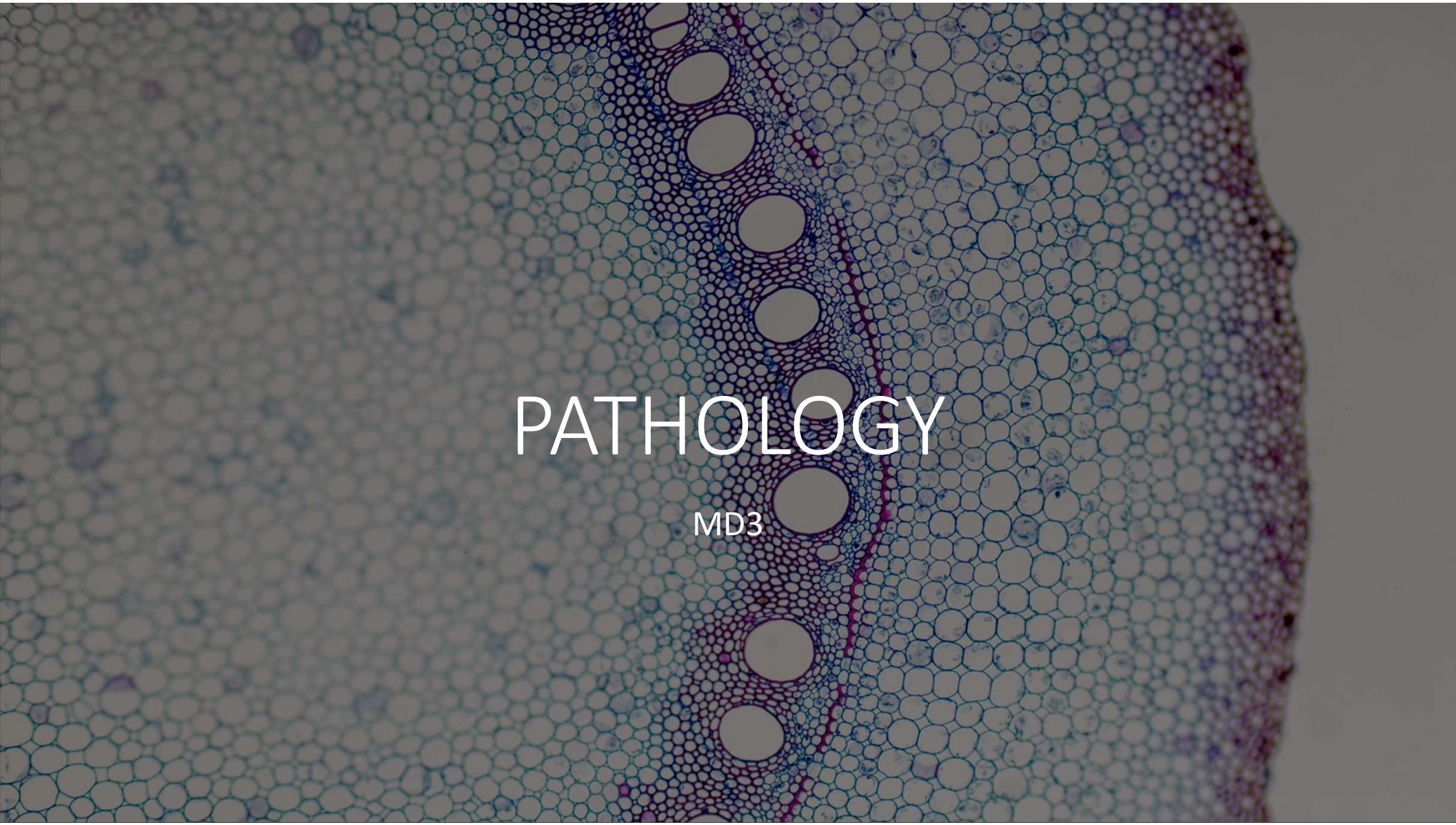


PATHOLOGY

MD3

PATHOLOGY

Inflammation

INFLAMMATION

Learning Objectives

- ❑ Solve problems concerning acute and chronic inflammation
- ❑ Describe tissue responses to infectious agents

INFLAMMATION

ACUTE INFLAMMATION

Acute inflammation is an immediate response to injury or infection, which is part of innate immunity.

- Short duration in normal host
- Cardinal signs of inflammation include Rubor (redness); Calor (heat); Tumor (swelling); Dolor (pain); Functio laesa (loss of function).

The important components of Acute Inflammation are hemodynamic changes, **neutrophils**, and chemical mediators.

Inflammation

Hemodynamic Changes

- Initial transient vasoconstriction
- Massive vasodilatation mediated by histamine, bradykinin, and prostaglandins
- Increased vascular permeability

