CHAPTER 1

Cellular Pathology and Biology of Aging

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LEARNING OBJECTIVES

CELL UNIT OF LIFE AND INTRODUCTION TO PATHOLOGY

- Cell unit of life
- Introduction to pathology

CELLULAR RESPONSE TO STRESS AND HARMFUL STIMULI

- Cellular adaptations
- Cell injury
  - Reversible cell injury
  - Irreversible cell injury
- Metabolic derangements

CELLULAR ADAPTATIONS

- Hyperplasia
- Hypertrophy
- Atrophy
- Metaplasia
- Dysplasia
- Reduction in size of organs in other pathologic processes

CELL INJURY AND CELL DEATH: OVERVIEW

- Causes of cell injury and cell death
  - Oxidative stress/hypoxia-induced cell injury
  - Ischemia-reperfusion-induced cell injury
  - Pathogen-induced cell injury
  - Physical agents induced cell injury
  - Chemical agents induced cell injury
  - Drug-induced cell injury

PATHOPHYSIOLOGY OF CELL INJURY, MORPHOLOGIC PATTERNS AND OUTCOME OF NECROSIS

- Reversible cell injury
  - Decreased ATP production in mitochondria
  - Plasma membrane Na^+/K^+ pump failure
  - Plasma membrane calcium pump failure
  - Plasma membrane bleb formation
  - Myelin figures
- Irreversible cell injury (cell death)
  - ATP depletion in mitochondria
  - Mitochondrial damage
  - Calcium influx and impaired calcium homeostasis
  - Reactive oxygen species production induced by cell stressors
  - Defects in permeability of plasma membrane and cell organelles
  - Rough endoplasmic reticulum disruption
  - Cytoskeleton disruption
  - Genetic apparatus disruption
- Morphologic patterns of necrosis
  - Coagulative necrosis
  - Liquefactive necrosis
  - Caseous necrosis
  - Fat necrosis
  - Gangrene
  - Fibrinoid necrosis
  - Gummatous necrosis
  - Subcutaneous necrosis in newborn
  - Zenker's necrosis in skeletal muscle
  - Postmortem autolysis
- Outcome of necrosis
  - Complete resolution
  - Injured tissue repair by fibrosis
  - Dystrophic calcification
  - Resorption of necrotic tissue

REGULATED CELL DEATH (RCD)

- Mitochondrial permeability transition pore driven necrosis
- Apoptosis
- Necroptosis
- Pyroptosis
- Ferroptosis
- Autophagy
- Lysosomal-dependent cell death

APOPTOSIS

- Three pathways of apoptosis
  - Extrinsic death receptor pathway of apoptosis
  - Intrinsic mitochondrial pathway of apoptosis
  - CD8+ cytotoxic T cells/NK cells (granzyme B/perforin) mediated pathway of apoptosis
- Family of cysteine proteins 'caspases'
  - Initiator/inducer caspases
  - Executioner/effector caspases
- Morphologic and biochemical changes in apoptotic cells
  - Histologic changes
  - Ultrastructural changes
  - Biochemical changes
- Apoptosis in health
  - Apoptosis during embryogenesis
  - Apoptosis during adult life
- Apoptosis in diseases
  - Apoptosis induced by viruses
  - Neuronal apoptosis and formation of red neurons in brain
  - Keratinocyte apoptosis in epidermis
  - Apoptosis of neutrophils in acute inflammation
  - Apoptosis of parenchymal organ's cells due to obstruction in ducts
  - Apoptosis of cells with damaged DNA
  - Apoptosis of cells with accumulated misfolded proteins
  - Apoptosis of cancer stem cells
- Laboratory diagnosis
  - Light microscopy
  - Electron microscopy
  - Electrophoresis
  - Flow cytometry
  - TUNEL assay
  - Immunohistochemistry

INTRACELLULAR ACCUMULATION OF SUBSTANCES

- Lipid accumulation
  - Triglyceride accumulation inducing fatty change in liver
  - Cholesterol and its esters accumulation inducing atherosclerosis, xanthomas and gallbladder cholesterolosis
- Glycogen accumulation
  - Glycogen storage diseases: types 1 to 10
- Protein accumulation
  - Increased protein droplets reabsorption in the proximal renal tubule in renal disease with proteinuria
  - Increased protein production by plasma cells forming Russell bodies
  - Accumulation of cytoskeleton proteins
  - α_1-Antitrypsin protein accumulation

- Pigment accumulation
  - Endogenous pigments
    - Lipofuscin pigment
    - Melanin pigment
    - Bilirubin pigment
    - Hemosiderin pigment
    - Hematin pigment
    - Homogentisic acid pigment
    - Hamazaki-Wesenberg bodies
  - Exogenous pigments
    - Coal pigment
    - Tattoo ink pigment

EXTRACELLULAR ACCUMULATION OF SUBSTANCES

- Intracellular and extracellular hyaline change
- Aggregation of misfolded proteins (amyloidosis)
- Fibrinoid necrosis of arterioles
- Hyalinization of glomenular basement membrane
- Dysgenetic hyalinization in seminiferous tubules

PATHOLOGIC CALCIFICATION

- Dystrophic calcification
- Metastatic calcification
- Pulmonary alveolar microlithiasis (PAM)

CELLULAR BIOLOGY OF AGING

- DNA damage theory of aging
- Cellular senescence
  - Telomere attrition
  - Activation of tumor suppressor genes
- Oxygen-derived free radicals theory linked to cellular aging
- Defective protein homeostasis and cellular aging
- Genetic disorders linked to premature aging
  - Hutchinson-Gilford progeria syndrome
  - Werner syndrome
  - Cockayne's syndrome (Weber-Cockayne's syndrome or Neill-Dingwall syndrome)
- Mammalian sirtuin system
  - Sirtuins in health and disease

CELL UNIT OF LIFE AND INTRODUCTION TO PATHOLOGY

Cell is defined as the most basic structural and functional unit of life. Normal cells handle physiological demands and maintains a steady state called homeostasis. More severe physiologic stresses stimuli may bring about a number of physiologic and morphologic cellular adaptations, during which new but altered steady states are achieved, preserving the viability of the cell. The adaptive response may consist of an increase in the size of the individual cell called hypertrophy and increase in the number of cells called hyperplasia. Conversely, **atrophy** is an adaptive response in which there is decrease in the size and function of cells.

CELL UNIT OF LIFE

Cell consists of cell membrane (plasma membrane), the nucleus and cytoplasm. The cell membrane is a phospholipid bilayer containing many different molecular components, including proteins and cholesterol, some with carbohydrate groups attached. A phospholipid molecule consists of a polar phosphate "head," which is hydrophilic and a nonpolar lipid "tail," which is hydrophobic. Unsaturated fatty acids result in links in the hydrophobic tails.

- The lipid bilayer provides the basic structure and serves as a relatively impermeable barrier to most water-soluble substances. Transmembrane proteins that span the phospholipid bilayer of cell membranes serve a variety of structural, transport, signaling and enzymatic functions.
- Cytoplasm is internal material between the cell membrane and nucleus of a cell. It consists of a clear, semi-fluid, water-based fluid called cytosol, within which are all specialized membrane-bound cell organelles (mitochondria and lysosomes) in the cell and cellular solute and suspended materials. Each organelle has its specific function, that is essential for cell survival.
- The cytoskeleton in cell is formed by rod-like proteins that support the cell's shape and provide other functions, locomotive abilities. Cytoskeleton consists of microtubules, microfilaments, and intermediate filaments, which plays an important role in maintaining cell shape and structure, in promoting cellular movement, and aiding cell division.
- Mitochondria are the energy-conversion factories of the cell. Mitochondrion, one of the cellular organelles, is bound by a double lipid bilayer membrane that functions primarily in the production of cellular energy (ATP).
- The endoplasmic reticulum (ER) is a winding network of thin interconnected membranous sacs found in close association with the cell nucleus.
- The smooth and rough endoplasmic reticula are very different in appearance and function.
  - Rough ER is studded with numerous ribosomes, which are sites of protein synthesis. Smooth endoplasmic reticulum is formed by a series of flattened, membrane-bound sacs that functions in protein modification, tagging, packaging, and transport within the other areas of cytoplasm. Some of these products are exported from the cell through exocytosis.
  - Enzymatic proteins are packaged and sent for fusion with existing lysosomes. Lysosomes and membrane-bound cellular organelles are originating from the Golgi apparatus and containing digestive enzymes.
  - Smooth ER synthesizes phospholipids, steroid hormones, regulates the concentration of cellular Ca^{++}, metabolizes some carbohydrates, and breaks down certain toxins.
- Peroxisome is a small membrane-bound organelle in the cytoplasm of many cells, which contains the reducing enzyme catalase and some oxidase for detoxifying harmful substances and lipid synthesis.

