

Complimentary
Online
Student
Resources

PATHOLOGY SIMPLIFIED

*A Quick Review for
Examination Preparation*

HIGHLIGHTS

- Thoroughly updated and comprehensive content in Q & A format
- Richly illustrated with labelled and easy-to-understand line sketches
- Online content—approximately 1,200 high yield MCQs, clinicopathologic vignettes and figure-based questions with answers and brief explanations

Harsh Mohan
Ivan Damjanov



Contents

SECTION I: GENERAL PATHOLOGY

Chapter 1: Introduction to Pathology	1
Chapter 2: Molecular Cell Biology in Health and Ageing	4
Chapter 3: Cellular Adaptations and Cell Injury	19
■ Cell Injury, Responses and Etiology	19
■ Cellular Adaptations	20
■ Pathogenesis of Cell Injury	27
■ Morphology of Cell Injury	33
■ Programmed Cell Death (Apoptosis)	40
■ Intracellular Accumulations and Pigments	44
Chapter 4: Inflammation and Repair	51
■ Definition and General Features	51
■ Acute Inflammatory Response	51
■ Chemical Mediators of Inflammation	56
■ Inflammatory Cells	62
■ Acute Inflammation—Factors in Response, Morphologic Types, Effects and Outcome	64
■ Chronic Inflammation—Types and General Features	67
■ Common Granulomatous Diseases	69
■ Tissue Repair	82
Chapter 5: Immunopathology Including Amyloidosis	87
■ Normal Immune System	87
■ Major Histocompatibility Complex and Transplantation	91
■ Immunodeficiency Diseases	94
■ Hypersensitivity Reactions	102
■ Autoimmune Diseases	106
■ Amyloidosis	114
Chapter 6: Derangements of Homeostasis and Haemodynamic Disorders	121
■ Homeostasis	121
■ Derangements of Body Water	122
■ Disturbances of Electrolytes and pH of Blood	129
■ Haemodynamic Derangements	130
■ Obstructive Circulatory Disturbances	137

Chapter 7: Neoplasia 148

- Nomenclature and Classification 148
- Characteristics of Tumours 150
- Epidemiology of Cancer 155
- Molecular Basis of Cancer 158
- Carcinogens and Carcinogenesis 166
- Clinical Aspects of Neoplasia 174

Chapter 8: Infectious Diseases 180

- General Aspects 180
- Bacterial Diseases 181
- Fungal Diseases 184
- Viral Diseases 185
- Parasitic Diseases 189

Chapter 9: Environmental and Nutritional Diseases 194

- Environmental Diseases 194
- Nutritional Diseases 199

Chapter 10: Genetic and Paediatric Diseases 209

- Genetic Diseases 209
- Paediatric Diseases 218

SECTION II: HAEMATOPOIETIC SYSTEM AND LYMPHORETICULAR TISSUES

Chapter 11: Introduction to Haematopoietic System and Disorders of Erythroid Series 221

- Bone Marrow and Haematopoiesis 221
- Erythropoiesis 224
- General Aspects of Anaemias 227
- Hypochromic Anaemias 230
- Megaloblastic Anaemias 235
- Haemolytic Anaemias and Anaemias of Blood Loss 238
- Aplastic Anaemia and Primary Bone Marrow Disorders 252

Chapter 12: Haemostatic System, Bleeding Disorders and Transfusion Medicine 254

- Haemostatic System 254
- Bleeding Disorders 258
- Blood Transfusion 266

Chapter 13: White Blood Cells—Proliferations and Myeloid Neoplasms 272

- White Blood Cells—Normal and Reactive Proliferations 272
- Haematolymphoid Malignancies—General Aspects 279
- Myeloid Neoplasms 281

Chapter 14: Lymphoid Cells of Blood and Lymphoreticular Tissues 291

- Normal Lymph Nodes and Reactive Lymphadenitis 291
- Pathology of the Spleen 293
- Thymus 296
- Lymphoid and Histiocytic Neoplasms 297

SECTION III: SYSTEMIC PATHOLOGY

Chapter 15: Blood Vessels and Lymphatics	317
Chapter 16: Heart	338
Chapter 17: Respiratory System	371
■ Lungs 371	
■ Pleura 407	
Chapter 18: Eye, ENT and Neck	410
■ Eye 410	
■ Ear 417	
■ Nose and Paranasal Sinuses 418	
■ Pharynx 419	
■ Larynx 420	
■ Neck 421	
Chapter 19: Oral Cavity and Salivary Glands	423
■ Oral Soft Tissues 423	
■ Teeth and Periodontal Tissues 428	
■ Salivary Glands 432	
Chapter 20: Gastrointestinal Tract	436
■ Oesophagus 436	
■ Stomach 440	
■ Small Intestine 453	
■ Appendix 468	
■ Large Intestine 470	
■ Peritoneum 478	
Chapter 21: Liver, Biliary Tract and Exocrine Pancreas	480
■ Liver 480	
■ Biliary Tract 515	
■ Exocrine Pancreas 521	
Chapter 22: Kidney and Lower Urinary Tract	526
■ Kidneys 526	
■ Lower Urinary Tract 564	
Chapter 23: Male Genital System	570
■ Testis and Epididymis 570	
■ Penis 580	
■ Prostate 582	
Chapter 24: Female Genital Tract	588
■ Vulva 588	
■ Vagina 590	
■ Cervix 591	

- Uterus 595
- Ovary 600
- Placenta 609

Chapter 25: Breast	613
--------------------	-----

Chapter 26: Skin	625
------------------	-----

Chapter 27: Endocrine System	641
------------------------------	-----

- Basic Concept of Endocrines 641
- Pituitary Gland 642
- Adrenal Gland 645
- Thyroid Gland 651
- Parathyroid Glands 663
- Endocrine Pancreas 666

Chapter 28: Musculoskeletal System	675
------------------------------------	-----

- Bone and Cartilage 675
- Joints 687
- Skeletal Muscles 692

Chapter 29: Soft Tissue Tumours	695
---------------------------------	-----

- General Features 695
- Specific Types of Soft Tissue Tumours 699

Chapter 30: Nervous System	705
----------------------------	-----

- Central Nervous System 705
- Peripheral Nervous System 729

APPENDIX

Chapter 31: Basic Diagnostic Cytopathology	735
--	-----

- Overview 735
- Exfoliative Cytology 737
- Interventional Cytology 743

Index	747
-------	-----

Inflammation and Repair

■ DEFINITION AND GENERAL FEATURES

Q1. Define inflammation. Briefly comment on its etiology.

Definition Inflammation is local response of living mammalian tissues to injury from any agent. It is a body defense reaction to eliminate or limit the spread of injurious agent, followed by removal of the necrosed cells and tissues.