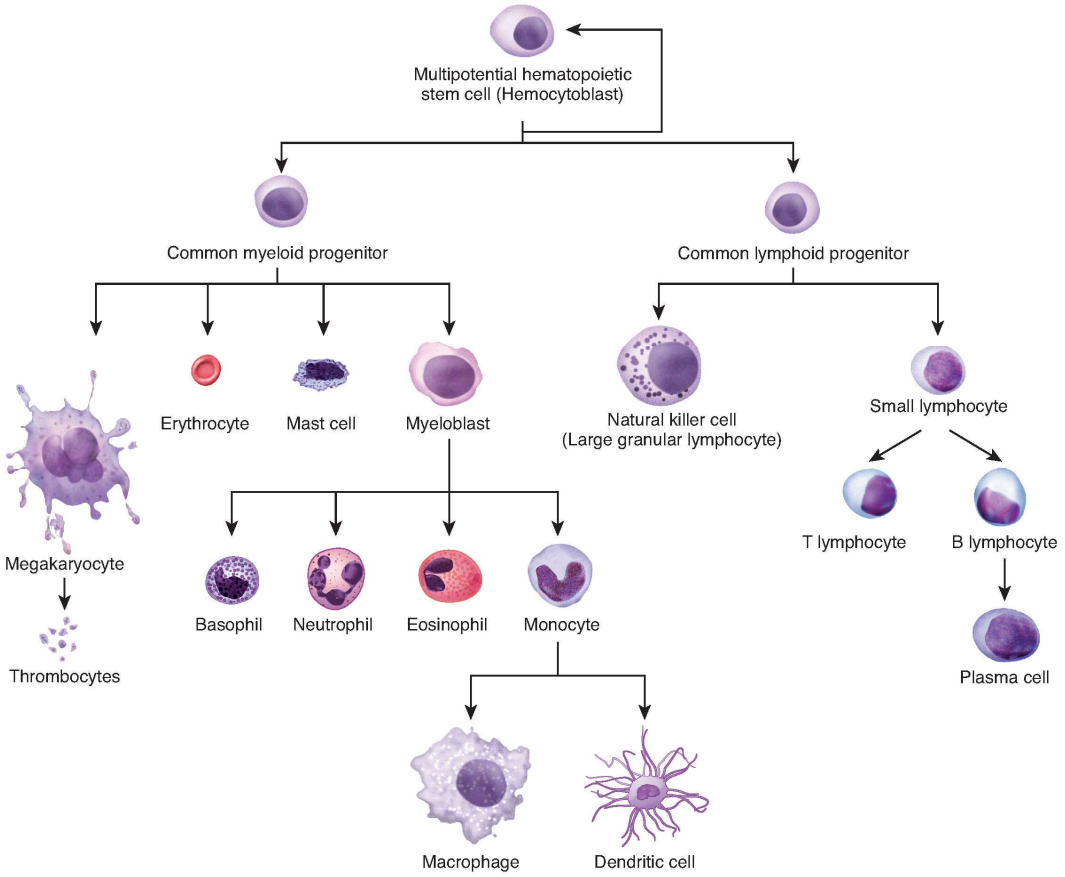
° Chemical mediators of increased permeability include vasoactive amines (histamine and serotonin), bradykinin (an end-product of the kinin cascade), leukotrienes (e.g., LTC4, LTD4, LTE4).

° The mechanism of increased vascular permeability involves endothelial cell and pericyte contraction; direct endothelial cell injury; and leukocyte injury of endothelium.

- Blood flow slows (stasis) due to increased viscosity, allows neutrophils to marginate

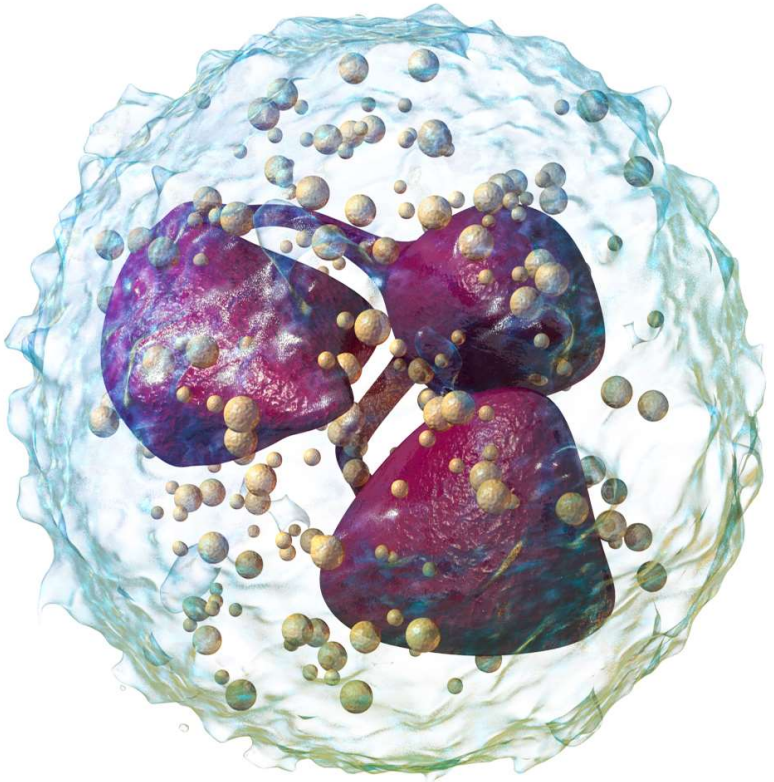
Inflammation

Cellular Component



Inflammation

Neutrophils



Inflammation

Neutrophils

- Life span in tissue 1–2 days
- Synonyms: segmented neutrophils, polymorphonuclear leukocytes (PMN)
- Primary (azurophilic) granules contain myeloperoxidase, phospholipase A2, lysozyme (damages bacterial cell walls by catalysing hydrolysis of 1,4- beta- linkages), and acid hydrolases. Also present are elastase, defensins (microbicidal peptides active against many gram-negative and gram-positive bacteria, fungi, and enveloped viruses), and bactericidal permeability increasing protein (BPI).
- Secondary (specific) granules contain phospholipase A2, lysozyme, leukocyte alkaline phosphatase (LAP), collagenase, lactoferrin (chelates iron), and vitamin B12-binding proteins.
- **Macrophages** (life span in tissue compartment is 60–120 days) have acid hydrolases, elastase, and collagenase.

Inflammation

Neutrophil margination and adhesion. Adhesion is mediated by complementary molecules on the surface of neutrophils and endothelium.

- In **step 1**, the endothelial cells at sites of inflammation have increased expression of *E-selectin* and *P-selectin*.
- In **step 2**, Neutrophils weakly bind to the endothelial selectins and roll along the surface.
- In **step 3**, Neutrophils are stimulated by chemokines to express their integrins.
- In **step 4**, binding of the integrins to cellular adhesion molecules (ICAM-1 and VCAM-1) allows the neutrophils to firmly adhere to the endothelial cell.

