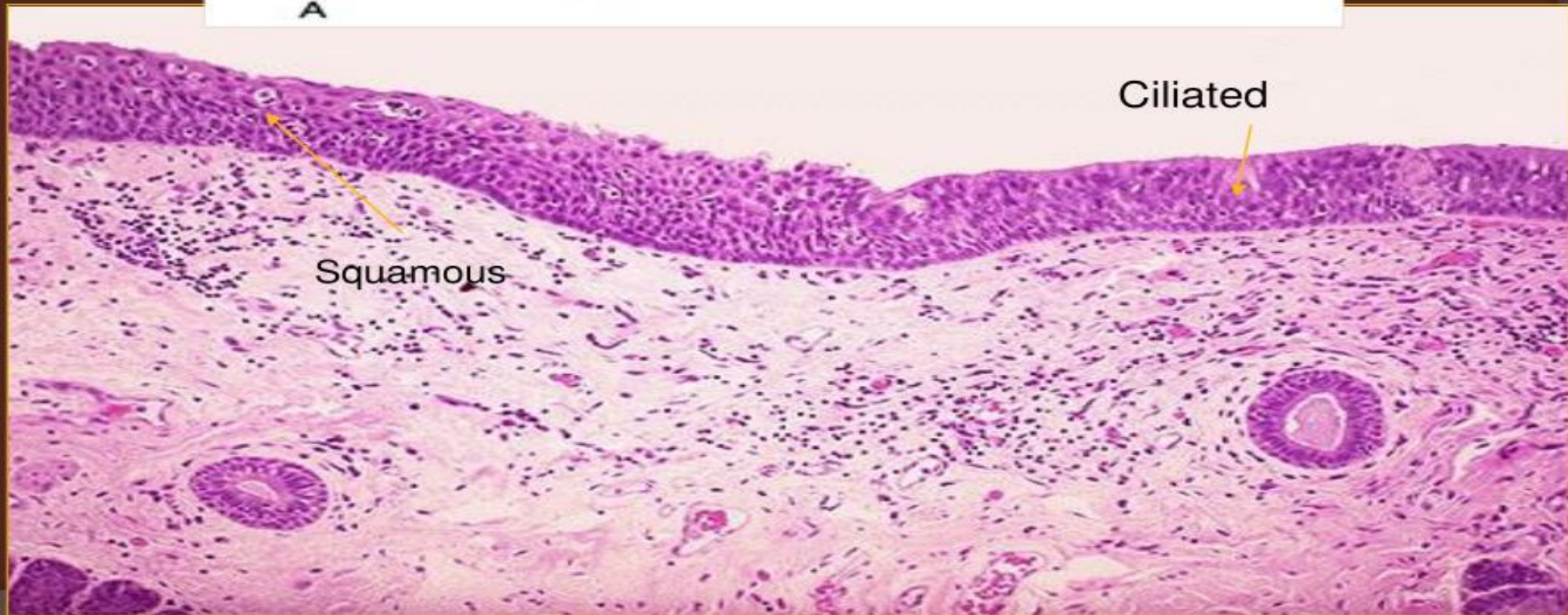
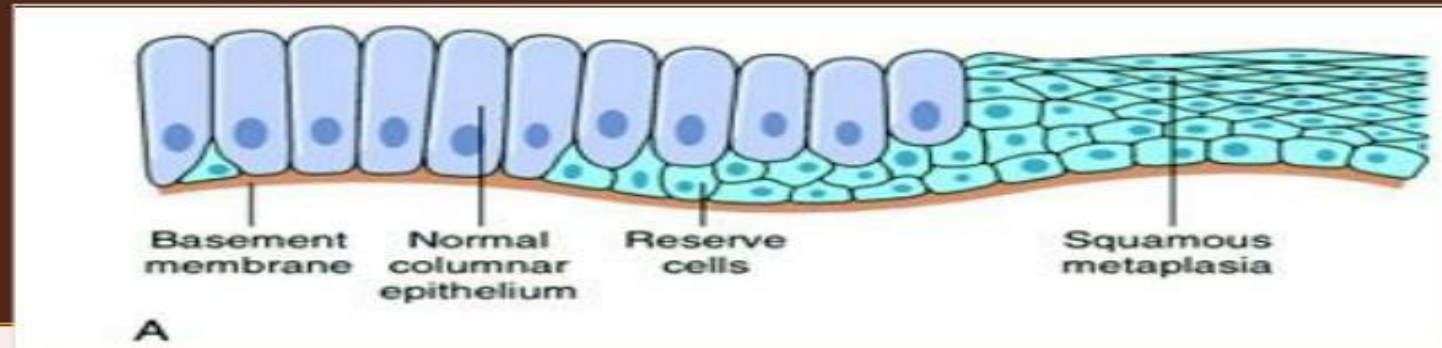
Occurs owing to altered/aberrant differentiation of stem cells due to their reprogramming.

Examples

- **Columnar to squamous metaplasia** in respiratory tract, in response to chronic irritation (cigarette smoking) and vitamin-A deficiency. Stones in excretory ducts of salivary glands, pancreas and gall bladder may also result in squamous metaplasia. Squamous metaplasia in cervix is usually associated with chronic infection (Fig. 1.5).
- **Connective tissue metaplasia** (formation of cartilage, bone or adipose tissue in tissues that normally do not contain these elements), eg, bone formation in muscle (myositis ossificans), which occurs after bone fracture.

Note: The factors that predispose to metaplasia, if persistent, may eventually lead to induction of cancer in metaplastic epithelium, eg, metaplasia from squamous to columnar epithelium in Barrett's oesophagus may progress to adenocarcinoma oesophagus.

Metaplasia



- **Q. Define dysplasia.**

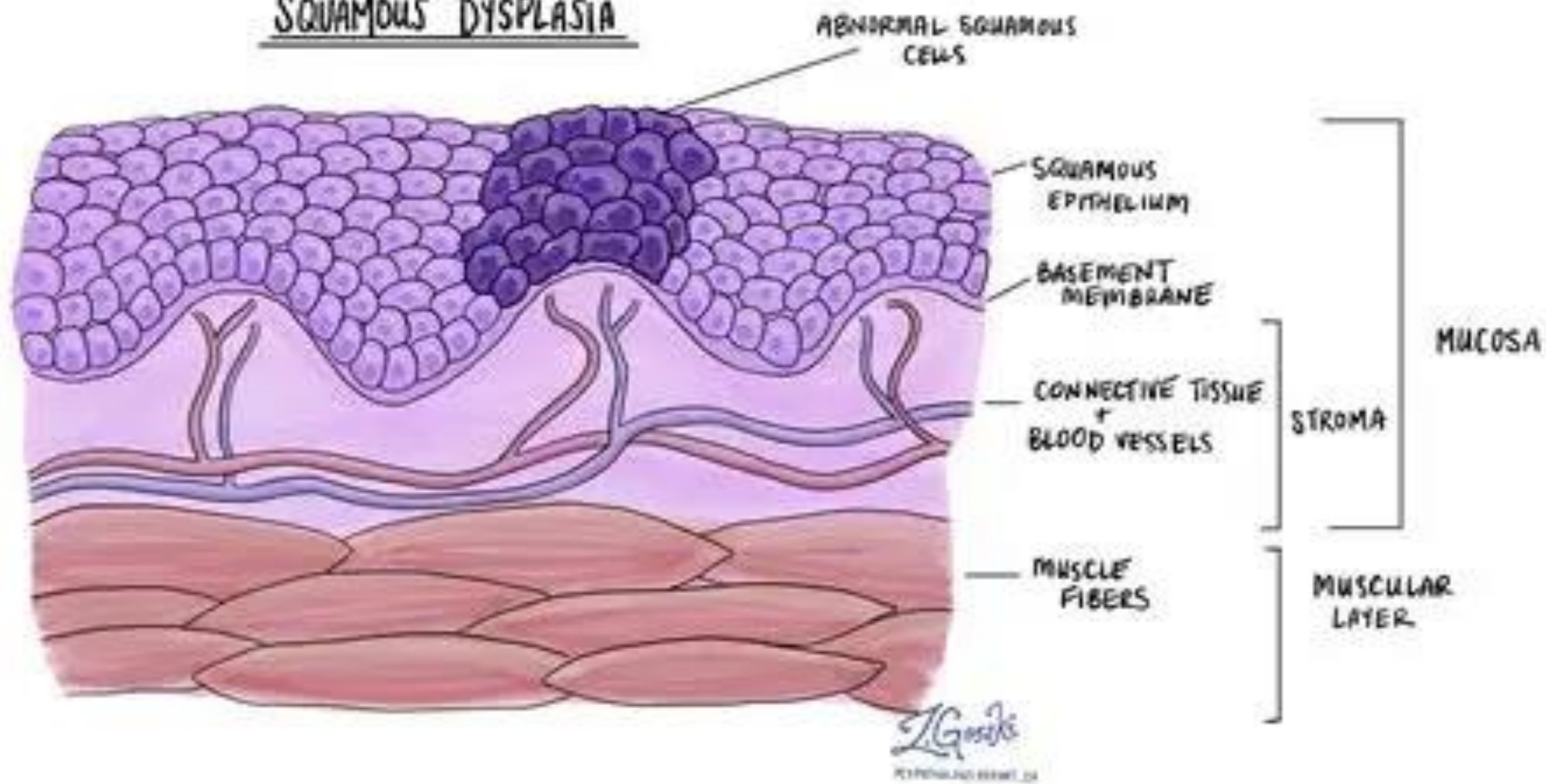
Dysplasia indicates disordered cellular development **characterized by**

- **Loss of orientation** of cells with respect to one another, eg, disorderly arrangement of the cells from basal to surface layer as in stratified squamous epithelium (architectural disorientation).
- **Lack of uniformity** of individual cells (cellular pleomorphism).
- Causes of dysplasia include diverse cellular insults, including physical, chemical and biological.
- It is typically seen in epithelial cells and may be reversible (at least in its early stage).

More severe dysplasia is known to progress to carcinoma in situ and invasive carcinoma.

- **Dysplastic cells are characterized by the following cellular features:**
- **Accelerated cell proliferation** (increased mitoses);
- **Nuclear abnormalities** such as hyperchromasia (increased basophilia on staining with haematoxylin) and pleomorphism (altered nuclear size and nuclear shape).
- **Increased nuclear-cytoplasmic ratio.**

