

General pathology

Inflammation

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MSc pathology

- Q. Define inflammation

Inflammation is a complex reaction to injury that comprises 'vascular responses' and 'migration and activation of leukocytes'. It basically starts as the body's defence reaction, But may turn potentially harmful.

Q. What are the different stimuli for inflammation?

Stimuli for inflammation include

1. Physical agents: heat, radiation and mechanical trauma
2. Chemical agents: organic and inorganic poisons
3. Infectious agents: bacteria, viruses and parasites
4. Immunological agents: hypersensitivity reactions

Q. What are the cardinal signs of inflammation?

Cardinal signs of inflammation:

1. Rubor (redness)

2. Tumour (swelling)

3. Calor (heat)

4. Dolour (pain)

5. Functio laesa (loss of function)-added later by Virchow

Q. What are the different types of inflammation?

1. Acute: It is a transient process, which occurs within minutes of injury, lasts for hours or days and represents the early body reaction. It is usually followed by repair, a process by which tissue is restored to its original state as far as possible.

2. Chronic: It occurs when the causative agent of acute inflammation persists for a longtime. Fibrosis and tissue necrosis usually accompany chronic inflammation.

TABLE 2.1.

Comparison between acute and chronic inflammation

Feature	Acute	Chronic
Causative agents	Physical (heat, radiation and mechanical trauma) Chemical agents (organic and inorganic poisons) Infectious agents (bacteria, viruses and parasites) Immunological agents (hypersensitivity reactions)	Persistent acute inflammation due to nondegradable pathogens Persistent foreign bodies Autoimmune reactions
Major cells involved	Mainly neutrophils; also eosinophils and basophils	Mononuclear cells (monocytes, macrophages, lymphocytes, plasma cells) and fibroblasts
Primary mediators	Vasoactive amines, eicosanoids	Interferon gamma (IFN- γ) and other cytokines, growth factors, reactive oxygen species, and hydrolytic enzymes
Onset	Immediate/rapid	Insidious/delayed
Duration	Few days	Up to many months or years
Outcomes	Resolution, fibrosis and chronic inflammation	Tissue destruction and scarring
Cardinal signs and systemic manifestations	1. Pain (dolor) 2. Heat (calor) 3. Redness (rubor) 4. Swelling (tumor) 5. Loss of function (functio laesa)	Absence of any cardinal signs Patient is asymptomatic or presents with low-grade fever, lethargy, loss of appetite and weight loss Patient may also present with high-grade fever
Oedema	Present	Absent
Angiogenesis	Absent	Present
Tissue destruction	Absent	Present
Attempts at repair	Absent	Present
Fibrosis	Absent	Present

Q. What are the major components of acute inflammation?

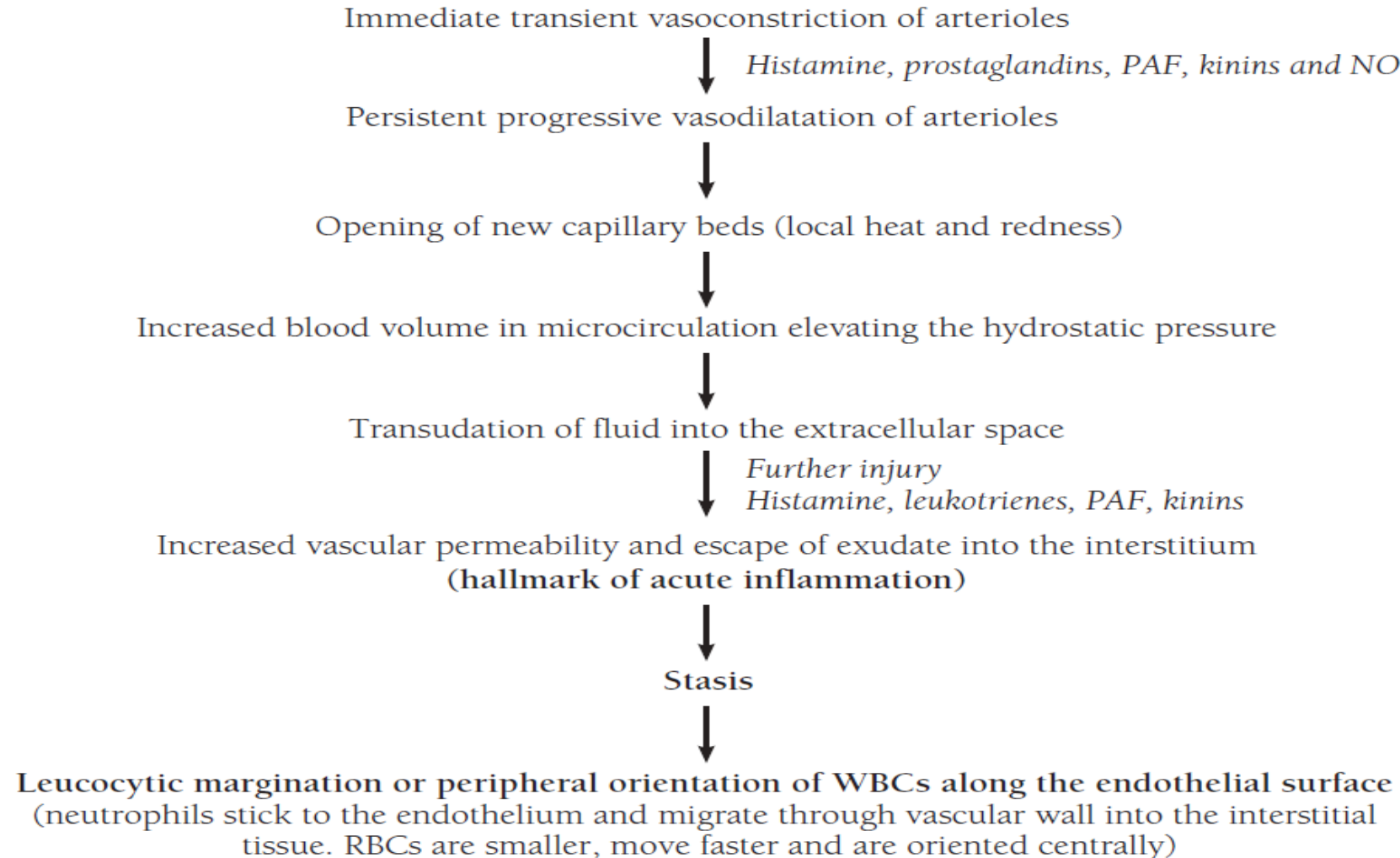
There are two major components of acute inflammation:

1. Vascular events

- (a) Alterations in vascular calibre that lead to an increase in blood flow
- (b) Structural changes in microvasculature, which permit plasma proteins and leukocytes to leave the circulation

2. Cellular events: Immigration of leukocytes from microcirculation and their accumulation in the focus of injury

Vascular events in acute inflammation occur in the sequence shown in Flowchart



FLOWCHART 2.1. Vascular events in acute inflammation.

Write briefly on the cellular events involved in acute inflammation

The two main cellular events involved in acute inflammation are

1. Extravasation of leukocytes (movement from vessel lumen to interstitial space)

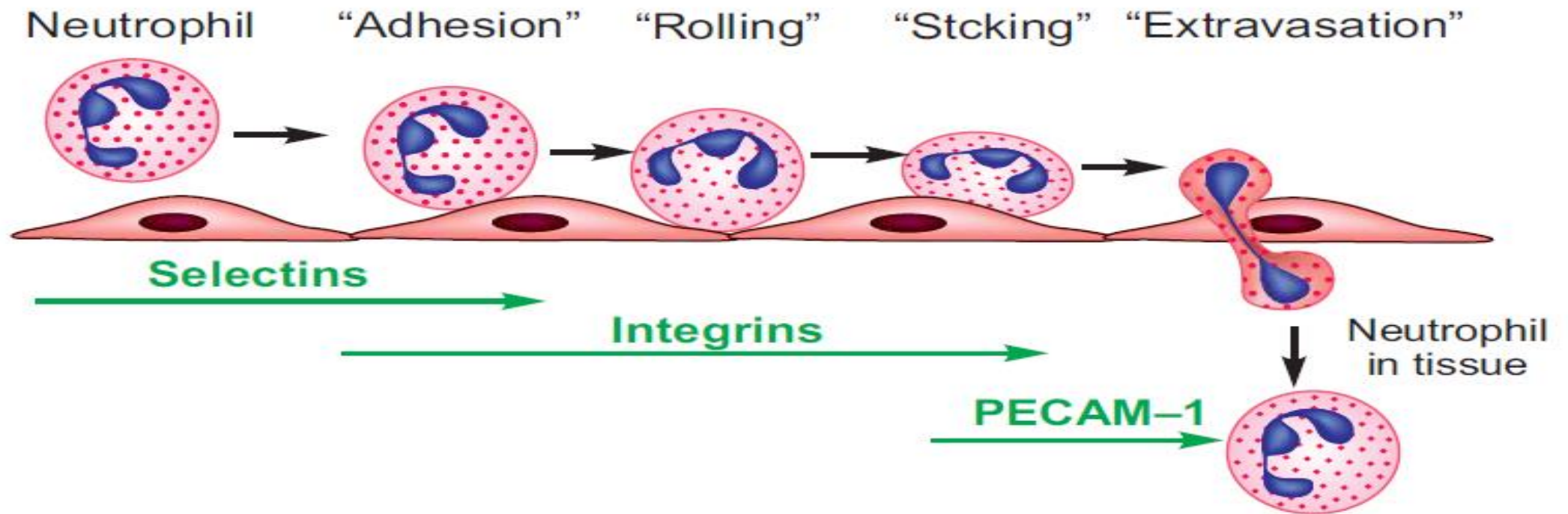


FIGURE 2.2. Mechanism of extravasation of leukocytes.