Inflammation

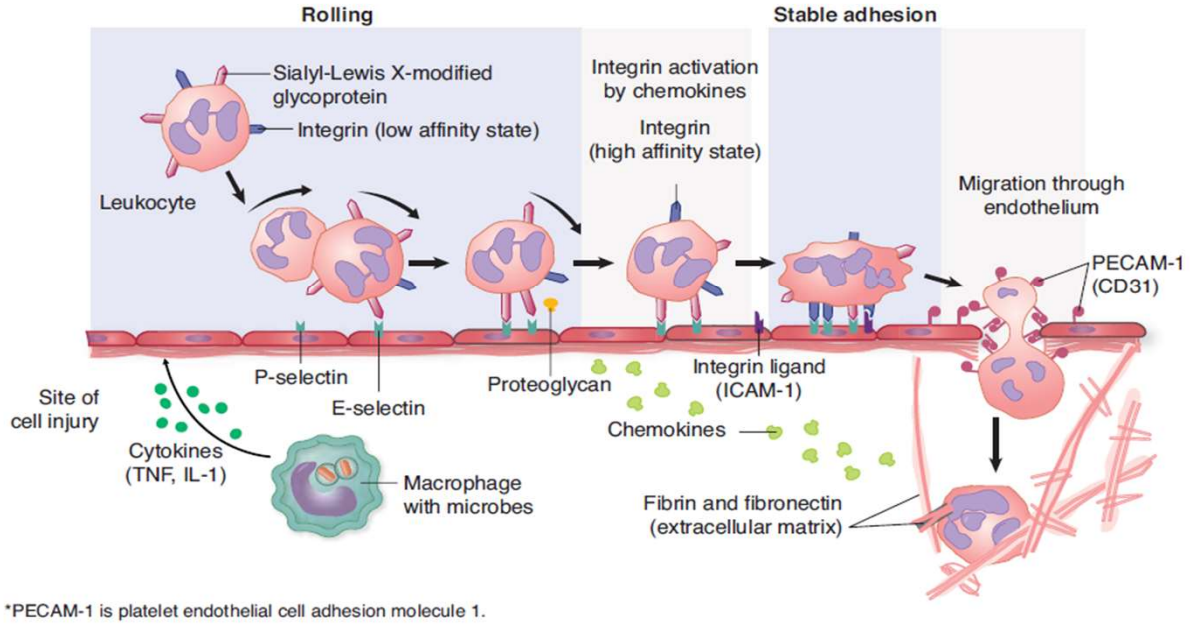
Neutrophils adhesion molecule

- **Selectins:** weak binding; initiate rolling
- **Integrins:** stable binding and adhesion

	Endothelium	Leukocyte
Selectins	P-Selectin	Sialyl-Lewis X & PSGL-1
	E-Selectin	Sialyl-Lewis X & PSGL-1
	GlyCam-1/CD34	L-Selectin
Integrins	ICAM-1	LFA-1 & MAC-1
	VCAM-1	VLA-4

Inflammation

Neutrophils adhesion molecule



*PECAM-1 is platelet endothelial cell adhesion molecule 1.

Inflammation

Modulation of adhesion molecules in inflammation occurs as follows. The fastest step involves redistribution of adhesion molecules to the surface; for example, P-selectin is normally present in the Weibel-Palade bodies of endothelial cells and can be mobilized to the cell surface by exposure to inflammatory mediators such as histamine and thrombin.

- Additionally, synthesis of adhesion molecules occurs. For example, proinflammatory cytokines IL-1 and TNF induce production of E-selectin, ICAM-1, and VCAM-1 in endothelial cells.
- There can also be increased binding affinity, as when chemotactic agents cause a conformational change in the leukocyte integrin LFA-1, which is converted to a high-affinity binding state.

Inflammation

Defects in adhesion can be seen in diabetes mellitus, corticosteroid use, acute alcohol intoxication, and leukocyte adhesion deficiency (Autosomal recessive condition with recurrent bacterial infections).

In **emigration (diapedesis),** leukocytes emigrate from the vasculature (postcapillary venule) by extending pseudopods between the endothelial cells. They then move between the endothelial cells, migrating through the basement membrane toward the inflammatory stimulus.

Chemotaxis is the attraction of cells toward a chemical mediator that is released in the area of inflammation. Important chemotactic factors for neutrophils include bacterial products such as *N*-formyl-methionine and host derived molecules such as leukotriene B4 (LTB4), complement system product C5a, and α-chemokines (IL-8).

Inflammation

Clinical Correlate

Leukocyte adhesion deficiency type I

- Autosomal recessive
- Deficiency of β2 integrin subunit (CD18)
- Recurrent bacterial infection
- Delay in umbilical cord sloughing

Inflammation

Phagocytosis and degranulation.

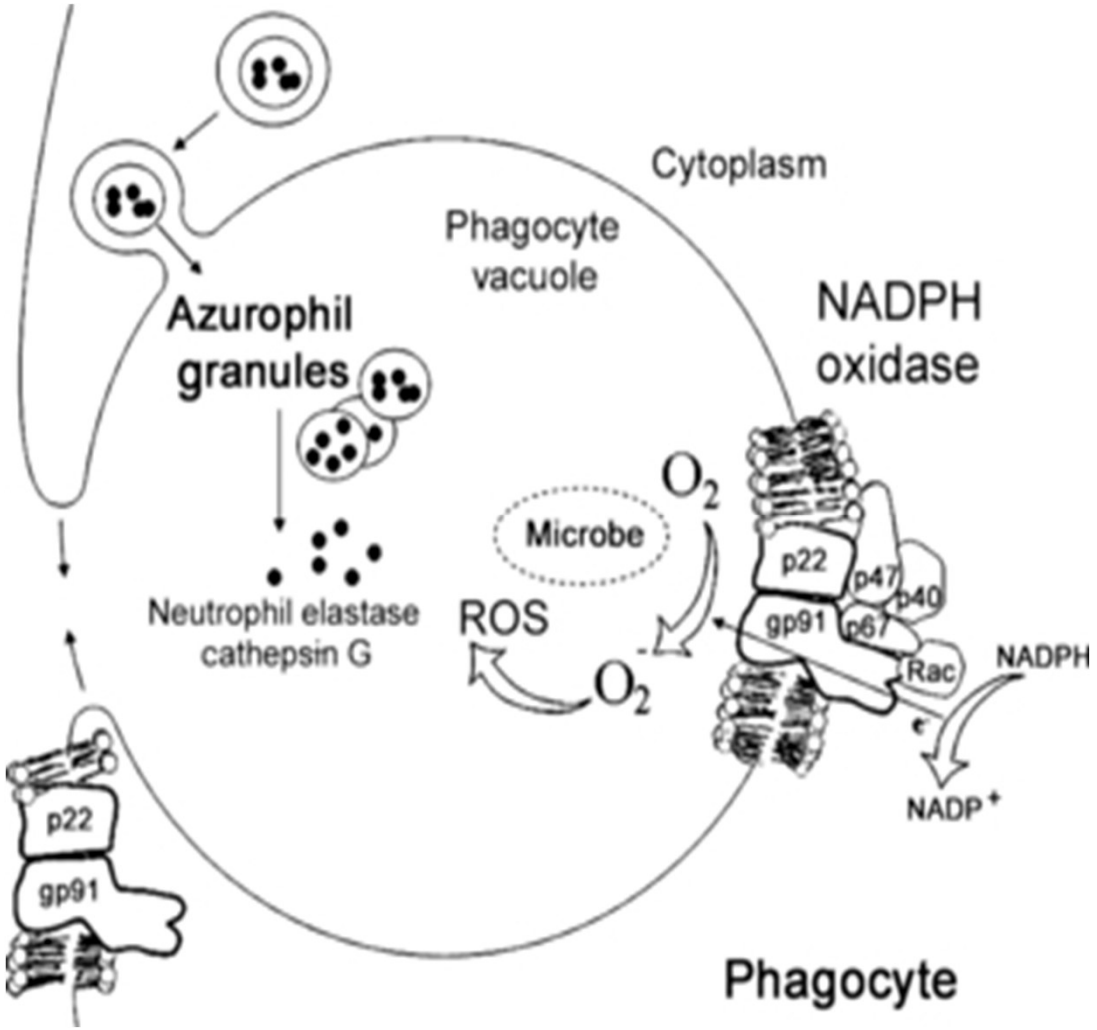
Opsonin coat microbes to enhance their detection and phagocytosis. Important opsonin include the Fc portion of IgG isotypes, complement system product C3b, and plasma proteins such as collectins (which bind to bacterial cell walls). Engulfment occurs when the neutrophil sends out cytoplasmic processes that surround the bacteria. The bacteria are then internalized within a phagosome. The phagosome fuses with lysosomes (degranulation). Defects in phagocytosis and degranulation include Chédiak-Higashi syndrome, an autosomal recessive condition characterized by neutropenia. The neutrophils have giant granules (lysosomes) and there is a defect in chemotaxis and degranulation.