- The centrosome contains the small replicating organelle 'centriole' that provides the origin for microtubule growth and moves DNA during cell division.
- The nuclear envelope, a double membrane, surrounding the nucleus contains nuclear pores that control the movement of substances into and out of the nucleoplasm.
- Human DNA is described as a double helix that resembles a molecular spiral staircase. DNA has an antiparallel configuration with one strand arranged 5′ to 3′ in one direction and the other strand in the opposite direction. A purine is bound to pyrimidine by the hydrogen bonds: adenine:thymine and guanine:cytosine. The double helix of DNA is the result of bonds in the sugar-phosphate backbone. DNA is organized around histone proteins into nucleosomes, which are compacted and progressively coiled and finally supercoiled into 46 chromosomes. DNA is inactive in the coiled form and must be uncoiled for biological processes such as transcription and translation into proteins. The dense nucleolus is the site of ribosome production. The nucleus of a eukaryotic cell directs the cell's activities and stores DNA.

Pathology Pearls: Conditions Associated with Alteration in Cell Organelles

- Certain conditions are associated with alterations in cell organelles (lysosomes, smooth endoplasmic reticulum, and mitochondria) or the cytoskeleton.
- Lysosomal catabolism occurs by heterophagy or autophagy
- Smooth endoplasmic reticulum hypertrophy occurs due to induction of drug tolerance to barbiturates and alcohol
- Mitochondrial defects (number, size and shape)
- Cytoskeleton defects (phagocytosis and locomotion)
- Nucleus (pyknosis, karyorrhexis and karyolysis)
- Membranes (plasma membrane and subcellular membrane such as endoplasmic reticulum)

CELL ADHESION MOLECULES (CAMs)

Cell adhesion molecules are transmembrane-linked glycoproteins that mediate connections between cells or the attachment of cells to basement membrane. There are at least six groups of cell adhesion molecules: selectins, integrins, cadherins, members of immunoglobulin superfamily, mucins and lymphocyte homing receptors (CD44). Cell adhesion receptors enable cells to recognize and bind cell adhesion molecules on other cells or in the extracellular matrix. Cell adhesion receptors form homophilic adhesions (cadherin-cadherin) or heterophilic adhesions between different types of molecules (selectin-mucin). Major family of cell adhesion molecules (CAMs) is given in Table 1.1.

Table 1.1 Major family of cell adhesion molecules (CAMs)

Selectins (calcium-dependent)
Integrins (calcium-dependent)
Cadherins (calcium-dependent)
Members of immunoglobulin superfamily (calcium-dependent)
Lymphocyte homing receptor (CD44) (calcium-dependent)

Selectins

The selectins are a family of carbohydrate-binding transmembrane molecules found on the surface of endothelial cells, leukocytes and platelets. Members of selectin family include endothelial selectin (E-selectin), leukocyte selectin (L-selectin) and platelet selectin (P-selectin). E-selectin adheres to integrins, P-selectin interacts with platelets, and L-selectin interacts with leukocytes. Selectins mediate the adhesion of white blood cells and platelets to endothelial cells. In collaboration with other CAM families, selectins play important roles in leukocyte trafficking to the sites of inflammation.

Integrins

Integrins are the principal cell surface receptors that function mechanically by binding the cell microfilament (actin) of cytoskeleton to the extracellular matrix (ECM). The integrin family of proteins consists of α and β subtypes, which form transmembrane heterodimers. Integrins are responsible for transduction of external signals to the cytoskeleton.

Cadherins

Cadherins are calcium-dependent transmembrane proteins that constitute the major intercellular link at adherens junctions and bind to catenin and other proteins inside cell to link to the microfilament (actin) of the cytoskeleton. Different members of cadherin family are found in different locations: E-cadherin (epithelial cells), N-cadherin (neurons) and P-cadherin (placenta). Cadherins form homophilic adhesions (cadherin-cadherin). Failure of cadherin mediated cell-to-cell adhesion cascade is observed in breast lobular carcinoma.

Members of Immunoglobulin Superfamily CAMs

The immunoglobulin superfamily CAMs are calcium-independent transmembrane. Members of immunoglobulin superfamily include intercellular adhesion molecule (ICAM), vascular adhesion molecule 1 (VCAM-1), neural cell adhesion molecule (NCAM), and platelet endothelial cell adhesion molecule 1 (PECAM 1 or CD31). Nectins have been recently identified as new calcium-independent CAMs consisting of four members.

- Each immunoglobulin superfamily CAM has an extracellular domain, which contains several Ig-like intra-chain disulphide-bonded loops with conserved cysteine residues, a transmembrane domain, and an intracellular domain that interacts with the cytoskeleton.
- Immunoglobulin superfamily CAMs function by both homophilic and heterophilic binding. These are involved in recognition, binding or adhesion processes of cells.

Lymphocyte Homing Receptors

Lymphocyte homing receptor (CD44) is involved in lymphocyte adhesion to endothelial cells of venules and lymphocyte exit from the blood circulation. It may also be involved in hematogenous dissemination of malignant lymphoma.

CELL JUNCTIONS

At molecular level, intercellular junctions consist of three multiprotein components which differ depending on the type of junctions: transmembrane adhesion protein, cytoplasmic adapter protein and cytoskeleton proteins.

- Five types of cellular junctions are present between the epithelial cells: tight junctions (zona occludens), adherent junctions (zona adherens), desmosomes (macula adherens), gap junctions and hemidesmosomes.
- Cell junctions provide contact between neighboring cells or between a cell and the extracellular matrix. They also build up the paracellular barrier of epithelia and control the paracellular transport. Functional classification of cell junctions is given in Table 1.2.

Table 1.2 Functional classification of cell junctions

Occluding Junctions
Tight junctions (zona occludens)
Anchoring Junctions

▪ Intermediate filament attachment sites
  • Desmosomes (cell-to-cell junction)
  • Hemidesmosomes (cell-extracellular matrix junction)
▪ Actin filament attachment sites
  • Zonula adherens (cell-to-cell junctions)
  • Focal adhesions (cell-extracellular matrix junction)

Communicating Junctions
Gap junctions
Signal Relaying Junctions
▪ Chemical synapses in the nervous system ▪ Immunological synapses in the immune system ▪ Transmembrane ligand-receptor cell-to-cell signaling contacts

Zona Occludens (Tight Junctions)

Zona occludens is a membrane protein complex composed of occludens and claudins, which are attached to three proteins called ZO1, ZO2 and ZO3, which help in holding occludens and claudins properly in their positions. Occludens and claudins exit cell membrane and interact with each other and seal the surface of two adjacent cells. Zona occludens is present in the lateral surfaces of epithelial cells, which prevents floating of protein channels from apical surface to basal surface. Zona occludens regulates fluid movement through paracellular route.

Zonula Adherens (Cell-to-Cell Junctions)

Zonula adherens is a cell-to-cell adherens junction that forms a belt in the apical most region of the lateral cell surface of many epithelia.

Desmosomes

Desmosomes are specialized adhesive proteins that localize intercellular junctions of epithelia and cardiac muscle. Desmosomes resist mechanical stress and maintain the mechanical integrity of tissues.

Hemidesmosomes

Hemidesmosomes are the only cellular junctions present on the basal surface of the epithelium, which link the cell to the basal lamina and through integrin attaches to extracellular matrix. Intermediate filaments are present inside hemidesmosomes.

Gap Junction Channels

Gap junction channels are formed by docking of two connexons, that are present at cell-to-cell appositions. Gap junction channels are responsible for direct intercellular transfer of ions and small molecules including propagation of inositol triphosphate-dependent calcium waves.

