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2nd Edition

Essential PATHOLOGY for Physiotherapy Students

Harsh Mohan

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2ND YEAR BPT COURSE IN PATHOLOGY (CODE BPT-201)

I. DURATION OF TEACHING AND ANNUAL EXAMINATION SCHEME

Internal Assessment	*University Examination*	*Total Marks*	*Theory Hours*	*Practical Hours*	*Total Hours*	*Credits Theory*	*Credits Practical*	*Credits Total*
Theory 10 Practical 0	Theory 40 Viva 0 Practical 0	50	60	0	60	8	0	8

II. CURRICULUM

UNIT 1

- Discuss the causes of disease and cell injury.
- Describe the mechanism of cell injury—hypoxia, free radical injury, necrosis, and gangrene.
- Explain the pathology of inflammation.
- Differentiate acute and chronic inflammation.
- Explain the process of primary healing and secondary healing.
- Discuss the factors affecting healing and repair of soft tissues and skin.

UNIT 2

- Describe fluid and hemodynamic derangements.
- Discuss the pathophysiology of edema, hyperemia, hemorrhage, shock, embolism, thrombosis, and infarction.
- Discuss immune mechanisms (natural and acquired).
- Discuss the features of autoimmune diseases and immunodeficiency diseases.
- Describe the hypersensitivity reactions.
- Discuss the characteristic of benign and malignant tumors.
- Describe grading and staging of malignant tumors.
- Describe general effects of malignancy on the host.
- Outline the carcinogenic agents.
- Outline the methods of diagnosis of malignancy.
- Classify the nutritional disorders.
- Discuss the deficiency disorders [protein deficiency, vitamin deficiency (A, B, C, D, E, K), iodine deficiency].
- Discuss the effect of nutrition deficiency on skeletal muscles, bones, and neurological functions.

UNIT 3

- Discuss the causative factors, pathology, clinical features, diagnosis, and management of disorders of blood (anemias, leukemia).

- Discuss the causative factors, pathology, clinical features, diagnosis, and management of disease of circulatory system (atherosclerosis, thromboangiitis obliterans, varicose vein, DVT, thrombophlebitis, lymphedema, congestive cardiac failure, rheumatic heart disease).
- Explain the causative factors, pathology, clinical features, diagnosis, and management of ischemic heart disease.
- Explain the causative factors, pathology, clinical features, diagnosis, and management of congenital heart disease.
- Explain the causative factors, pathology, clinical features, diagnosis, and management of diseases of respiratory system (pneumonias, bronchiectasis, emphysema, chronic bronchitis, asthma, occupational lung diseases, carcinoma of lungs).
- Explain the causative factors, pathology, clinical features, diagnosis, and management of disorders of musculoskeletal system (arthritis: rheumatoid, degenerative, infective, metabolic; osteoporosis, Paget's disease, osteogenesis imperfecta, osteomyelitis; a brief outline of bone tumors. Muscular dystrophy, myasthenia gravis, myositis).
- Explain the causative factors, pathology, clinical features, diagnosis, and management of diseases of nervous system (meningitis, encephalitis, vascular diseases of brain, peripheral nerve lesions; degenerative diseases, parkinsonism, Alzheimer's disease).
- Describe the causative factors, pathology, clinical features, diagnosis, and management of diseases endocrine system (diabetes mellitus, thyroiditis, thyrotoxicosis, myxedema).

UNIT II

Inflammation and Repair

Lecture 4: Acute Inflammation, 20
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LECTURE 4
ACUTE INFLAMMATION

DEFINITION AND CAUSES

Inflammation (literally meaning burning) is defined as the local response of living mammalian tissues to injury from any agent. It is a body defense mechanism in order to eliminate or limit the spread of injurious agent, followed by removal of the necrosed cells and tissues. In fact, inflammatory reaction is an all-important change that distinguishes living tissue from tissues in the dead.

The injurious agents causing inflammation may be as under:

1. *Infective agents* like bacteria, viruses and their toxins, fungi, parasites.
2. *Necrotic tissue* resulting from various agents such as ischemia, physical agents (e.g. heat, cold, radiation, mechanical trauma), or chemical agents (e.g. organic and inorganic toxins).
3. *Immunological agents* like cell-mediated and antigen-antibody reactions.
4. *Foreign materials* such as foreign bodies, dirt, sutures, thorn etc.

Thus, it can be inferred from above that *inflammation is distinct from infection*—infection is invasion into the body by harmful microbes and their resultant ill-effects, while inflammation is a general protective response by the body to a variety of etiologic agents (infectious or non-infectious).

Inflammation involves 2 basic processes with some overlapping—early *inflammatory response,* and later followed by *repair*. Though both these processes generally have protective role against injurious agents, inflammation and healing may also cause considerable harm to the body sometimes, e.g. anaphylaxis to bites by insects or reptiles, drugs, toxins, atherosclerosis, chronic rheumatoid arthritis, fibrous bands and adhesions in intestinal obstruction.

SIGNS OF INFLAMMATION

Although the word inflammation means burning, we know that burning is only one of the features of inflammation. Roman medical writer Celsus in 1st century AD described famous four *cardinal signs of inflammation* as:

i) *rubor* (redness),
ii) *tumor* (swelling),
iii) *calor* (heat), and
iv) *dolor* (pain).

To these, fifth sign *functio laesa* (loss of function) was later added by Galen, a pupil of Hippocrates.

TYPES OF INFLAMMATION

Depending upon the defense capacity of the host and duration of response, inflammation can be classified as acute and chronic:

I. Acute inflammation is of short duration (lasting less than 2 weeks) and represents the early body reaction, resolves quickly and is usually followed by healing.

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The main features of acute inflammation are:
i) accumulation of fluid and plasma at the affected site,
ii) intravascular activation of platelets, and
iii) polymorphonuclear neutrophils as acute inflammatory cells.

II. Chronic inflammation is of longer duration and occurs after a delay, either when the causative agent of acute inflammation persists for a long time, or the stimulus is such that it induces chronic inflammation from the beginning.

The characteristic features of chronic inflammation are:
i) presence of chronic inflammatory cells such as lymphocytes, plasma cells and macrophages, and granulation tissue formation, and
ii) granuloma formation as a specific type of chronic inflammatory response.

ACUTE INFLAMMATORY RESPONSE

Acute inflammatory response by the host to any etiologic agent is a continuous process, but for the purpose of discussion, it can be divided into following two aspects:
I. Vascular events
II. Cellular events

Closely linked to these two processes is the release of mediators of acute inflammation.

I. VASCULAR EVENTS

Alteration in the microvasculature (arterioles, capillaries and venules) is the earliest response to tissue injury. These alterations include:
A. hemodynamic changes, and
B. altered vascular permeability.