Inflammation

Intracellular killing.

In oxygen-dependent killing, respiratory burst requires oxygen and NADPH oxidase and produces superoxide, hydroxyl radicals, and hydrogen peroxide.

Myeloperoxidase requires hydrogen peroxide and halide (Cl–) and produces HOCl (hypochlorous acid).



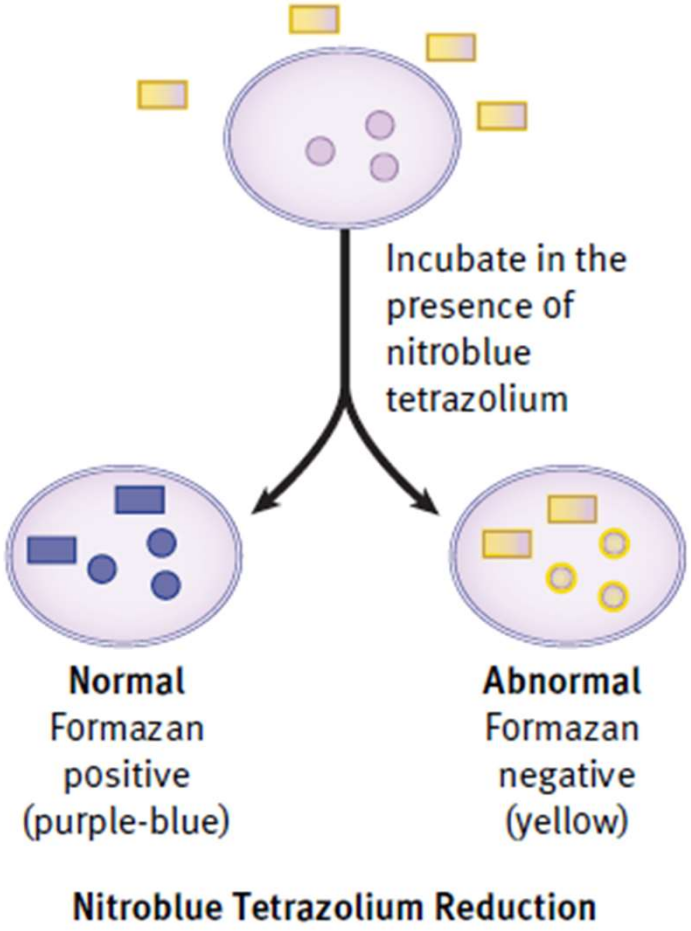
Inflammation

Oxygen-independent killing involves lysozyme, lactoferrin, acid hydrolases, bactericidal permeability increasing protein (BPI), and defensins. Deficiencies of oxygen-dependent killing include:

- Chronic granulomatous disease of childhood can be X-linked or autosomal recessive. It is characterized by a deficiency of NADPH oxidase, lack of superoxide and hydrogen peroxide, and recurrent bacterial infections with catalase-positive organisms (*S. aureus*). The nitroblue tetrazolium test will be negative.
- Myeloperoxidase deficiency is an autosomal recessive condition characterized by infections with *Candida*. In contrast to chronic granulomatous disease, the nitroblue tetrazolium test will be positive.

Inflammation

Nitro blue Tetrazolium



Nitroblue Tetrazolium Reduction

Inflammation

Chemical Mediators of Inflammation

Vasoactive amines

• **Histamine** is produced by basophils, platelets, and mast cells. It causes vasodilation and increased vascular permeability. Triggers for release include IgE-mediated mast cell reactions, physical injury, anaphylatoxins (C3a and C5a), and cytokines (IL-1).

• **Serotonin** is produced by platelets and causes vasodilation and increased vascular permeability.

Kinin system

• Activated Hageman factor (factor XII) converts prekallikrein → kallikrein

• Kallikrein cleaves high molecular weight kininogen (HMWK) → bradykinin

• Effects of bradykinin include increased vascular permeability, pain, vasodilation, bronchoconstriction, and pain

Inflammation

Arachidonic acid products

Cyclooxygenase pathway

° Thromboxane A2 is produced by platelets and causes vasoconstriction and platelet aggregation.

° Prostacyclin (PGI2) is produced by vascular endothelium and causes vasodilation and inhibition of platelet aggregation.

° Prostaglandin E2 causes pain.