2. Phagocytosis (leukocytic engulfment of microbes, foreign particles, and cellular debris).

Extravasation of leukocytes has the following steps:

- (a) In the lumen: margination (peripheral orientation of leukocytes), rolling (weak attachment of leukocytes to endothelium, detachment and binding again, causing a rolling movement), pavementing or adhesion (activation of leukocytes and firm binding of leukocytes to endothelium)
- (b) Transmigration across the endothelium (emigration or diapedesis): emigration is facilitated by focal dissolution of the exposed basement membrane by leukocytederived collagenase
- (c) Migration in interstitial tissue towards a chemotactic stimulus (chemotaxis)

Q. Write briefly on chemotaxis

Chemotaxis is defined as a locomotion oriented along a chemical gradient. All granulocytes, monocytes and to some extent lymphocytes exhibit directed movement to the area of injury, which is facilitated by chemotactic agents (chemoattractants).

Chemoattractants

1. Exogenous—bacterial products
2. Endogenous—C5a, leukotrienes and cytokines

Q. Write briefly on phagocytosis

Phagocytosis is defined as leukocytic engulfment of microorganisms, foreign particles and cellular debris. The two most important phagocytic cells are:

1. Polymorphs

2. Circulating monocytes or macrophages

Steps in Phagocytosis (Fig. 2.4)

1. Recognition and attachment

(a) Typically, phagocytosis is initiated by recognition of the microorganisms and particles by receptors expressed on the leukocyte surface.

(b) Mannose receptors and scavenger receptors are two important receptors that function to bind and ingest microbes. Mannose/fucose residues are typically a part of the microbial cell wall; where as, mammalian cells instead contain sialic acid and N-acetylgalactosamine residues. Mannose receptors, therefore, recognize only the microbe and not the host cell. Macrophage scavenger receptors bind a lot of microbes.

- (c) The efficiency of phagocytosis is greatly enhanced by opsonization of bacteria (or foreign material).
- (d) The process of coating of a particle, such as a microbe, to target it for phagocytosis is called opsonization and the substances that do this are called opsonins. Phagocytes express high-affinity receptors for opsonins.
- (e) Major opsonins are 'IgG antibodies', 'C3b breakdown products of complement' and plasma carbohydrate-binding lectins called 'collectins', which bind to the microbial cell wall sugar groups.
- (f) Leukocytes express receptors for opsonins that facilitate phagocytosis of the coated microbes, eg, Fc receptor for IgG (FcγRI), complement receptors 1 and 3 (CR1 and 3) for complement fragments and C1q for the collectins.

2. Engulfment

- (a) Bacteria are engulfed by pseudopodia (extensions of cytoplasm) and trapped within phagosomes forming a phagocytic vacuole.
- (b) The limiting membrane of the phagocytic vacuole fuses with the limiting membrane of the lysosomal granule, resulting in discharge of the contents of the granule into the phagolysosome.

3. Killing and degradation

- (a) Neutrophils and monocytes are armed with both 'oxygen-dependent' (MPO system and O₂-derived free radicals) as well as 'oxygen-independent' (lysosomal enzymes and reactive nitrogen species, mainly derived from nitric oxide) mechanisms for killing bacteria.

(b) The oxygen-dependent MPO system is the most potent bactericidal mechanism available to neutrophils and monocytes.

Other constituents of leukocyte granules which are also capable of killing microorganisms include

- **Bactericidal/permeability-increasing** (causes phospholipase activation and degradation of phospholipids)
- **Lysozymes** (causes degradation of bacterial coat oligosaccharides)
- **Major basic protein** (important eosinophilic granule constituent, which is toxic to parasites)
- **Defensins** (peptides that kill microbes by creating holes in their membranes)
- **Neutrophil extracellular traps or NETs** (Extracellular fibrillary networks consisting a viscous meshwork of nuclear chromatin of neutrophils that trap the microbe at the site of infection by fibrils and prevent their spread)

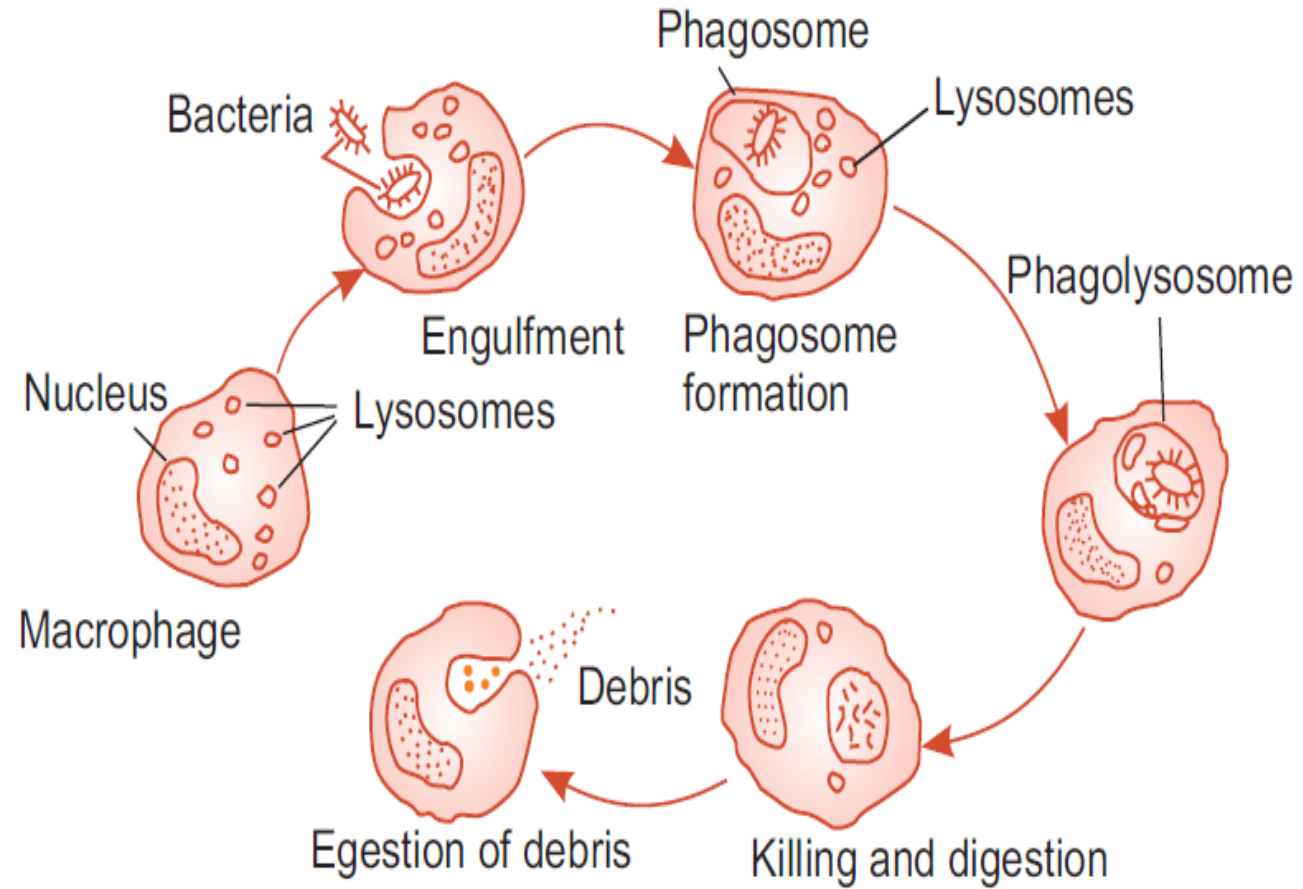


FIGURE 2.4. Mechanism of phagocytosis.

Enumerate the defects in leukocyte functions.