Etiology Inflammation may be caused by numerous injurious agents, the most important of which are the following:

- i. Infectious agents
- ii. Necrotic tissues resulting from the action of ischaemia, physical agents (e.g. heat, cold, mechanical force, etc.), chemical agents
- iii. Immunologic agents
- iv. Inert foreign material such as sutures or thorns

Pathophysiology Infection involves two processes: *inflammatory response* and *repair*.

Classification According to the duration and the defense capacity of the organism, there are two principal forms of inflammation: *acute* and *chronic inflammation*.

Q2. What are the cardinal signs of inflammation?

The cardinal signs of inflammation, as described by the Roman medical writer Celsus, and expanded by Galen are as follows:

- i. *Rubor* (redness)
- ii. *Tumor* (swelling)
- iii. *Calor* (heat)
- iv. *Dolor* (pain)
- v. *Functio laesa* (loss of function)

■ ACUTE INFLAMMATORY RESPONSE

Q3. How does inflammation begin?

Inflammation begins through the interaction of i) receptors on the etiologic agent and the host cells, as well as ii) some host proteins in the interstitial tissue and blood.

I. Receptors on etiologic agents and host cells Three sets of receptors play a key role in the initiation of inflammation. They are expressed on: i) infectious agents (e.g. pathogen associated molecular patterns, PAMPs), ii) necrotic cells, and iii) leucocytes.

i. *Receptors for the recognition of microbes* These include several proteins expressed on lymphocytes, macrophages and many other participating cells. The most important of these receptors are toll-like receptors (TLR), NOD-like receptors (NLRs) and RIG-like receptors (RIR).

ii. *Receptors for recognition of necrotic cells* Cytosolic and nuclear molecules released from necrotic leucocytes react with cytosolic receptors such as NLRs, forming inflammasomes, which directly activate caspase-1, triggering the release of proinflammatory cytokines, such as interleukin-1.

iii. *Receptors for the opsonised microbes* Two most important opsonins, the Fc component of immunoglobulins and C3 component of the complement system, are ligands for the receptors on leucocytes, thus stimulating inflammation.

II. **Circulating host proteins** These initiators of inflammation are certain circulating proteins liberated by activation of complement system after microbial infection. These include:

- i. mannose-binding lectins, and
- ii. collectins.

These act against invading organisms and trigger inflammation.

Q4. What are the key events in acute inflammatory response?

There are two principal components of the acute inflammatory response:

I. **Vascular events** These include:

- i. Haemodynamic changes
- ii. Altered vascular permeability

II. **Cellular events** These are:

- i. Exudation of leucocytes
- ii. Phagocytosis

Q5. What is the sequence of haemodynamic changes in acute inflammation?

- i. *Transient vasoconstriction* of arterioles, that lasts 3–5 seconds, except in more severe injury when it can last longer, up to 5 minutes.
- ii. *Persistent progressive vasodilatation*, involving all compartments of the microcirculation. It is obvious within half an hour and it accounts for the increased blood volume and redness of the involved area.
- iii. *Increased local hydrostatic pressure* and transudation of the fluids into the extracellular space.
- iv. *Slowing or stasis* of microcirculation and increased viscosity of the blood.
- v. *Margination of leucocytes* along the endothelium, followed by their emigration into the perivascular spaces.

Q6. What is the triple response in Lewis 'flare and wheel' experiment?

Lewis experiment included stroking the skin of the forearm with a blunt point object. The response included sequentially the following changes, corresponding to signs of inflammation (redness, heat and swelling) as follows (**Fig. 4.1**):

- i. *Red line* due to the dilatation of the capillaries and venules.
- ii. *Flare* of reddish colour surrounding the red line due to the vasodilation of arterioles.
- iii. *Wheel* of the surrounding skin due to transudation of fluids to form oedema.

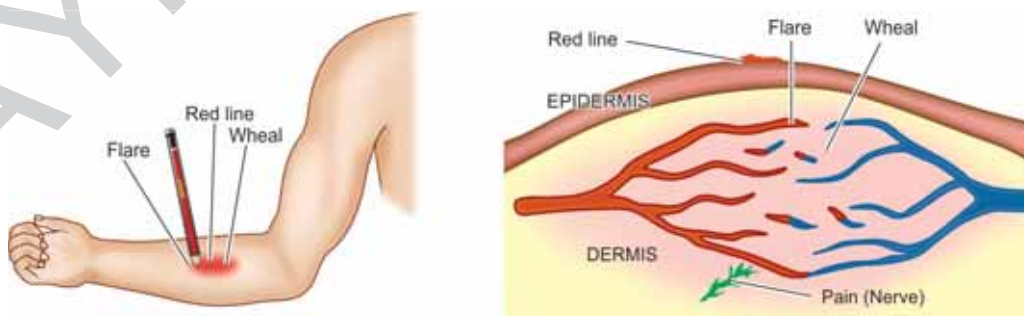


FIGURE 4.1: A, 'Triple response' elicited by firm stroking of skin of forearm with a pencil. B, Diagrammatic view of microscopic features of triple response of the skin.

Q7. What are the mechanisms of oedema formation due to altered vascular permeability?

These are as under (Fig. 4.2):

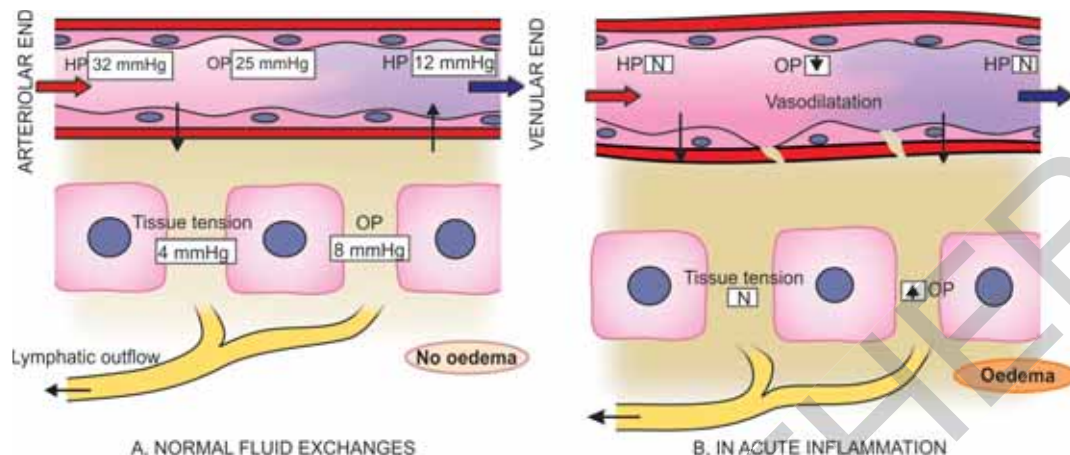


FIGURE 4.2: Fluid interchange between blood and extracellular fluid (ECF). (HP, hydrostatic pressure; OP, osmotic pressure).