Signal Relaying Junctions

Chemical synapses are specialized junctions through which neurons signal to each other and to non-neuronal cells such as those in the glands and muscles. Chemical synapses allow neurons to form circuits within the central nervous system. Their key feature is the presence of synaptic vesicles at presynaptic terminals, which are filled with one or more neurotransmitters, which act as messengers between the communicating neurons.

CYTOSKELETON

Cytoskeleton of a cell represents network of protein filaments in the cytosol that maintains cell shape, cell movement, cell division, intracellular organization and intracellular transport of organelles and molecules.

- There are three main components of the cytoskeleton: microtubules, microfilaments and intermediate filaments, along with other proteins that support these components. All three components of cytoskeleton interact with each other noncovalently.
- Cytoskeleton helps cells in maintaining their shape and internal organization, and also provides mechanical support that enables cells to perform essential functions like cell division and cell movement. Hypoxic injury may cause damage to cytoskeleton.
- Blebs are observed on cell surface, most likely caused by disorderly function of the cellular cytoskeleton. Components of cytoskeleton, their arrangement, functions and disorders are given in Table 1.3.

Pathology Pearls: Disorders of Cytoskeleton

Disorders of Microfilaments

The membrane skeleton composed of spectrin, actin, and protein provides structural integrity to the cell membrane of red blood cells. Congenital spherocytosis, an autosomal dominant disease, is an example of a defect in spectrin resulting in a hemolytic anemia.

Disorders of Microtubules

- **Male sterility:** Defects in microtubules inhibit sperm motility results in sterility.
- **Kartagener's syndrome (immotile cilia syndrome):** It refers to immobilization of cilia of respiratory epithelium causes interference of clearance of pathogens resulting in bronchiectasis.
- **Dysfunctional leukocytes:** Colchicine drug used in acute attacks of gout binds to tubulin and prevents the assembly of microtubules, thus prevents migration and phagocytosis of leukocytes in response to urate crystals.
- **Chédiak-Higashi syndrome:** It is autosomal recessive disorder due to defect in the assembly (polymerization) of microtubules in the cytoplasm. It is characterized by defective degranulation of neutrophils, impaired microbial killing, and recurrent *Staphylococcus aureus* bacterial infections forming soft tissue abscess. This disorder results from a mutation in the '**LYST gene**' on chromosome 1q42 that encodes a protein for microtubules involved in intracellular trafficking of proteins.

Disorders of Intermediate Filaments

- **Mallory hyaline:** In chronic alcoholic persons, Mallory hyaline demonstrated in hepatocytes. It is an example of intermediate filaments (cytokeratins) abnormality.
- **α_1-Antitrypsin deficiency:** Structurally abnormal α_1-antitrypsin molecules accumulate in the liver.
- **Parkinson disease:** α-Synuclein accumulates in neurons in the substantia nigra of patients with Parkinson disease.

Microfilaments

Microfilaments or actin filaments (6–8 nm) are the thinnest, linear and strong filaments of the cytoskeleton; predominantly of a contractile protein called actin subunits. These are protein filaments primarily composed of polymers of actin and found in the cytoplasm of eukaryotic cells, which interact with numerous other proteins in the cell.

- Microfilaments are intimately involved in many plasma and internal membrane functions. Functions of microfilaments include cytokinesis, cell motility, amoeboid movement leukocytes, changes in cell shape, endocytosis (phagocytosis) and exocytosis, cell contractility, transmembrane signaling and mechanical stability.

Table 1.3 Components of cytoskeleton, their arrangement, functions and disorders

Cytoskeleton Component Size	Arrangement	Functions	Disorders
Microfilaments			
8 nm	Microfilaments thin, twisted strands of protein molecules	Movement of pigment granules	Impairment of leukocytes
Microtubules			
25 nm	Microtubules hollow, tough and durable fibers have spiral arrangement of protein subunits	▪ Maintenance of shape of cells, intracellular transport, movement of organelles and chromosomes ▪ Colchicine drug disrupts microtubules hence impairs movement of chromosomes	▪ Male sterility ▪ Kartagener's syndrome ▪ Dysfunctional leukocytes ▪ Chédiak-Higashi syndrome
8–10 nm	Intermediate filaments are thick hollow tubes, twisted protein strands (e.g. keratin, glial filaments, desmin and vimentin)	In most of the cells, intermediate filaments are forming a basket around the nucleus and present in cell-to-cell junction	▪ Mallory's hyaline ▪ α_1-Antitrypsin deficiency ▪ Parkinson disease

- Microfilaments in leukocytes participate in leukocytic movement and phagocytosis. Phalloidin toxin (*Amanita phalloides*) inhibit actin filaments resulting in disruption of phagocytic activity of the cells.

Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome protein (WASp) regulates remodeling of actin filaments of cytoskeleton to regulate cell movement, cell signaling and cell division.

- Abnormality of microfilaments is linked to Wiskott-Aldrich syndrome, a X-linked recessive immunodeficiency disorder characterized by recurrent bacterial sinopulmonary infections, eczema (atopic-like), platelet dysfunction (thrombocytopenia), bloody diarrhea (secondary to low platelet count) and T cell defect.
- Wiskott-Aldrich syndrome is treated with stem cell transplant by using bone marrow, peripheral blood or umbilical cord blood from a healthy suitably tissue matched donor.

Microtubules

Microtubules are the major components of the cytoskeleton and formed by the polymerization of a dimer of two globular proteins, tubulin α and β subunits, assembled into linear protofilaments that can then associate laterally to form hollow tubes, the microtubules with a diameter of 20–25 nm.

- Microtubules are capable of undergoing rapid assembly and disassembly in the cytosol. Microtubules function in maintenance of cell shape, intracellular organelle motility, structural support, keeping cell organelles in place and chromosome segregation during cell division (mitosis and meiosis, i.e. movement of chromosomes and creation of the mitotic spindle).
- Microtubules are essential for leukocytic migration and phagocytosis. Cytochalasin B drug prevents the assembly of microtubules also results in disruption of phagocytic activity of the cells.
- Microtubule abnormalities are linked to male sterility, Kartagener's syndrome (immotile cilia syndrome), dysfunctional leukocytes and Chédiak-Higashi syndrome (defective degranulation of neutrophils, impaired microbial killing).
- Male infertility can be caused by low sperm production, abnormal sperm function or blockages that prevent the delivery of the sperm. A sperm (spermatozoon) has three parts: head, neck, midpiece and tail (exoneme).

Clinical Pearls: Structure of Spermatozoon

- **Head of spermatozoon:** The head of the sperm contains nucleus with haploid number of chromosomes, that holds DNA of the cell. The head also contains numerous enzymes such as hyaluronidase, corona penetrating enzyme and zona lysine (acrosin) collectively called 'spermatolysins', which help the sperm breakthrough the cell membrane of ovarian ovum.
- **Neck of spermatozoon:** Neck of the sperm contains proximal and distal centrioles that form the cilium of the sperm. And after fertilization form the major microtubule-organizing center of the zygote.
- **Midpiece of spermatozoon:** Midpiece of the sperm contains mitochondria.
- **Tail of spermatozoon:** The structure of tail (exoneme) of sperm consists of 9+2 microtubules, molecular motors (flagellar dyneins), and their regulatory linker proteins. Microtubules are the prime component of the cytoskeleton, which are vital for organelle transport and cellular division during spermatogenesis, sperm motility and functional capacity of sperm. Tail (exoneme) of the sperm is well preserved. Defects in the microtubules in axonemal structure cause defects in sperm abnormality (teratozoospermia, oligospermia, oligozoospermia, asthenozoospermia or even azoospermia), sperm motility and often leads to male infertility.

Kartagener's Syndrome (Immotile Cilia Syndrome)

Kartagener's syndrome, also called immotile cilia syndrome, is an autosomal recessive ciliary microtubule associated disorder and characterized by triad of situs inversus, chronic sinusitis and bronchiectasis. The basic defect lies in the defective movement of cilia lining nose, paranasal sinuses, and bronchus. Eustachian tube and fallopian tube that cause interference of clearance of pathogens leading to recurrent infections of upper respiratory tract, otitis media and infertility. These patients are treated with colchicine drug.