A. Hemodynamic Changes

The earliest features of inflammatory response result from changes in the vascular flow and caliber of small blood vessels in the injured tissue. The sequence of these changes is as under:

1. Irrespective of the type of cell injury, immediate vascular response is of **transient vasoconstriction** of arterioles. With mild form of injury, the blood flow may be re-established in 3–5 seconds, while with more severe injury the vasoconstriction may last for about 5 minutes.
2. Next follows **persistent progressive vasodilatation** which involves mainly the arterioles, but to a lesser extent, affects other components of the microcirculation like venules and capillaries. This change is obvious within half an hour of injury. Vasodilatation results in increased blood volume in microvascular bed of the area, which is responsible for redness and warmth at the site of acute inflammation.
3. Increased blood volume, in turn, may elevate the **local hydrostatic pressure** resulting in transudation of fluid into the extracellular space. This is responsible for swelling at the local site of acute inflammation.
4. **Slowing or stasis** of microcirculation follows which causes increased concentration of red cells, and thus, increased blood viscosity.
5. Stasis or slowing is followed by **leukocytic margination** or peripheral orientation of leukocytes (mainly neutrophils) along the vascular endothelium. The leukocytes stick to the vascular endothelium briefly, and then move and migrate through the gaps between the endothelial cells into the extravascular space.

TRIPLE RESPONSE The features of hemodynamic changes in inflammation are best demonstrated by the Lewis experiment. In this experiment, the skin of inner aspect of forearm is stroked firmly with a blunt point such as pencil and changes observed. The reaction so elicited is known as triple response or red line response consisting of the following **(Fig. L-4.1)**:

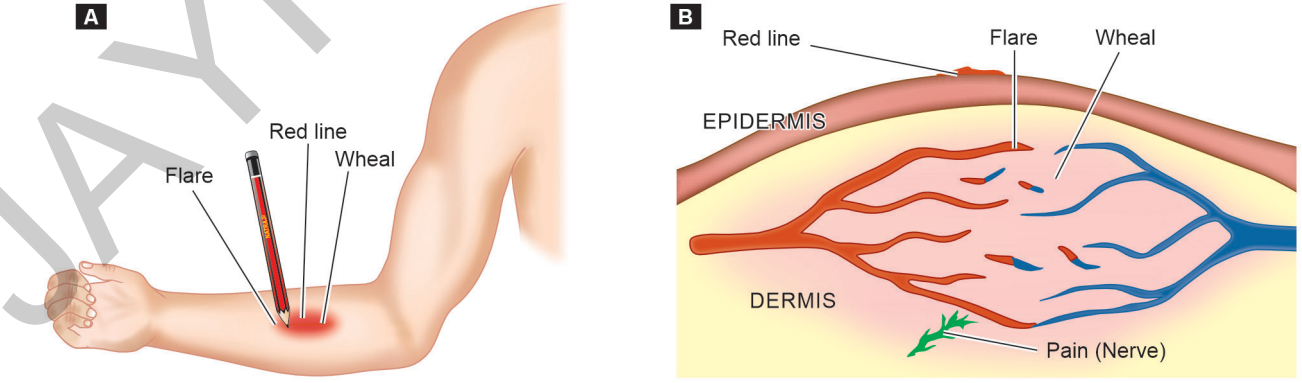


Figure L-4.1 A, 'Triple response' elicited by firm stroking of skin of forearm with a pencil. B, Diagrammatic representation of morphologic features of triple response of the skin.

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TABLE L-4.1 Differences between transudate and exudate.

	Feature	Transudate	Exudate
1.	*Definition*	Filtrate of blood plasma without changes in endothelial permeability	Edema of inflamed tissue associated with increased capillary permeability
2.	*Mechanism*	Elevated hydrostatic pressure, or decreased oncotic pressure	Increased capillary permeability
3.	*Character and appearance*	Non-inflammatory edema, pale-yellow, clear	Inflammatory edema, yellowish-white, turbid
4.	*Protein content*	Low (<3 g/dL) Mainly albumin, low fibrinogen; hence no tendency to coagulate	High (>3 g/dL) Readily coagulates due to high content of fibrinogen and other coagulation factors
5.	*Specific gravity*	Low (<1.015)	High (>1.018)
6.	*Microscopy*	Few cells, mainly mesothelial cells and cellular debris	Many cells, inflammatory as well as parenchymal
7.	*Examples*	Edema in congestive cardiac failure, nephrotic syndrome	Purulent exudate such as pus

i) *Red line* appears within a few seconds after stroking; this is due to local vasodilatation of capillaries and venules.
ii) *Flare* is the bright reddish appearance or flush surrounding the red line; this results from vasodilatation of the adjacent arterioles.
iii) *Wheal* is the swelling or edema of the surrounding skin; this occurs due to transudation of fluid into the extravascular space.

These features, thus, elicit the classical signs of inflammation—redness, heat and swelling; fourth feature is pain due to mild trauma to cutaneous nerve endings.

B. Altered Vascular Permeability

In and around the inflamed tissue, there is accumulation of edema fluid in the interstitial compartment which comes from blood plasma by its escape through the endothelial wall of peripheral vascular bed. In the initial stage, escape of fluid is due to vasodilatation and consequent increased volume of blood, elevating hydrostatic pressure. This is transudate in nature. But subsequently, the characteristic inflammatory edema, exudate, appears by increased vascular permeability of microcirculation and by appearance of inflammatory cells (*discussed under vascular events*). The differences between transudate and exudate are summarized in **Table L-4.1**.

The appearance of inflammatory edema due to increased vascular permeability of microvascular bed is explained on the basis of **Starling hypothesis**. According to this, normal fluid balance is maintained by two opposing sets of forces (page 58):
i) Forces that cause **outward movement** of fluid from microcirculation: These are *intravascular hydrostatic pressure* and *colloid osmotic pressure of interstitial fluid*.
ii) Forces that cause **inward movement** of interstitial fluid into circulation: These are *intravascular colloid osmotic pressure* and *hydrostatic pressure of interstitial fluid*.

Whatever little fluid is left in the interstitial compartment is drained away by lymphatics and, thus, no edema results normally **(Fig. L-4.2, A)**.

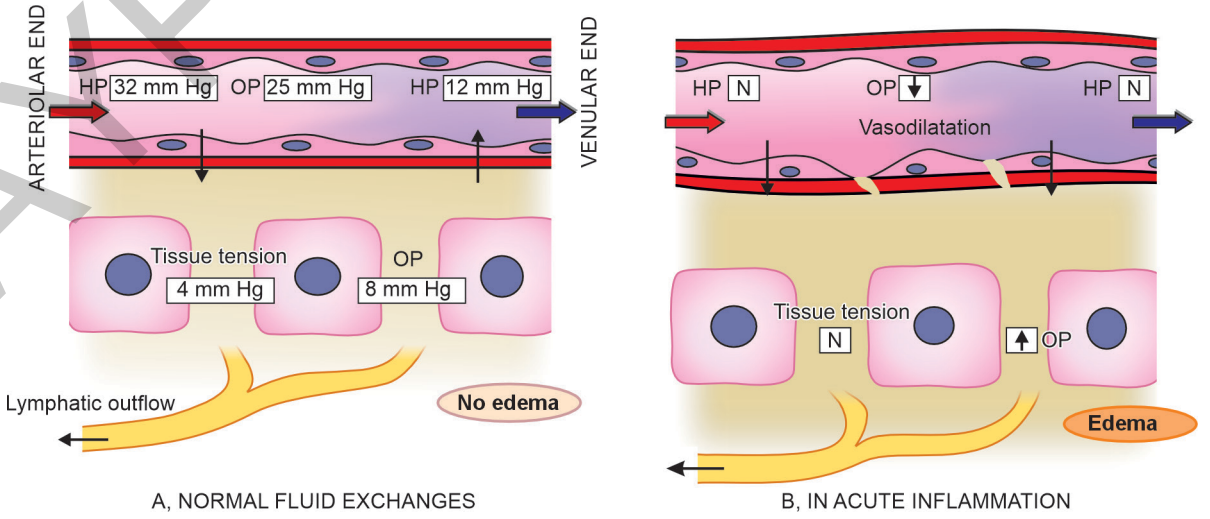


Figure L-4.2 Fluid interchange between blood and extracellular fluid (ECF). (HP, hydrostatic pressure; OP, osmotic pressure).