- i. Transudation of fluid due to increased intravascular pressure following vasodilation of arterioles and the flooding of the microcirculation with arterial blood.
- ii. Increased permeability of blood vessel walls.
- iii. Increased colloid osmotic pressure of the interstitial fluid that now contains more albumin.
- iv. Decreased intravascular colloid osmotic pressure due to a loss of albumin from circulating blood.

Q8. What are the mechanisms of increased vascular leakiness?

These changes include the following (Fig. 4.3):

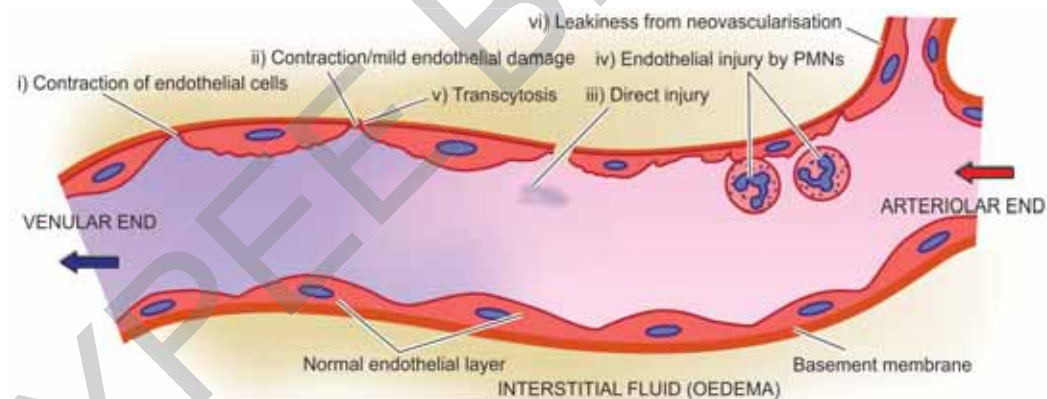


FIGURE 4.3: Schematic illustration of pathogenesis of increased vascular permeability in acute inflammation. The serial numbers in the figure correspond to six numbers described in the text.

- i. *Contraction of endothelial cells*, e.g. transient, short (15–30 minutes) response to mild thermal injury. It is mediated by histamine and bradykinin and other mediators of inflammation. It affects venules and it is the most common form of increased vascular leakiness.
- ii. *Contraction/mild damage of endothelial cells*, e.g. longer reaction (4–6 hours) sunburn skin injury, mediated by interleukin-1 (IL-1) and tumour necrosis factor- α (TNF- α).
- iii. *Direct injury*, e.g. severe bacterial infection or moderate thermal and irradiation injury. It may start immediately or be delayed in onset. It affects all parts of the microcirculation, and lasts hours and days and may be associated with thrombosis.
- iv. *Endothelial cell injury by PMNs*, e.g. pulmonary oedema due to the adherence of leucocytes to endothelial cells in lung capillaries. It is a late response affecting venules.

v. *Transcytosis*, e.g. VEGF-induced oedema.

vi. *Leakiness from neovascularisation*, e.g. granulation tissue or oedema in tumours.

Q9. What are the cellular events during the exudation of leucocytes?

The sequential changes are illustrated in **Figure 4.4** and listed as follows:

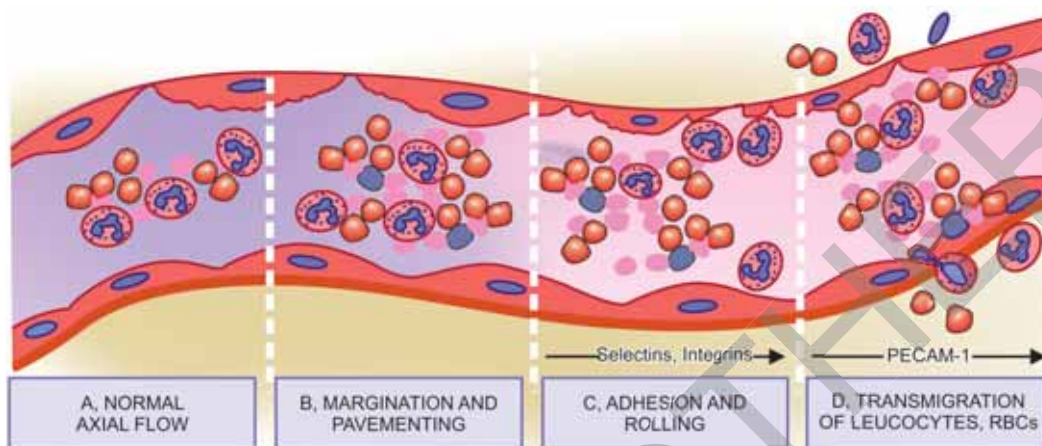


FIGURE 4.4: Sequence of changes in the exudation of leucocytes. A, Normal axial flow of blood with central column of cells and peripheral zone of cell-free plasma. B, Margination and paving of neutrophils with narrow plasmatic zone. C, Adhesion of neutrophils to endothelial cells with pseudopods in the intercellular junctions. D, Emigration of neutrophils and diapedesis with damaged basement membrane.

- i. **Margination** of PMNs due to the blood flow changes, followed by paving of PMNs on the surface of endothelial cells.
- ii. **Rolling** of PMNs and their early contact with endothelial cells mediated by selectins. Stronger **adhesion** of PMNs to endothelial cells is mediated by integrins.
- iii. **Transmigration** or **diapedesis** is mediated by platelet-endothelial cell adhesion molecule (PECAM-1 or CD31). RBCs may passively follow it and this gives the exudate a haemorrhagic appearance.
- iv. **Chemotaxis** and movement of PMNs toward the chemoattractants.

Q10. What are chemoattractants? How are they classified?

Definition Chemoattractants are biologically active compounds, which mediate chemotaxis, i.e. they direct the neutrophils (PMNs) to migrate along a chemical gradients toward them.

Pathogenesis of cell movement Chemoattractants bind to specific transmembrane G-protein coupled receptors (GPCR), which upon activation, increase the influx into the cytoplasm of PMNs, leading to cytoskeletal changes, resulting in directional migration of these cells.