Dysfunctional Leukocytes

Gout is caused by excessive uric acid in blood resulting from breakdown of purine. Defective metabolism of uric acid causes arthritis especially of smaller bones of the feet, due to deposition of uric acid crystals. Gout is characterized by sudden, severe episodes of acute pain, swelling and tenderness in the small joints, often at the base of the big toe resulting from dysfunctional leukocytes due to microtubule defects.

- Colchicine drug works by decreasing swelling and lessening the buildup of uric acid crystals that cause severe acute pain in the affected joints. Colchicine is a classical antimitotic drug which blocks mitotic cells in metaphase.

- Colchicine binds to tightly to ends of unpolymerized tubulin and forms a colchicine-tubulin complex resulting in inhibition of microtubule polymerization essential for cell mitosis.
- Colchicine may enhance activation, migration and phagocytic activity of neutrophils to the site of inflammation in response urate crystals.

Chédiak-Higashi Syndrome

Chédiak-Higashi syndrome is an autosomal recessive disorder caused by mutation in the 'LYST gene' on chromosome 1q42 that encodes a protein essential for assembly of microtubules in neutrophils.

- Defect in assembly of microtubules in neutrophils results in impaired chemotaxis, defective degranulation of neutrophils, impaired microbial killing, and recurrent *Staphylococcus aureus* bacterial infections forming soft tissue abscess with fatal outcome.
- Neutrophils contain giant granules due to aberrant organelles. Accelerated phase of the syndrome results in fatal outcome due to multiorgan failure in 85% of cases.

Intermediate Filaments

Intermediate filaments are composed of a variety of proteins. These are 8–10 nm diamtere filaments highly stable cytoskeletal component expressed in different types of cells. Examples of intermediate filaments are keratin, microfilaments, glial filaments, desmin and vimentin. Immunochemical stains utilizing monoclonal antibodies against individual intermediate filaments (e.g. desmin to identify muscle) are useful in identifying the origin of neoplasms.

- The most important function of intermediate filaments is to provide mechanical support for the plasma membrane where it comes in contact with other cells and extracellular matrix for maintenance of cell shape.
- Unlike microtubules and microfilaments, intermediate filaments do not participate in cell motility.
- Abnormalities of intermediate filaments are linked to Mallory hyaline formation in liver diseases, accumulation of α-synuclein in neurons in the substantia nigra in Parkinson disease, and other diseases like epidermolysis bullosa simplex (EBS) and desmin myopathy.

Mallory Hyaline (Mallory-Denk Body)

In histopathology, Mallory hyaline also known as Mallory-Denk body or Mallory body, is an irregular eosinophilic intracytoplasmic inclusion, that represents aggregates of intermediate filaments (cytokeratins 8 and 18). The cytokeratins form a filamentous support within the hepatocytes. Liver disorders associated with Mallory-Denk bodies in hepatocytes are given in Table 1.4.

Table 1.4 Liver disorders associated with Mallory-Denk bodies

Alcoholic liver disease
Biliary atresia
Extrahepatic bile duct obstruction
Primary biliary cirrhosis
Primary sclerosing cholangitis
α_1-Antitrypsin deficiency
Abetalipoproteinemia
Hepatic adenomatosis in glycogen storage disease type 1a (von Gierke disease)
Wilson disease
Ethanol-induced hepatocellular injury
Amiodarone-induced hepatocellular injury
Indian childhood cirrhosis
Nonalcoholic steatohepatitis
Hepatic adenoma
Hepatocellular carcinoma
Focal nodular hyperplasia of liver

Neuronal Intermediate Filaments Related Neurodegenerative Diseases

Neuronal intermediate filaments (NIFs) are most abundant cytoskeleton component in mature neurons. These are composed of different protein units encoded by separate genes such as neurofilament light chain (NFL), neurofilament medium chain (NFM), neurofilament heavy chain (NFH), α-internexin and peripherin.

- Neuronal intermediate filament proteins give cells shape, determine axonal caliber, which control signal conduction, and regulate the transport of synaptic vesicles and modulate synaptic plasticity by binding to neurotransmitter receptors.
- Mutations in genes encoding neuronal intermediate filaments result in their aggregation in neurons responsible for neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, Charcot-Marie-Tooth disease, dementia with Lewy bodies and giant axonal neuropathy.
  - **Parkinson disease:** α-Synuclein is normally wavy-like presynaptic neuronal protein. In Parkinson disease, α-synuclein protein misfolds and forms toxic aggregates, which damage neurons in the part of the brain called the substantia nigra. Normally,

neurons in this part of brain are responsible for production of a chemical called dopamine. Neuronal damage in this part of brain results in reduction of dopamine production. An antibody that binds the misfolded α-synuclein can be used to intercept the protein as it passes between neurons.

- **Alzheimer's disease:** It is a neurodegenerative disorder characterized by brain pathology of intracellular neurofibrillary tangles made of hyperphosphorylated R-protein and extracellular amyloid plaques present in cortical and limbic areas of human brain. It is characterized by memory loss and progressive neurocognitive dysfunction.
- **Amyotrophic lateral sclerosis (ALS):** It is also known as motor neuron disease or Lou Gehrig's disease affecting 50–60 years elderly persons. Peripherin is an intermediate filament protein detected in spheroids, a hallmark of amyotrophic lateral sclerosis. Increased levels of peripherin mRNA have been observed in some cases of amyotrophic lateral sclerosis. Disorder is characterized by death of neurons controlling voluntary muscles. Patient presents with muscle stiffness, muscle twitching and gradually worsening muscle weakness. Life expectancy is 2–4 years.
- **Charcot-Marie-Tooth disease type 2:** Neurofilaments (NFs) are the major intermediate filaments of mature neurons. Charcot-Marie-Tooth disease type 2 is a hereditary disorder involving motor and sensory neuropathies of the peripheral nervous system characterized by progressive skeletal muscle weakness and decreased touch sensation across various parts of the body. Recently, two mutations in the neurofilament light subunit have been detected in families affected by Charcot-Marie-Tooth disease type 2.
- **Dementia with Lewy bodies:** In dementia, Lewy bodies are intracytoplasmic inclusion bodies composed of the neurofilament (intermediate filament) protein, ubiquitin, α-synuclein and α-crystallin. Lewy bodies may occasionally be surrounded by neurofibrillary tangles.
- **Giant axonal neuropathy:** Giant axonal neuropathy (GAN) is an autosomal recessive slowly progressive neurodegenerative disorder caused by mutation in GAN gene that encodes gigaxonin, a member of the BTH/Kelch family of E3 ligase adaptor proteins. The disease is characterized by the aggregation of intermediate filaments of cytoskeleton. Patient presents with progressive motor and sensory peripheral neuropathy, central nervous system involvement (including cerebellar and pyramidal signs), and kinky hair in most cases.

Epidermolysis Bullosa Simplex

Epidermolysis bullosa simplex (EBS) is an inherited skin disorder caused by mutation in the keratin 5 (KRT5) and keratin 14 (KRT14). Genes with fragility of basal keratinocytes resulting in epidermal cytolysis and blistering produced with even a slight mechanical stress. Cells with severe mutations in KRT5 and KRT14 are more sensitive to osmotic stress and take longer time to recover from it.

Desmin Myopathy

Desmin myopathy is an autosomal dominant or autosomal recessive disorder caused by mutation in desmin or α-crystallin B. Patient presents with lower limb muscle weakness slowly spreading to involve truncal, neck-flexor, facial, bulbar and respiratory muscles. Histologic examination of tissue section shows abnormal fiber area containing amorphous eosinophilic deposits seen as granular or granulofilamentous material. Immunohistochemical examination demonstrates positive staining for desmin in each region containing abnormal structures.

MITOCHONDRIA

Mitochondria are cylindrical-shaped double membrane-bound organelle with inner part being folded inwards to form cristae and found in the cytoplasm of eukaryotic cells. Numerous mitochondria are found in human liver cells, with 1000–2000 mitochondria per cell, making up one fifth of the cell volume.