SQUAMOUS DYSPLASIA



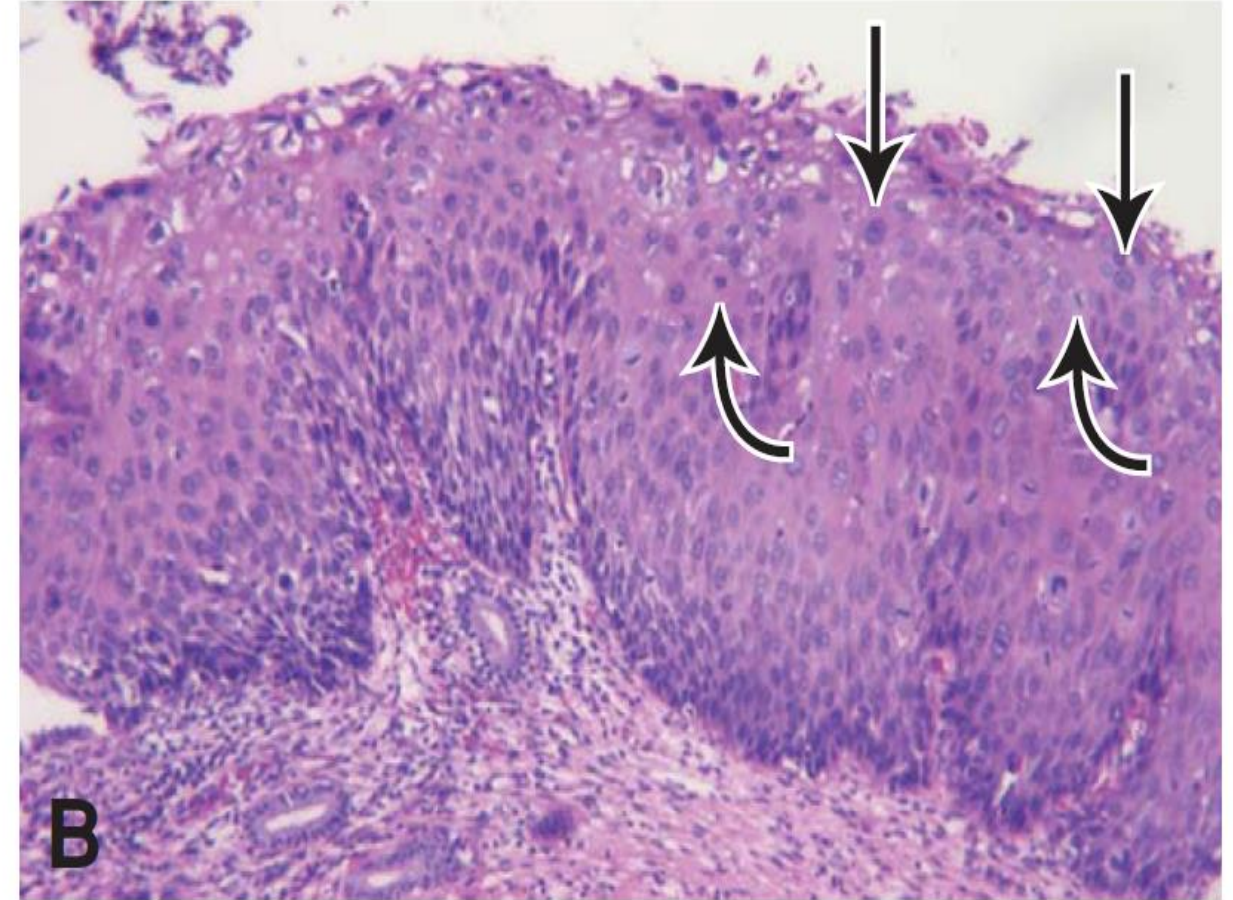
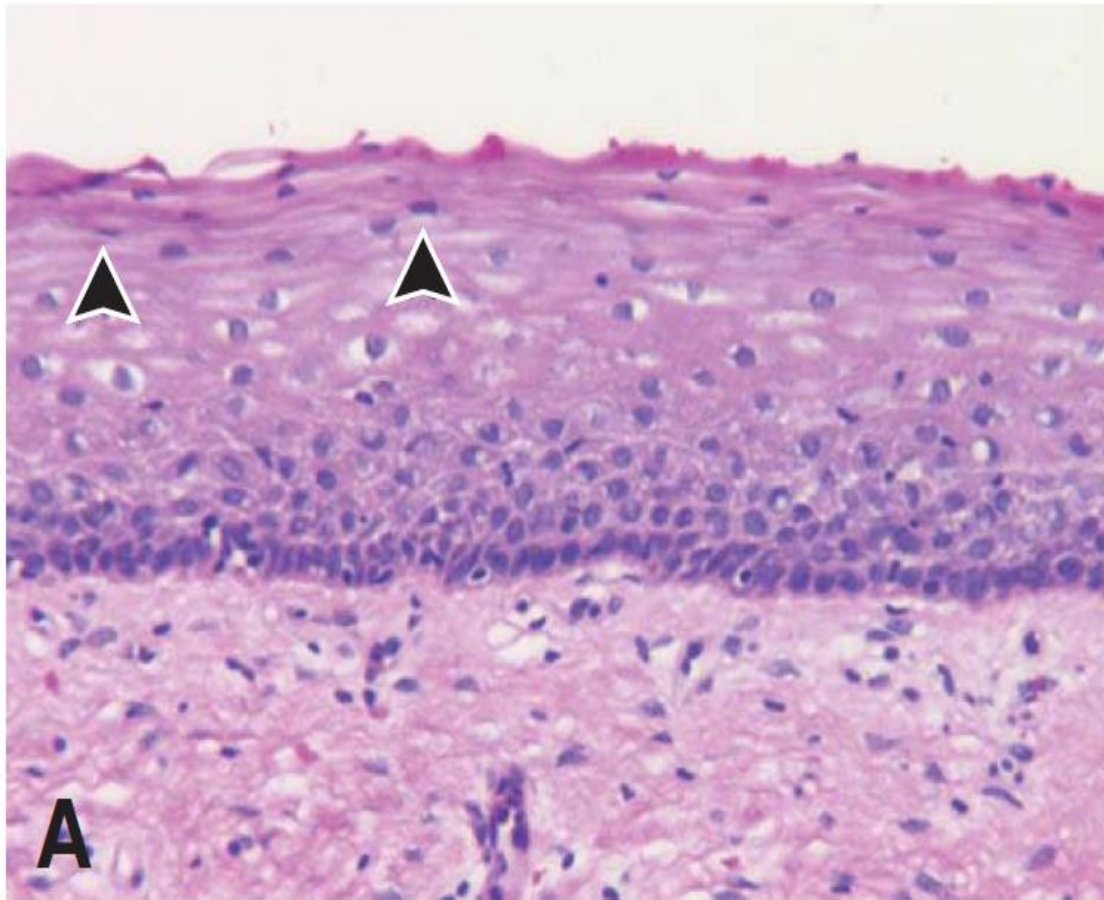


FIGURE 1-16. Dysplasia. A. Nondysplastic cervical epithelium. Normal cervix shows no mitotic activity above the most basal layers, but rather shows epithelial maturation, with flattening of the cells and progressive diminution of nuclei (*arrowheads*). **B.** At the same magnification, dysplastic epithelium of the uterine cervix lacks normal polarity, and individual cells show hyperchromatic nuclei and a greater than normal nucleus-to-cytoplasm ratio. Compare, for example, the size and hyperchromaticity of nuclei in the dysplastic cells (*straight arrows*) with the characteristics of normal counterparts at comparable height in the normal cervix. In contrast to normal cervix, cellular arrangement in dysplastic epithelium is disorderly, largely lacking appropriate histologic maturation, from the basal layers to the surface. Mitotic figures far above the basal layers (*curved arrows*) are common.

TABLE 1.1.**Differences between metaplasia and dysplasia**

Features	Metaplasia	Dysplasia
Definition	Replacement of one adult epithelial or mesenchymal cell type by another	Disordered cellular development characterized by (a) Loss of orientation of cells with respect to one another (b) Lack of uniformity of individual cells
Types	Squamous, columnar (epithelial) and osseous, cartilaginous (mesenchymal)	Epithelial only
Cellular pleomorphism	Mature cellular development; no pleomorphism	Disordered cellular development due to aberrant/delayed maturation or differentiation; pleomorphism present
Natural history	Reversible on withdrawal of stimulus	May regress on withdrawal of inciting stimulus or progress to higher grades of dysplasia or carcinoma in situ

- Q. Write briefly on aetiopathogenesis and biochemical basis of cell injury.

Sublethal or chronic injurious stimuli can cause ‘reversible and irreversible cell injury’.

Causes of Cell Injury

- Genetic

- Development defects (errors in morphogenesis)
- Cytogenetic defects (chromosomal abnormalities)
- Single gene defects (Mendelian disorders)
- Multifactorial inheritance disorders

- Acquired

- Hypoxia (ischaemia, anemia, carbon monoxide poisoning, cardiorespiratory failure).
- Physical agents (trauma, thermal injury, radiation, electric shock, pressure changes)
- Chemical agents/drugs (heavy metals, acids/alkalies, insecticides/herbicides, alcohol, smoking)
- Microbial agents (bacteria, viruses, fungi, rickettsiae, parasites)
- Immunological agents (autoimmunity, hypersensitivity)
- Nutritional imbalance (deficiency of protein, calories, trace elements, vitamins, excess cholesterol).
- Psychological factors

- The cellular responses to pathological stimuli depend on
- (a) Type, duration and severity of the injury.
- (b) Type, status and adaptability of the target cell.
- The most important targets of injurious stimuli are
- (a) Aerobic respiration (involving mitochondrial oxidative phosphorylation and production of ATP)
- (b) Cell membrane
- (c) Protein synthesis
- (d) Cytoskeleton
- (e) Genetic apparatus

- Biochemical Basis of Cell Injury

Cell injury occurs due to the following mechanisms:

- ATP depletion: ATP is required for
- Membrane transport
- Protein synthesis
- Lipogenesis
- Phospholipid turnover

ATP depletion results in dysfunction in the above functions/mechanisms.

- Damage due to oxygen and oxygen-derived free radicals.
- Loss of calcium homeostasis:
- Normal cytosolic-free calcium levels are very low
- Most intracellular calcium sequestered in endoplasmic reticulum and mitochondria
- Injury causes influx of calcium across cell membrane and its release into cytosol from mitochondria and endoplasmic reticulum.
- Increase in cytosolic calcium leads to activation of enzymes initiating cell injury

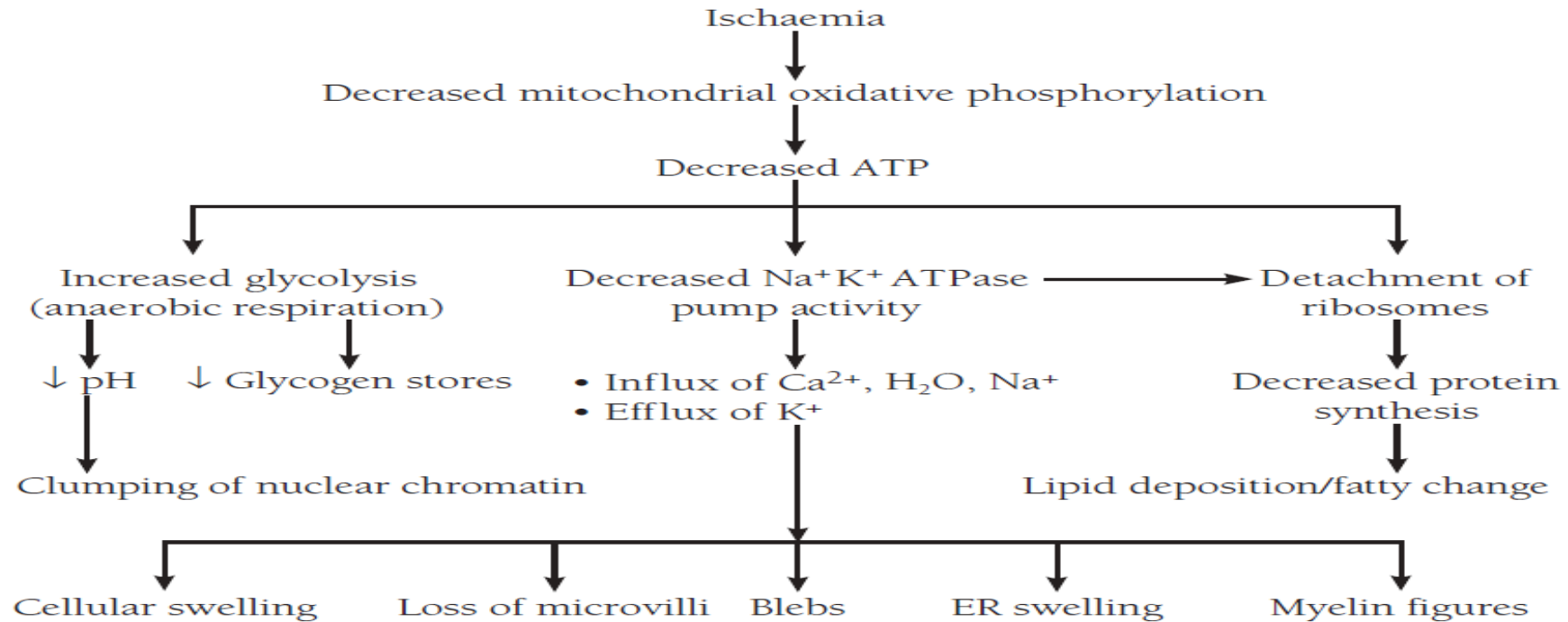
Q. Differentiate between reversible and irreversible cell injury.

Ans. Differences between reversible and irreversible cell injury are shown in Table 1.2.

TABLE 1.2.

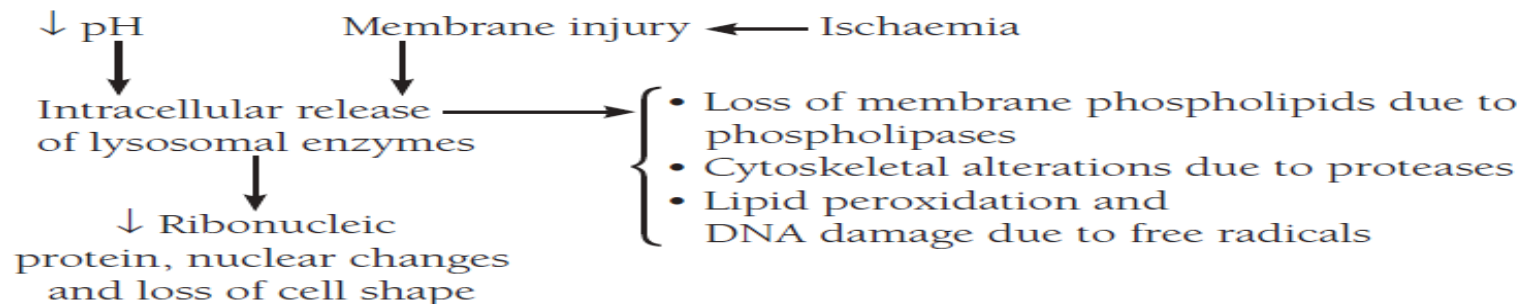
Differences between reversible and irreversible cell injury

Features	Reversible injury	Irreversible injury
Definition	If the structural and functional changes, induced by an injurious stimulus, <i>can</i> revert to normal on removal of the same, it is called reversible injury	If the structural and functional changes, induced by an injurious stimulus, <i>cannot</i> be reversed even after removal of the same, it is called irreversible injury
Cell membrane		
(a) Blebbing, blunting, distortion	Present	Present; more prominent than reversible injury
(b) Defect	Absent	Present
Endoplasmic reticulum	Shows swelling only	Shows swelling and lysis
Ribosomes	Dispersed	Dispersed and destroyed
Lysosomes	Autophagy of organelles by lysosomes, no rupture	Rupture of lysosomes and autolysis of cell
Mitochondria	Swelling, small densities present	Swelling, large densities present
Nucleus	Clumping of nuclear chromatin	Pyknosis, karyolysis or karyorrhexis
Calcification	Absent	Dystrophic calcification may be seen



FLOWCHART 1.4. Sequence of events in reversible injury.