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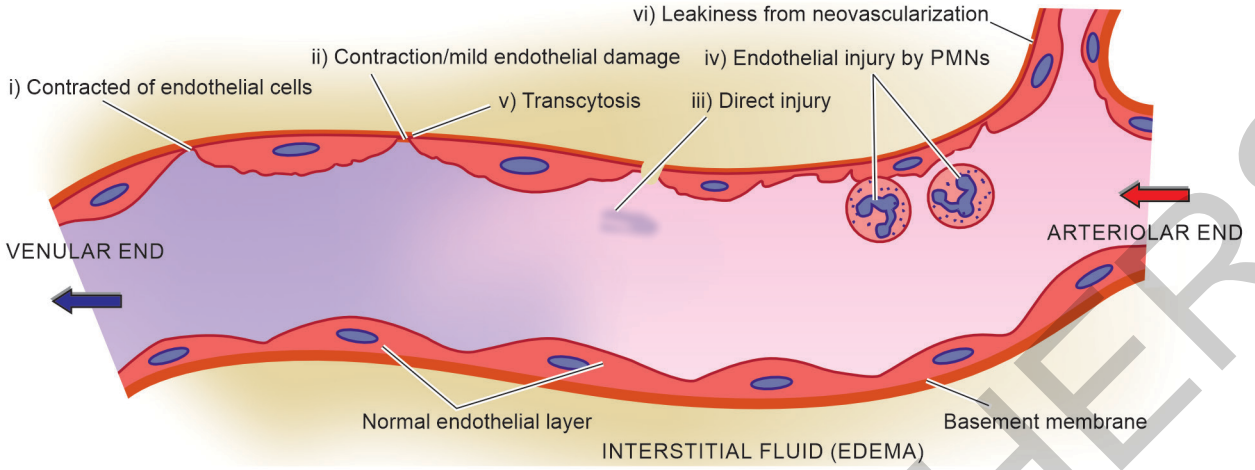


Figure L-4.3 Schematic illustration of pathogenesis of increased vascular permeability in acute inflammation. (PMNs, polymorphonuclear neutrophils).

However, in inflamed tissues, the endothelial lining of microvasculature becomes leaky. Consequently, intravascular colloid osmotic pressure decreases and osmotic pressure of the interstitial fluid increases, resulting in excessive outward flow of fluid into the interstitial compartment which is exudative inflammatory edema **(Fig. L-4.2, B)**.

Mechanisms of vascular leakage, acting singly or in combination, by which normally non-permeable endothelial layer of microvasculature becomes leaky from increased vascular permeability in acute inflammation, are as follows **(Fig. L-4.3)** and summarized in **Table L-4.2**:

i) Contraction of endothelial cells
ii) Contraction or mild endothelial damage
iii) Direct injury to endothelial cells
iv) Leukocyte-mediated endothelial injury
v) Transcytosis across the endothelial cytoplasm
vi) Leakiness in neovascularization

II. CELLULAR EVENTS

The cellular phase of acute inflammation includes recruitment of leukocytes at the site of infection, their activation to recognize the microbe, and eventually phagocytose and clear off the offending agent. Thus, cellular phase includes:

A. exudation of leukocytes, and
B. phagocytosis

A. Exudation of Leukocytes

Escape of leukocytes from the lumen of microvasculature to the interstitial tissue is the most important feature of inflammatory response. In acute inflammation, polymorphonuclear neutrophils (PMNs) comprise the first line of body defense, followed later by phagocytes (monocytes and macrophages).

The changes leading to migration of leukocytes are as follows **(Fig. L-4.4):**

1. CHANGES IN THE FLOW OF BLOOD In the early stage of inflammation, the rate of flow of blood is increased due to vasodilatation. But subsequently, there is slowing or stasis of bloodstream. With stasis, changes in the normal axial flow of blood in the microcirculation take place. The normal axial flow consists of central stream of cells comprised by leukocytes and RBCs

TABLE L-4.2 Mechanisms of increased vascular permeability.

	Mechanism	*Microvasculature*	*Onset and Effect*	*Examples*
1.	*Endothelial cell contraction*	Venules	Onset immediate after injury; transient effect (15–30 min)	Mild thermal injury
2.	*Contraction or mild endothelial injury*	Venules, capillaries	Onset after delay (4–6 hrs); effect prolonged (24 hrs to days)	Sunburns
3.	*Direct endothelial cell injury*	Arterioles, venules, capillaries	Onset either immediate, lasting hrs to days; or onset after delay (2–12 hrs), effect prolonged (hrs to days)	Severe bacterial infection, moderate to severe burns, radiation injury
4.	*Leukocyte-mediated endothelial injury*	Venules, capillaries	Late response, lasts longer	Pulmonary venules and capillaries
5.	*Transcytosis*	All levels	Any type	Macromolecules
6.	*Neovascularization*	All levels	Any type	Healing, tumors

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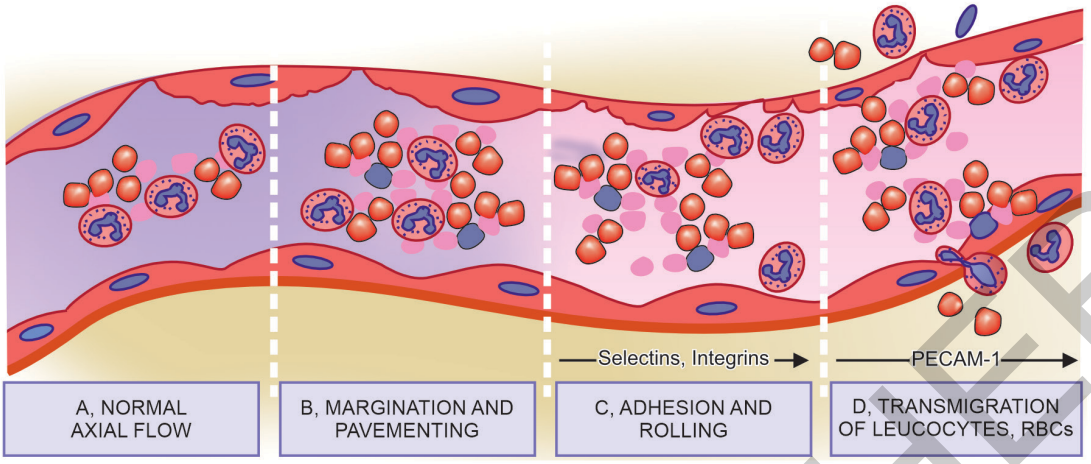