- Mitochondria utilize cytoplasmic proteins to degrade sugars and produce cellular energy in the form of ATP (i.e. phosphorylation of ADP) through cellular respiration for regulation of cellular metabolism. The set of reaction involved in ATP production are collectively known as the citric acid cycle, or the Krebs cycle.
- The Krebs cycle occurs in the mitochondrial matrix and generates chemical energy (ATP, NADH, and $FADH_2$) from the oxidation of pyruvate, the end product of glycolysis. When acetyl-CoA is oxidized to carbon dioxide in the Krebs cycle, chemical energy is released and captured in the form of ATP, NADH, and $FADH_2$.
- $FADH_2$ is high energy electron carrier used to transport electrons generation in glycolysis and Krebs cycle to the electron transport chain.

Mitochondrial Dysfunction

Mitochondrial dysfunction results in cell injury and apoptosis. Mitochondrial dysfunction has been indicated as a potential player of development of cardiac hypertrophy. Mitochondrial number is increased in hypertrophy and decreased in atrophy.

Mitochondrial Hypertrophy

Hypertrophy of mitochondria termed megamitochondria can be induced by a variety of processes. By electron microscopy, megamitochondria demonstrate normal cristae and matrix density; and associated with normal oxidative phosphorylation. It should be differentiated from swollen mitochondria, which have swollen cristae and irregular densities in the matrix; and associated with uncoupling of oxidative phosphorylation and reduction in ATP production induced by NSAIDs and tolcapone.

- Mild to severe hypertrophy of mitochondria is seen with disruption of mitochondrial β-oxidation of drug-induced hepatocellular injury. By electron microscopy, the amount of mitochondrial matrix increases and becomes electron lucent. By light microscopy, these changes may be observed as cytoplasmic vacuolation.
- Microvesicular steatosis, inflammation and necrosis occur in human beings as a feature of severe interference with mitochondrial β-oxidation of free fatty acid.
- Hypertrophy of mitochondria (megamitochondria) may be seen in alcohol liver disease, mitochondrial myopathies, certain nutritional diseases and benign tumors arising from oncocytes of salivary glands, thyroid, parathyroid and kidneys (known as oncocytes).

Mitochondrial Gene Mutations Associated Disorders

Mitochondrial disorders may be caused by inherited or acquired mutations in mitochondrial DNA or nuclear genes that code for mitochondrial components. Acquired mitochondrial dysfunction can be caused by drugs, infections and environmental factors. Mitochondrial gene mutations and associated disorders are given in Table 1.5.

- Mitochondrial diseases caused by mutations in mitochondrial genes include mitochondrial myopathies, cardiomyopathy, exercise intolerance, diabetes mellitus and deafness (DAD), Kearns-Sayre syndrome (KSS), Leigh syndrome, mitochondrial depletion syndrome (MDS), mitochondrial encephalopathy, subacute sclerosing encephalopathy, Leber's hereditary optic neuropathy (LHON); and neuropathy, ataxia, retinitis pigmentosa and ptosis (NARP).
- Even autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis and Sjögren syndrome appear to have a mitochondrial basis. Mitochondrial diseases can occur at any age.
- Mitochondrial diseases can be diagnosed by biochemical tests on blood, urine and cerebrospinal fluid, skeletal muscle biopsy to examine the mitochondria and test enzyme levels, magnetic resonance imaging of the brain and spinal cord.
- Prognosis is variable in mitochondrial diseases. Minimally affected individuals live a normal life. Severely affected persons manifest with mitochondrial disease. The progression of mitochondrial disease is unpredictable and different for each individual.

Table 1.5 Mitochondrial gene mutations and associated disorders

Mitochondrial myopathies
Cardiomyopathy
Exercise intolerance, diabetes mellitus and deafness (DAD)
Kearns-Sayre syndrome (KSS)
Leigh syndrome
Mitochondrial depletion syndrome (MDS)
Mitochondrial encephalopathy
Subacute sclerosing encephalopathy
Leber's hereditary optic neuropathy (LHON)
Neuropathy, ataxia, retinitis pigmentosa and ptosis (ANRP)

LYSOSOMES

Lysosomes are sphere-shaped important membrane-enclosed cytoplasmic organelles, that contain numerous acid hydrolases (acid phosphatase, glucuronidase, sulfatase, ribonuclease, and collagenase). The pH in lysosomal lumen ranges between 4.5 and 5.0. Lysosomes degrade macromolecules (proteins, carbohydrates, some lipids) taken up into the cells by endocytosis (heterophagy). Major proteins present in lysosomes are given in Table 1.6. Lysosomal disorders are given in Table 1.7.

- Lysosomal proteases make up a great contribution to the overall process of intracellular degradation of most of proteins and carbohydrates. However, some lipids remain undigested. When examined under electron microscope, newly formed 'primary lysosomes' are more uniform in size, with an amorphous electron-opaque content. After fusion of lysosomes with phagocytic vesicles or other cell contents, these form 'secondary lysosomes', whose size and internal density is more variable. Lysosomes

Table 1.6 Major proteins present in lysosomes

Lysosomal Luminal Proteins
Acid hydrolases (enzymes) or their activators
Lysosomal Integral Proteins
▪ Structural proteins (amino acids and lipid transporters) ▪ Ion channels like calcium channels ▪ Trafficking and fusion machinery ▪ Vesicular ATPase which functions both as a proton pump and nutrient sensor
Lysosomal Associated Proteins

Table 1.7 Lysosomal disorders

Categories	Diseases
Sphingolipidosis	Niemann-Pick disease: types A, B and C, Gaucher's disease: types 1, 2 and 3, Fabry disease (classic and late-onset types), metachromatic leukodystrophy, globoid leukodystrophy, multiple sulfatase deficiency, GM1 gangliosidosis: types 1, 2, GM2 gangliosidosis: Tay-Sachs disease, and Sandhoff disease and GM2 activator deficiency
Mucopolysaccharidosis	Hurler syndrome, Scheie syndrome, Hunter syndrome, Sly syndrome, Morquio syndrome: types A, B, Sanfilippo syndrome: types A, B, C and D, and Maroteaux-Lamy syndrome
Oligosaccharidosis	Schindler disease, fucosidosis, α-mannosidosis and aspartylglucosaminuria
Neuronal ceroid lipofuscinosis	Neuronal ceroid lipofuscinosis 1 through neuronal ceroid lipofuscinosis 14 (lipofuscin pigment)
Sialic acid disorders	Galactosialidosis, infantile sialic acid storage disease, salla disease and sialuria
Mucolipidosis	Mucolipidosis I (sialidosis I and II), mucolipidosis II (I cell disease), mucolipidosis III (pseudo-Hurler polydystrophy), and mucolipidosis IV
Miscellaneous disease	Pompe disease (glycogen storage disease type 2), Dannon disease (glycogen storage disease), cystinosis and lysosomal acid lipase deficiency (infantile and childhood/adult types—accumulation of cholesterol esters, triglycerides)

containing indigestible material often remain in the cytoplasm as residual bodies (e.g. lipofuscin pigment in elderly persons).

- Lysosomes participate in removal of damaged cell organelles during cell injury and the cellular remodeling of differentiation, and atrophic cells due to nutrient deprivation. Chloroquine antimalarial drug raises the intracellular pH of the lysosomes, thus inactivating its enzymes reduces tissue damage in inflammatory reactions.
- Certain substances are not metabolized by cells resulting in abnormal accumulation of glycogen and phospholipids in lysosomes and impairment of functions. Deficiency of enzyme results in accumulation of endogenous substances and causes lysosomal storage diseases. Insoluble endogenous pigments such as lipofuscin and melanin accumulate in the cells. Exogenous particulate particles accumulate such as silica, carbon and asbestos in the lungs.

Pathology Pearls: Autophagy and Heterophagy

Autophagy

- Autophagy usually inhibits apoptosis; however, if uncontrolled, it can cause lysosomal digestion of the cell's own components. Autophagy participates in removal of damaged cell organelles during cell injury and the cellular remodeling of differentiation, and atrophic cells due to nutrient deprivation.
- Chloroquine antimalarial drug raises the intracellular pH of the lysosomes, thus inactivating cell enzymes reduces tissue damage in inflammatory reactions.
- Autophagy is categorized as macroautophagy, microautophagy (direct pinocytosis by the lysosomes) and chaperone-assisted autophagy.
- In macroautophagy, portions of cytosol and cell organelles are enveloped in a double-membrane autophagosome, which subsequently fuses with a lysosome to form a single-membrane bound autophagolysosome resulting in degradation of the cell's own cytoplasmic organelles by releasing proteolytic enzymes.