Classification Chemoattractants can be exogenous (e.g. derived from bacteria) or endogenous:

- I. *Exogenous chemoattractants* are mostly formylated peptides.
- II. *Endogenous chemoattractants* include several groups of substances as given below:
 - i. Leukotriene B₄ formed from arachidonic acid through the lipoxygenase pathway
 - ii. Activated fragments of the complement system like C5a
 - iii. Cytokines such as IL-8, MCP-1, MIP
 - iv. Kallikrein

Q11. Define phagocytosis. How do leucocytes phagocytise microbes?

Definition Phagocytosis is a cellular process during which the cells engulf solid particles. Microbes are phagocytised like any other foreign material by two types of cells:

- Polymorphonuclear leucocytes (PMNs) called microphages
- Circulating monocytes and their descendant in tissue called macrophages

Phagocytosis of microbes is a specialised form of phagocytosis, which occurs in three phases: i) recognition, ii) engulfment, and iii) killing and degradation (**Fig. 4.5**).

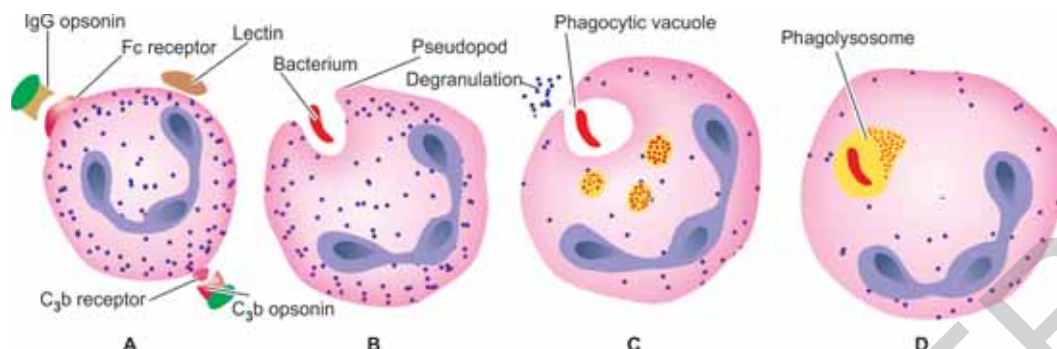


FIGURE 4.5: Stages in phagocytosis of a foreign particle. A, Opsonisation of the particle. B, Pseudopod engulfing the opsonised particle. C, Incorporation within the cell (phagocytic vacuole) and degranulation. D, Phagolysosome formation after fusion of lysosome of the cell.

I. **Recognition** is mediated by mannose receptor and scavenger receptor on the cell membrane of macrophages. It is facilitated by opsonisation with one of the following three *opsonins*:

- i. C3b component of complement
- ii. Fc part of IgG
- iii. Collectins (carbohydrate binding lectin in the plasma which bind to the bacterial wall).

II. **Engulfment** involves formation of a phagocytic invagination of the plasma membrane which becomes a vesicle called phagosome.

Phagosomes fuse with lysosomes forming *phagolysosomes*. Phagolysosome is a membrane-bound vesicle that contains the microbe and is full of lysosomal lytic enzymes.

III. **Killing and degradation** in the phagolysosomes is mediated by the following substances:

- i. Reactive oxygen species generation which may be:
 - myeloperoxidase (MPO) dependent, or
 - myeloperoxidase independent
- ii. Nitric oxide (mostly in macrophages and endothelial cells)
- iii. Lysosomal enzymes (in PMNs and macrophages)

Q12. Which is the most efficient form of bacterial killing?

Reactive oxygen species (ROS) are the most potent bactericidal substances in the phagolysosomes containing microbes. They include superoxide, hydrogen peroxide and hydroxyl radical, and halide derivatives such as hypochlorous acid.

ROS are generated by two ways:

- MPO dependent, and
- MPO independent pathway.

These include several steps:

- i. Both processes begin with an oxygen burst mediated by *NADPH oxidase*, resulting in the production of superoxide anion.
- ii. *MPO dependent system* works in PMNs and monocytes. It involves a conversion of superoxide into hydrogen peroxide, which is then converted by MPO into *hypochlorous acid*, in the presence of chloride ion.
- iii. *MPO independent system* takes place in mature macrophages which lack the enzyme MPO and, therefore, cannot form halide derivatives like hypochlorous acid. Instead, macrophages form *hydroxyl radical* and *superoxide* that have a less potent bactericidal activity.

Q13. Which extracellular mechanisms are used for bacterial killing?

i. **Release of granules** from the cytoplasm of PMNs and macrophages floods the tissue with lytic enzymes, which have bactericidal activity. Unfortunately, these lytic enzymes act non-selectively; they not only kill microbes but may also cause tissue damage by proteolysis.

ii. Another mechanism is formation of **neutrophil extracellular traps** (NETs), a fibrillar network composed of nuclear material of dead neutrophils. This fibrillar network may trap microbes and prevent the spread of infection.

iii. **Immune mechanism** also provides a defense against the bacteria.

CHEMICAL MEDIATORS OF INFLAMMATION

Q14. What are the common properties of all chemical mediators of inflammation?

Mediators of inflammation have the following common properties:

- i. They belong to two groups: cell derived and plasma derived.
 - *Cell derived mediators* are stored in cytoplasmic granules from which they are released when needed.
 - *Plasma derived mediators* circulate in an inactive form in blood and require activation. Most of these plasma proteins are synthesised by the liver.
- ii. Spectrum of their actions include the following: increased vascular permeability, vasodilation, chemotaxis, fever, pain and tissue damage.
- iii. Mediators have a short life span after their release.
- iv. All mediators are released in response to certain stimuli.
- v. Mediators act on different targets.

Q15. Classify chemical mediators of inflammation.

Two main groups of substances acting as chemical mediators of inflammation—released from the cells and those from the plasma proteins, and members in each group are listed in **Table 4.1**.

TABLE 4.1 Mediators of inflammation.

I. CELL-DERIVED MEDIATORS

1. Vasoactive amines (Histamine, 5-hydroxytryptamine, neuropeptides)
2. Arachidonic acid metabolites (eicosanoids)
 - i. Metabolites via cyclo-oxygenase pathway (prostaglandins, thromboxane A_2 , prostacyclin, resolvins)
 - ii. Metabolites via lipo-oxygenase pathway (5-HETE, leukotrienes, lipoxins)
3. Cytokines: interleukins (IL-1, IL-6, IL-8, IL-12, IL-17) TNF- α , TNF- β ; IFN- γ ; other chemokines
4. Platelet activating factor
5. Free radicals (oxygen intermediates, nitric oxide)

II. PLASMA PROTEIN-DERIVED MEDIATORS (PLASMA PROTEASES) PRODUCTS OF:

1. The kinin system (kallikrein, bradykinin)
2. The clotting system (fibrin, fibrinopeptides)
3. The fibrinolytic system (plasmin)
4. The complement system (C3a, C3b, C5a, MAC)

Q16. Discuss histamine as a chemical mediator of inflammation briefly.