- Irreversible injury (Flowchart 1.5)



FLOWCHART 1.5. Sequence of events in irreversible injury.

Q. Write briefly on free radical-mediated cell injury.

Free radicals are chemical species with an unpaired electron in their outer orbit. They react with inorganic and organic molecules (proteins, lipids and carbohydrates), which are mainly present in membranes and nucleic acids.

Free radical production is induced by

- Absorption of radiant energy: UV rays, X-rays.
- Enzymatic metabolism of exogenous chemicals/drugs: CCl_4 to CCl_3 .
- Reduction–oxidation reaction processes that occur during normal metabolism: Formation of superoxide anion

(O_2^-), hydrogen peroxide (H_2O_2), hydroxyl ion ($\cdot\text{OH}$).

- Reactions involving transition metals: iron (Fenton reaction), copper, etc.
- Reactions involving nitric oxide (NO): acts as a free radical and can be converted to highly reactive peroxynitrite anion (ONOO^-) as well as NO_2 and NO_3^- .

Effects of free radicals:

- **Lipid peroxidation**: Lipid and free radical interactions produce peroxides (initiation).

Peroxides are reactive and unstable species, which start a chain reaction of lipid peroxidation (propagation).

In some cases, chain reaction may be terminated by antioxidants.

- **Modification of proteins by oxidation**: Oxidation of amino acid residue side chain leads to formation of protein–protein cross-linkage and disruption of the protein backbone resulting in protein fragmentation.

- **DNA lesions**: Attack thymine and other nucleotides of nuclear and mitochondrial DNA to produce single- or double-stranded breaks in DNA as well as cross-linking of DNA strands.

Inactivation of free radicals is brought about by

- **Antioxidants**: vitamins A, C, E and b-carotene.
- **Iron- and copper-binding proteins**: transferrin, ferritin, lactoferrin, ceruloplasmin (decrease available free metal by binding to it).
- **Enzymes**: catalase, superoxide dismutase, glutathione peroxidase (catalyse free radical breakdown)

- Q. Define necrosis and describe its various morphological patterns.

Disturbances of the external environment beyond the limits of homeostasis lead to premature cell death, which is called necrosis.

Necrosis may be caused by ischaemia, infection, poisoning, etc., and is invariably pathological.

It usually precipitates an inflammatory response and is accompanied by cell swelling, lysis and lysosomal leakage.

Self-digestion of cells by enzymes liberated from its own lysosomes on the other hand is labelled autolysis

The morphological features of necrosis vary with its type.

Changes common to most types include

1. Cytoplasmic changes

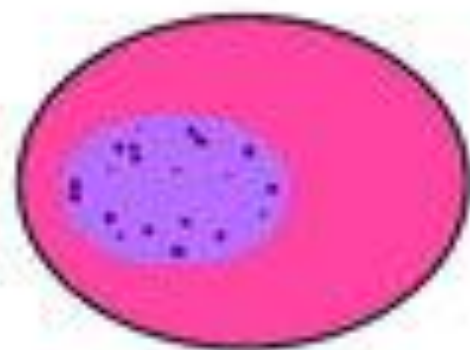
- **Increased eosinophilia** of the cytoplasm, which is due to loss of normal cytoplasmic basophilia caused by the loss of RNA and denaturation of cytoplasmic proteins which then bind strongly to the dye eosin.
- **Glassy homogenous cytoplasm** due to loss of glycogen.
- **Swelling and vacuolation of the cytoplasm** (occurs after enzymatic digestion has started).
- **Cellular and organelle swelling** may eventually lead to discontinuities in cell and organelle membranes and ultimately rupture.
- **Formation of myelin figures** (phospholipid masses derived from damaged cell membranes).

2. Nuclear changes

The changes in nucleus appear in one of the following three patterns:

- **Nuclear shrinkage and increased basophilia** (pyknosis)
- **Nuclear fragmentation** (karyorrhexis)
- **Loss or fading of basophilia** due to DNase activity (karyolysis)

KARYOLYSIS



Nuclear fading

chromatin dissolution due to action of DNases & RNases

PYKNOSIS



Nuclear shrinkage

DNA condenses into shrunken basophilic mass

KARYORRHEXIS

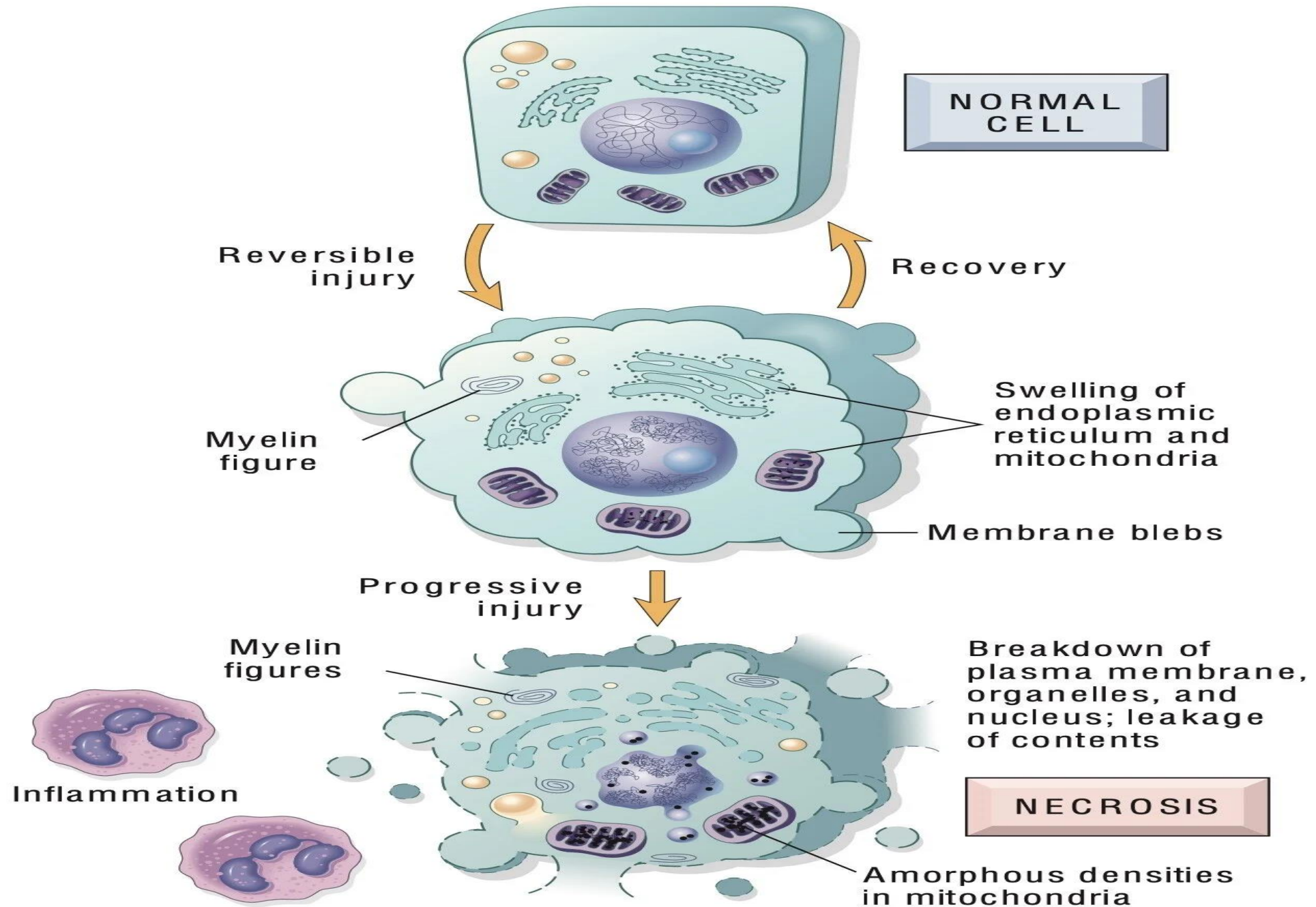


Nuclear fragmentation

Pyknotic nuclei membrane ruptures & nucleus undergoes fragmentation

Nuclear dissolution

ANUCLEAR NECROTIC CELL



Morphological patterns of necrosis include

1. Coagulative necrosis

- It is the most common pattern of necrosis and is caused by ischaemic injury resulting in hypoxic death of cells in all tissues except the brain.
- There is preservation of the basic architectural outlines and type of tissue can be recognized but cellular details are lost.
- Cell injury leads to increasing intracellular acidosis, which denatures not only structural proteins but also enzymatic proteins, and so blocks the proteolysis of the cell, thereby preventing loss of architecture of the tissue.
- **On gross examination**, the affected tissue is pale in colour and firm in texture.
- **Microscopically**, increased eosinophilia of the cytoplasm and decreased basophilia of the nucleus are observed. Myocardial infarction is an excellent example in which acidophilic, coagulated anucleate cells are seen

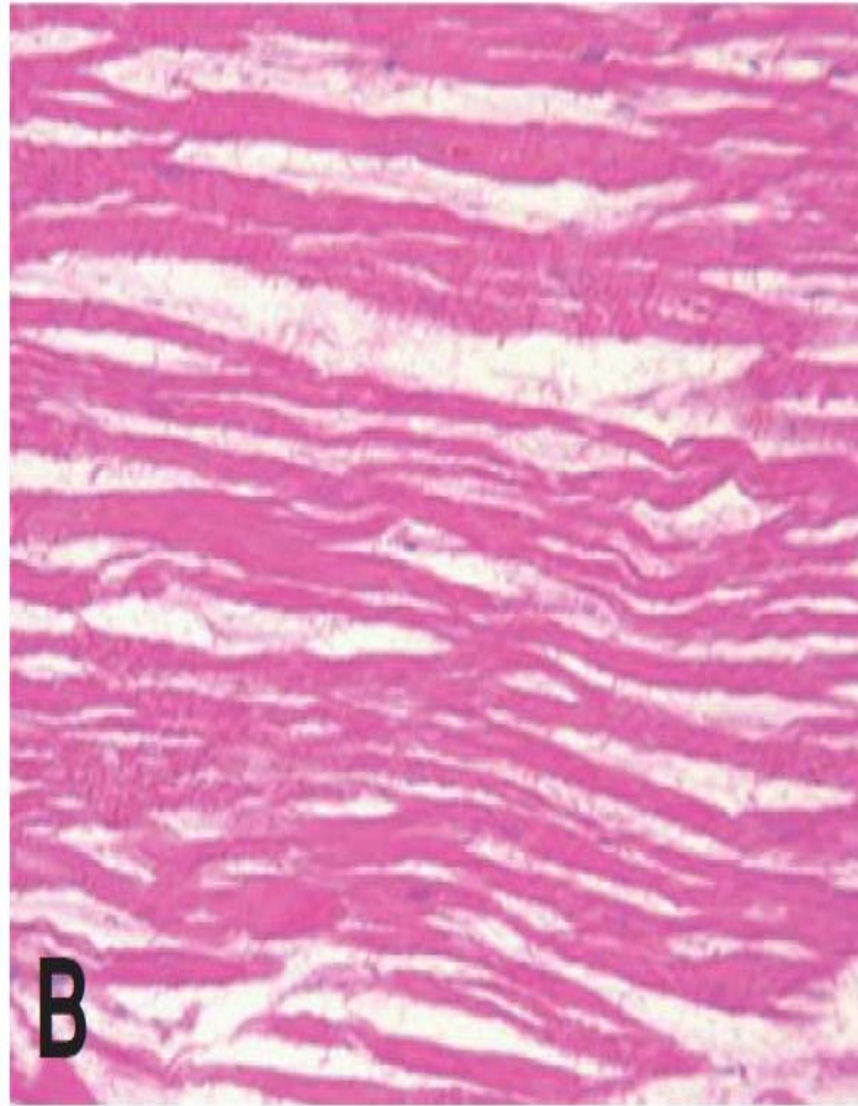


FIGURE 1-31. Coagulative necrosis. **A. Normal heart.** All myocytes are nucleated, and striations are clear. **B. Myocardial infarction.** The heart from a patient following acute myocardial infarction. The necrotic cells are deeply eosinophilic and most have lost their nuclei.