Heterophagy

- Heterophagy is the process of lysosomal degradation of materials ingested from the extracellular environment by the general process of endocytosis.
- Ingestion of particulate particles by the cells is known as phagocytosis, and uptake of soluble smaller macromolecules is called pinocytosis.
- Extracellular materials are endocytosed into phagosomes, which eventually fuse with lysosomes to form phagolysosomes, where the engulfed extracellular material is degraded.
- Heterophagy is the most common in the professional phagocytes, such as neutrophils and macrophages. Examples of heterophagy include the uptake and degradation of bacteria by neutrophils and the removal of apoptotic cells by macrophages.

ENDOPLASMIC RETICULUM

The smooth endoplasmic reticulum is a multifunctional membranous organelle found in most eukaryotic cells, which lacks ribosomes. It participates in lipid biosynthesis, steroid hormones synthesis and detoxification of harmful metabolic byproducts, protein folding and processing; and storage of calcium ions in the cell.

- Smooth endoplasmic reticulum is especially abundant in mammalian liver and gonad cells. When cells exposed to chemical agents, the endoplasmic reticulum shows hypertrophy as an adaptive response.
- Proper functioning of endoplasmic reticulum is disturbed by a number of physiologic, pathologic conditions and pharmacologic agents resulting in impairment of protein folding and risk of proteotoxicity.

- Smooth endoplasmic reticulum stress is triggered by intracellular alterations (e.g. calcium or redox imbalances), microenvironmental conditions (e.g. hypoxia, hypoglycemia, and acidosis), high sugar-diet, high-fat diet, natural compounds (e.g. tunicamycin and geldanamycin), and several drugs (e.g. bortezomib (Velcade®), Celebrex and nelfinavir). The cell reacts to smooth endoplasmic reticulum stress by initiating a defensive cellular mechanism, known as the unfolded protein response (UPR) aimed at cellular adaptations and safeguarding cellular survival.
- A malfunction of the endoplasmic reticulum stress response induced by aging, genetic mutations, or environmental factors can result in various diseases such as diabetes mellitus type 2, obesity, inflammation, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, atherosclerosis and nonalcoholic fatty liver. Obesity also induces endoplasmic reticulum stress. Hyperglycemia and free fatty acids disrupt endoplasmic reticulum homeostasis and induce pancreatic β cell death through C/EBP homologous protein, which has a central role in apoptotic execution pathways triggered by endoplasmic reticulum stress.
- Endoplasmic stress triggers a protective cellular mechanism, which includes the unfolded protein response (UPR). When activation of the UPR is severe and prolonged, the final cellular outcome is pathologic apoptotic cell death. Stress that impairs endoplasmic reticulum homeostasis leads to accumulation of unfolded or misfolded proteins such as amyloid β (Aβ) peptide, the major component of amyloid plaques in Alzheimer's disease.
- Endoplasmic reticulum stress has been implicated in the pathogenesis of Parkinson's disease. Accumulation of a substrate of Parkin in the endoplasmic reticulum activates endoplasmic reticulum stress. Human ubiquitin ligase HRD1 is associated with protection against endoplasmic reticulum stress. Human ubiquitin ligase HRD1 also prevents apoptosis of neurons.
- Dysfunction in protein handling in endoplasmic reticulum has been implicated in the pathogenesis of amyotrophic lateral sclerosis. Mutation in Cu/Zn-superoxide (SOD1) induces endoplasmic reticulum and motor neuron death resulting in amyotrophic lateral sclerosis (ALS). Exact mechanism of SOD1 induced death is unknown.
- Prolonged endoplasmic reticulum stress has been implicated in the pathogenesis and progression of atherosclerosis. Oxidized phospholipids, homocysteinemia and cholesterol loading induce death of macrophages, vascular smooth muscle cells and endothelial cells via CHOP.
- Disruption of endoplasmic reticulum homeostasis, often termed endoplasmic reticulum has been observed in liver and adipose tissue with nonalcoholic fatty liver disease and/or obesity. Endoplasmic reticulum contributes to hepatic SREBP-Ic activation and lipid accumulation in fructose-evoked nonalcoholic fatty liver disease (NAFLD).

INTRODUCTION TO PATHOLOGY

A disease is an alteration from the normal function/structure of an organ or system, which manifests as a characteristic of signs and symptoms. Disease can be congenital (genetic or nongenetic) or acquired. Pathology emphasized three aspects of disease process: (a) mechanism of development of disease (pathogenesis), (b) the alterations of structure and forms (morphology), and (c) functional alterations (pathophysiology).

- Etiopathogenesis refers to study the causes such as genetic defects, environmental including iatrogenic or idiopathic.
- Pathogenesis is defined as the mechanism that leads to a diseased state by progression of processes of cellular lineage, maturation, migration, and eventual morphogenesis of both individual cells and their architecture in formation of a tissue or organ.
- Pathophysiology refers to the study of functional changes in body functions that are the causes, consequences or concomitants of disease processes.
- Most important aspects in clinical practice of medicine and surgery are diagnosis, prognosis, treatment and prophylaxis.

PATHOLOGY

Pathology is the scientific study of disease, that identifies etiology, mechanism and functional changes in cells, tissues and organs that underlie disease. Pathology lays a strong foundation of every aspect of patient care from diagnostic testing and treatment. Alterations at the molecular level and cellular level correlate with the clinical manifestations of the disease. Understanding the processes of the disease helps in the accurate recognition, diagnosis (biochemical investigations, hematologic tests, surgical pathology and immunohistochemistry) and treatment of diseases.

Pathology Divisions

Pathology is divided into following clinical discipline: general pathology, systemic pathology, chemical pathology and forensic pathology. There are three main subtypes of pathology: anatomic pathology, clinical pathology, and molecular pathology.

General Pathology

General pathology is the study of the reactions of cells or tissues to injury with a focus on the mechanisms of that response, which involves all aspects of pathology. It deals with clinical history, examination of patient, diagnosis and management of the disease by use of laboratory medicine and diagnostic techniques.

Systemic Pathology

Systemic pathology is the pathology of systems in the human body. Anatomic pathology is the study of tissues, organs and tumors. Systemic pathology is not a separate discipline from general pathology, but a different approach at the level of the tissue or organ or even the entire body. Pathologists are specialists in the disciple of pathology. Although general pathology and systemic pathology are educationally useful divisions of pathology discipline. Pathologists can be specialists in a particular organ system.

Histopathology

Histopathology is the study of histologic abnormalities of diseased cells and tissues under a microscope, which enables pathologists to look for changes in cells or tissues that explain the actual cause of the patient's illness. Pathologists are able to reach a diagnosis by examining a biopsy (punch, wedge, excision) from various organs. Histopathology is essential as it broadens and progresses treatment options.

Cytopathology

Cytopathology is the study of cellular changes related to cells and mainly used to diagnose or screen for cancer. Cell samples can be obtained during routine diagnostic procedures, such as bronchoscopy and cystoscopy or fine needle aspiration from specific body's sites for diagnosis. Cytopathology is also used to screen for fetal abnormalities and Papanicolaou smears are prepared from cells taken from the cervix to diagnose cervical cancer and infectious organisms. Two methods can be used in a Papanicolaou test: conventional and automated liquid tests.

Immunopathology

Immunopathology is a branch and manifestation of conditions concerned with immune responses associated with the production of diseases through the analysis of humoral and cellular immune function. There is a great deal of synergy between the adaptive immune system and its innate immune system, and defects in either of immune system can provoke disease such as inappropriate inflammation, autoimmune diseases, immunodeficiency diseases and hypersensitivity reactions.