Storage site Biogenic amine stored in cytoplasmic granules of basophils, mast cells and platelets.

Stimulants for release Agents in acute inflammation, e.g. heat, cold, trauma, irritant chemicals, irradiation, type I hypersensitivity (anaphylactic or allergic) reaction.

Actions Acts on blood vessels and nerves:

- i. Vasodilation of arterioles
- ii. Increased vascular permeability
- iii. Itching
- iv. Pain

NOTE: Histamine is similar to another biogenic amine which has similar actions, i.e. *serotonin* (5-hydroxytryptamine); the latter is stored in platelets granules. Serotonin has similar pro-inflammatory activities as histamine, even though serotonin actions are much weaker.

Q17. Which are the mediators of inflammation produced from the arachidonic acid and how are they formed?

Arachidonic acid (eicosanoids) derivatives are the most potent mediators of inflammation. They are fatty acids released from the phospholipids in the cell membrane through the action of phospholipases. The biologically active derivatives are formed through one of the two pathways: cyclo-oxygenase pathway and lipo-oxygenase pathways (**Fig. 4.6**):

- I. **Cyclo-oxygenases** (two enzymes, COX-1 and COX-2) generate the following biologically active compounds:
 - i. Prostaglandins

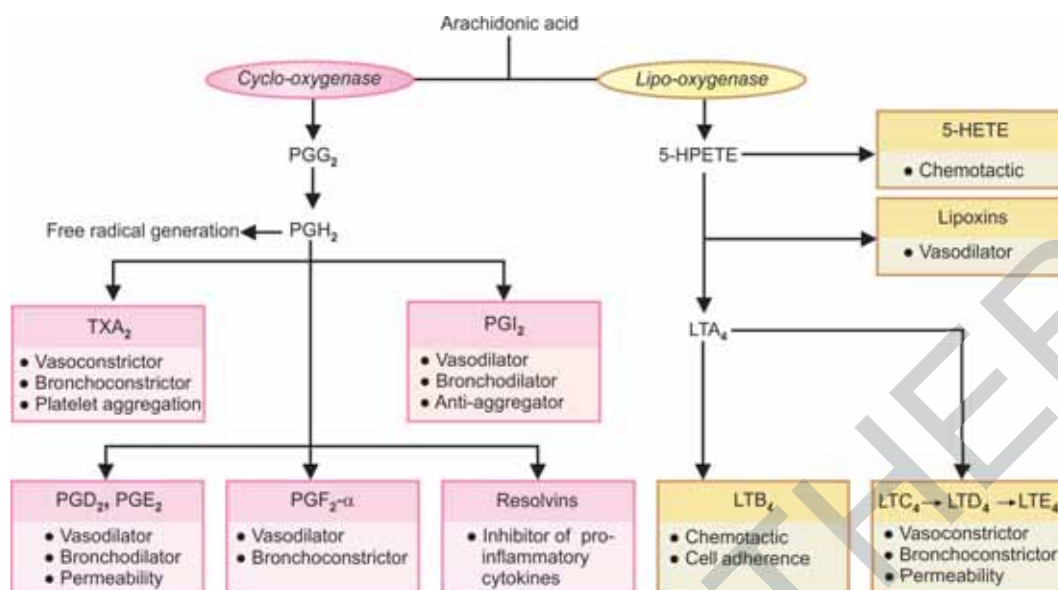


FIGURE 4.6: Arachidonic acid metabolites via cyclooxygenase and lipo-oxygenase pathway and their major actions.

ii. Prostacycline (also known as PGI₂)

iii. Thromboxane

iv. Resolvins

II. **Lipo-oxygenase** (an enzyme most abundant in PMNs) acts on the activated arachidonic acid to form hydroxyperoxy-eicosatetraenoic acid (5-HPETE), which then gives rise to:

i. 5-HETE, a potent chemoattractant of neutrophils

ii. Leukotrienes (chemoattractants, bronchoconstrictors, and vasoconstrictors)

iii. Lipoxins (vasodilators, bronchodilators, counteracting leukotrienes)

Certain key facts on arachidonic acid metabolites:

i. Arachidonic acid derivatives are called **autacoids** because they have predominantly autocrine and paracrine actions.

ii. **Prostaglandins** act on blood vessels, bronchial smooth muscles, or uterine smooth muscle, in synergy or opposing each other's actions (for details see **Fig. 4.6**).

iii. **Thromboxane and prostacyclin** counteract one another: Thromboxane is produced by platelets favouring aggregation of platelets and promoting vasoconstriction. Prostacyclin is produced by endothelial cells, counteracting aggregation of platelets and acting as a vasodilator.

iv. **Resolvins** inhibit production of pro-inflammatory cytokines.

v. The effects of pro-inflammatory prostaglandins can be inhibited by *acetylsalicylic acid* (aspirin), which **inhibits COX-2**.

vi. **Leukotrienes** are synthesised and slowly released from mast cells as type I hypersensitivity (anaphylactic) reactions, e.g. hay fever or bronchial asthma. Therefore, they are also known as slow reacting substances of anaphylaxis SRS-As.

vii. **Lipoxins** counteract leukotrienes.

Q18. What are cytokines and chemokines? Discuss their classification and their major functions.

Definition Cytokines are polypeptides produced by activated lymphocytes (thus also known as *lymphokines*) or monocytes (*monokines*). Cytokines may act on 'self' cells (autocrine action) or on other cells. The term *chemokine* is used for small cytokines that act as chemoattractants.

Sources Most cytokines are produced by a variety of cells:

i. The most common sources of cytokines are monocytes/macrophages, lymphocytes, dendritic cells, mast cells, neutrophils.

ii. Some connective tissue cells such as fibroblasts, endothelial cells and smooth muscle cells.

iii. Some epithelial cells such as pulmonary alveolar cells.

Targets Many cytokines have multiple target cells, and many act on almost all cells in the body. Selective targets are most often T or B lymphocytes, NK cells and other white blood cells.

Classification Several groups of cytokines are recognised, the most important of which are as follows:

i) interleukins, ii) tumour necrosis factor family, and iii) interferons (**Table 4.2**).