2. Liquefactive necrosis (colliquative necrosis)

- This occurs in situations in which enzymatic breakdown is more prominent than protein denaturation unlike coagulative necrosis.

- It is usually associated with bacterial or fungal infections because microbes stimulate

the accumulation of leukocytes and liberation of enzymes from these cells.

- The organ–cellular architecture is lost, and the tissue is digested and converted into

a liquefied mass, which appears creamy yellow in colour and is called ‘pus’.

- Liquefactive necrosis is most commonly seen in organs that have a high-fat and lowprotein content (eg, the brain), or those with a high-enzymatic content (eg, the pancreas), and typically causes gangrene of intestine and limbs and hypoxic death in brain.

- Lack of a proper collagenous connective tissue framework in an organ also aids to this type of necrosis.

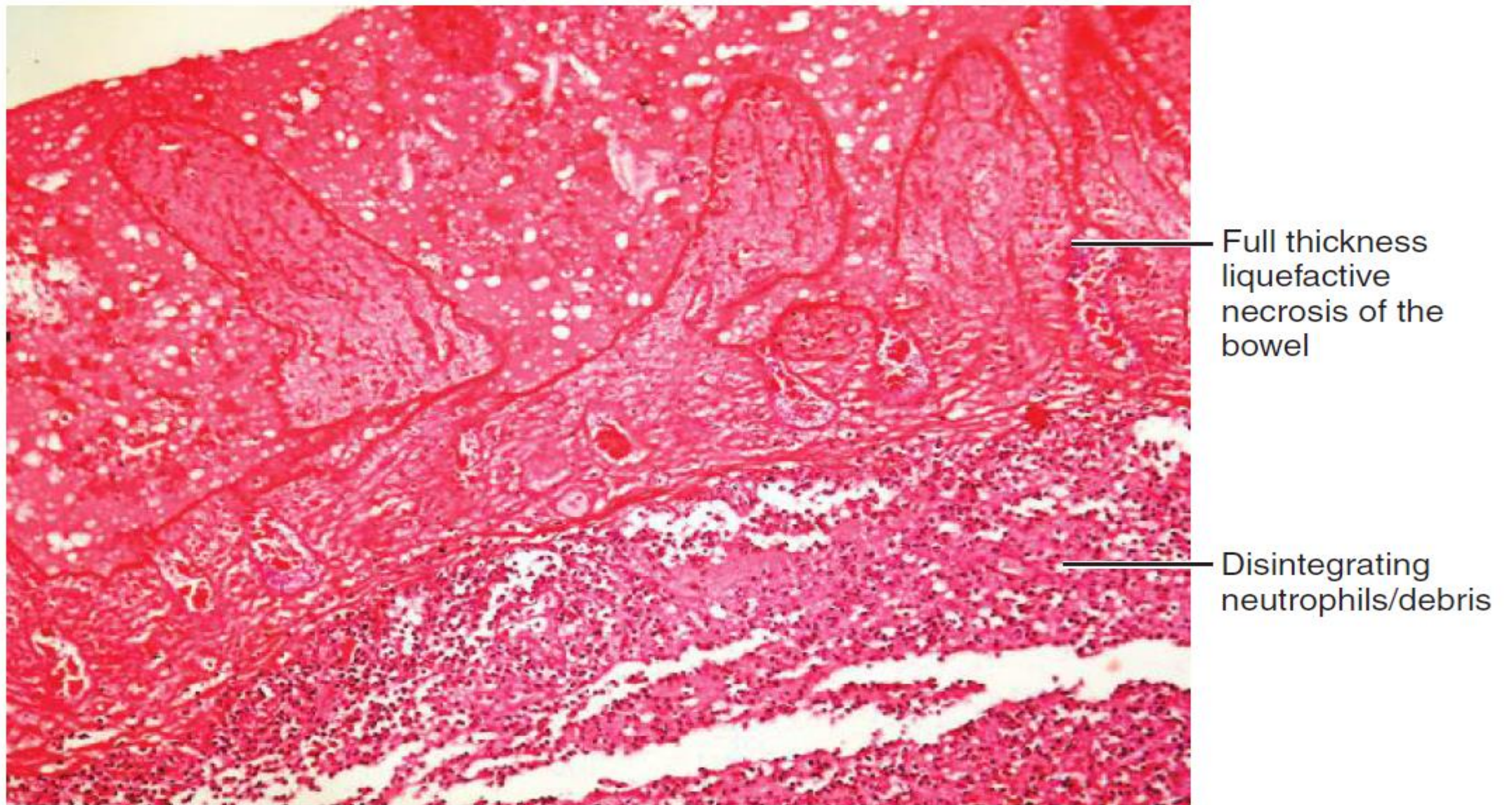


FIGURE 1.8. Liquefactive necrosis/gangrene of intestine (H&E; 100X).

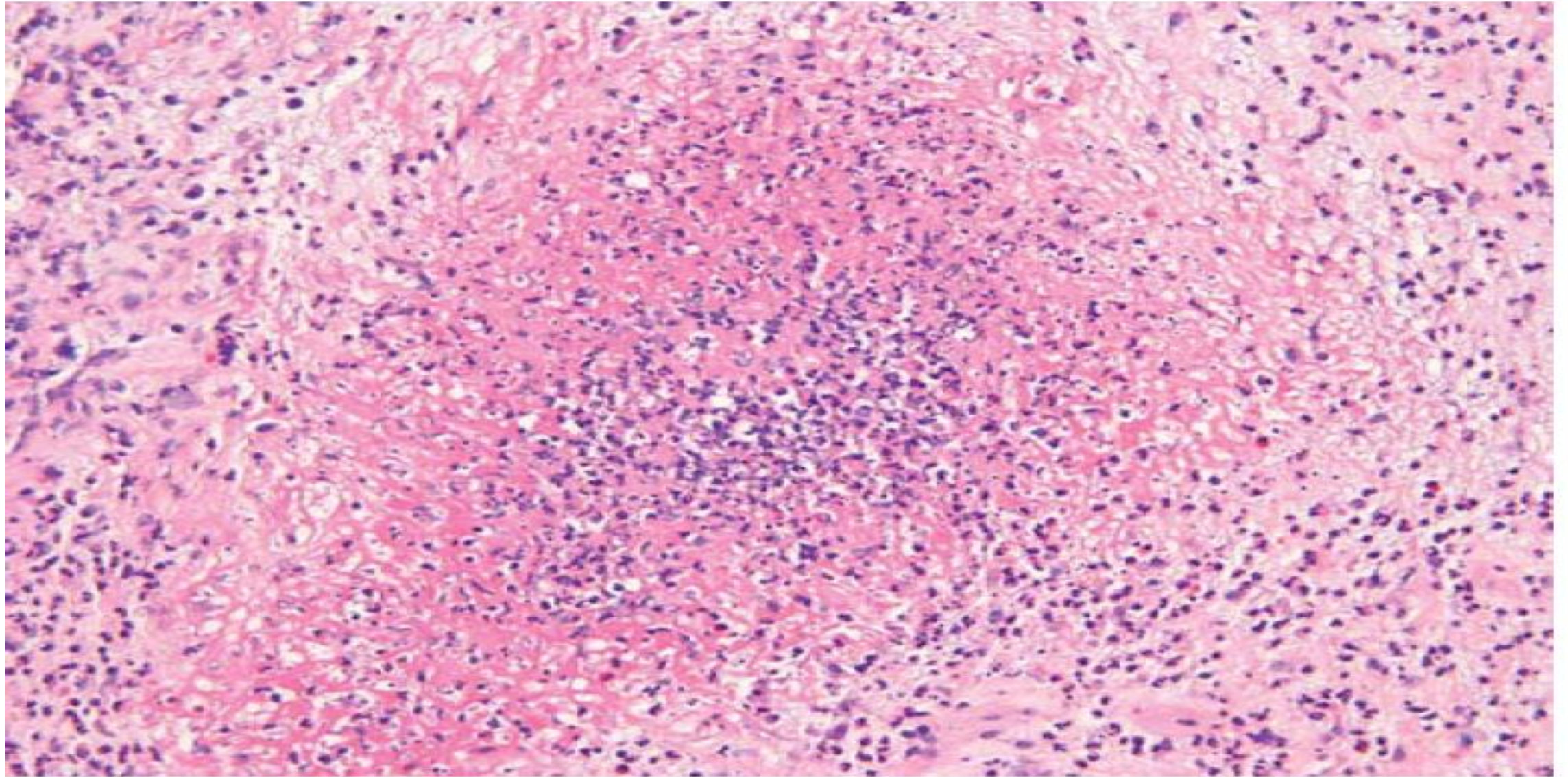


FIGURE 1-32. Liquefactive necrosis in an abscess of the skin. The abscess cavity is filled with polymorphonuclear leukocytes.

3. Gangrenous necrosis

This is a clinical term, not a specific pattern of necrosis. It is usually used in context of the lower limbs, which have lost their blood supply and have undergone necrosis, initially coagulative (dry gangrene), and later liquefactive due to secondary bacterial infection and immigrating leukocytes (wet gangrene) .

Mechanism of evolution of gangrenous necrosis .

- 1-Bacterial infections and accumulation of inflammatory cells
- 2-Release of enzymes
- 3-Autolysis and heterolysis

4. Caseous necrosis

- This type of necrosis is typically associated with tuberculous infection.
- **On gross examination**, the necrotic areas appear cheesy white (caseous).

Microscopically, the debris appears amorphous, eosinophilic and granular , and is surrounded by a distinct inflammatory reaction called granulomatous reaction.

- Tissue architecture is completely obliterated unlike coagulative necrosis. Dystrophic calcification may be seen.

5. Enzymatic fat necrosis

- It refers to a focal area of fat destruction that converts adipocytes to necrotic cells with shadowy outlines and basophilic calcium deposits, surrounded by an inflammatory reaction .
- It is typically seen in acute pancreatitis and traumatic fat necrosis of breast.