Molecular Pathology

Molecular pathology is the study of disease at the molecular level by testing deoxyribose nucleic acid (DNA), ribonucleic acid (RNA) and proteins found in tissues, organs, and even body fluids within a clinical context. The applications of molecular diagnostics span a range of human disorders including hereditary, neoplastic and infectious diseases. Molecular-based *in vitro* biological assays such as polymerase chain reaction enzyme-linked immunosorbent assay (PCR-ELISA) or fluorescence *in situ* hybridization (FISH) are used to detect a molecule, often in low concentrations, that is a marker of disease or risk in a sample from a patient.

Hematology

Hematology is a branch of internal medicine in relation to health and disease, that deals with the pathophysiology, diagnosis, treatment, prognosis and prevention of blood-related disorders such as anemias, leukemias, lymphoma, bleeding and coagulation disorders. Hematology tests are performed on the blood, blood proteins and hematopoietic organs. Full blood count is a routine test that evaluates three major components found in the blood: red blood cells, white blood cells and platelets.

Chemical Pathology

Chemical pathology is the study of biochemical abnormalities associated with disease, which involves biochemical investigations of body fluids such as blood, urine and cerebrospinal fluid.

Forensic Pathology

Forensic pathology refers to perform autopsies and legal pathology tests. Autopsy room sessions can provide students with an excellent opportunity to correlate the gross and histopathologic features with the natural history of the disease.

Basis of Pathology Study

Understanding the processes of the disease help in the accurate recognition, diagnosis (biochemical investigations, hematological tests, surgical pathology and immunohistochemistry) and treatment of diseases.

Etiology

The word etiology refers to the scientific study of disease process, which generally falls into three main categories: intrinsic, extrinsic and idiopathic (unknown cause).

- Pathologic change that has occurred from inside the body as a result of intrinsic factors such as inherited, metabolic, neoplastic and immune system disorders. Hemophilia is an example of inherited disorder that

leads to excessive bleeding. Diabetes mellitus is a metabolic and endocrine disorder that causes high blood sugar.

- Pathologic change that has occurred from outside as a result of extrinsic factors include: (a) infectious agents such as bacteria, viruses, fungi and parasites, (b) animal bites or stings, (c) physical trauma, chemical agents, electricity burns and radiation; and (d) iatrogenic causes resulting from medical professional's actions or within a medical setting, and (e) idiopathic of unknown cause.
- Reactive oxygen species (ROS) is a group of extremely reactive peroxides and oxygen-containing radicals that may contribute to cellular damage.
- Autophagy refers lysosomal breakdown of a cell's own components. Autolysis refers to breakdown of cells by their own enzymatic action.

Risk Factors

A risk factor confers an increased risk of developing a disease. For example, tobacco smoking is a risk factor for lung cancer and obesity is a risk factor for heart disease.

- Types of risk factors include tobacco smoking, alcoholism, nutritional, physical inactivity, prolonged exposure to sunlight, not having certain vaccination and unprotected sexual activity leading to sexual transmitted diseases.
- The risk factors of chronic diseases are modifiable for men and women such as unhealthy diet, physical inactivity and tobacco use. These risk factors are expressed through the intermediate risk factors of raised blood pressure, raised blood glucose levels, abnormal lipids, overweight and obesity.
- Chronic diseases are the major causes of mortality and disability worldwide, which include heart disease (coronary artery disease, ischemic heart disease), cerebral stroke, chronic respiratory diseases (chronic obstructive pulmonary disease, bronchial asthma), bone and joint disorders, genetic orders and neoplastic disorders.

Predisposition

Predisposition is a term applied for patients having an increased susceptibility to develop a disease. A genetic predisposition is an increased likelihood of developing a genetic disorder. For example, familial adenomatous polyposis (FAP) patients have a mutated APC gene associated risk of developing colorectal carcinoma resulting from succession of mutations in one or more polyps. Other examples of genetic disorders include Down syndrome, thalassemia, cystic fibrosis and sickle cell disease.

Pathogenesis

Pathogenesis is the pathologic mechanism which results in clinically evident disease. For example, the way in which the interaction between *Mycobacterium tuberculosis* and the host immune system produces the caseating epithelioid granulomatous lesion in tuberculosis.

- Atherosclerosis is a chronic inflammatory disease, which begins with fatty streak due to accumulation of lipid laden foam cells in the intimal layer of large elastic and medium-sized arteries and then progresses to formation of atheromatous plaque.
- The atheromatous plaque has cellular component (e.g. smooth muscle cells and inflammatory cell), a fibrous component composed of connective tissue, and central core fat component of lipids. Major risk factors of atheromatous plaque are hypertension, diabetes mellitus, dyslipidemia, tobacco smoking, obesity, sedentary lifestyle and family history.

Morphologic Changes in Cells and Tissues

Morphologic changes are characterized by structural alterations in the cells and tissues and altered cellular functions such as cell–pathogen interaction, tumor formation and stem cell differentiation.

- Cellular adaptation is the ability of cells to respond to various types of stimuli and adverse environmental changes. If cells are unable to sustain to the adverse injurious insults, cell undergoes apoptosis or cell death in the form of necrosis.
- Morphology is a branch of life science dealing with the study of gross structure of diseased tissue and microscopic examination of tissue.

Functional Derangements and Clinical Manifestations

External and internal factors adversely affecting cell, tissue, organ or person cause structural and functional changes and cellular adaptation and response from cellular to whole person level resulting in symptoms and signs.

- For example, *Streptococcus pneumoniae* causes acute inflammatory response (consolidation is structural change in lung parenchyma that becomes solid, reduced exchange of gases in alveoli is functional change) resulting in symptoms (cough, breathlessness, hemoptysis) and signs such as reduced chest movements, dull percussion notes and radiologic changes.
- Injury to the cells and extracellular matrix results in tissue and organ injury, which determines the morphologic and clinical patterns of the disease.

Diagnosis

Understanding the processes of the disease help in the accurate recognition, diagnosis (biochemical investigations, hematological tests, surgical pathology and immunohistochemistry) and treatment of diseases.

CELLULAR RESPONSE TO STRESS AND HARMFUL STIMULI

Normal cells are the structural and functional units of tissues, which remain in a state of homeostasis with the extracellular fluid and respond to changes in their environment. The cells are capable of adjusting their structure and functions in response to various physiologic and pathologic mild to severe stimuli throughout life. Genetic or acquired metabolic defects and chronic cell injury cause intracellular accumulation of glycogen, proteins and pigments; and pathologic dystrophic and metastatic calcification. Cellular response to injurious stimuli is given in Table 1.8. Cellular response to injurious stimuli is shown in Fig. 1.1.

- Altered physiologic stimuli and some nonlethal stimuli produce cellular adaptations: atrophy, hypertrophy, hyperplasia and metaplasia. Intracellular accumulations occur due to altered metabolism.
- Cellular stress beyond the level of adaptive response results in cell injury. Cellular injury occurs when a stress exceeds the cells ability to adapt due to altered physiologic stimuli, reduced oxygen supply, extremes of temperature, electrical injury, radiation, biologic agents, and nutritional deficiency, metabolic alteration and cumulative aging.
- Cell injury depends on injurious stimuli: (a) type, duration and severity of injury, (b) ability of the tissues to regenerate (e.g. labile or dividing cells/stable cells/permanent cells), (c) metabolic needs of cell, (d) adaptability of cell, and (e) genetic constitution. Neurons are highly susceptible to ischemic injury; whereas skeletal muscle is relatively more resistant to ischemic injury.
- Depending on severity of cell injury, various cellular changes occur: (a) subcellular alterations (intracellular accumulation of biomolecules and calcium), (b) reversible cell injury, (c) irreversible cell injury

Table 1.8 Cellular response to injurious stimuli

Cellular Adaptations
▪ Hyperplasia ▪ Atrophy ▪ Hypertrophy ▪ Metaplasia
Cell Injury
▪ Reversible cell injury ▪ Irreversible cell injury (necrosis and apoptosis)
Intracellular Accumulations
▪ Normal endogenous substances (e.g. fatty liver and protein droplets in renal tubules) ▪ Normal endogenous substances due to enzyme defects (e.g. glycogen storage diseases and lipid storage disorders) ▪ Mutated gene products (misfolded proteins) ▪ Abnormal exogenous products (e.g. silicosis and anthracosis)
Subcellular Changes
▪ Lysosomal catabolism (heterophagy or autophagy) ▪ endoplasmic reticulum hypertrophy (induction of drug tolerance to barbiturates and alcohol) ▪ Mitochondrial defects (number, size and shape) ▪ Cytoskeleton defects (phagocytosis and locomotion) ▪ Membranes (plasma membrane and subcellular membrane such as endoplasmic reticulum) ▪ Nucleus (pyknosis, karyorrhexis and karyolysis)