Figure L-4.4 Sequence of changes in the exudation of leukocytes. A, Normal axial flow of blood with central column of cells and peripheral zone of cell-free plasma. B, Margination and pavementing of neutrophils with narrow plasmatic zone. C, Adhesion of neutrophils to endothelial cells with pseudopods in the intercellular junctions. D, Emigration of neutrophils and diapedesis with damaged basement membrane. (PECAM-1, platelet-endothelial cell adhesion molecule 1).

and peripheral cell-free layer of plasma close to vessel wall. Due to slowing and stasis, the central stream of cells widens and peripheral plasma zone becomes narrower because of loss of plasma by exudation. This phenomenon is known as *margination*. As a result of this redistribution, neutrophils of the central column come close to the vessel wall; this is known as *pavementing*.

2. ROLLING AND ADHESION Peripherally marginated and pavemented neutrophils slowly roll over the endothelial cells lining the vessel wall (*rolling phase*). This is followed by transient sticking of leukocytes to endothelial cells (*adhesion phase*). The process of rolling is facilitated by cell adhesion molecules (CAMs) or adhesion receptors (ARs). CAMs are expressed in response to cytokines (TNF, IL-1, chemokines) produced after exposure to microbial infection and cell damage:

i) Selectins These are a group of CAMs expressed on the surface of activated cells and are structurally composed of lectins or lectin-like protein molecules. Their role is to recognize and bind to glycoproteins and glycolipids on the cell surface of neutrophils. There are three types of selectins: P-selctins (expressed on platelets, E-selectin (expressed on endothelial cells), and L-slectins (expressed on surface of lymphocytes).

ii) Integrins These are a family of leukocyte surface proteins which mediate firm adhesion between endothelium and leukocytes. For each integrin, a corresponding ligand belonging to immunoglobulin gene superfamily is present on endothelial cells. These ligands are stimulated by cytokines (TNF, IL-1).

3. TRANSMIGRATION After leukocyte-endothelium adhesion, neutrophils move along the endothelial surface till a suitable site between the endothelial cells is found where the neutrophils throw out cytoplasmic pseudopods. Subsequently, the neutrophils lodged between the endothelial cells and basement membrane cross the basement membrane by damaging it locally with secreted collagenases and escape out into the extravascular space; this is known as *transmigration* or *diapedesis*. The damaged basement membrane is almost immediately repaired. As already mentioned, neutrophils are the dominant cells in acute inflammatory exudate in the first 24 hours, while monocyte-macrophages appear in the next 24–48 hours. However, neutrophils are short-lived (24–48 hours) while monocyte-macrophages survive much longer.

4. CHEMOTAXIS Chemotaxis is movement of leukocytes towards the direction of chemical molecules or factors called chemoattractants. Transmigration of leukocytes after crossing several barriers (endothelium, basement membrane, perivascular myofibroblasts and matrix) to reach the interstitial tissues is a chemotactic factor-mediated process. Chemoattractants for leukocytes may be of two types:

1. *Exogenous agents* Most important exogenous substances are soluble bacterial products such as formylated peptide.
2. *Endogenous agents* These include several chemical mediators (discussed later):

i) Leukotriene B4 (LT-B4), a product of lipoxygenase pathway of arachidonic acid metabolites
ii) Components of complement system (C5a in particular)
iii) Cytokines/chemokines (e.g. IL-8, MCP-1, MIP-α, eotaxin etc).

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B. Phagocytosis

After the site of infection has been infiltrated by leukocytes, process of clearing off of the microbial agent is set in action. Phagocytosis is defined as the process of cellular engulfment of a solid particulate material (e.g. microbes, foreign particulate material). In other words, phagocytosis is cell-eating (on the other hand, cell-drinking is called pinocytosis). The cells performing this function are called *phagocytes*. There are two main types of cells performing this function:

i) Polymorphonuclear neutrophils (PMNs) which appear early in acute inflammatory response, sometimes called as *microphages*.

ii) Circulating monocytes and fixed tissue mononuclear phagocytes, commonly called as *macrophages*.

Neutrophils and macrophages on reaching the tissue spaces at the site of infection produce several proteolytic enzymes—lysozyme, protease, collagenase, elastase, lipase, proteinase, gelatinase, and acid hydrolases. These enzymes degrade collagen and extracellular matrix.

Phagocytosis of the microbe by polymorphs and macrophages occurs through the following three processes **(Fig. L-4.5)**:

1. Recognition and attachment
2. Engulfment
3. Killing and degradation

1. RECOGNITION AND ATTACHMENT Phagocytosis is initiated by the expression of cell surface receptors on macrophages which recognize microorganisms; these are *mannose receptor* and *scavenger receptor*. The process of phagocytosis is further enhanced when the microorganisms are coated with specific proteins, *opsonins*, from the serum and the process is called opsonization (meaning preparing for eating). Opsonins establish a bond between bacteria and the cell membrane of phagocytic cell. The main opsonins present in the serum and their corresponding receptors on the surface of phagocytic cells (PMNs or macrophages) are as under:

i) *IgG opsonin* is the Fc fragment of immunoglobulin G (IgG); it is the naturally-occurring antibody in the serum that coats the bacteria. Corresponding receptor on PMNs is Fc receptor for IgG called FcγRI.

ii) *C3b opsonin* is the breakdown product generated by activation of complement pathway. It is strongly chemotactic for attracting PMNs to bacteria. Corresponding receptor or C3b is complement receptor 1 and 3 (CR1 and 3).

iii) *Collectins* are carbohydrate-binding lectins in the plasma which bind to bacterial cell wall. Corresponding receptor for collectins is C1q.

2. ENGULFMENT The opsonized particle or microbe bound to the surface of phagocyte is ready to be engulfed. This is accomplished by formation of cytoplasmic pseudopods around the particle due to activation of actin filaments beneath cell wall, enveloping it in a phagocytic vacuole. Eventually, plasma membrane enclosing the particle breaks from the cell surface so that membrane-lined phagocytic vacuole or phagosome becomes internalized in the cell and lies free in the cell cytoplasm. The phagosome fuses with one or more lysosomes of the cell and form bigger vacuole called *phagolysosome*.

3. KILLING AND DEGRADATION The major function of phagocytes as scavenger cells is killing and degradation of microbe to dispose it off. The microorganisms after being killed by antibacterial substances are degraded by hydrolytic enzymes. However, this mechanism fails to kill and degrade certain bacteria such as tubercle bacilli.