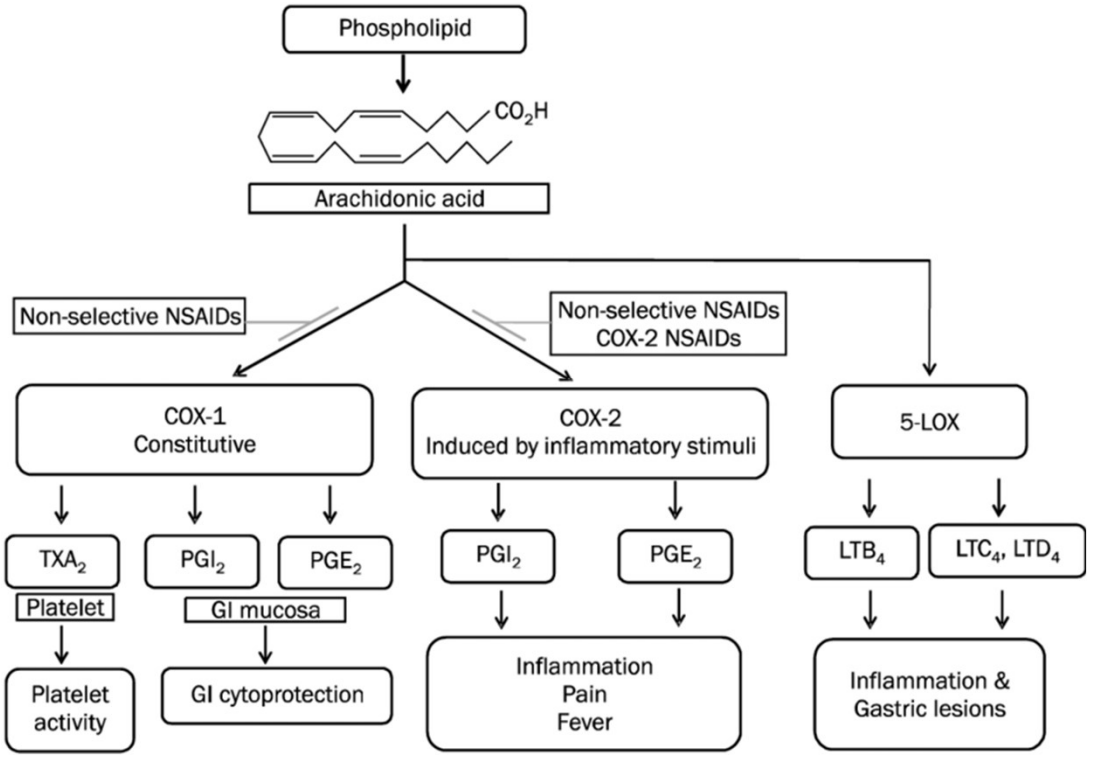
° Prostaglandins PGE2, PGD2, and PGF2 cause vasodilatation.

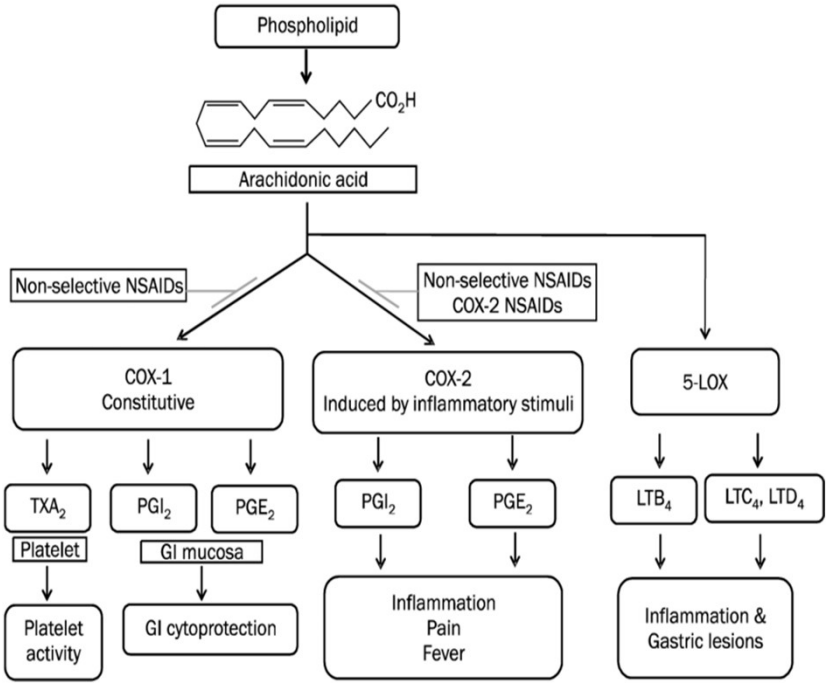
Mediators of Pain

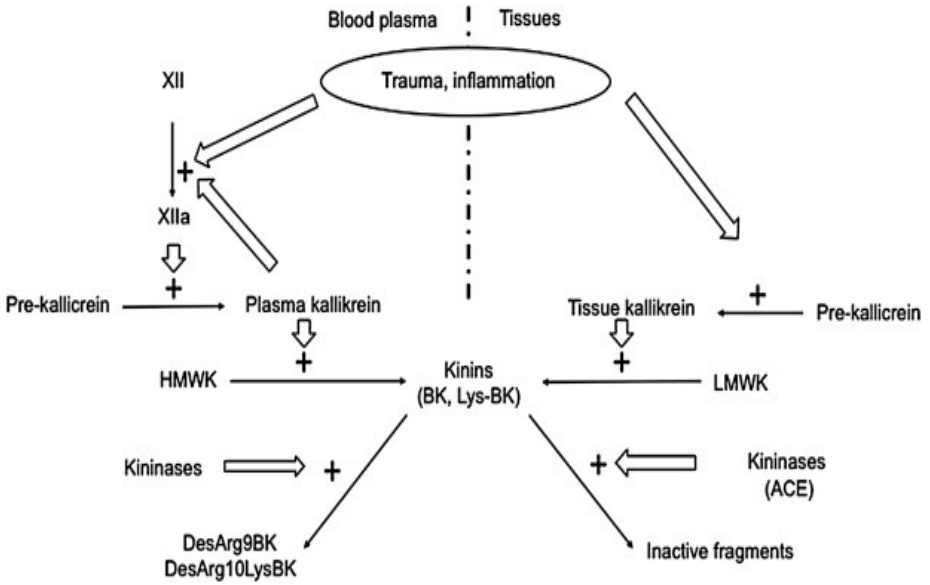
- Bradykinin
- Prostaglandins (E2)

Inflammation

COX and LOX pathway







Inflammation

COX and LOX pathway

Inflammation

Lipoxygenase pathway

Leukotriene B4 (LTB4) causes neutrophil chemotaxis, while leukotriene

C4, D4, E4 cause vasoconstriction.