Defects in leukocyte functions may be:

1. Genetic

- (a) Chediak–Higashi syndrome: disorder of lysosomal granules; prevents fusion of lysosomes with phagosomes to form phagolysosomes
- (b) Chronic granulomatous disease of childhood: X-linked/autosomal recessive disease characterized by absence of NADPH oxidase
- (c) Myeloperoxidase deficiency: absent MPO–H₂O₂ system

2. Acquired

- (a) Defective chemotaxis: thermal injury, diabetes, malignancy, sepsis and immunodeficiencies
- (b) Defective adhesion: haemodialysis and diabetes
- (c) Defective phagocytosis and microbicidal activity: leukaemia, anaemia, sepsis, diabetes, neonates and malnutrition

1. Cell derived

Sources	Mediator	Action
Mast cells, basophils and platelets	Histamine ^a	Vasodilatation, increased permeability, endothelial activation, itching and pain
Platelets and entero-chromaffin cells	Serotonin ^a	Actions like histamine but less potent
Neutrophils and macrophages	Lysosomal enzymes ^a	Tissue damage
All leukocytes and endothelial cells	Platelet-activating factor ^b	Increased vascular permeability
All leukocytes	Leukotrienes ^b (slow reacting substances of anaphylaxis)	LTC₄, LTD₄ and LTE₄ • Increased permeability of vessels • Smooth muscle contraction • Vasoconstriction • Bronchoconstriction LTB₄ • Chemotaxis • Cell adherence PGD₂ and PGE₂ • Vasodilatation • Bronchodilatation • Increased permeability of vessels PGF₂α • Vasodilatation • Bronchoconstriction TXA₂ • Vasoconstriction • Bronchoconstriction • Platelet aggregation PGI₂ • Vasodilatation • Bronchodilatation • Inhibition of platelet aggregation
All leukocytes, platelets and endothelial cells	Prostaglandins ^b	IL8 chemotactic for neutrophils, PF4 chemotactic for neutrophils, monocytes and eosinophils, MCP-1 chemotactic for monocytes and eotaxin chemotactic for eosinophils)
Lymphocytes, macrophages and endothelial cells	Cytokines ^b	Increased leukocyte adherence, thrombosis, fibroblastic proliferation and acute phase reaction
Macrophages	Nitric oxide ^b	Vasodilatation, antiplatelet effect and microbicidal action
Neutrophils and macrophages	Oxygen-derived free radicals	Endothelial damage and increased vascular permeability

chemical mediators
of inflammation

2. Plasma derived

Sources	Mediator	Action
Clotting and fibrinolytic system	Fibrin split products	Increased vascular permeability
Kinin system	Kinin/bradykinin	Increased vascular permeability
Complement system	Anaphylatoxins, C3a, C4a and C5a	Increased vascular permeability

What are cytokines? Describe their role in inflammation.

Cytokines are messenger proteins secreted by some cell types (activated lymphocytes, macrophages, endothelial, epithelial and connective tissue cells) which modulate the function of other cell types.

- TNF and IL-1 are the prototypes.
- TNF mediates the effects of septic shock (causes hypotension, decrease vascular resistance, increase heart rate and decrease blood pH).

It was earlier classified into TNF- α and - β .

Presently, TNF- α is actually considered TNF; TNF- β is thought to be a lymphotoxin (produced by activated T lymphocytes).

Secretion of TNF and IL1 is induced by:

- Bacterial products
- Immune complexes
- Toxins
- Cytokines
- Physical injury

homework

- Write briefly on chemokines
- Write briefly on complement system

Enumerate the factors determining variation in inflammatory response of different individuals

Factors determining variation in individual inflammatory responses are as follows:

1. Factors involving the organism:

- (a) Type of injury
- (b) Virulence and dosage of infective organism
- (c) Portal of entry

2. Factors involving the host:

- (a) General health of host; starvation, chronic debilitating diseases like diabetes mellitus and alcoholism render the host more susceptible to infections
- (b) Immune status of host
- (c) Neutropenia
- (d) Site or type of tissue involved
- (e) Local host factors—ischæmia, presence of foreign bodies, necrosis, etc.

What are the systemic effects of inflammation?

Systemic changes associated with inflammation are collectively called acute phase response or systemic inflammatory response syndrome (SIRS)

Bacterial products (lipopolysaccharides or LPS)



Release of cytokines



SIRS

FLOWCHART 2.11. Systemic inflammatory response syndrome.

Manifestations of SIRS include

1. **Fever:** The mechanism underlying development of fever is depicted in [Flowchart 2.12](#).

Bacterial products (exogenous pyrogens) act on leukocytes to release
cytokines IL-1 and TNF (endogenous pyrogens)



Increased cyclooxygenase



Increased conversion of arachidonic acid to prostaglandins



Prostaglandin E stimulates production of neurotransmitters
(eg, cyclic AMP) in hypothalamus



Resetting of the temperature at a higher level

FLOWCHART 2.12. Mechanism of development of fever in SIRS.

2. Release of acute phase proteins: Acute phase proteins/reactants, eg, C reactive protein (CRP), fibrinogen and serum amyloid A (SAA) protein, are mostly synthesized in the liver. They bind to the cell wall (act as opsonins) and complement, and their synthesis is regulated by cytokines IL-1, IL-6 and TNF.

3. Leukocytosis: Accelerated release of cells from the bone marrow post-mitotic reserve pool with a shift to left (due to IL-1 and TNF) is common in inflammation and this may result in counts as high as 40,000–100,000 cells/ μ L (leukaemoid reaction).

4. Other manifestations: Increased pulse and blood pressure, decreased sweating, rigours, chills, anorexia, somnolence and malaise

Enumerate and describe the various morphological patterns of acute inflammation?

1-Serous inflammation: It is characterized by collection of a watery, protein-poor fluid; derived from either the plasma or secretions of mesothelial cells (lining peritoneal, pleural and pericardial cavities). It is usually associated with burns, viral infections, etc.

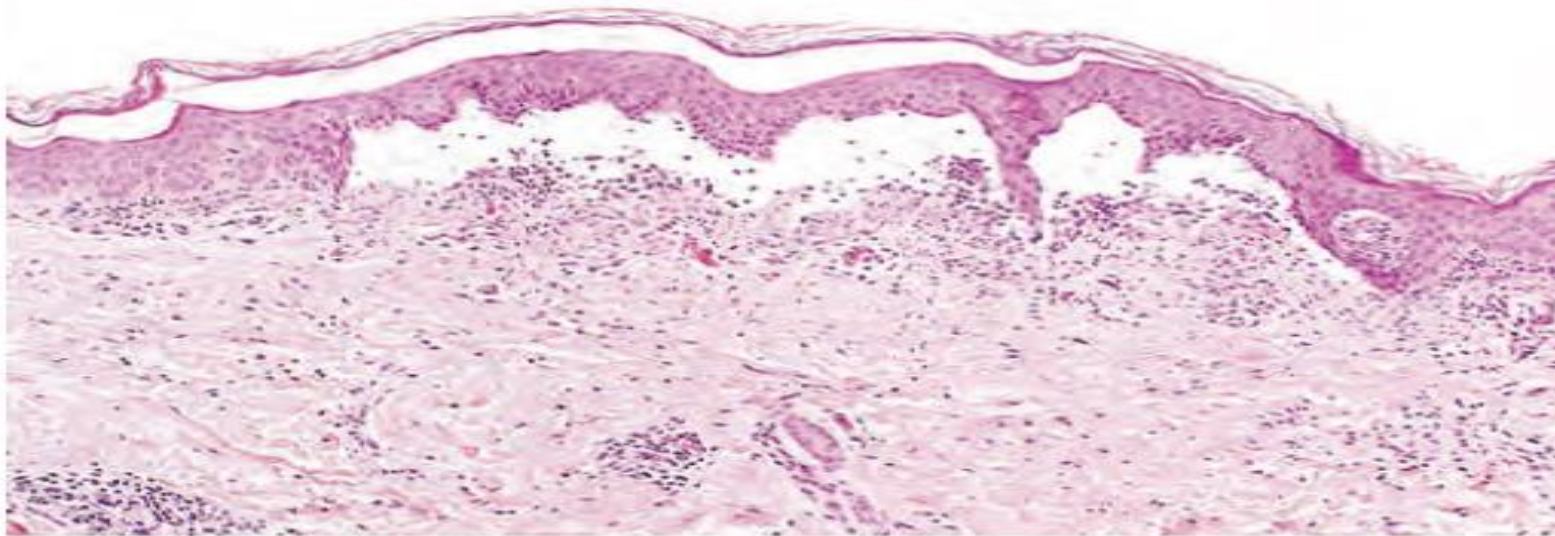
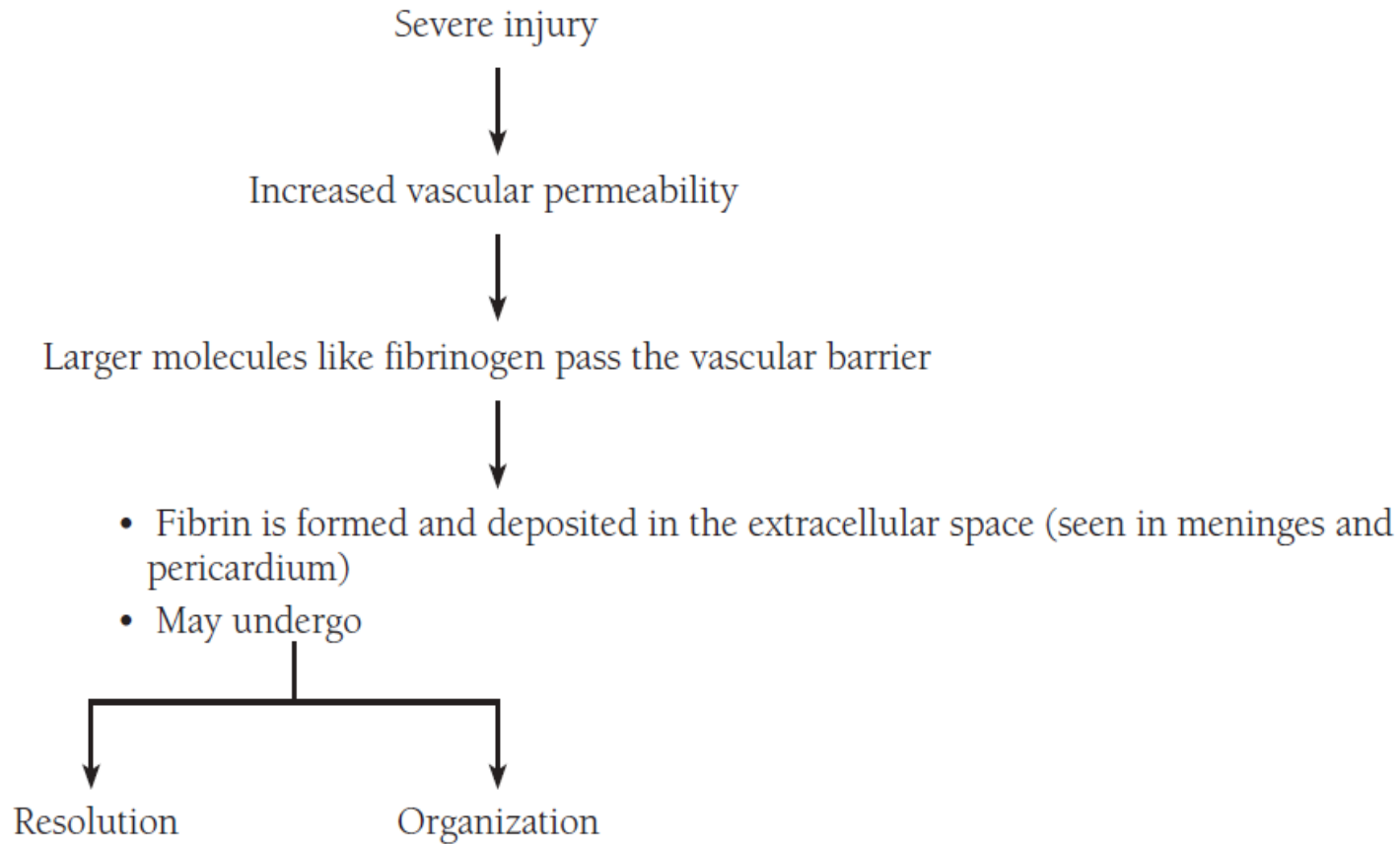