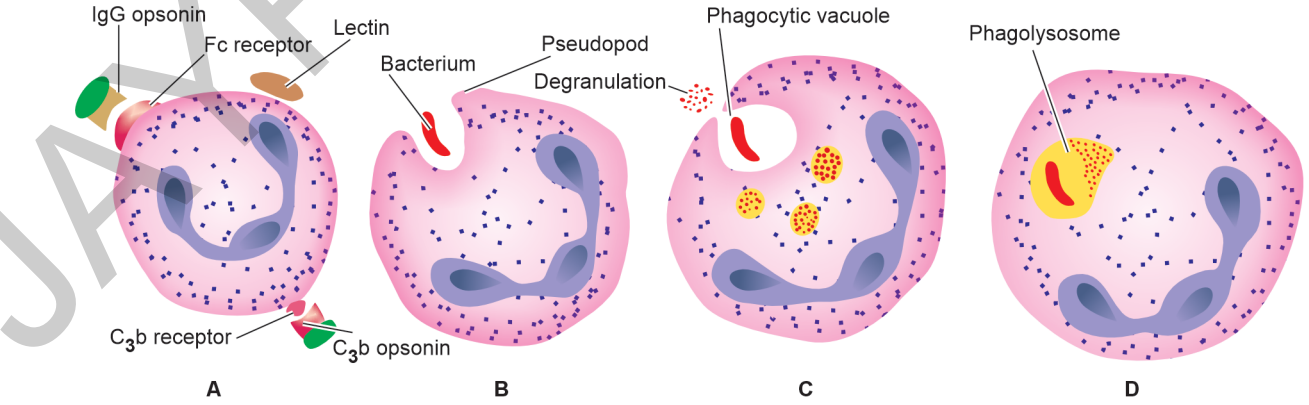


Figure L-4.5 Stages in phagocytosis of a foreign particle. A, Opsonization of the particle. B, Pseudopod engulfing the opsonized particle. C, Incorporation within the cell (phagocytic vacuole) and degranulation. D, Phagolysosome formation after fusion of lysosome of the cell.

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In general, following mechanisms are involved in disposal of microbes:

A. *Intracellular mechanisms*
i) Reactive oxygen species
a) Myeloperoxidase (MPO)-dependent
b) Myeloperoxidase (MPO)-independent
ii) Nitric oxide
iii) Lysosomal granules
B. *Extracellular mechanisms*
i) Activated leukocytes
ii) Neutrophil extracellular traps (NETs)
iii) Immune mechanisms

KEY POINTS **Acute Inflammatory Response**

- Inflammation is the local response of living mammalian tissues to injury from any agent which could be microbial, immunological, physical or chemical agents.
- Cardinal signs of inflammation are: redness, swelling, heat, pain and loss of function.
- Inflammation is of two types: 1) acute when it is due to early response by the body, is of short duration and has infiltration by neutrophils, and 2) chronic when it is for longer duration, occurs after a delay and is characterized by response by chronic inflammatory cells.
- Acute inflammatory response by the host to an etiologic agent is a continuous process consisting of vascular and cellular events.
- Vascular changes include hemodynamic changes and altered vascular permeability.
- Sequential hemodynamic changes in microvasculature are: initial transient vasoconstriction, followed by persistent progressive vasodilatation, raised local hydrostatic pressure and transudation in extracellular space. At the same time, there is slowing and margination of blood stream.
- Mechanisms of increased vascular permeability and subsequent inflammatory edema depend upon type and extent of cellular injury.
- 'Triple response' is demonstration of cardinal features of inflammation by firm stroking of the skin surface.
- Cellular phase of inflammation consists of exudation of leukocytes and phagocytosis.
- Leukocyte exudation begins from change of normal axial blood flow to slowing and stasis, followed by margination, pavementing, rolling, adhesion, and finally transmigration of leukocytes across the endothelial wall directed to chemoattractants.
- Phagocytosis is cellular eating. The process engulfment of foreign particulate material involves its initial recognition and opsonization. The mechanisms of phagocytosis are largely intracellular (by reactive oxygen species, nitric oxide, lysosomal granules) while there are a few extracellular mechanisms (activated leukocytes, NETs, immune).

CHEMICAL MEDIATORS OF INFLAMMATION

These are a large and increasing number of endogenous chemical substances which mediate the process of acute and chronic inflammation.

Mediators of inflammation have some common properties as under:

1) They are released *from the cells or derived from plasma proteins*:
- Cell-derived mediators are released either from their storage in the cell granules or are synthesized in the cells.
- Most common site of synthesis of plasma-derived mediators is the liver. After their release from the liver, these mediators require activation.

2) All mediators are *released in response to certain stimuli*. These stimuli may be a variety of injurious agents, dead and damaged tissues, or a mediator itself.

3) Mediators *act on different targets*. They may have similar action on different target cells or differ in their action on different target cells.

4) General *spectrum of actions* of various mediators is: increased vascular permeability, vasodilatation, chemotaxis, fever, pain and tissue damage.

5) Mediators have *short lifespan* after their release. After release, they are rapidly removed from the body by various mechanisms, e.g. by enzymatic inactivation, antioxidants, regulatory proteins, or they may even decay spontaneously.

There are two main groups of substances acting as chemical mediators of inflammation;

I. Those released from the cells, and
II. Those from the plasma proteins.

They have further members in both groups as under; their range of actions in acute inflammation is schematically illustrated in **Fig. L-4.6**.

I. CELL-DERIVED MEDIATORS

This group includes chemical substances which are either preformed or are newly synthesized in different cells of the body. On stimulation of the cell, they are released and act as potent mediators of inflammation. The group includes following examples:

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)

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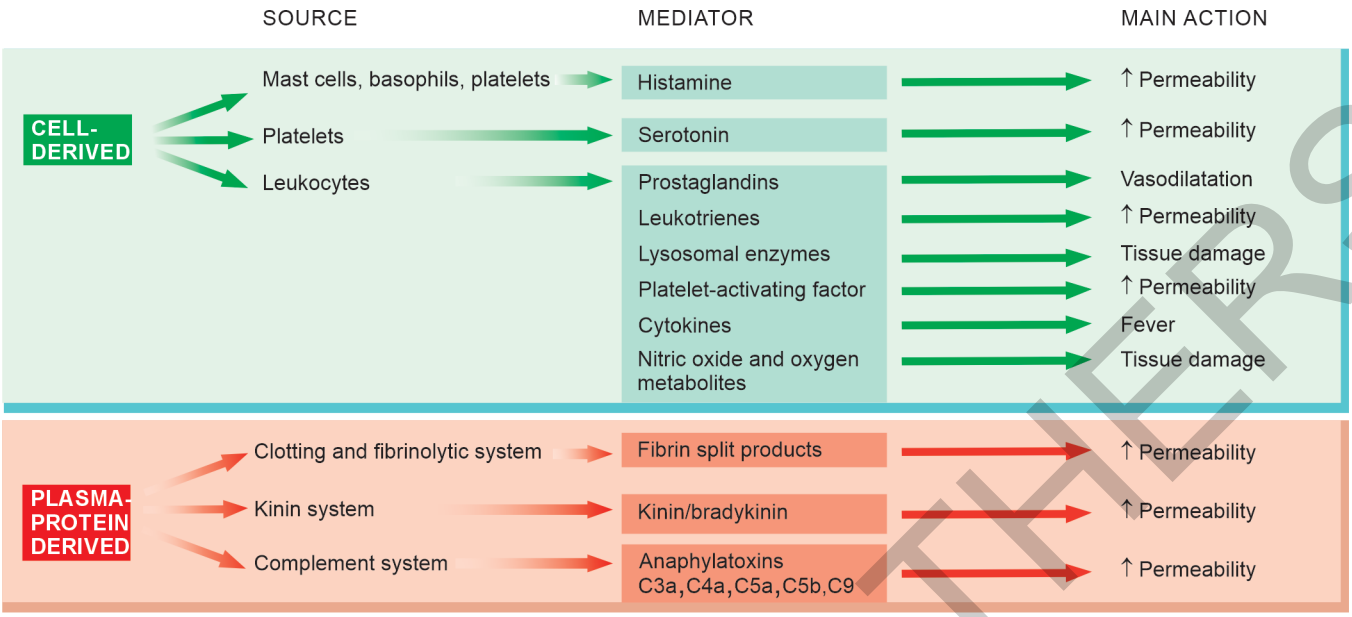