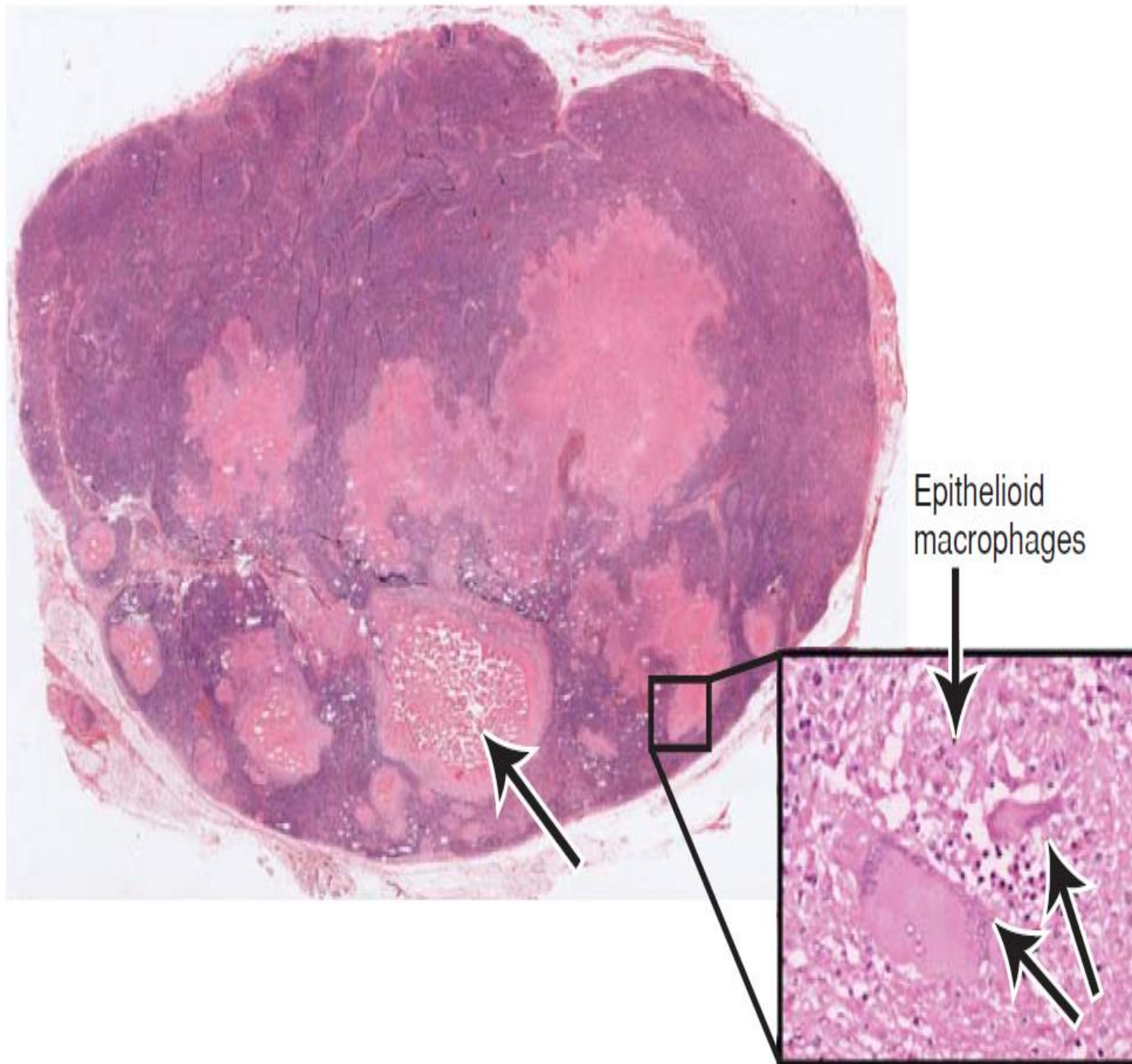
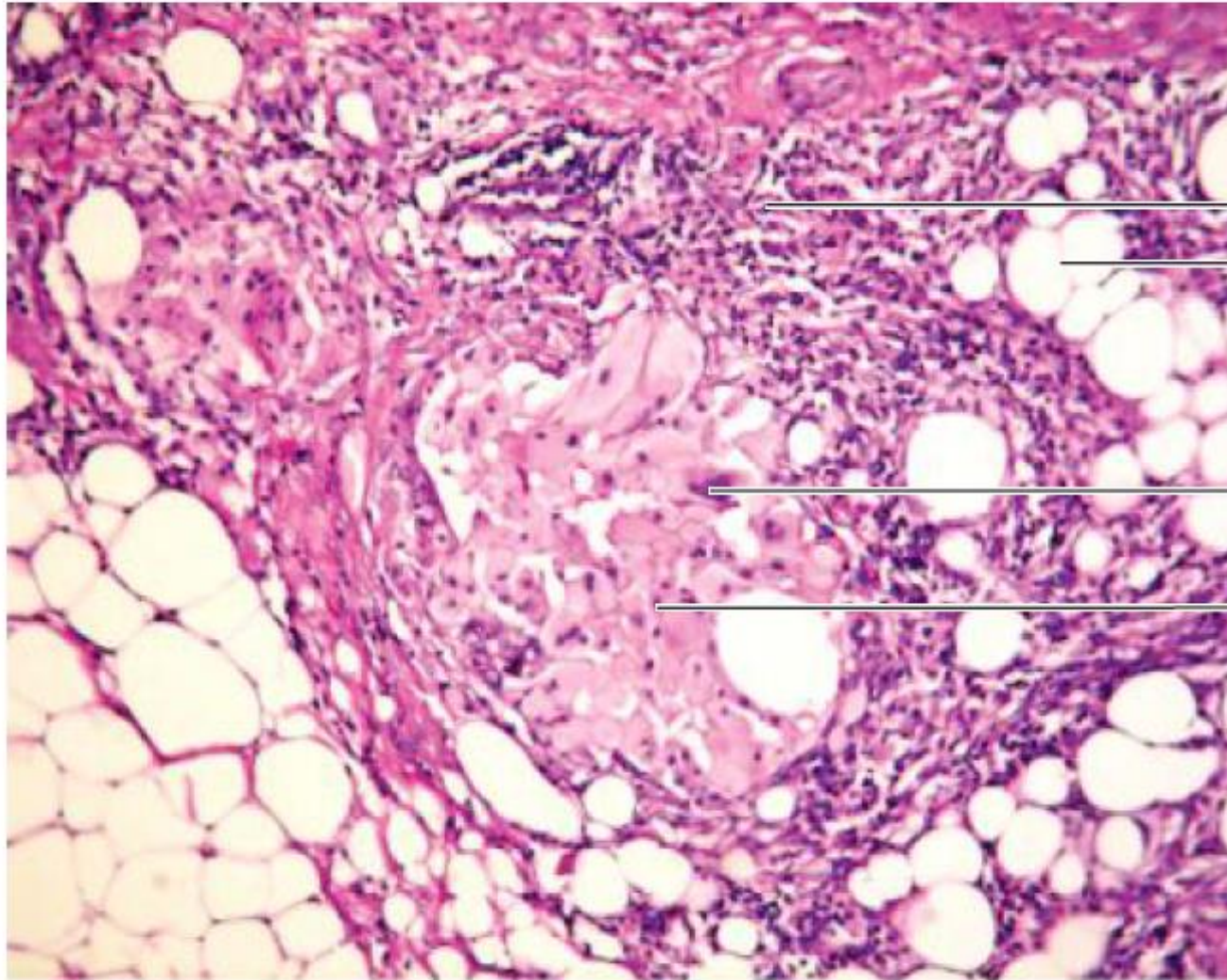


FIGURE 1-34. Caseous necrosis in a tuberculous lymph node. Hilar lymph node from a patient with active tuberculosis. Irregular pink areas of caseous necrosis (*arrow*) are evident against a background of lymphocytes. **Inset:** Granulomas on the periphery of necrotic areas show epithelioid macrophages and multinucleated giant (Langhans) cells (*arrows*).



Inflammatory cells

Mature adipose tissue

Multinucleate
giant cell

Foamy histiocytes

FIGURE 1.10. Fat necrosis in the breast showing disruption of normal adipocytes and accumulation of lipid-laden foamy histiocytes and a multinucleate giant cell (H&E; 200X).

6. Fibrinoid necrosis

- Deposition of bright, smudgy, eosinophilic fibrin-like material in vessel wall
- The fibrinoid material is composed of degenerated collagen and ground substance.
- It is usually seen in patients with malignant hypertension and immunological injury (vasculitis—polyarteritis nodosa).

It may also be seen in rheumatic fever, rheumatoid arthritis, hepatitis B virus (HBV) infection, systemic lupus erythematosus (SLE), etc.

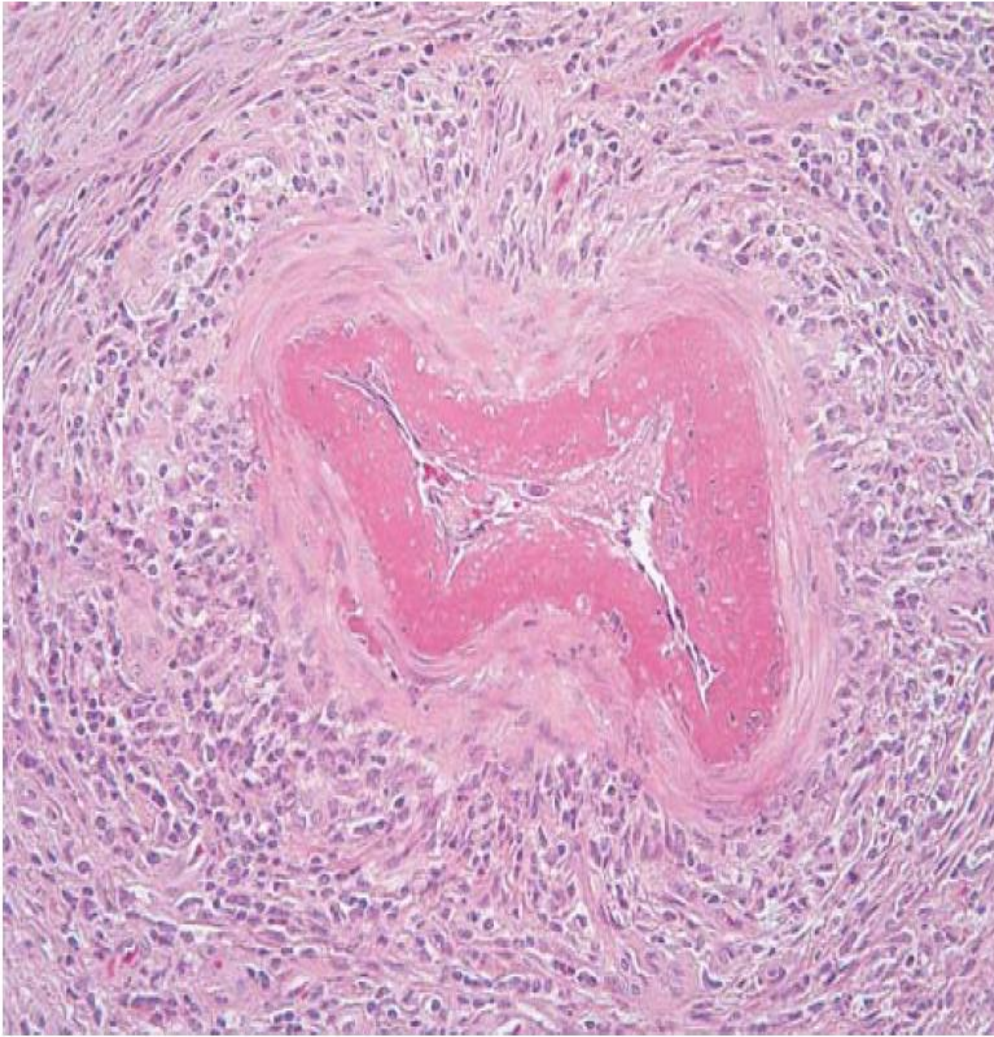
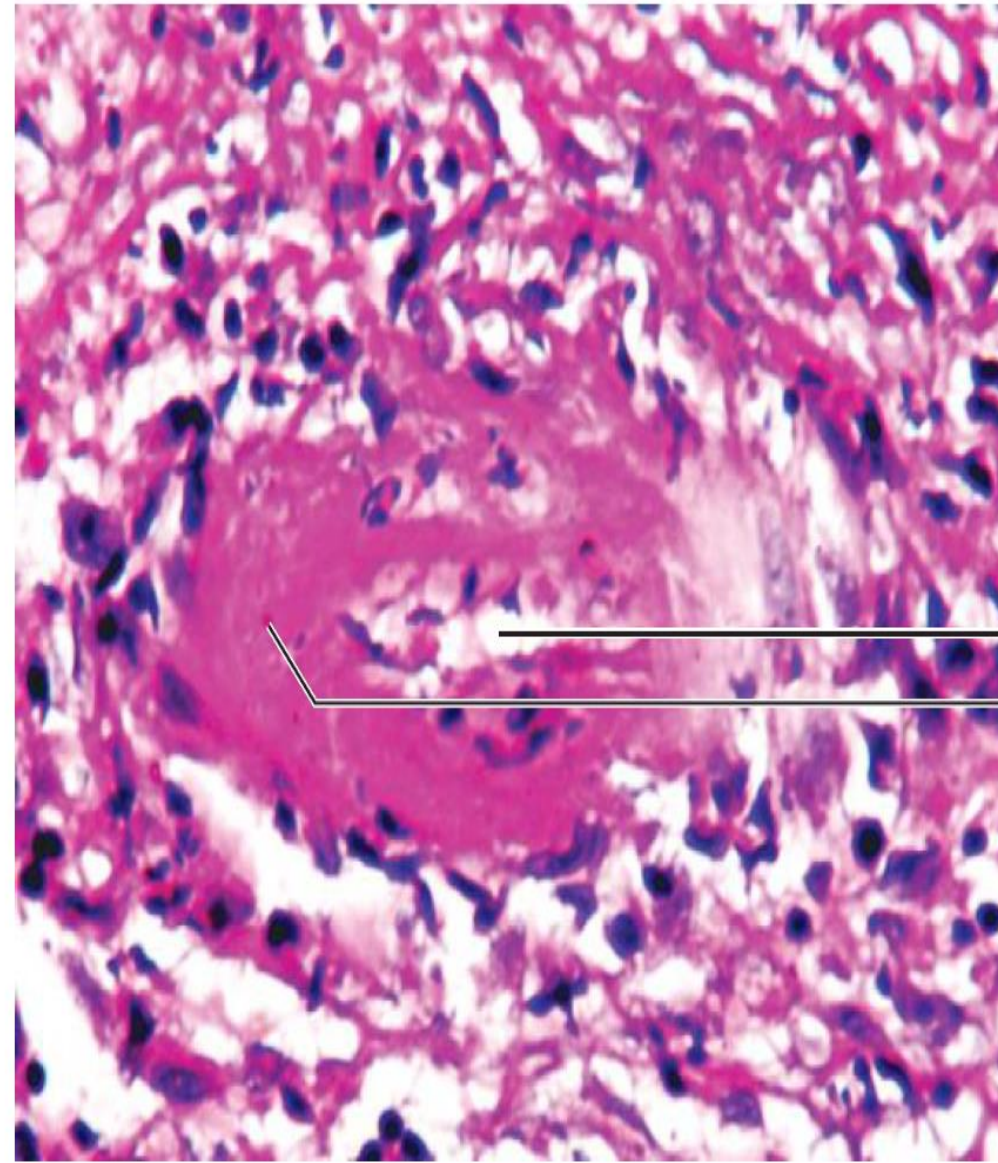


FIGURE 1-35. Fibrinoid necrosis. An inflamed muscular artery in a patient with systemic arteritis shows a sharply demarcated, homogeneous, deeply eosinophilic zone of necrosis.