Figure 3.13 Serous inflammation. Low-power view of a cross section of a skin blister showing the epidermis separated from the dermis by a focal collection of serous effusion.

2. Fibrinous inflammation (Flowchart 2.13): Examples of fibrinous inflammation include 'bread and butter' pericarditis seen in acute rheumatic fever and fibrinous pleuritis.



FLOWCHART 2.13. Pathogenesis and outcomes of fibrinous inflammation.

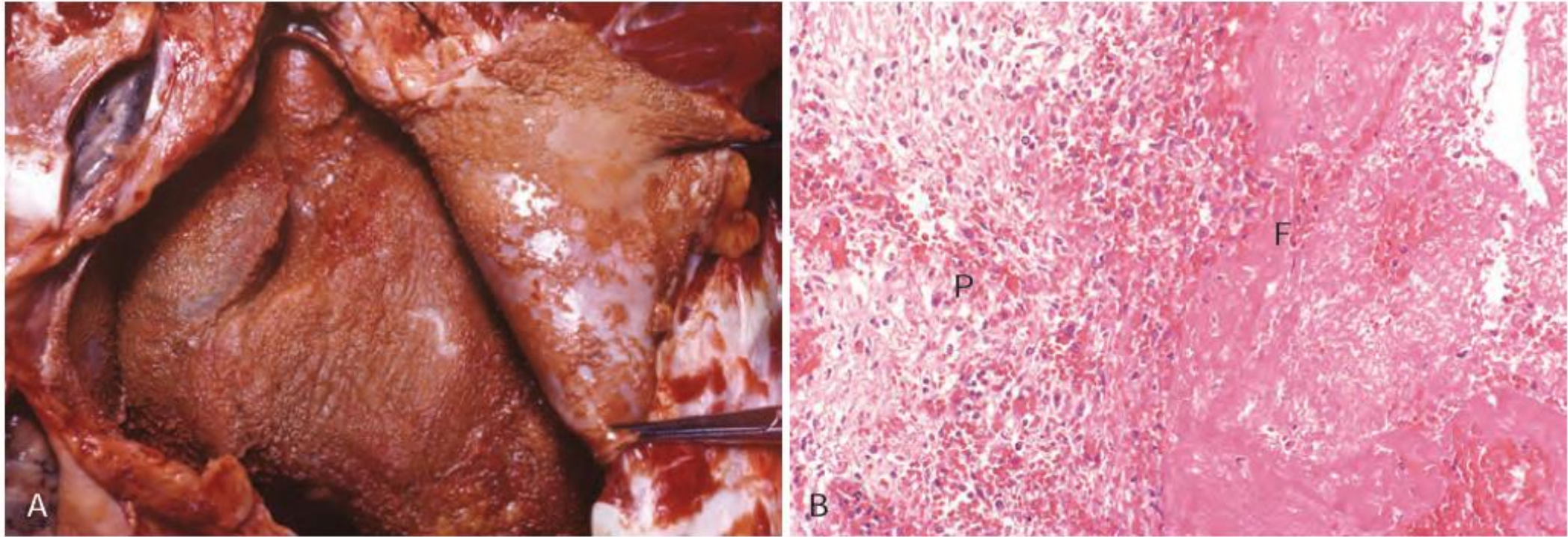


Figure 3.14 Fibrinous pericarditis. (A) Deposits of fibrin on the pericardium. (B) A pink meshwork of fibrin exudate (*F*) overlies the pericardial surface (*P*).

3. Suppurative inflammation:

- It is characterized by production of large amount of pus or purulent exudates comprising neutrophils, necrotic cells and oedema fluid. The pus may collect locally to form an abscess (abscesses, typically have a large central necrotic cavity rimmed by a layer of preserved neutrophils and may be surrounded by a zone of dilated vessels and proliferating fibroblasts).
- Occurs secondary to infections with pyogenic (pus-producing organisms), eg, staphylococci

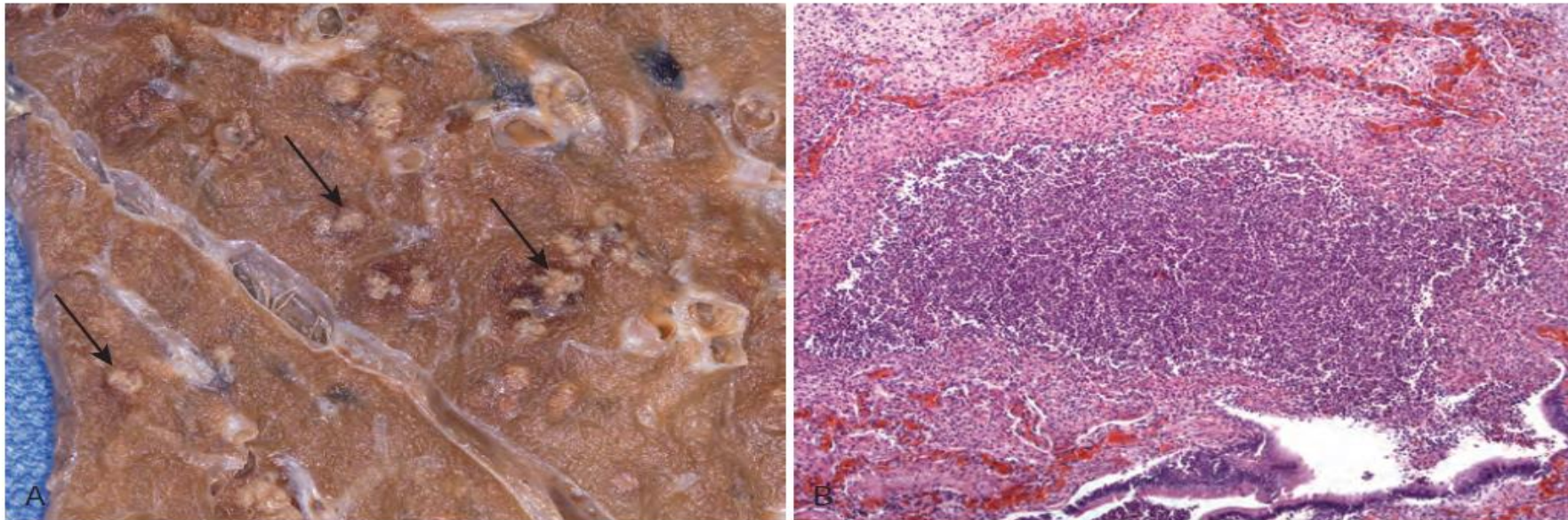


Figure 3.15 Purulent inflammation. (A) Multiple bacterial abscesses (arrows) in the lung in a case of bronchopneumonia. (B) The abscess contains neutrophils and cellular debris and is surrounded by congested blood vessels.