Lipoxins are anti inflammatory products which inhibit neutrophil chemotaxis.

Important products in the complement cascade include C5b-C9 (membrane attack complex), C3a, C5a (anaphylatoxins stimulate the release of histamine), C5a (leukocyte chemotactic factor), and C3b (opsonin for phagocytosis).

Inflammation

Cytokines

• IL-1 and TNF cause fever and induce acute phase reactants; enhance adhesion molecules; and stimulate and activate fibroblasts, endothelial cells, and neutrophils.

• IL-8 is a neutrophil chemoattractant produced by macrophages.

Four Outcomes of Acute Inflammation

• Complete resolution with regeneration

• Complete resolution with scarring

• Abscess formation

• Transition to chronic inflammation

Inflammation

CHRONIC INFLAMMATION

Causes of chronic inflammation include the following:

- Following a bout of acute inflammation
- Persistent infections
- Infections with certain organisms, including viral infections, mycobacteria, parasitic infections, and fungal infections
- Autoimmune diseases
- Response to foreign material
- Response to malignant tumors

There are several **important cells** in chronic inflammation.

Inflammation

Macrophages are derived from blood monocytes. Tissue-based macrophages (life span in connective tissue compartment is 60–120 days) are found in connective tissue (histiocyte), lung (pulmonary alveolar macrophages), liver (Kupffer cells), bone (osteoclasts), and brain (microglia). During inflammation circulating monocytes emigrate from the blood to the periphery and differentiate into macrophages.

° Respond to chemotactic factors: C5a, MCP-1, MIP-1α, PDGF, TGF-β

° Secrete a wide variety of active products (monokines)

° May be modified into epithelioid cells in granulomatous processes

Inflammation

Lymphocytes include B cells and plasma cells, as well as T cells. Lymphotoxin is the lymphocyte chemokine

- **Eosinophils** play an important role in parasitic infections and IgE-mediated allergic reactions. The eosinophilic chemokine is eotaxin. Eosinophil granules contain major basic protein, which is toxic to parasites.

- **Basophils** contain similar chemical mediators as mast cells in their granules. Mast cells are present in high numbers in the lung and skin. Both basophils and mast cells play an important role in IgE-mediated reactions (allergies and anaphylaxis) and can release histamine.

Inflammation

Chronic granulomatous inflammation is a specialized form of chronic inflammation characterized by small aggregates of modified macrophages (epithelioid cells and multinucleated giant cells) usually populated by CD4+ Th1 lymphocytes. Composition of a granuloma is as follows:

• Epithelioid cells, located centrally, form when IFN-γ transforms macrophages to epithelioid cells. They are enlarged cells with abundant pink cytoplasm.

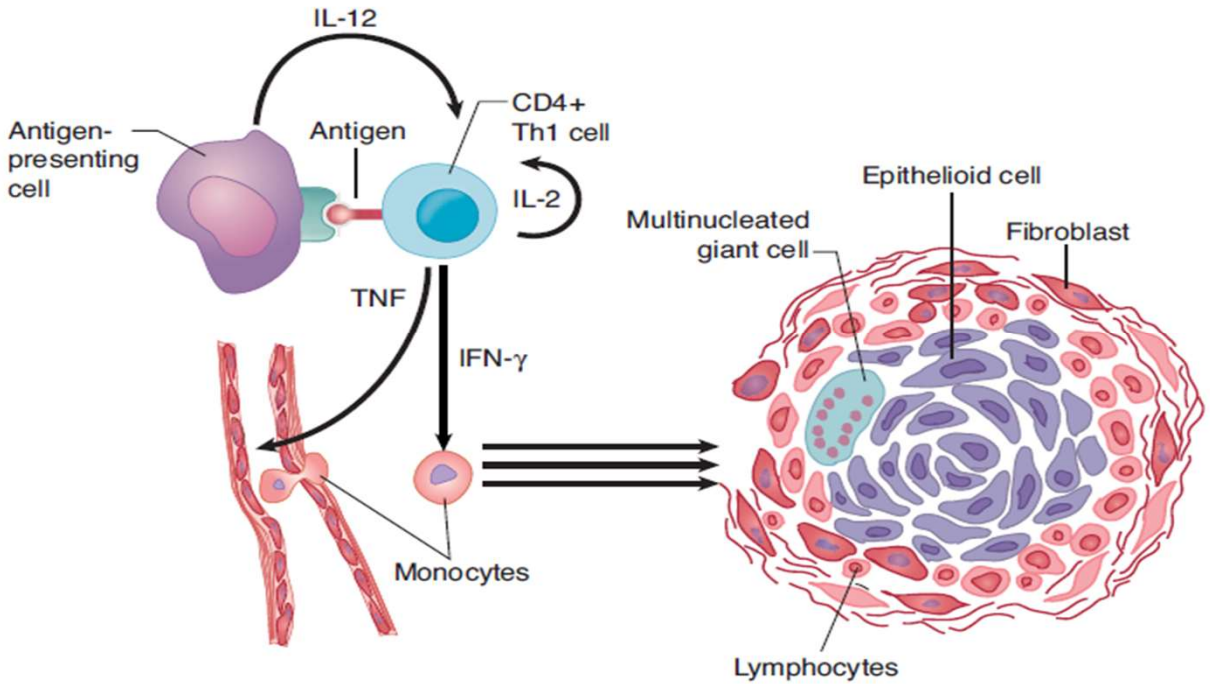
• Multinucleated giant cells, located centrally, are formed by the fusion of epithelioid cells. Types include Langhans-type giant cell (peripheral arrangement of nuclei) and foreign body type giant cell (haphazard arrangement of nuclei).

• Lymphocytes and plasma cells are present at the periphery.

• Central necrosis occurs in granulomata due to excessive enzymatic breakdown and is commonly seen in *Mycobacterium tuberculosis* infection as well as fungal infections and a few bacterial infections. Because of the public health risk of tuberculosis, necrotizing granulomas should be considered tuberculosis until proven otherwise.