Lumen of the vessel
Fibrinoid deposits in vessel wall

FIGURE 1.11. Fibrinoid necrosis of vessel wall seen as bright pink smudgy deposits (H&E; 200X).

Q. Differentiate between autolysis and necrosis.

Ans. Differences between autolysis and necrosis are shown in Table 1.3.

TABLE 1.3. Differences between autolysis and necrosis		
Features	Autolysis	Necrosis
Definition	Self-digestion of cells by enzymes liberated from its own lysosomes	Spectrum of morphologic changes that follow cell death in living tissue, resulting from the progressive degradative action of enzymes on lethally injured cells
Reaction	• In <i>living tissue</i>, inflammatory cells may be present • In <i>post-mortem</i> cases, there is complete absence of inflammatory cells	• Presence of inflammatory cells • Does not occur post-mortem
Calcification	Absent	Dystrophic calcification may be present

- Q. Define apoptosis and describe its morphology, biochemical basis and underlying mechanism.

Apoptosis is a form of genetically programmed cell death designed to eliminate unwanted host cells through activation of a coordinated series of events. It occurs in physiological and pathological conditions. in contrast with necrosis, which is always

- **Physiological apoptosis:**

- During development/embryogenesis (implantation and organogenesis)
- Hormone-dependent involution (regression of lactational changes in breast and prostatic atrophy)
- Cell deletion in proliferating cell population such as intestinal crypt epithelia
- Apoptosis of immune T and B cells as in clonal deletion or cell death induced by cytotoxic T cells
- Cell ageing

- **Pathological apoptosis:**

- Cellular damage by diseases/noxious agents, eg, councilman bodies in hepatitis
- Pathological atrophy in parenchymal organs after duct obstruction, eg, salivary gland and pancreas
- Pathological atrophy in hormone-dependent organs, eg, prostate
- Cell death in the tumours
- Low doses of thermal injury, radiation and anticancer drugs

- Sequence of Morphological Changes in Apoptosis (Fig. 1.12)
- **1. Cell shrinkage** (increased density of the cytoplasm with tightly packed organelles)
- **2. Chromatin condensation** under the nuclear membrane followed by nuclear fragmentation
- **3. Formation of cytoplasmic blebs** followed by fragmentation into apoptotic bodies (surface blebbing followed by fragmentation into membrane-bound apoptotic bodies)
- **4. Phagocytosis of apoptotic bodies** (ingestion by macrophages followed by lysosomal degradation).

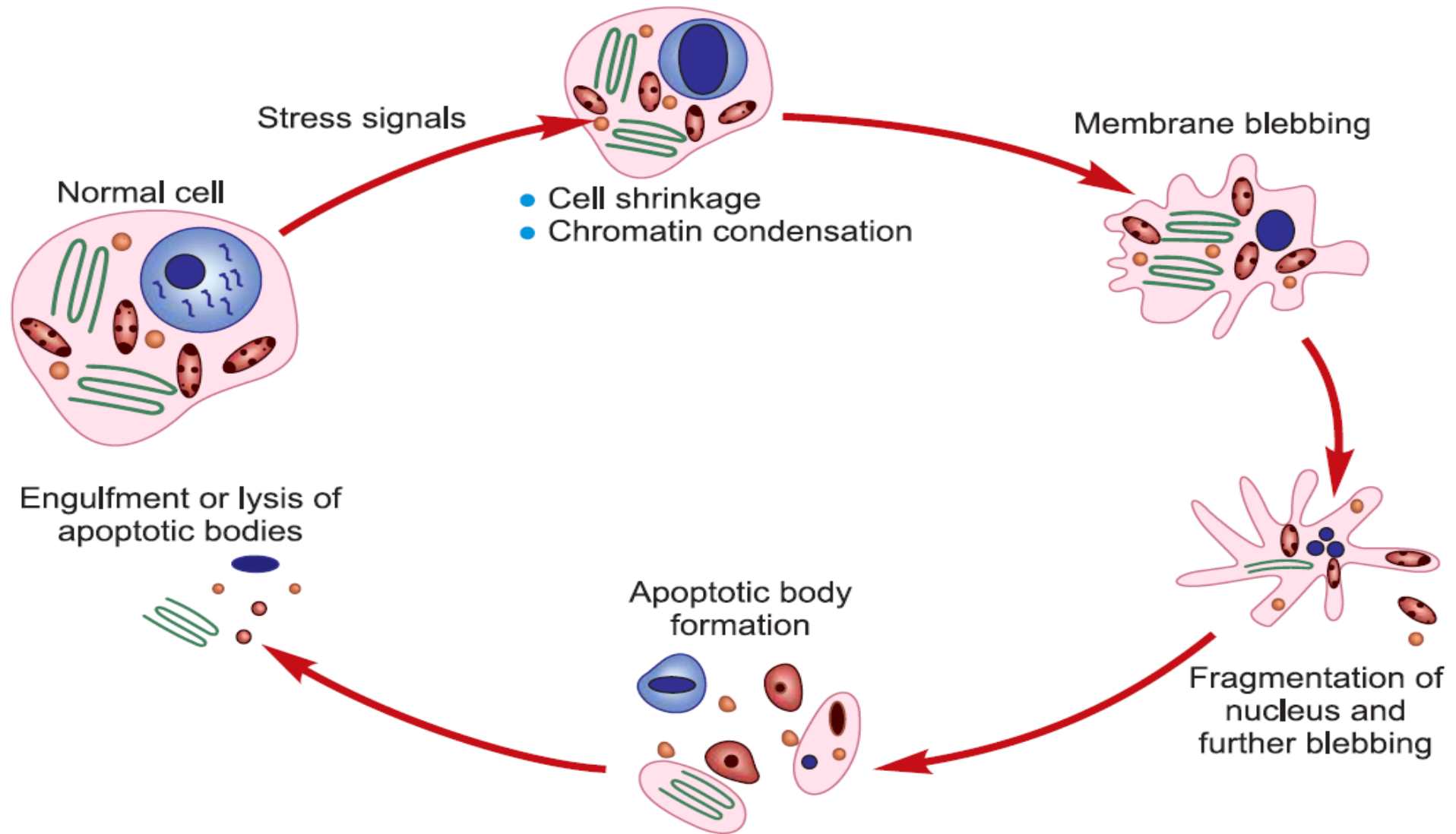


FIGURE 1.12. Sequence of morphological changes in apoptosis.

- **Mechanism of Apoptosis**

Apoptosis is the end point of an energy-dependent cascade of molecular events having four steps.

1. Initiation of apoptosis by activation of signalling pathways:

There are two main signalling pathways in apoptosis.

(a) Extrinsic/death receptor-initiated pathway

(b) Intrinsic/mitochondrial pathway (the major mechanism of apoptosis)

2. Control and integration: Commitment or abortion of lethal signals is controlled by BCL2 family of proteins which include 'antiapoptotic proteins' (BCL2, BCLXL and MCL1); 'proapoptotic proteins' (BAX and BAK); and 'BCL2 sensor proteins' (BAD, BIM, Puma, Noxa). Also, the cytoplasm of normal cells contains inhibitors of apoptosis (IAP) which are neutralized by proapoptotic factors.

3. Execution phase: Proteolytic cascade involving execution caspases (caspases 3 and 6). Caspase 3 also converts a cytoplasmic DNase into an active form by cleaving the inhibitor of this enzyme (this DNase induces internucleosomal cleavage of DNA).

4. Removal of dead cells: Early recognition and removal by macrophages. Removal is aided by:

(a) Expression of phosphatidylserine: in normal cells phosphatidylserine is present in the inner leaflet of the plasma membrane; during apoptosis there is turning out of the phosphatidylserine so that it is expressed on the outer membrane and is easily recognized by the macrophage.

(b) Secretion of soluble factors by apoptotic cells, eg, thrombospondin, which recruit macrophages.

(c) Coating of apoptotic cells by natural antibodies and proteins of the complement system, which are easily recognized by macrophage receptors.

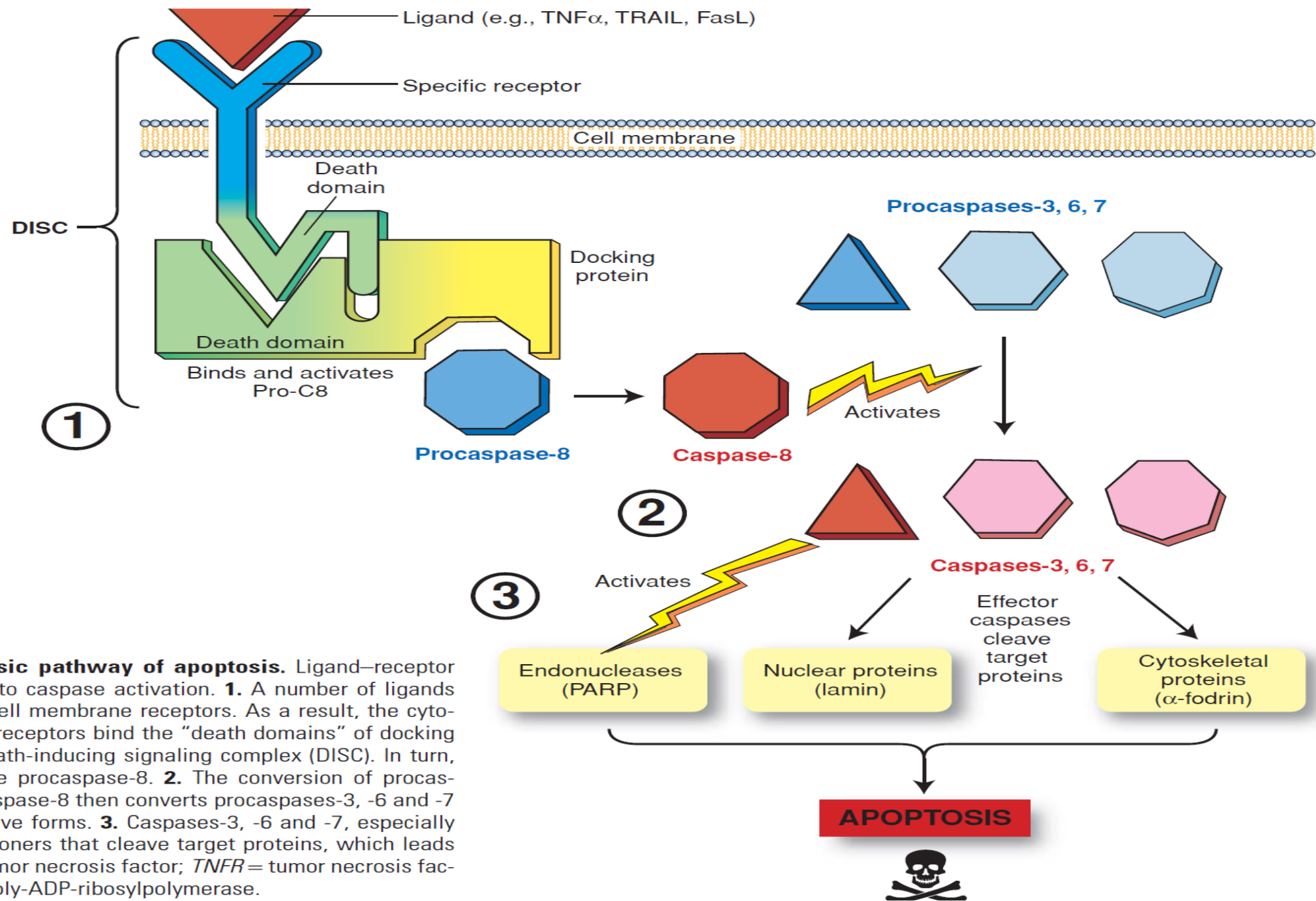


FIGURE 1-40. Extrinsic pathway of apoptosis. Ligand–receptor interactions that lead to caspase activation. **1.** A number of ligands bind their respective cell membrane receptors. As a result, the cytoplasmic tails of these receptors bind the “death domains” of docking proteins, to form a death-inducing signaling complex (DISC). In turn, these proteins activate procaspase-8. **2.** The conversion of procaspase-8 to activated caspase-8 then converts procaspases-3, -6 and -7 to their respective active forms. **3.** Caspases-3, -6 and -7, especially caspase-3, are executioners that cleave target proteins, which leads to apoptosis. *TNF*= tumor necrosis factor; *TNFR*= tumor necrosis factor receptor; *PARP*= poly-ADP-ribosylpolymerase.