4. Catarrhal inflammation: Also called phlegmonous inflammation, it is characterized by acute inflammation of the mucous membranes resulting in excessive mucous production(eg, running nose).

5. Membranous inflammation: This type of inflammation involves formation of a membrane over the epithelial surfaces. The membrane is constituted by fibrin, desquamated epithelial and inflammatory cells, eg, membrane formation is pharyngitis associated with *Corynebacterium diphtheriae*.

Q. Define cellulitis.

Cellulitis is caused by thin, watery exudate that spreads throughout subcutaneous tissue.

Q. Define an ulcer.

An ulcer is a local defect, or excavation on the surface of an organ or tissue that results due to sloughing of inflammatory necrotic material. During the acute stage, there is intense polymorphonuclear infiltration and vascular dilatation. With chronicity, the base and margins of the ulcer develop fibroblastic proliferation, scarring and infiltration by chronic inflammatory cells

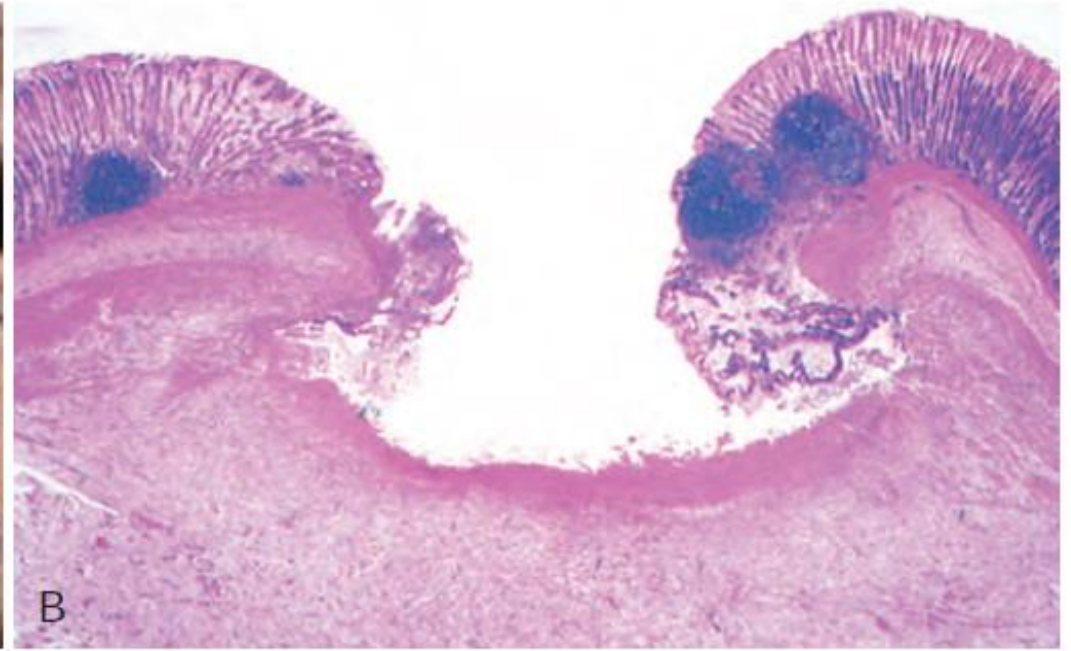
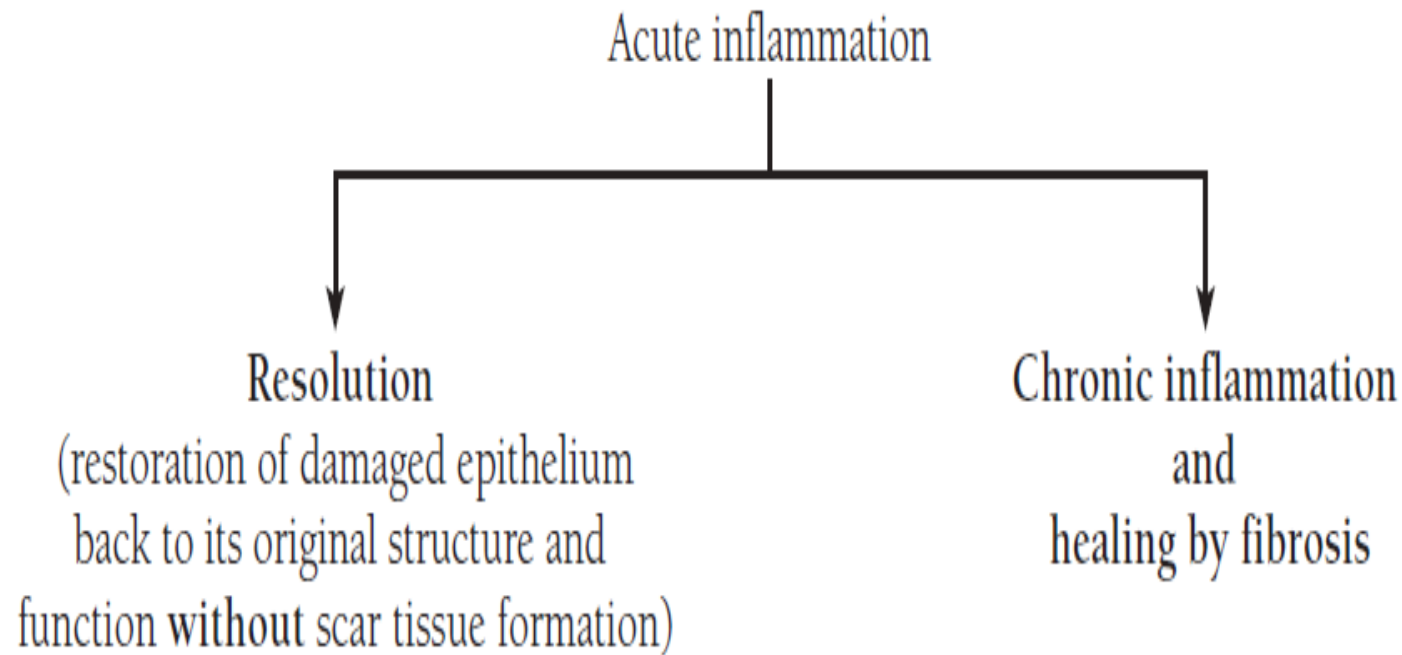


Figure 3.16 The morphology of an ulcer. (A) A chronic duodenal ulcer. (B) Low-power cross-section view of a duodenal ulcer crater with an acute inflammatory exudate in the base.

Q. What are the possible outcomes of acute inflammation?

Ans. Possible outcomes of acute inflammation are given in Flowchart 2.14.



FLOWCHART 2.14. Outcomes of acute inflammation.

Q. Define chronic inflammation.

Inflammation of prolonged duration (lasting weeks or months) is labelled chronic inflammation. It is characterized by three simultaneously ongoing components:

1. Active inflammation

2. Tissue destruction

3. Attempts at repair

Typically, chronic inflammation is low grade and associated with an asymptomatic clinical response.