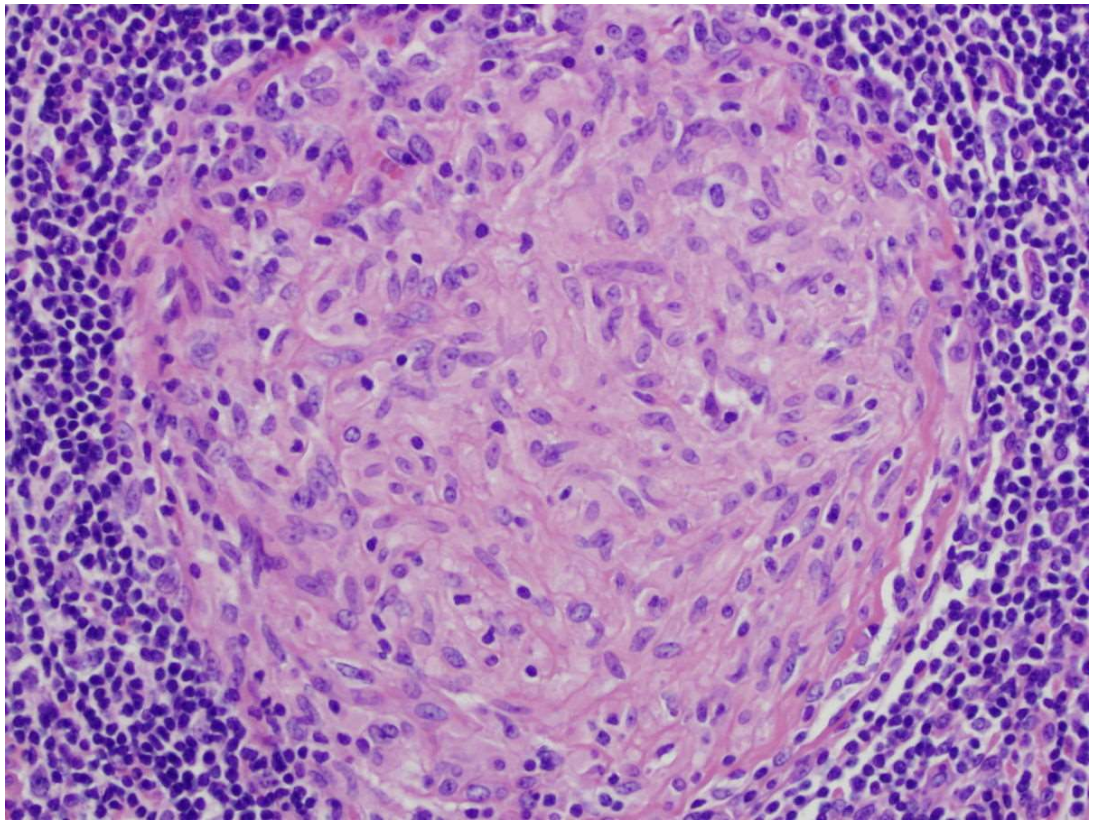
Inflammation

Granulomatous diseases include tuberculosis (caseating granulomas), cat-scratch fever, syphilis, leprosy, fungal infections (e.g., coccidioidomycosis), parasitic infections (e.g., schistosomiasis), foreign bodies, beryllium, and sarcoidosis.



Inflammation

Granuloma formation



Inflammation

TISSUE RESPONSES TO INFECTIOUS AGENTS

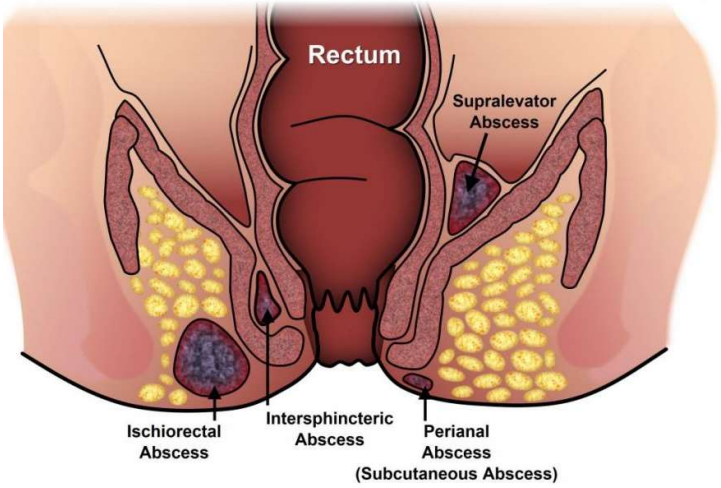
Infectious diseases are very prevalent worldwide and are a major cause of morbidity and mortality. Infectious agents tend to have **tropism** for specific tissues and organs.