Q. Differentiate between apoptosis and necrosis.

Ans. Differences between apoptosis and necrosis are shown in Table 1.7.

TABLE 1.7. Differences between apoptosis and necrosis		
Features	Apoptosis	Necrosis
Definition	Programmed and coordinated cell death, which eliminates unwanted/harmful cells or removes cells damaged beyond repair	Spectrum of morphologic changes that follow cell death in living tissue, largely resulting from the progressive degradative action of enzymes on lethally injured cells
Causes	May be physiological or pathological	Always pathological, eg, hypoxia, toxins
Involves	Single or small groups of cells	Large groups of cells
Inflammation	Absent	Present
Cellular change	Cell shrinkage	Cell swelling
Cell membrane	Bleb formation	Membrane disruption
Nucleus	Chromatin condensation followed by fragmentation	Nuclear pyknosis, karyolysis and karyorrhexis
Removal of cell	Phagocytosis of apoptotic bodies by macrophages	Enzymatic digestion or phagocytosis of cell debris by macrophages
Lysosomes/other organelles	Intact	Hydrolytic enzyme release due to rupture
Mechanism	Genetically coordinated	Due to ATP depletion, free radicals, mitochondrial damage, etc.
Agarose gel electrophoresis	Stepladder DNA pattern	Diffuse DNA pattern

- Q. Enumerate the disorders associated with apoptosis.

1. Disorders associated with decreased apoptosis: cancer, autoimmunity

2. Disorders associated with increased apoptosis:

- (a) Neurodegenerative diseases (Alzheimer, Huntington, Parkinson)

- (b) Ischaemic injury in stroke and myocardial infarction

- (c) Death of virus-infected cells as in AIDS

Accumulation of Normal Cellular Constituent in Excess

1. Water

(a) Cloudy swelling

- (i) A form of reversible injury, cloudy swelling is also called granular degeneration (named so because of the presence of prominent protein granules in the cytoplasm)
- (ii) It commonly affects hepatocytes, renal tubular cells and myocardium

b) Hydropic/vacuolar degeneration

- (i) This is an extension of changes seen in cloudy swelling
- (ii) Affected cells are ballooned, pale, watery and vacuolated
- (iii) Vacuoles coalesce and push nucleus towards the periphery
- (iv) Cell bursts and nucleus undergoes karyorrhexis/lysis

2. Fat: Abnormal accumulation of triglycerides in the cytosol of parenchymal cells is called fatty change (steatosis). It mainly affects liver and heart but can also be seen in muscle and kidney.

Causes of fatty liver

- Alcohol abuse.
- Starvation/malnutrition.
- Diabetes mellitus.
- Obesity.
- Hepatotoxins like CCl₄, ether, aflatoxins.
- Certain drugs, like steroids, tetracycline and aspirin (Reye syndrome).
- Hypoxia in anaemia and cardiac failure.
- Late pregnancy.
- Chronic illness, like tuberculosis.

3. Carbohydrates: Accumulation of carbohydrates is seen in conditions such as glycogenosis and mucinous degeneration.

4. Proteins:

Proteins can accumulate as

(a) Colloid droplets (reabsorption droplets in proximal renal tubules seen in renal diseases associated with excessive protein loss in the urine).

(b) Russell bodies (active synthesis of immunoglobulins leads to excessive amounts of secretory protein in plasma cells causing huge distension of endoplasmic reticulum, which appear as large eosinophilic inclusions).

(c) Defective secretion and transport of proteins, as in α -1 antitrypsin deficiency, results in accumulation of misfolded protein in ER causing ER stress as well as loss of protein function inducing emphysema and cirrhosis.

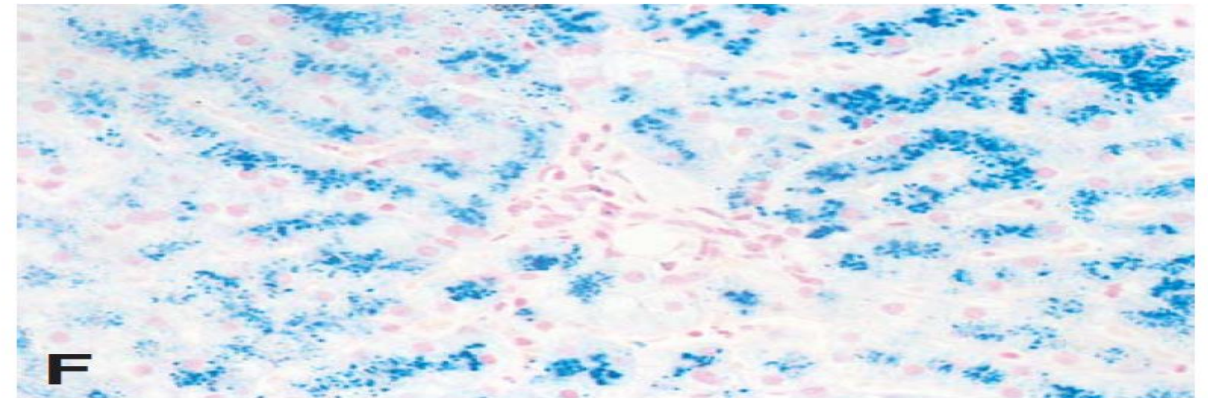
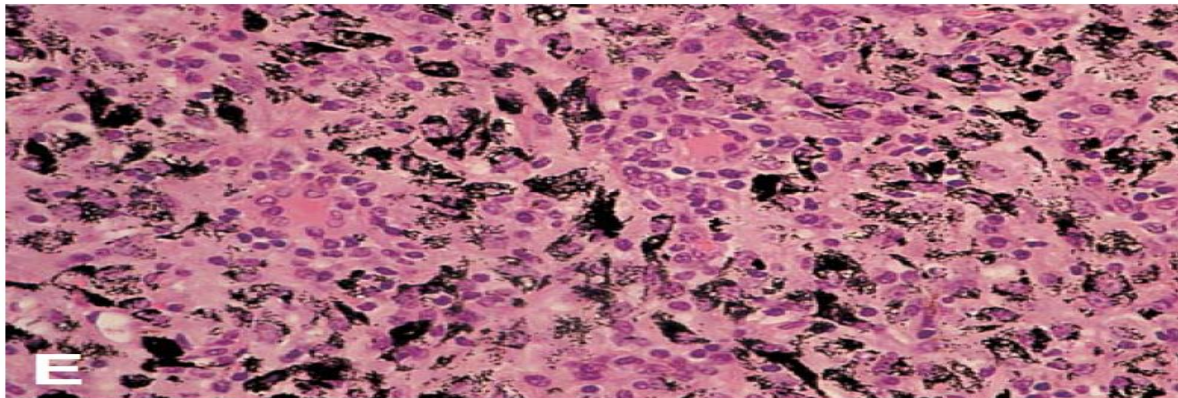
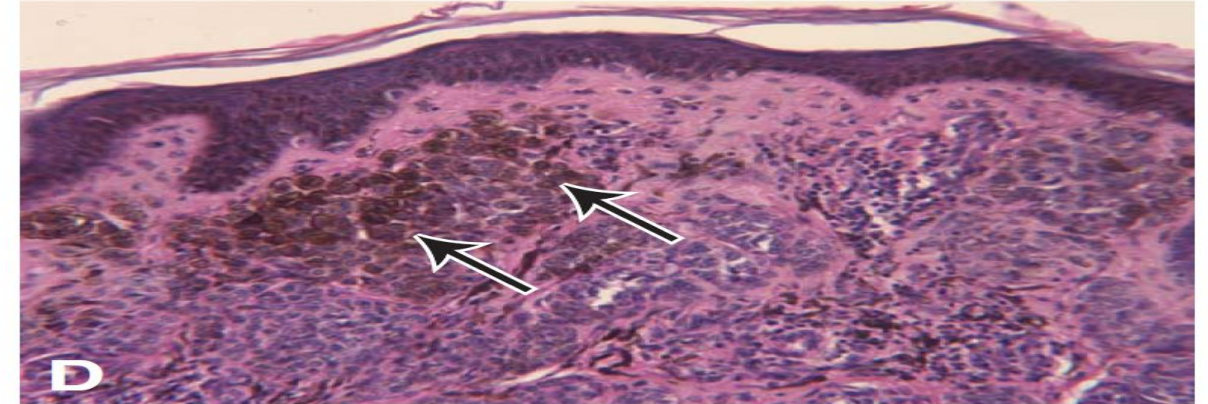
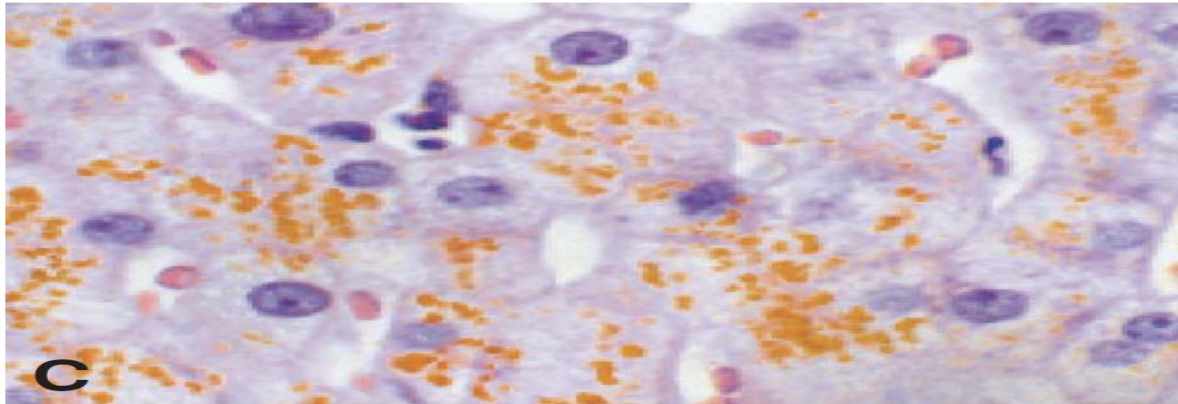
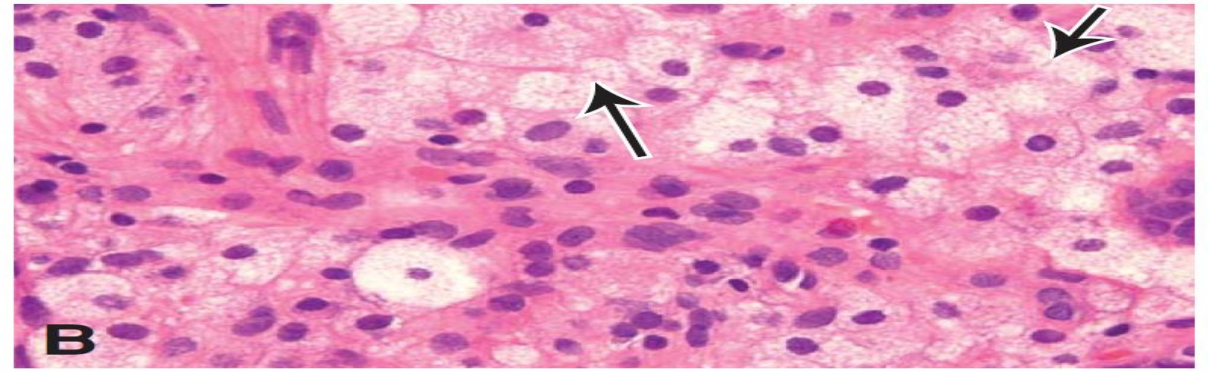
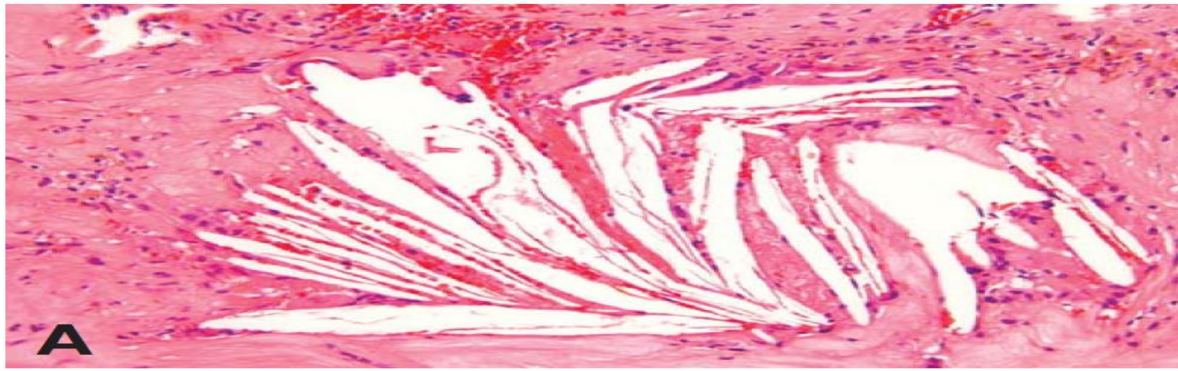


FIGURE 1-12. Abnormal intracellular storage. **A.** Abnormal cholesterol accumulation is characterized by transparent clefts, shown here in an atherosclerotic plaque. **B.** Lipid is stored in macrophages (*arrows*) in a cutaneous xanthoma. **C.** Lipofuscin in the liver from an 80-year-old man appears as golden cytoplasmic granules in lysosomes. **D.** Melanin (*arrows*) is stored in the cells of an intradermal nevus. **E.** Carbon pigment storage. A mediastinal lymph node, which drains the lungs, exhibits numerous macrophages that contain black anthracotic (carbon) pigment. This material was inhaled and originally deposited in the lungs. **F.** Iron storage in hereditary hemochromatosis. Prussian blue stain of the liver reveals large deposits of iron within hepatocellular lysosomes.