Figure L-4.6 Mediators of inflammation.

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-DERIVED MEDIATORS (PLASMA PROTEASES)

These include various products derived from activation and interaction of four interlinked systems:

1. Kinin system (kallikrein, bradykinin)
2. Clotting system (fibrin, fibrinopeptides)
3. Fibrinolytic system (plasmin)
4. Complement system (C3a, C3b, C5a, MAC)

Each of these systems has its inhibitors and accelerators in plasma with negative and positive feedback mechanisms respectively. *Hageman factor (factor XII) of clotting system plays a key role in interactions of the four systems.* Activation of factor XII *in vivo* by contact with basement membrane and bacterial endotoxins, and *in vitro* with glass or kaolin, leads to activation of clotting, fibrinolytic and kinin systems. In inflammation, activation of factor XII is brought about by contact of the factor leaking through the endothelial gaps. The end-products of the activated clotting, fibrinolytic and kinin systems activate the complement system that generates permeability factors. These permeability factors, in turn, further activate clotting system. Thus, these four pathways are interlinked as illustrated in **Fig. L-4.7**.

KEY POINTS — Chemical Mediators of Inflammation

- These are endogenous chemical substances which mediate the process of inflammation.
- They have some common properties: i) released either from the cells or are derived from plasma proteins, ii) released in response to certain stimuli, iii) act on different targets, iv) have a short lifespan after their release, and v) have several actions, most important being increased vascular permeability.
- Cell-derived mediators of inflammation are: vasoactive amines (histamine, 5-HT, neuropeptides), arachidonic acid metabolites (prostaglandins, 5-HETE, leukotrienes, lipoxins), platelet activating factor, cytokines (ILs, TNF, IFN, chemokines), and free radicals (reactive oxygen species and nitric oxide).
- Plasma protein derived mediators are products of: kinin (i.e. kallikrein, bradykinin), clotting (i.e. fibrin, fibrinopeptides), fibrinolytic (i.e. plasmin) and complement (i.e. C3a, C5a, C4a, C5a, MAC) system.

A FEW SELECTED EXAMPLES OF ACUTE INFLAMMATION

Inflammation of an organ is usually named by adding the suffix *-itis* to its Latin name, e.g. appendicitis, hepatitis, cholecystitis, meningitis etc. A few examples of acute inflammation are briefly described below.

APPENDICITIS

Acute inflammation of the appendix, acute appendicitis, is the most common acute abdominal condition confronting

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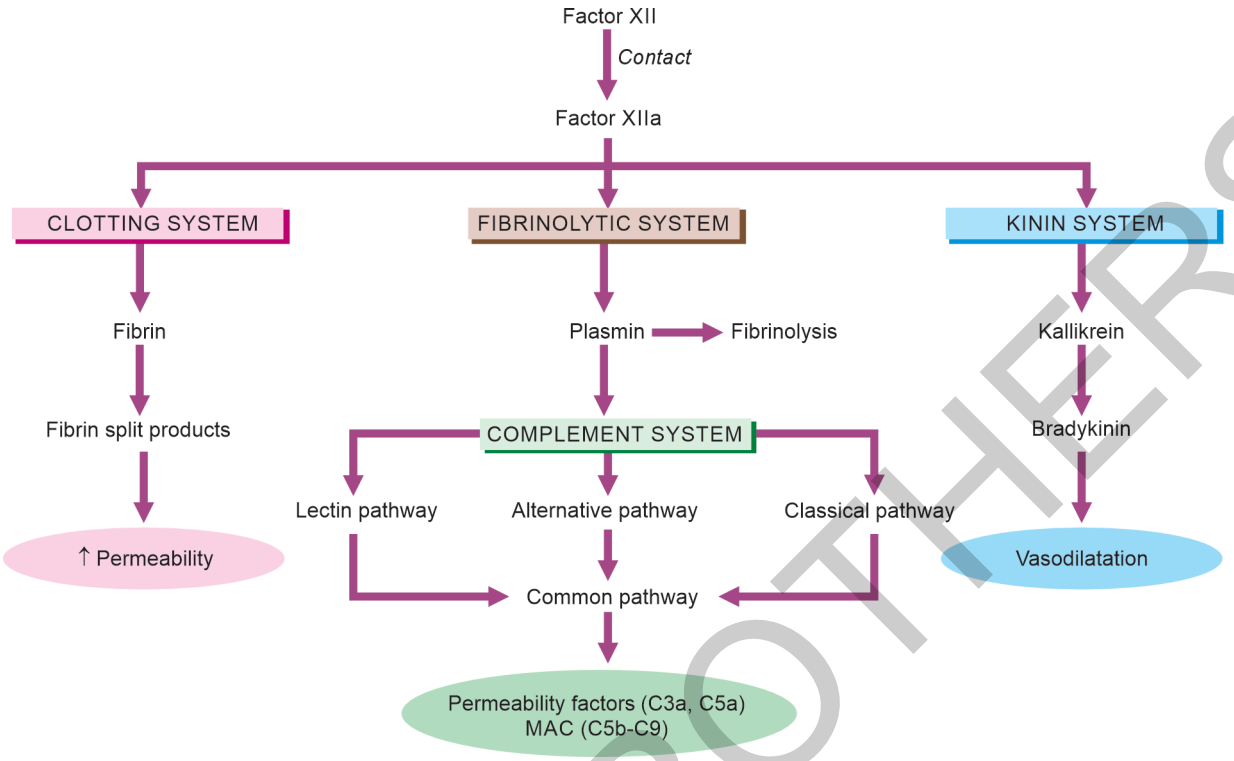


Figure L-4.7 Inter-relationship among clotting, fibrinolytic, kinin and complement systems. (MAC, membrane attack complex).

the surgeon. The condition is seen more commonly in older children and young adults, and is uncommon at the extremes of age. The disease is seen more frequently in the West and in affluent societies which may be due to variation in diet—a diet with low bulk or cellulose and high protein intake more often causes appendicitis.