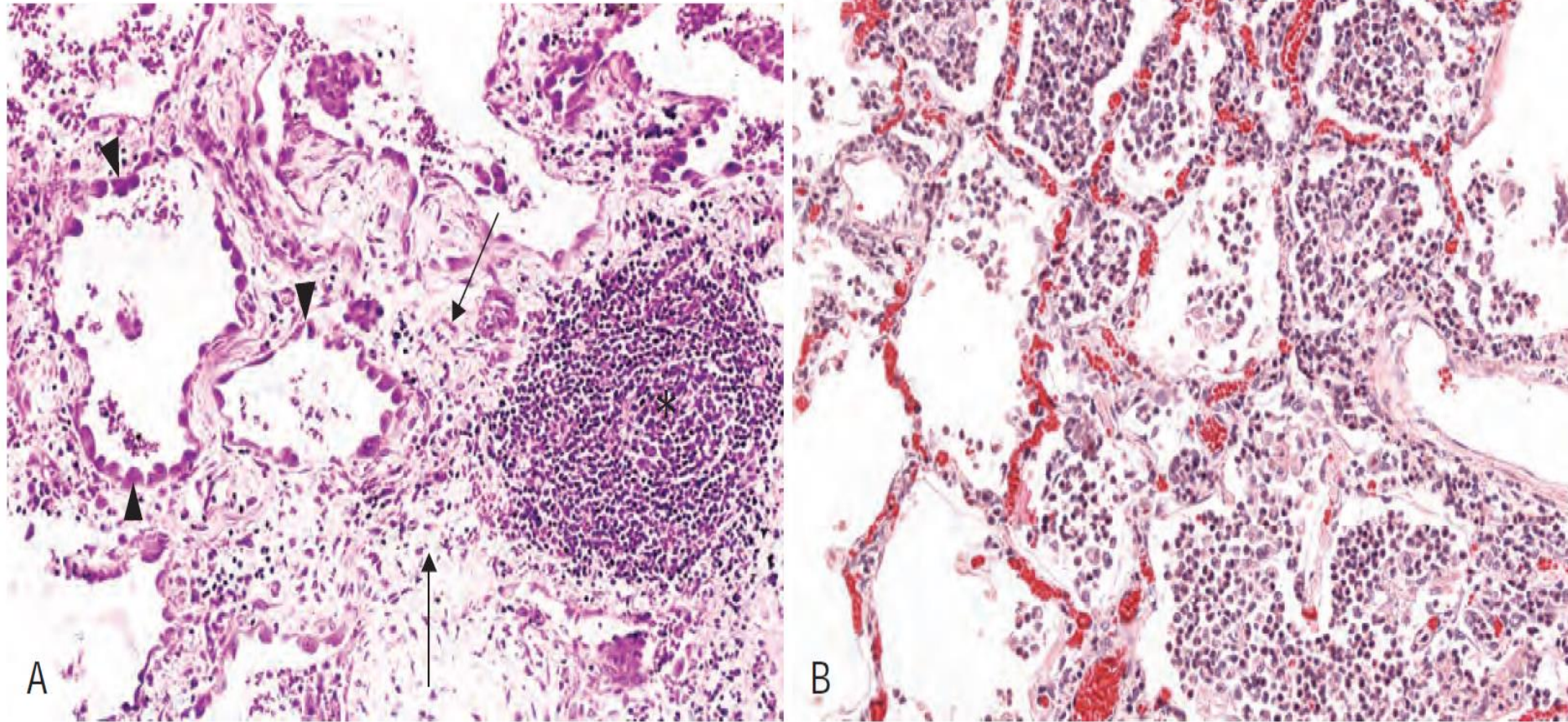


Figure 3.18 (A) Chronic inflammation in the lung, showing all three characteristic histologic features: (1) collection of chronic inflammatory cells (*asterisk*), (2) destruction of parenchyma (normal alveoli are replaced by spaces lined by cuboidal epithelium) (*arrowheads*), and (3) replacement by connective tissue (fibrosis) (*arrows*). (B) In contrast, in acute inflammation of the lung (acute bronchopneumonia), neutrophils fill the alveolar spaces, and blood vessels are congested.

Q. Enumerate the causes of chronic inflammation and write briefly on its morphology.

Causes

1. Persistent infections, such as tuberculosis, syphilis, infections due to certain viruses, fungi and parasites. Typically, these organisms

(a) Are of low toxicity.

(b) Evoke an immune response called delayed hypersensitivity.

(c) Are characterized by a specific inflammatory response called a granulomatous reaction.

2. Prolonged exposure to potentially toxic agents:

Exogenous—Silica cause Silicosis

Endogenous—Toxic lipid components cause Atherosclerosis

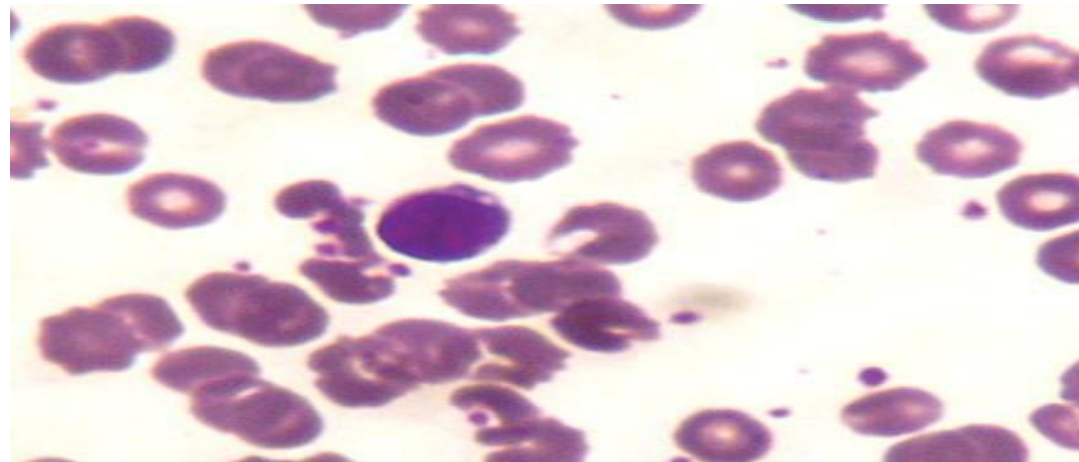
3. Autoimmunity: Immune reaction against one's own antigens can result in chronic tissue damage.

Morphologic Features of Chronic Inflammation

1. Infiltration by mononuclear cells (lymphocytes, macrophages and plasma cells)
2. Tissue destruction due to persistent offending agent/inflammation
3. Healing by connective tissue replacement of damaged tissue includes proliferation of blood vessels (angiogenesis and fibrosis)

Cells Involved in Chronic Inflammation

1. Lymphocytes are mobilized in antibody-mediated, cell-mediated as well as nonimmune inflammation (both T and B lymphocytes are involved)



2. Macrophages bring about phagocytosis, initiate tissue repair, secrete mediators of inflammation and influence lymphocyte function



3. Eosinophil

- Recruitment and extravasation from blood driven by adhesion molecules like neutrophils and by eotaxin (chemokine derived from leukocytes and epithelial cells which is specific for eosinophils)
- Involved in IgE-mediated immune reactions and parasitic infections
- Major basic protein is a highly toxic protein contained in eosinophil granules. It is toxic to parasites and mammalian epithelial cells

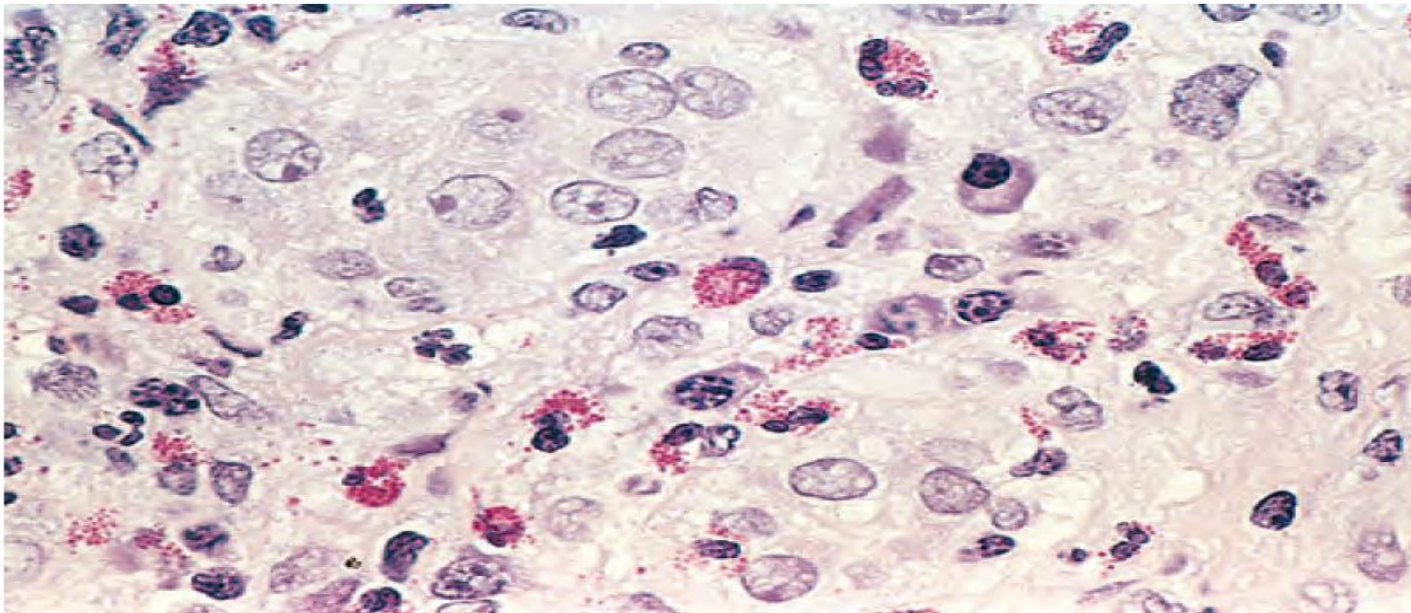
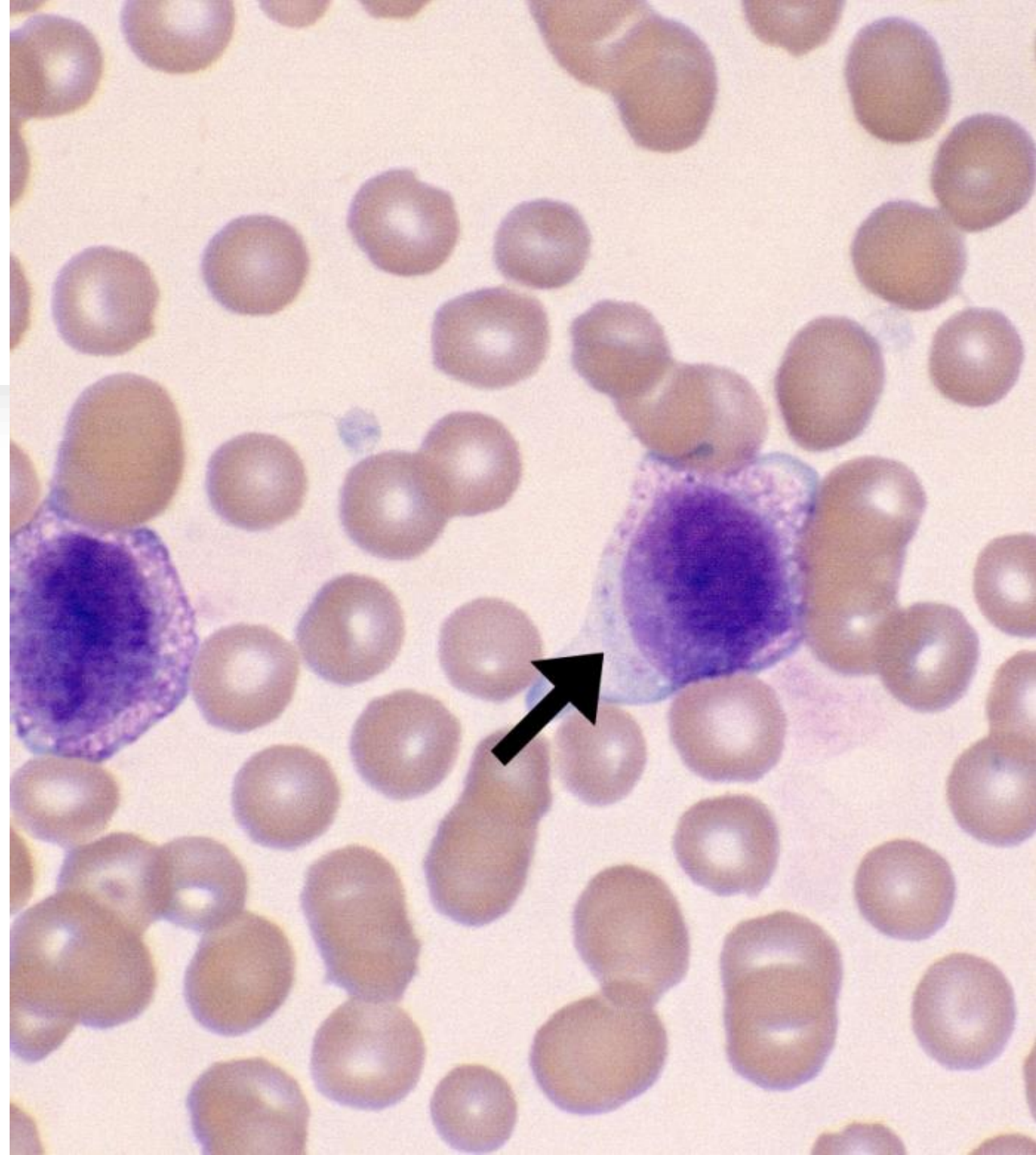