I. **Interleukins (IL-1, IL-2, IL-3, etc.)** which have the following main functions:

- i. Emigration of neutrophils and macrophages
- ii. Expression of adhesion molecules
- iii. Regulation of fever, shock
- iv. Hepatic production of acute phase reactants
- v. Increased production of IFN- γ or other cytokines
- vi. Induction of formation of T-cell subsets, like T helper or cytotoxic T cells
- vii. Promote CTL activity
- viii. Stimulate angiogenesis

II. **Tumour necrosis factors (TNF- α TNF- β)** which is produced by T cells and NK cells and has the following main functions:

- i. Fever, shock, anorexia
- ii. Hepatic production of acute phase reactants
- iii. Increased production of pro-inflammatory cytokines
- iv. Expression of endothelial cell adhesion molecules

III. **Interferon (IFN- γ):**

- i. Activation of macrophages and NK killer cells
- ii. Stimulation of immunoglobulins by B cells
- iii. Differentiation of T helper cells

IV. **Chemokines** (*monocyte chemoattractant protein, MCP-1; macrophage inflammatory protein, MIP1- α ; eotaxin; regulated and normal T cell expressed and secreted, RANTES*):

- i. Chemoattractant action for specific inflammatory cell types
- ii. Release of histamine from basophils

Q19. What is platelet activating factor (PAF)?

Definition PAF is a phospholipid-derived mediator of inflammation, initially identified as a mediator of platelet aggregation and degranulation. It is a multifunctional molecule synthesised by leucocytes, endothelial cells and many other cells. Receptors of PAF are found on numerous cells.

Main functions Binding of PAF to cell receptor may have the following effects:

- i. Increase vascular permeability
- ii. Vasodilatation or vasoconstriction depending on the concentration of PAF
- iii. Bronchoconstriction
- iv. Chemotaxis
- v. Adhesion of PMNs to endothelium

Q20. What are the main plasma-derived mediators of inflammation?

Mediators circulating in the blood are mostly synthesised by the liver and belong to four interlinked systems:

- i. Kinin
- ii. Clotting
- iii. Fibrinolytic
- iv. Complement

Hageman factor (clotting factor XII) plays a key role in interactions of the four systems (**Fig. 4.7**).

Q21. What are the components of the kinin system and the main functions?

Kinin system is involved in the production of bradykinin from kininogen which is activated by kallikrein. Kallikrein is formed from prekallikrein under the action of prekallikrein activator derived from Factor XII (**Fig. 4.8**).

TABLE 4.2 Major cytokines in inflammation.

CYTOKINE	CELL SOURCE	CELL TARGET	MAIN ACTIONS
I. INTERLEUKINS			
IL-1	Monocytes/macrophages, B cells, fibroblasts, endothelial cells, some epithelial cells	All cells	➤ Expression of adhesion molecules ➤ Emigration of neutrophils and macrophages ➤ Role in fever and shock ➤ Hepatic production of acute phase reactant
IL-6	Same as for IL-1	T and B cells, epithelial cells, hepatocytes, monocytes/macrophages	➤ Hepatic production of acute phase reactant ➤ Differentiation and growth of T and B cells
IL-8	Monocytes/macrophages, T cells, neutrophils, fibroblasts, endothelial cells, epithelial cells	Neutrophils, basophils, T cells, monocytes/macrophages, endothelial cells	➤ Induces migration of neutrophils, macrophages and T cells ➤ Stimulates release of histamine from basophils ➤ Stimulates angiogenesis
IL-12	Macrophages, dendritic cells, neutrophils	T cells, NK cells	➤ Induces formation of T helper cells and killer cells ➤ Promotes CTL cytolytic activity ➤ Increases production of IFN-γ ➤ Decreases production of IL-17
IL-17	CD4+T cells	Fibroblasts, endothelial cells, epithelial cells	➤ Increases secretion of other cytokines ➤ Migration of neutrophils and monocytes
II. TNF FAMILY			
TNF- α	Monocytes/macrophages, mast cells/basophils, eosinophils, B cells, T cells, NK cells	All cells except RBCs	➤ Hepatic production of acute phase reactant ➤ Systemic features (fever, shock, anorexia) ➤ Expression of endothelial adhesion molecules ➤ Enhanced leucocyte cytotoxicity ➤ Induction of pro-inflammatory cytokines
III. INTERFERON FAMILY			
IFN- γ	T cells, NK cells	All cells	➤ Activation of macrophages and NK cells ➤ Stimulates secretion of Igs by B cells ➤ Differentiation of T helper cells
IV. OTHER CHEMOKINES (BESIDES IL-8)			
MCP-1	Fibroblasts, smooth muscle cells, blood mononuclear cells	Monocytes/macrophages, NK cells, T cells	➤ Chemoattractant for monocytes, T cells and NK cells ➤ Stimulates release of histamine from basophils
MIP-1 α	Monocyte—macrophages	Monocyte-macrophages, T cells, NK cells	Chemoattractant for monocytes, dendritic cells, T cells, NK cells
Eotaxin	Alveolar cells, myocardium	Eosinophils, basophils	➤ Chemoattractant for eosinophils and basophils ➤ Induces allergic pulmonary disease
RANTES	Monocytes—macrophages, T cells, fibroblasts and eosinophils	Monocytes-macrophages, T cells, NK cells, dendritic cells, eosinophils	Chemoattractant for monocytes—macrophages, T cells and NK cells
Lymphotactin	NK cells, T cells, mast cells	T cell and NK cells	Chemoattractant specific for lymphocytes
Fractalkine	Endothelial cells	NK cells, T cells, monocytes-macrophages	Dual role for monocytes and T cells: ➤ as cell-surface chemoattractant ➤ as cell adhesion molecule

(IL, interleukin; TNF, tumour necrosis factor; IFN, interferon; MCP, monocyte chemotactic protein; RANTES, regulated and normal T cell expressed and secreted).

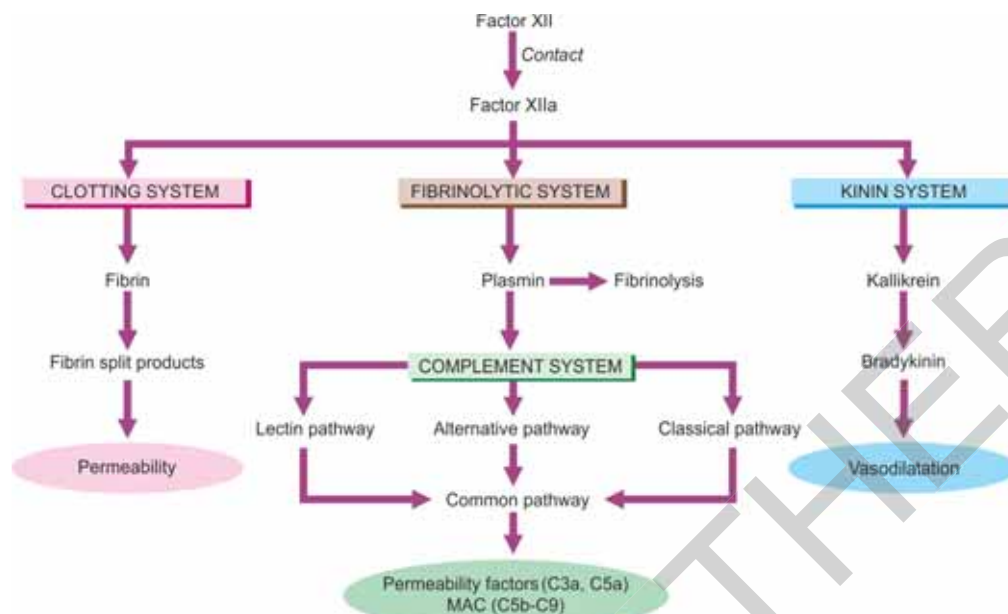


FIGURE 4.7: Inter-relationship among clotting, fibrinolytic, kinin and complement systems.