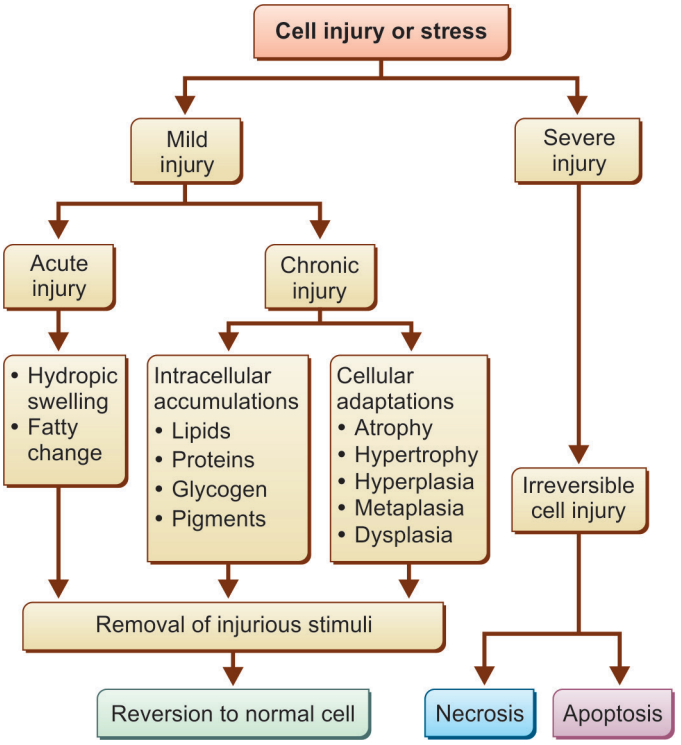

Fig. 1.1: Cellular response to injurious stimuli. Cellular adaptations, reversible injury and cell death may be stages of progressive impairment following different types of insults depending on type and duration of injurious stimuli. Acute cell mild injury can cause hydropic change and fatty change. Chronic cell injury can cause intracellular accumulation of biomolecules and cellular adaptations. Severe cell injury can cause necrosis and apoptosis.

and (d) ischemic/reperfusion injury. Initially, cellular injury may be reversible, but prolonged or severe stress leads to irreversible cell injury (necrosis or apoptosis). Reversible cell injury is the ability to heal without permanent damage.

- Ultrastructural signs in both reversible and irreversible cell injury include: (a) cellular swelling occurs due to diminished activity of the sodium/potassium pump in the cell membrane causing influx of sodium along with water and efflux of potassium, (b) mitochondrial swelling results in reduced adenosine triphosphate (ATP), aerobic respiration (oxidative phosphorylation), (c) dilatation and degranulation of rough endoplasmic reticulum results in cessation of protein synthesis, and (d) autophagocytosis occurs due to ingestion of damaged cell organelles by the lysosomes.

CELLULAR ADAPTATIONS

Cellular adaptations are usually reversible changes that result in increased, decreased, or altered functions of cells, tissues and organs, which can be physiologic or pathologic and have many causes. Cellular adaptations encompass several processes: (a) hyperplasia, (b) hypertrophy, (c) atrophy, (d) metaplasia, and (e) dysplasia. Cellular adaptations are shown in Fig. 1.2.

- **Hyperplasia:** Hyperplasia is the enlargement of the tissue/organ caused by an increase in the reproduction rate of its cells. Physiologic hyperplasia occurs in normal cells: (a) hormones-driven increase in the thickness of endometrium during menstrual cycle, lactating breast and uterus during pregnancy, (b) tissue damage-driven proliferation of connective tissue cells in wound healing, and (c) hepatocellular regeneration after partial resection. Pathologic hyperplasia is linked to cancer in endometrium and breast.
- **Hypertrophy:** Hypertrophy is defined as an increase in the size of the cell due to the synthesis of structural components and expression of embryonic genes triggered by mechanical and trophic factors (growth factors and stretch receptors). Physiologic hypertrophy occurs due to increased functional demands placed on the cell (e.g. skeletal muscle hypertrophy from weight lifting). Pathologic hypertrophy occurs when the limit of cardiac hypertrophy is exceeded and the cells can longer compensate for the increased burden (e.g. congestive heart failure and systemic hypertension).
- **Atrophy:** Atrophy refers to reduction in size of cell and tissues. Physiologic atrophy of skeletal muscles occurs in bed-ridden persons. Pathologic atrophy occurs due to loss of stimulus to a specific region due to diminished blood supply, loss of hormone stimulation, and neurogenic diseases (poliomyelitis, Guillain-Barré syndrome, Charcot-Marie-Tooth disease, amyotrophic lateral sclerosis).
- **Metaplasia:** Metaplasia is the conversion of one adult tissue type into another in same tissue. It is an adaptive response to a hostile environment that increase risk of development lung carcinoma in tobacco smokers (glandular to squamous epithelium conversion in respiratory mucosa) and esophageal adenocarcinoma in 'Barrett's esophagus' (squamous to glandular epithelium conversion).
- **Dysplasia:** Dysplasia is used to describe acquired disorderly growth and maturation of cells that are abnormal but not obviously malignant under a light microscope. This type of preneoplastic condition is

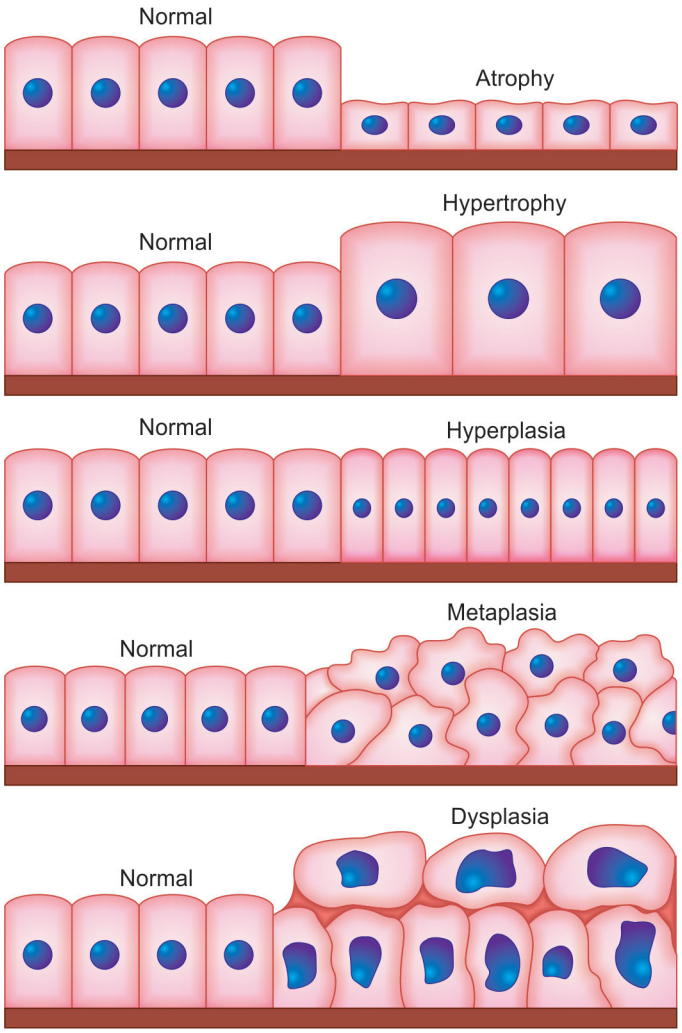

Fig. 1.2: Cellular adaptations. In cell biology and pathophysiology, cellular adaptation refers to alteration made by a cell in response to adverse or varying environmental changes. Cellular adaptations may be physiologic or pathologic (atrophy, hypertrophy, hyperplasia, metaplasia and dysplasia).