Figure 3.22 Focus of inflammation containing numerous eosinophils.

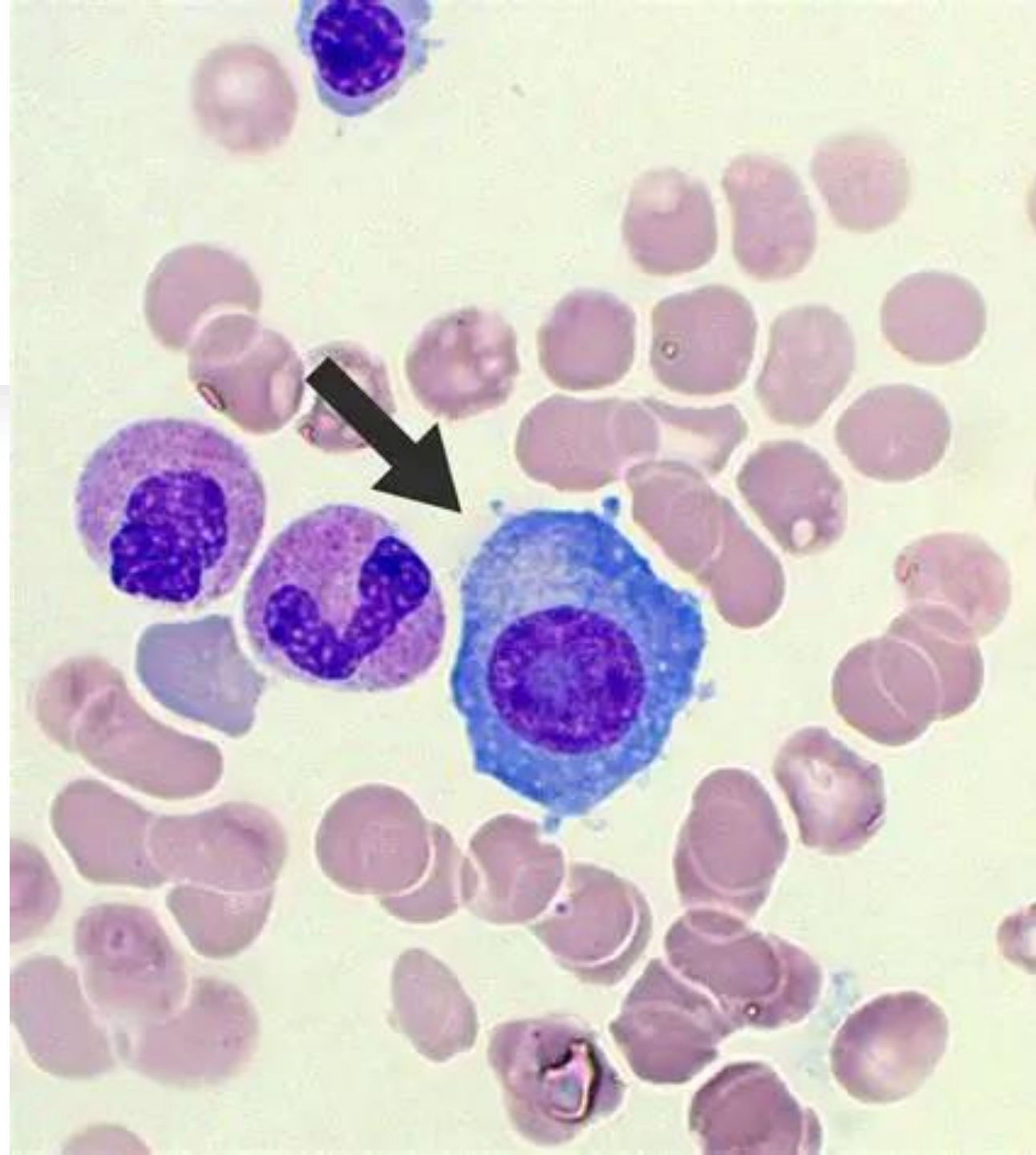
4. Mast cells

- Widely present in connective tissue.
- Participate in both acute and chronic inflammatory cells.
- Express on their surface the receptor that binds to the Fc portion of IgE antibody to degranulate mast cells and release mediators (histamines and prostaglandins).