Q. Write briefly on pathologic calcification.

Pathologic calcification is defined as abnormal deposition of calcium salts together with smaller amounts of iron, magnesium and mineral salt forms.

Types of Pathological Calcification:

1. Dystrophic calcification: Deposition of calcium in dead tissue, eg, areas of necrosis (coagulative/liquefactive/caseous/enzymatic fat), atheromas/focal intimal injuries in aorta and larger arteries or ageing heart valves. Dystrophic calcification occurs despite normal calcium metabolism.

2. Metastatic calcification: Deposition of calcium in viable tissue, eg, blood vessels, kidneys, lungs and gastric mucosa. Metastatic calcification has the same morphology and pathogenesis as dystrophic calcification; however, it is always seen in a background of deranged calcium metabolism (hypercalcaemia).

Causes of metastatic calcification include:

- Hyperparathyroidism and hyperthyroidism
- Vitamin-D intoxication
- Systemic sarcoidosis (macrophages activate vitamin D precursor)
- Milk–alkali syndrome (excessive calcium ingestion with antacids and milk)
- ‘Williams syndrome’ or idiopathic hypercalcaemia of infancy (hypersensitivity to vitamin D)
- Renal failure (causes retention of phosphate leading to secondary hyperparathyroidism)
- Increased bone catabolism associated with disseminated bone tumours

Pathogenesis of Pathological Calcification

Pathological calcification has two major phases:

- **Initiation**: may occur in Extracellular sites in membrane-bound vesicles 200 nm in size. Calcium is concentrated in these vesicles due to its affinity for acidic phospholipids. Intracellular sites in mitochondria.
- **Propagation**: involves the formation of crystals of calcium hydroxyapatite.

Morphology of Pathological Calcification

Gross Pathology

Appears as fine white granules or clumps of gritty deposits.

Microscopy

- Seen on Hematoxylin and Eosin (H&E) sections as intracellular or extracellular basophilic amorphous granular deposits
- Sometimes single necrotic cells act as seeds which get encrusted with lamellar mineral deposits ('psammoma body') labelled so due to resemblance to grains of sand and commonly seen in some papillary cancers, eg, thyroid and meningiomas
- Calcium and iron salts may gather about long slender spicules of asbestos in lung, creating beaded, dumb-bell forms called 'asbestos bodies'

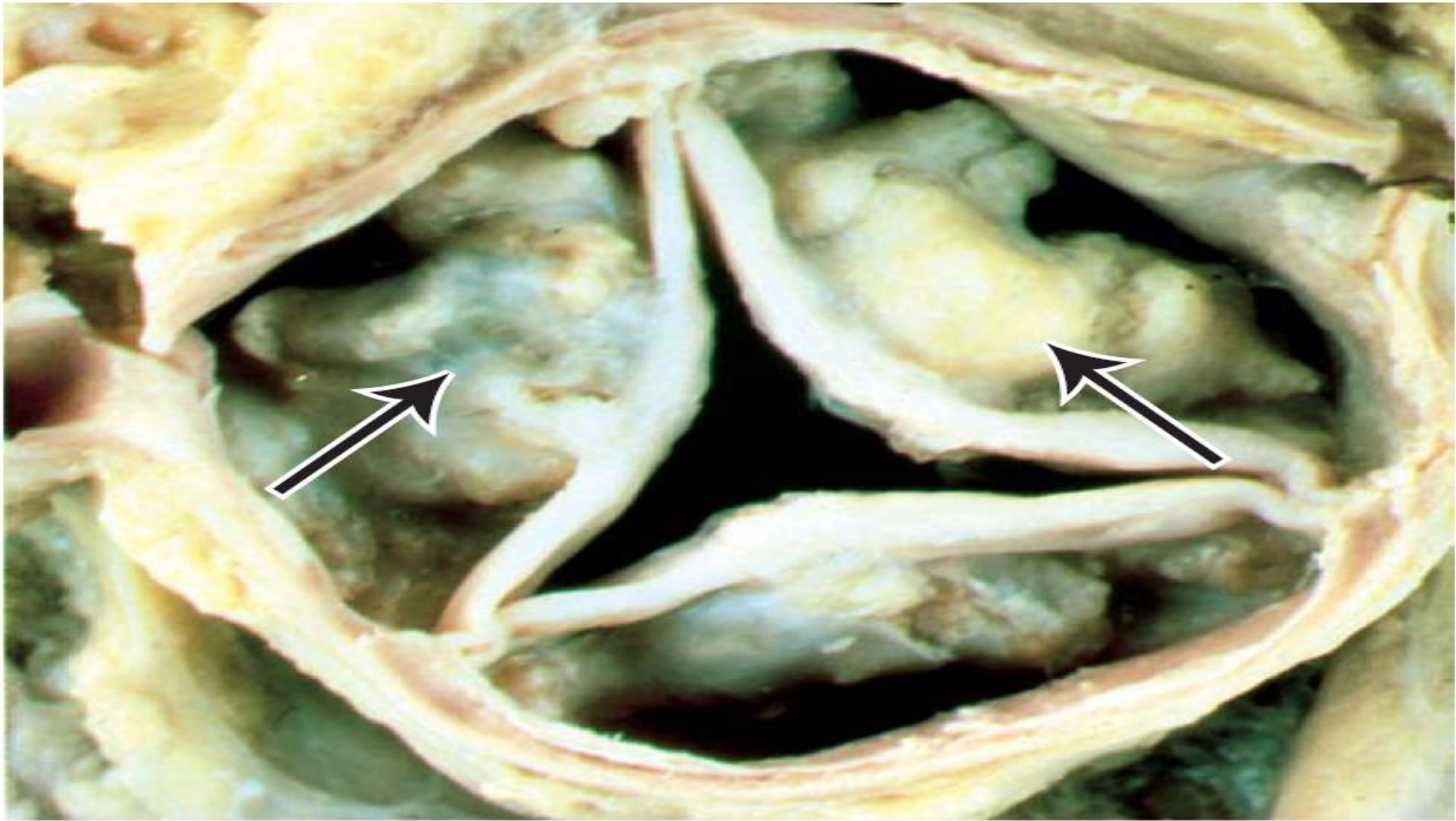
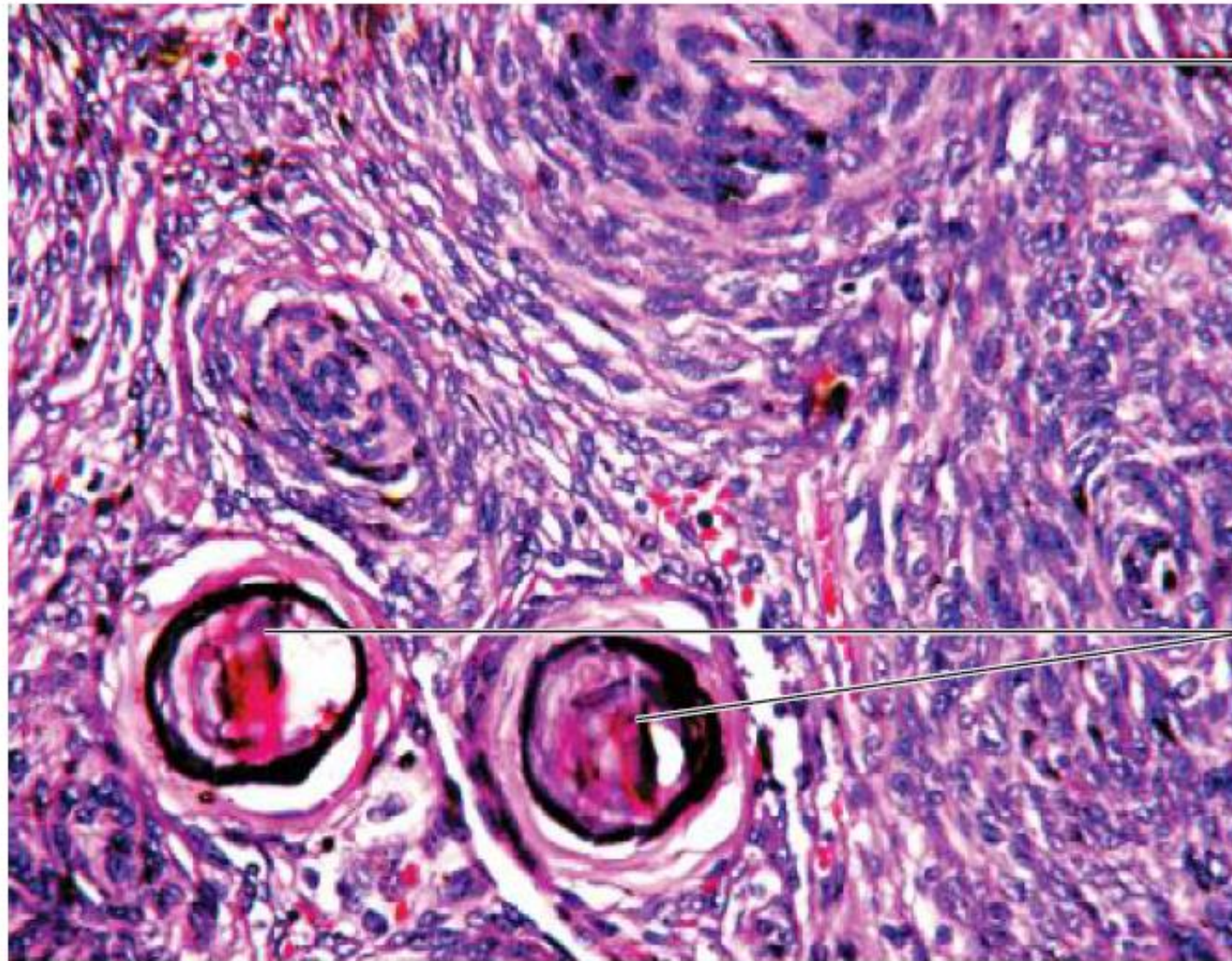


FIGURE 1-13. Calcific aortic stenosis. Deposits of solid calcium salts (*arrows*) are seen in the cusps and the free margins of the thickened aortic valve, viewed from above.



Whorled pattern of
meningotheelial cells

Psammoma bodies

FIGURE 1.19. Dystrophic calcification (psammoma bodies) in a meningioma (200X).

Q. Define cell ageing

Cell ageing is defined as loss of functional capacity and progressive decline in proliferative capacity, which ends in cell death.

Enumerate the biochemical and morphological alterations that occur during ageing.

Factors Contributing to Cell Ageing

- Genetic factors
 - Diet
 - Social conditions
 - Atherosclerosis
 - Diabetes mellitus
 - Age-related diseases, eg, osteoarthritis
- ### Indicators of Declining Cell Function Associated With Ageing
- Decreased oxidative phosphorylation
 - Decreased synthesis of Structural and enzymatic proteins
 - Decreased capacity for uptake of nutrients
 - Decreased repair of chromosomal damage

Thanks