ETIOPATHOGENESIS The most common mechanism is obstruction of the lumen from various etiologic factors that leads to increased intraluminal pressure. This presses upon the blood vessels to produce ischemic injury which in turn favors the bacterial proliferation and hence acute appendicitis. The common causes of appendicitis are as under:

A. *Obstructive:*
1. Fecolith
2. Foreign body
3. Tumor
4. Worms (especially *Enterobius vermicularis)*
5. Diffuse lymphoid hyperplasia, especially in children

B. *Non-obstructive:*
1. Hematogenous spread of generalized infection
2. Vascular occlusion

PATHOLOGY ***Grossly,*** in *early acute appendicitis,* the organ is swollen and serosa shows hyperemia. In well-developed acute inflammation called *acute suppurative appendicitis,* the serosa is coated with fibrinopurulent exudate and engorged vessels on the surface. In further advanced cases called *acute gangrenous appendicitis,* there is necrosis and ulcerations of mucosa which extend through the wall so that the appendix becomes soft and friable and the surface is coated with greenish-black gangrenous necrosis.

Microscopically, the most important diagnostic histological criterion is the *neutrophilic infiltration of the muscularis.* In early stage, besides acute inflammatory changes, other changes are congestion and edema of the appendiceal wall. In later stages, the mucosa is sloughed off, the wall becomes necrotic, the blood vessels may get thrombosed and there may be neutrophilic abscesses in the wall. In either case, an impacted foreign body, fecolith, or concretion may be seen in the lumen **(Fig. L-4.8)**.

Thus, there is good correlation between macroscopic and microscopic findings in acute appendicitis.

CLINICAL COURSE The patient presents with features of acute abdomen as under:

1. Colicky pain, initially around umbilicus but later localized to right iliac fossa
2. Nausea and vomiting
3. Pyrexia of mild grade
4. Abdominal tenderness
5. Increased pulse rate
6. Neutrophilic leukocytosis with toxic granules in neutrophils is most significant laboratory finding.

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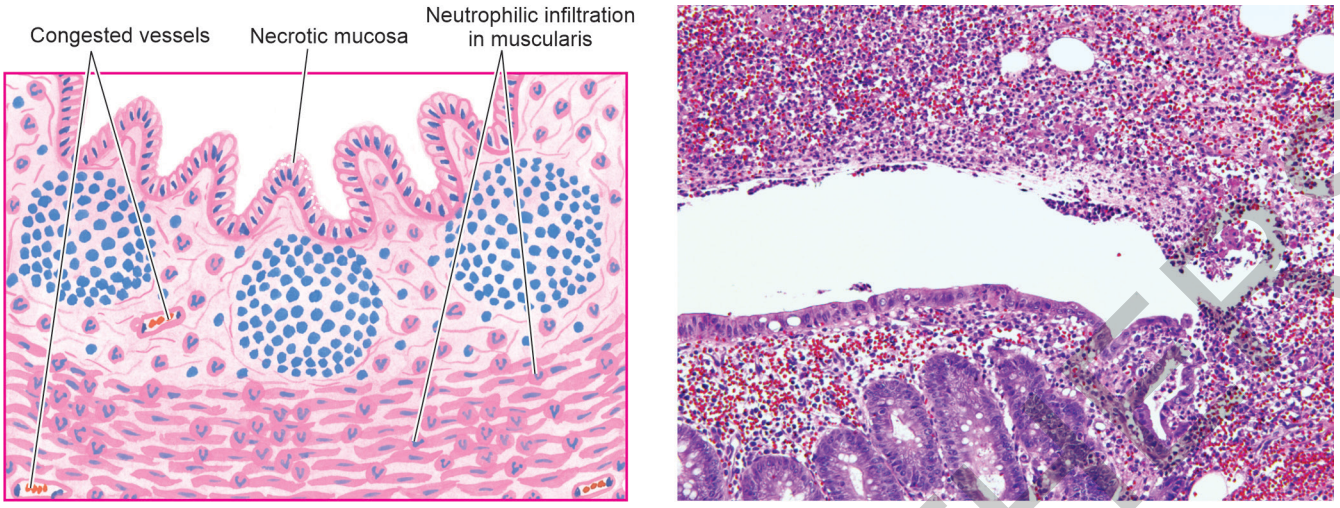


Figure L-4.8 Acute appendicitis. Microscopic appearance showing diagnostic neutrophilic infiltration into the muscularis. The mucosa is sloughed into the lumen. (Microimage courtesy of Dr Ivan Damjanov, Department of Pathology and Laboratory Medicine, The University of Kansas School of Medicine, Kansas, USA).

An attack of acute appendicitis predisposes the appendix to repeated attacks *(recurrent acute appendicitis)* and thus surgery has to be carried out. If appendicectomy is done at a later stage following acute attack *(interval appendicectomy),* pathological changes of healing by fibrosis of the wall and chronic inflammation are observed.

ULCER

Ulcers are local defects on the surface of an organ produced by inflammation. Some common sites for ulcerations are the stomach, duodenum, intestinal ulcers in typhoid fever, intestinal tuberculosis, bacillary and amoebic dysentery, ulcers of legs due to varicose veins etc. In the acute stage, there is infiltration by polymorphs with vasodilatation while long-standing ulcers develop infiltration by lymphocytes, plasma cells and macrophages with associated fibroblastic proliferation and scarring.

ABSCESS

When acute bacterial infection is accompanied by intense neutrophilic infiltrate in the inflamed tissue, it results in tissue necrosis. A cavity is formed which is called an abscess and contains purulent exudate or pus and the process of abscess formation is known as suppuration. The bacteria which cause suppuration are called pyogenic, e.g. *Staphylococcus aureus.*

Microscopically, pus is creamy or opaque in appearance and is composed of numerous dead as well as living neutrophils, some red cells, fragments of tissue debris and fibrin. In old pus, macrophages and cholesterol crystals are also present **(Fig. L-4.9)**.

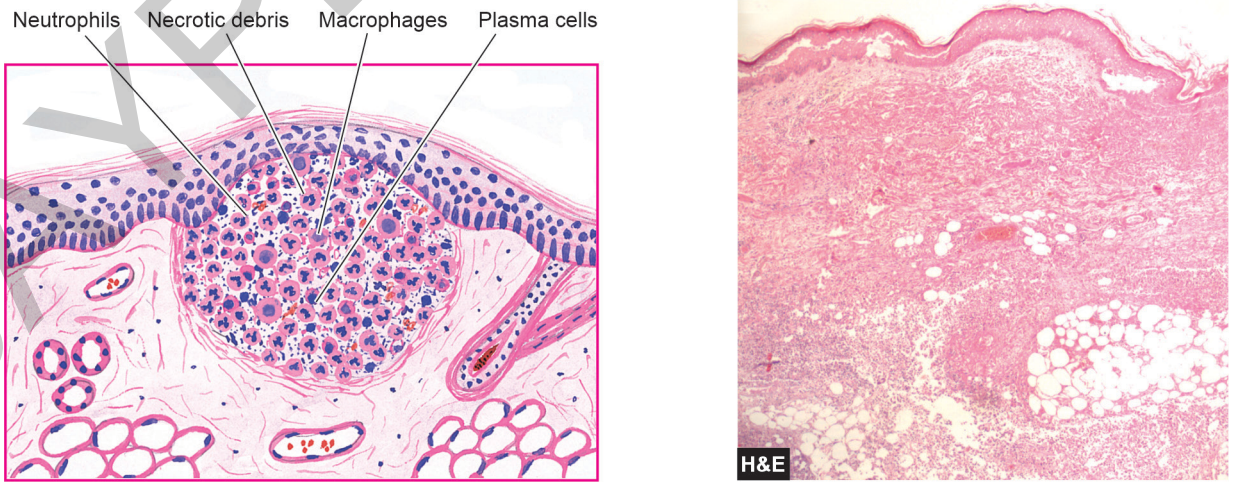


Figure L-4.9 An abscess in the skin. It contains pus composed of necrotic tissue, debris, fibrin, RBCs and dead and living neutrophils. Some macrophages are seen at the periphery.