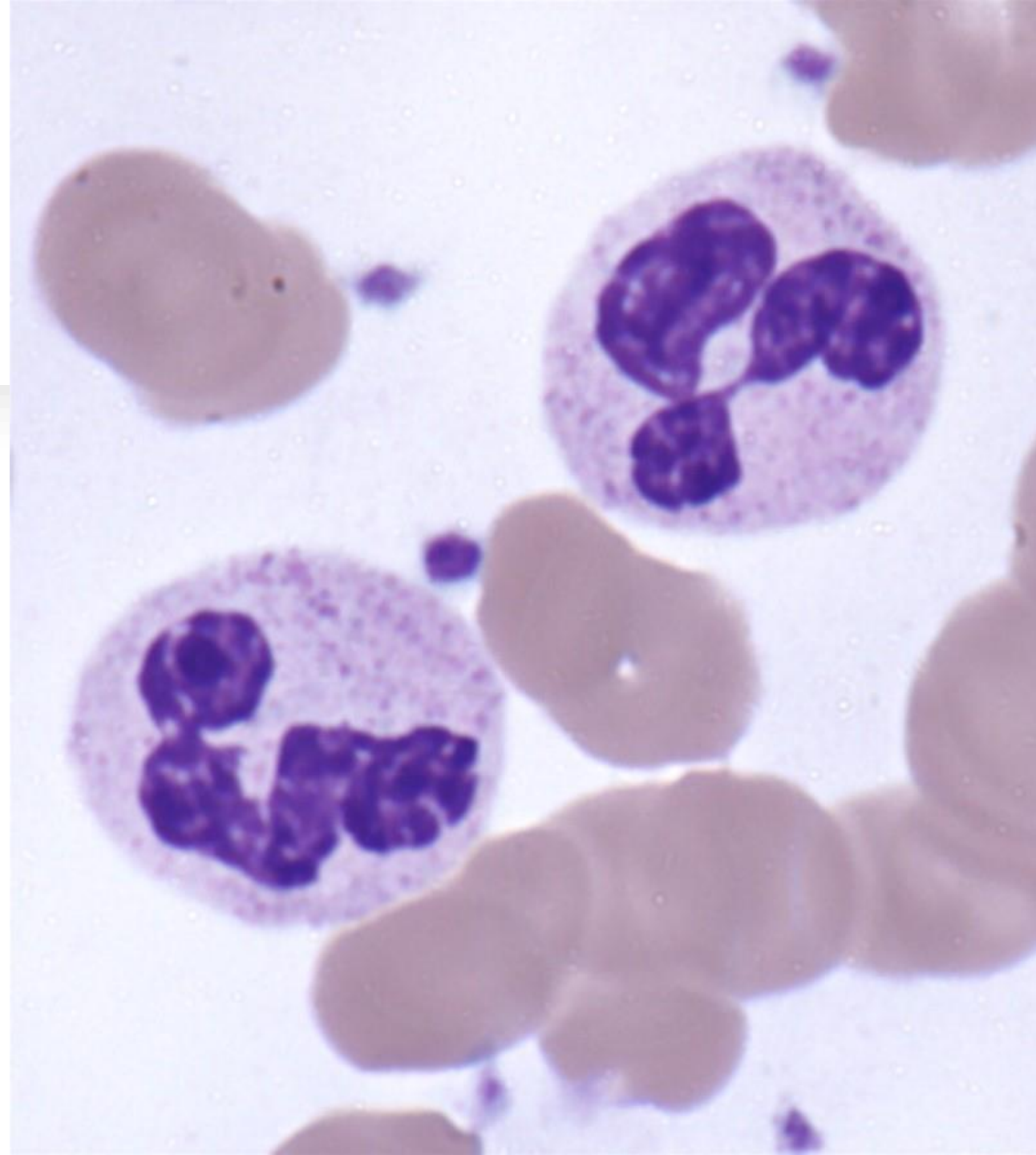
5. Plasma cells

- Plasma cells are large cells with amphophilic to basophilic cytoplasm, an eccentric nucleus with the chromatin arranged in a characteristic cart-wheel or clock-face pattern.
- Their cytoplasm contains a pale perinuclear zone that on electron microscopy shows an extensive Golgi apparatus and centrioles.
- Plasma cells have abundant rough endoplasmic reticulum coupled with a well-developed Golgi apparatus, which together are responsible for immunoglobulin secretion.



6. Neutrophils

Although neutrophils have been classically associated with acute inflammation, they may sometimes be seen in chronic inflammation as well (recruited by mediators produced by activated macrophages and lymphocytes), eg, chronic osteomyelitis (bacterial infection of bone). This is labelled 'acute on chronic inflammation'



Q. What is granulomatous inflammation? Enumerate some granulomatous diseases.

Granulomatous inflammation is a distinctive pattern of chronic inflammatory reaction characterized by the presence of granulomas. A granuloma is a microscopic aggregation of activated macrophages which transform into epithelioid (epithelial like) cells. Epithelioid cells have scanty to moderate, ill-defined, pale pink cytoplasm and a slipper-shaped vesicular nucleus. These are surrounded by a collar of mononuclear cells (lymphocytes and plasma cells). Older granulomas have an enclosing rim of fibroblasts and connective tissue. Epithelioid cells fuse to form 'giant cells' 40–50 microns in size with 20 or more nuclei arranged peripherally like a horse shoe.

Types of Granulomas

1. Infectious granulomas

- (a) **Tuberculosis** (prototype of granulomatous disease): Caused by *Mycobacterium tuberculosis*, tuberculosis is associated with the formation of caseating granulomas (granulomas showing presence of central granular debris with loss of all cellular detail and higher positivity for acid fast bacilli) or noncaseating granulomas (absence of caseation and low positivity for acid fast bacilli).

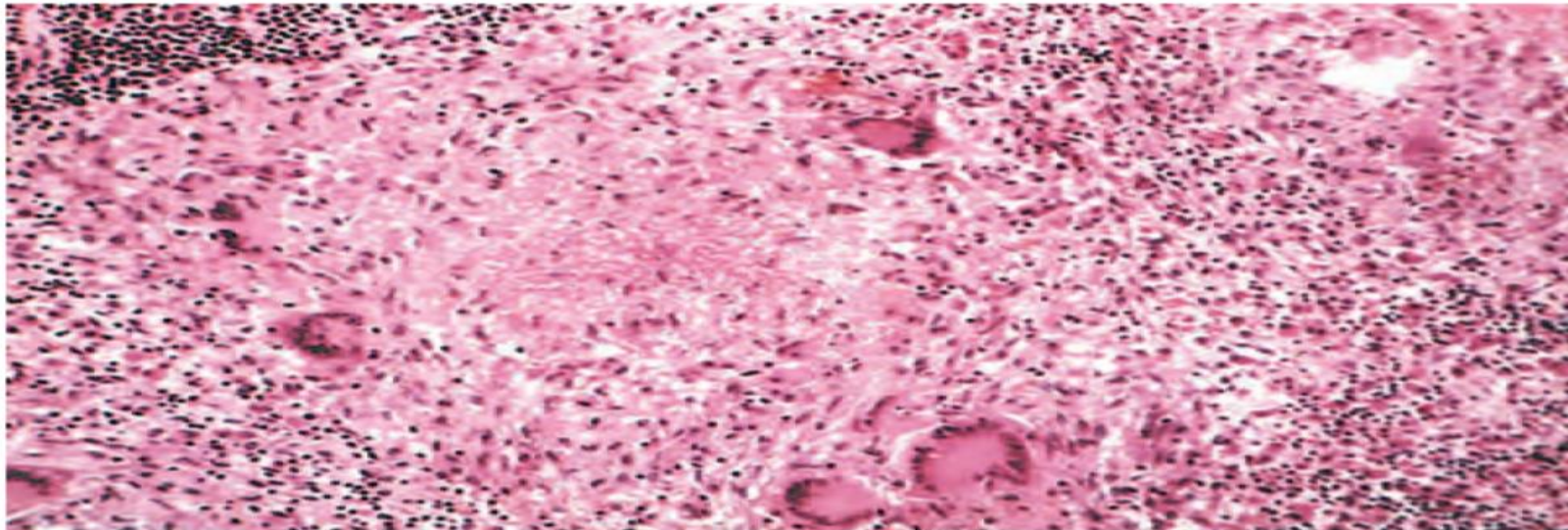


Figure 3.23 Typical tuberculous granuloma showing an area of central necrosis surrounded by multiple Langhans-type giant cells, epithelioid cells, and lymphocytes.

(b) Leprosy: It is caused by *Mycobacterium leprae*. Noncaseating granulomas are typically seen with or without acid fast lepra bacilli in the macrophages.

(c) Syphilis: It is caused by *Treponema pallidum*. Gumma formation is the disease hallmark. Gumma is histopathologically characterized by a central necrotic area without loss of cellular outline; plasma cell infiltrate with a wall of histiocytes.

(d) Cat scratch disease: It is caused by a Gram-negative bacillus. It typically shows rounded or stellate granulomas containing central granular debris and large number of neutrophils.

(e) Deep fungal infections: Fungal granulomas are caused by organisms like histoplasma and blastomyces and are typically suppurative (granulomas with neutrophilic inflammation).

2. Noninfectious or immune granulomas: Granulomas form in response to persistent presence of nondegradable or particulate material, which incites an immune response. These are usually noncaseating epithelioid cell granulomas. Examples includes sarcoidosis and hypersensitivity pneumonitis.

3. Foreign body granulomas are formed as a response to foreign bodies like talc, suture and drugs. The foreign material can be identified in the center of the granuloma or within the foreign body giant cells which have a haphazard distribution of nuclei unlike Langhans giant cell.

Table 3.9 Examples of Diseases With Granulomatous Inflammation

Disease	Cause	Tissue Reaction
Tuberculosis	<i>Mycobacterium tuberculosis</i>	Caseating granuloma (tubercle): focus of activated macrophages (epithelioid cells), rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cells; central necrosis with amorphous granular debris; acid-fast bacilli
Leprosy	<i>Mycobacterium leprae</i>	Acid-fast bacilli in macrophages; noncaseating granulomas
Syphilis	<i>Treponema pallidum</i>	Gumma: microscopic to grossly visible lesion, enclosing wall of histiocytes; plasma cell infiltrate; central cells are necrotic without loss of cellular outline
Cat-scratch disease	Gram-negative bacillus	Rounded or stellate granuloma containing central granular debris and recognizable neutrophils; giant cells uncommon
Sarcoidosis	Unknown etiology	Noncaseating granulomas with abundant activated macrophages
Crohn disease (inflammatory bowel disease)	Immune reaction against intestinal bacteria, possibly self antigens	Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate

KEY CONCEPTS

CHRONIC INFLAMMATION

- Chronic inflammation is a prolonged host response to persistent stimuli.
- It is caused by microbes that resist elimination, immune responses against self antigens and environmental antigens, and some toxic substances (e.g., silica), and it underlies many medically important diseases.
- It is characterized by coexisting inflammation, tissue injury, and attempted repair by scarring.
- The cellular infiltrate consists of macrophages, lymphocytes, plasma cells, and other leukocytes.
- It is mediated by cytokines produced by macrophages and lymphocytes (notably T lymphocytes); bidirectional interactions between these cells tend to amplify and prolong the inflammatory reaction.
- Granulomatous inflammation is a pattern of chronic inflammation induced by T-cell and macrophage activation in response to an agent that is resistant to eradication.

thanks