Bradykinin participates in early stages of inflammation and has the following effects:

- i. Smooth muscle contraction
- ii. Vasodilatation
- iii. Increased vascular permeability
- iv. Pain

Q22. What are the main components of the clotting system and their major functions?

Activation of Factor XII through contact of the blood with a hard surface leads to the initiation of the clotting cascade that ends in the formation of fibrin and clot formation (**Fig. 4.9**).

Plasmin acts on fibrin, splitting it into **fibrinopeptides**, which may act on the inflammatory process as follows:

- i. Increased vascular permeability
- ii. Chemotaxis for leucocytes
- iii. Anticoagulant activity

Q23. What are the main functions of the fibrinolytic system in inflammation?

Plasmin, the most important fibrinolytic protein, is formed from plasminogen. There are several plasminogen activators, including kallikrein, endothelial cells or leucocytes (**Fig. 4.10**).

Plasmin has the following effects in the inflammatory process:

- i. Activation of factor XII to form prekallikrein, ultimately leading to the formation of *bradykinin*.



FIGURE 4.8: Pathway of kinin system.

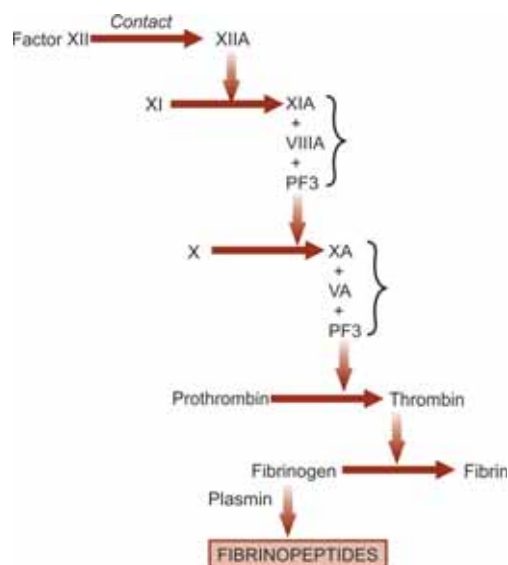


FIGURE 4.9: Pathway of the clotting system.

- ii. *Splitting of complement component C3* to form *C3a*, which leads to increased vascular permeability.
- iii. Breakdown of fibrin which gives rise to *fibrinopeptides* or *fibrin split products*. These compounds increase vascular permeability and are chemotactic for leucocytes.

Q24. What is the complement system? Briefly discuss its main features and its pathways of generation.

Definition Complement system comprises some 30 plasma proteins, cell surface proteins and receptors, as well as specific inhibitors.

Main features

- i. Complement plasma proteins, which circulate in blood in an inactive form, are labeled numerically from 1 to 9.
- ii. Upon activation, complement proteins form *fragments* which are labeled such as 3a, 3b, 5a, etc.
- iii. Fragments and activated complement proteins assemble into *intermediate complexes* and also form the final *membrane attack complex* (MAC), comprising C5b, C6, C7, C8, and C9).
- iv. *Activation of the complement pathway by one of the three pathways (Fig. 4.11):*

- a. *Classical pathway*, activated by antigen-antibody complexes containing IgG or IgM.
- b. *Alternative pathway* which can be activated by a non-immunologic agent such as bacterial toxins or lipopolysaccharides and cobra venom.
- c. *Mannose-binding lectin pathway* in which this lectin binds to mannose residues on the microbial surface and activates serine protease.
- v. All three pathways converge on the activation of *C3 convertase* which activates more complement proteins that have an important role in inflammation.
- vi. Excessive activity of complement components is controlled by specific inhibitors. Clinically, the most important *inhibitors* are as follows:
 - *C1 inhibitor*, blocking the first step of the classical pathway. Congenital deficiency of C1 INH causes *hereditary angioedema*.
 - *Decay accelerating factor (DAF)* prevents formation of C3 convertase. It is linked to plasma glycoposphatidyl and its deficiency causes *paroxysmal nocturnal haematuria*.
 - *CD59* prevents the formation of MAC.

Q25. What are the principal functions of complement in the inflammatory process?

Proteins forming the complements have many important functions in the inflammatory process in which they act as:

- i. **Anaphylatoxins**, which activate mast cells, stimulate release of histamine and increase vascular permeability.
- ii. **Chemoattractants**, which attract leucocytes to the area of inflammation.
- iii. **Opsonins**, which coat microbes and facilitate their phagocytosis.
- iv. **Membrane attack complex (MAC)**, which leads to perforation of the phospholipid cell membrane and lysis of cells (e.g. lysis of RBC in haemolysis) and killing of microbes.

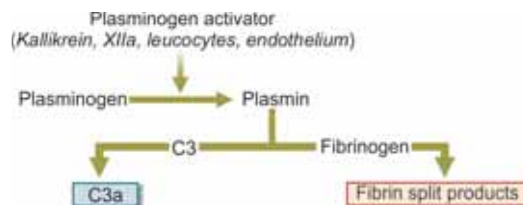


FIGURE 4.10: The activation of fibrinolytic system.

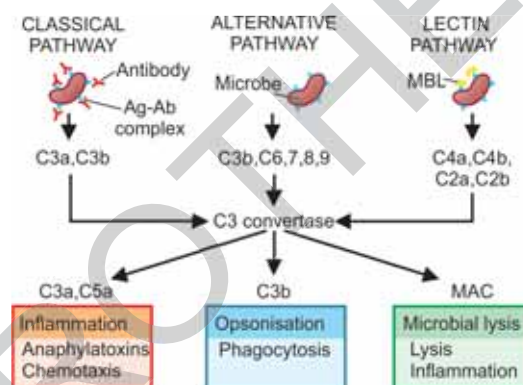


FIGURE 4.11: Activation pathways of complement system and actions of activated products.

INFLAMMATORY CELLS

Q26. What are the principal inflammatory cells and what are their major functions?