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An abscess may be discharged to the surface due to increased pressure inside or may require drainage by the surgeon. Due to tissue destruction, resolution does not occur but instead healing by fibrous scarring takes place.

Some common examples of abscesses are as under:

i) *Boil or furuncle* which is an acute inflammation via hair follicles in the dermal tissues.

ii) *Carbuncle* is seen in untreated diabetics and occurs as a loculated abscess in the dermis and soft tissues of the neck.

iii) *Abscesses* in organs, e.g. abscess in the lung, liver, kidney, spleen, brain etc.

BACTERIAL INFECTIONS OF BLOOD

Bacteria after entering the blood may produce any of the following three patterns:

i) *Bacteremia*, i.e. presence of small number of bacteria in the blood which do not multiply significantly. These are not detected by direct microscopy but blood culture is done for their detection.

ii) *Septicemia*, i.e. presence of rapidly multiplying pathogenic bacteria in the blood. Septicemia is generally accompanied by systemic features of toxemia such as fever, leukocytosis and may progress to disseminated intravascular coagulation (DIC).

iii) *Pyemia*, i.e. dissemination of small septic thrombi through the blood which produce effects at the site of lodgment. These effects may be in the form of pyemic abscesses in the organs or septic infarcts.

SYSTEMIC FEATURES

Most forms of acute inflammation is accompanied by a few general systemic features such as fever, neutrophilic leukocytosis, raised acute phase reactant (APR) proteins, and lymphangitis-lymphadenitis of the region that drains the acutely inflamed tissue. Septic shock may occur in severe and fulminant cases.

KEY POINTS

A Few Selected Examples of Acute Inflammation

- Acute appendicitis is an acute abdomen associated with colicky pain and neutrophilic leukocytosis. Characteristically, there is neutrophilic infiltration in the muscularis propria.
- Other common morphologic patterns of acute inflammation are various forms of exudates, ulcers, abscesses (in the skin and various inner organs), cellulitis, and bacterial infection through blood (bacteremia, septicemia, pyemia).
- Most forms of acute inflammation is associated with a few general systemic features, e.g. fever, neutrophilic leukocytosis, raised acute phase reactant proteins, and regional lymphangitis-lymphadenitis.

LECTURE 5
CHRONIC INFLAMMATION—SALIENT FEATURES

INFLAMMATORY CELLS

The cells participating in acute and chronic inflammation are circulating leukocytes, plasma cells, tissue macrophages and inflammatory giant cells. Their morphology, characteristics and functions in inflammation are summarized in **Table L-5.1**.

POLYMORPHONUCLEAR NEUTROPHILS (PMN)

Commonly called as neutrophils or polymorphs, these cells along with basophils and eosinophils are together known as granulocytes due to the presence of granules in their cytoplasm. The diameter of neutrophils ranges from 10 to 15 μm and these cells are actively motile. PMNs comprise 40–75% of circulating leukocytes and their number is increased in blood (neutrophilia) and tissues in acute bacterial infections. These cells arise from hematopoietic stem cells in the bone marrow.

The functions of neutrophils in inflammation are as follows:

i) **Initial phagocytosis** of microorganisms as they form the first line of body defense in bacterial infection. The steps involved are adhesion of neutrophils to vascular endothelium, transmigration through the vessel wall, chemotaxis, engulfment, degranulation, killing and degradation of the foreign material.

ii) **Engulfment** of antigen-antibody complexes and non-microbial material.

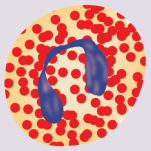
iii) **Harmful effects** of neutrophils are by causing basement membrane destruction of the glomeruli and small blood vessels in immunologic cell injury.

EOSINOPHILS

These are slightly larger than neutrophils but are fewer in number, comprising 1–6% of total blood leukocytes. Eosinophils share many structural and functional similarities with neutrophils such as their production in the bone marrow, locomotion, phagocytosis (weak), lobed nucleus and presence of granules in the cytoplasm

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TABLE L-5.1 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, alkaline phosphatase, 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	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) pathway ii) Release proteases (collagenase, elastase) iii) Activation of coagulation pathway iv) Prostaglandins, leukotrienes v) Chemoattractant for other leukocytes

(MPO, myeloperoxidase)

containing a variety of enzymes, of which major basic protein and eosinophil cationic protein are the most important which have bactericidal and toxic action against helminthic parasites.

The absolute number of eosinophils is increased due to inflammatory responses in the following conditions:

i) allergic conditions,
ii) parasitic infestations,
iii) skin diseases, and
iv) certain malignant lymphomas.

BASOPHILS AND MAST CELLS

The basophils comprise about 1% of circulating leukocytes while mast cells are their morphological and functional counterparts widely distributed in tissues. These cells contain coarse basophilic granules in the cytoplasm and a polymorphonuclear nucleus. These granules are laden with heparin and histamine.

The role of these cells in acute and chronic inflammation are:

i) in immediate and delayed type of hypersensitivity reactions, and
ii) release of histamine by IgE-sensitized basophils.

LYMPHOCYTES

Next to neutrophils, these cells are the most numerous of the circulating leukocytes in adults (20–45%). Apart from blood, lymphocytes are present in large numbers in the

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Harsh Mohan MD FAMS FICPath FUICC

A Gold Medallist in academics from Panjab University, Dr Mohan has served as founding Professor and former Head, Department of Pathology, Government Medical College and Hospital, Chandigarh, India, for about 22 years. An alumnus of Postgraduate Institute of Medical Sciences (PGIMS), Rohtak, Haryana, he initially served on the faculty of his alma mater in various capacities until 1993. Overall, he has experience in teaching and diagnostic pathology for over 45 years and has published more than 300 scientific articles in national and international indexed journals and has authored 8 books running successfully in multiple editions. He was the Editor-in-Chief of Indian Journal of Pathology and Microbiology (2003–7) and the President of Indian Association of Pathologists and Microbiologists (2008). Besides other awards and honors, he was conferred Haryana Vigyan Ratna award (2010–11) for the contribution to the medical science and education, and Lifetime Achievement Award conferred by National Medicos Organization in 2018. His keen interest in teaching, perfectionist attitude, and meticulous approach have won him love and adoration from his students and colleagues and are best reflected in his books.

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