The principal inflammatory cells are: i) polymorphonuclear neutrophils (PMNs), ii) eosinophils, iii) basophils/mast cells, iv) lymphocytes, v) plasma cells, and vi) monocytes/macrophages (**Table 4.3**). They are all found in the circulating blood except macrophages, mast cells and plasma cells, which are found only in tissues.

I. Polymorphonuclear leucocytes

- i. Most numerous white blood cells in circulation (40–75% of all leucocytes).
- ii. Nucleus is polymorphous, i.e. segmented in up to 5 lobes.
- iii. Cytoplasmic granules are classified as primary, secondary, tertiary → rich in lytic enzymes.
- iv. Phagocytic activity strong → killing of microbes.
- v. Lytic enzymes released from granules → damage tissues and basement membranes.
- vi. They are the first inflammatory cells to reach the area of bacterial infections.
- vii. In tissues, they live only 2 days.
- viii. *Main function*: Most prominent cells in acute inflammation caused by microbes or tissue necrosis.

TABLE 4.3 Morphology and functions of inflammatory cells.

MORPHOLOGY	MAIN FUNCTIONS	FEATURES
 A, POLYMORPH	i. Initial phagocytosis of bacteria and foreign body ii. Engulfment of antigen-antibody complexes iii. Basement membrane destruction iv. Acute inflammatory cell	i. Primary granules (MPO, lysozyme, cationic proteins, acid hydrolases, elastase) ii. Secondary granules (lysozyme, alk. phosph, collagenase, lactoferrin) iii. Tertiary granules (gelatinase, cathepsin)
 B, EOSINOPHIL	i. Allergic states ii. Parasitic infestations iii. Dermatoses iv. Malignant lymphomas v. Chronic inflammatory cell	i. Contains MPO ii. Granules contain major basic protein, cationic protein iii. Lack lysosomes
 C, BASOPHIL/MAST CELL	i. Receptor for IgE molecules ii. Electron-dense granules	i. Histamine ii. Leukotrienes iii. Platelet activating factor
 D, LYMPHOCYTE	i. Humoral and cell-mediated immune responses ii. Chronic inflammatory cell iii. Regulates macrophage response	i. B cells: antibody production ii. T cells: delayed hypersensitivity, cytotoxicity
 E, PLASMA CELL	i. Derived from B cells ii. Plasma cell dyscrasias iii. Chronic inflammatory cell	i. Antibody synthesis ii. Antibody secretion
 F, MONOCYTE/MACROPHAGE (MPO, myeloperoxidase).	i. Microbial phagocytosis and killing ii. Induce repair by fibrosis iii. Chronic inflammatory cell iv. Regulate lymphocyte response	i. Require activation by: classic (non-immunologic) or alternate (IL-4, IL-13) way ii. Release proteases (collagenase, elastase) iii. Activation of coagulation pathway iv. Prostaglandins, leukotrienes v. Chemoattractant for other leucocytes

PATHOLOGY SIMPLIFIED

A Quick Review for Examination Preparation

Pathology Simplified: A Quick Review for Examination Preparation is a joint Indo-US book in hybrid mode (print and online supplement) based on well-vetted and carefully selected high-yield topics that are often asked in various exams.

Key Features

- **Question and answer format** This user-friendly format of short questions and brief answers replicates the actual exams and contains many questions from previous exams, accompanied by succinct answers written in simple and easy-to-understand language.
- **Illustrations** The book is profusely illustrated with over 500 labelled line-sketches of gross and microscopy of specimens/slides, schematic drawings and photographs. Some of these figures were also used for questions, to show the students that some questions on the forthcoming examination will be based on pictorial material.
- **Tables** The book contains approximately 200 tables that include comparative features of closely resembling conditions, important classifications and listing of salient features.
- **Online learning resources** The electronic supplement to the book includes approximately 1,200 high-yield questions (MCQs, clinicopathologic vignettes and figure-based questions), followed by corresponding answers and brief explanatory notes for the correct answers, as well as a full rationale for all other answer options.
- **Self-assessment** Users have the facility for attempting online questions and knowing the score, followed by correct answers with explanatory notes.
- *In summary*, this compact but comprehensive and all-inclusive package at reasonable cost is primarily targeted at recent medical school graduates to help them revisit Pathology and learn it quickly for qualifying exam or for licensing exam. Furthermore, undergraduate students who are in a 'hurry' to quickly study and prepare the subject to take their Pathology exam will also find this book immensely useful.

Harsh Mohan MD FAMS FICPath FUICC has been former founding Professor and Head, Department of Pathology at Government Medical College and Hospital, Chandigarh, India for about 22 years. He is an alumnus of Postgraduate Institute of Medical Sciences (PGIMS), Rohtak, Haryana, India. Dr Mohan is a Gold medalist in academics, has over 44 years of rich professional experience in teaching and diagnostic pathology, has published over 300 scientific articles in indexed medical journals, and has authored 7 books. He was Editor-in-Chief of Indian Journal of Pathology and Microbiology from 2003 to 2007, and President of Indian Association of Pathologists and Microbiologists in 2008. He was conferred Haryana Vigyan Ratna in 2011 by the Government in recognition of his contribution.

Ivan Damjanov MD PhD dhc has taught undergraduate level Pathology for more than 50 years, first in his native Croatia and then in the United States of America. He has delivered many invited lectures and has served as visiting Professor in many countries worldwide. He is now Professor Emeritus of Pathology at the University of Kansas School of Medicine, Kansas City, Kansas, USA, where he worked for 24 years as Chair and Professor and Attending Pathologist in the University of Kansas Medical Center. For his teaching, he received numerous prestigious awards from his students and peers. He also received honorary doctorate degrees (dhc) from the University of Novi Sad, Serbia and the Charles University, Prague, Czechia, and was admitted to the Croatian Academy of Arts and Sciences (Zagreb, Croatia) and the Vojvodina Academy of Arts and Sciences (Novi Sad, Serbia). He served on the editorial board of ten biomedical journals and was the Associate Editor of the USCAP journal, Laboratory Investigation for 12 years. He has published more than 300 scientific articles in internationally indexed journals, and more than 30 medical books, many of which were translated into other languages.

Printed in India

**Available at all medical bookstores
or buy online at www.jaypeebrothers.com**



JAYPEE BROTHERS
Medical Publishers (P) Ltd.
EMCA House, 23/23-B, Ansari Road,
Daryaganj, New Delhi - 110 002, INDIA
www.jaypeebrothers.com

Join us on [facebook.com/JaypeeMedicalPublishers](https://www.facebook.com/JaypeeMedicalPublishers)

Shelving Recommendation
PATHOLOGY

ISBN 978-93-5465-133-5



9 789354 651335