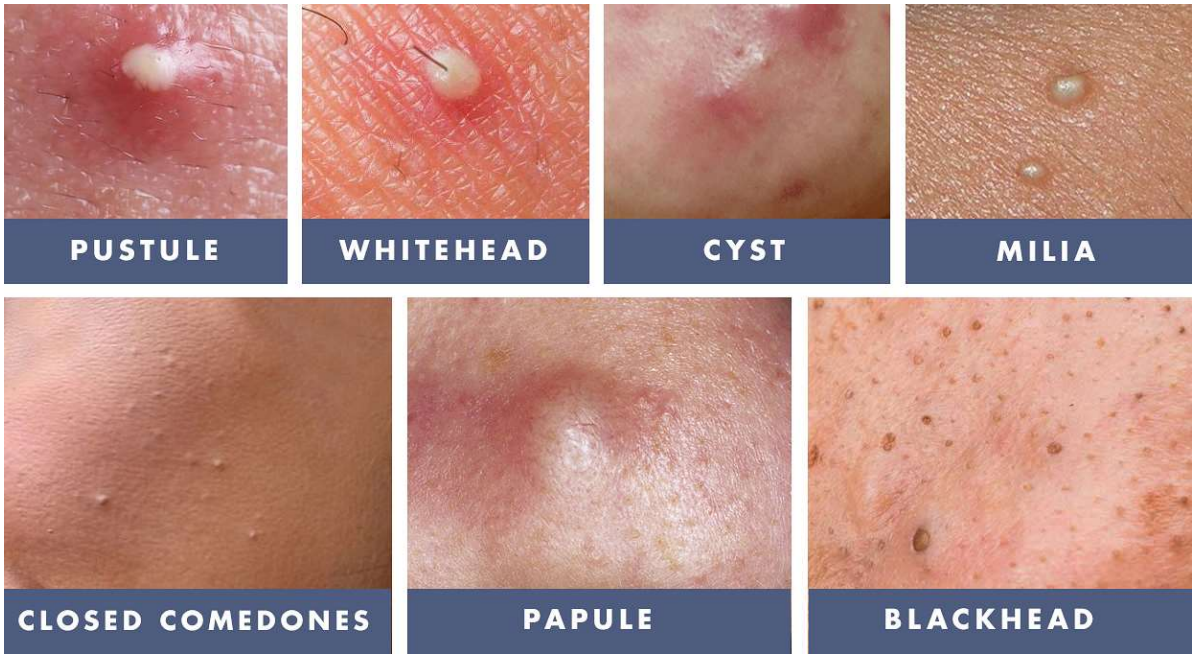
Inflammation

- Exudative inflammation
- Necrotizing inflammation
- Granulomatous inflammation
- Interstitial inflammation
- Cytopathic /cytoproliferative inflammation
- No inflammation

Inflammation

Exudative inflammation is acute inflammatory response with neutrophils. Examples include bacterial meningitis, bronchopneumonia, and abscess.





INFLAMMATION

Exudative Inflammation

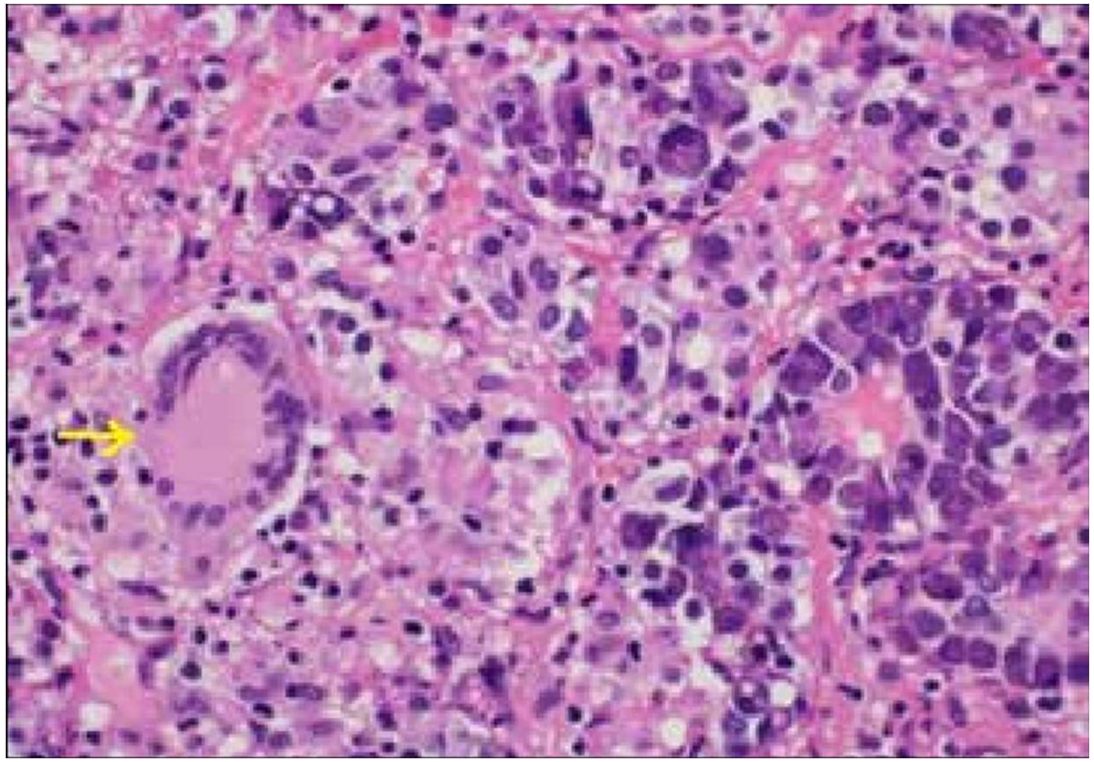
Examples

Inflammation

Necrotizing inflammation occurs when a virulent organism produces severe tissue damage and extensive cell death. Examples include necrotizing fasciitis and necrotizing pharyngitis.

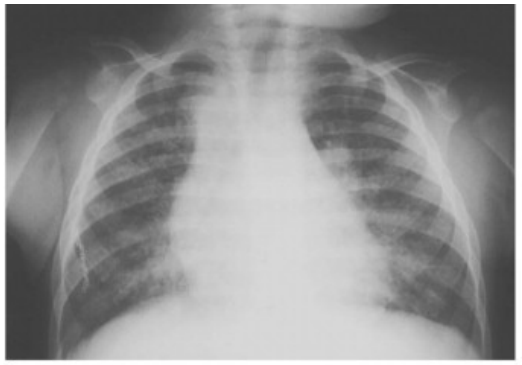
Inflammation

Granulomatous inflammation. Granulomatous response predominates with slow-growing organisms such as mycobacteria, fungi, and parasites.



Inflammation

Interstitial inflammation is a diffuse mononuclear interstitial infiltrate that is a common response to viral infectious agents. Examples include myocarditis (Coxsackie virus) and viral hepatitis.



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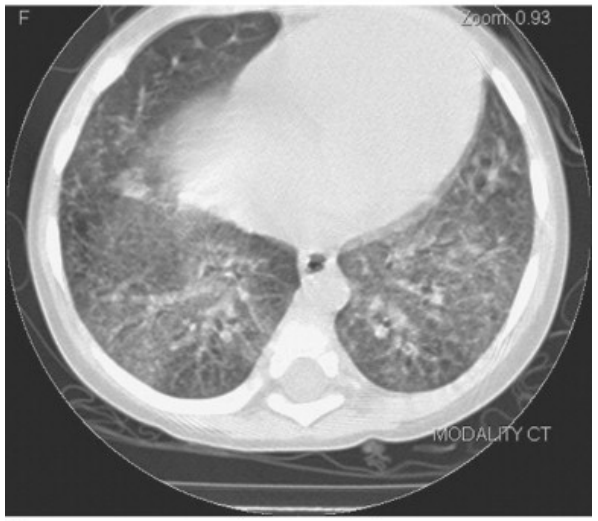

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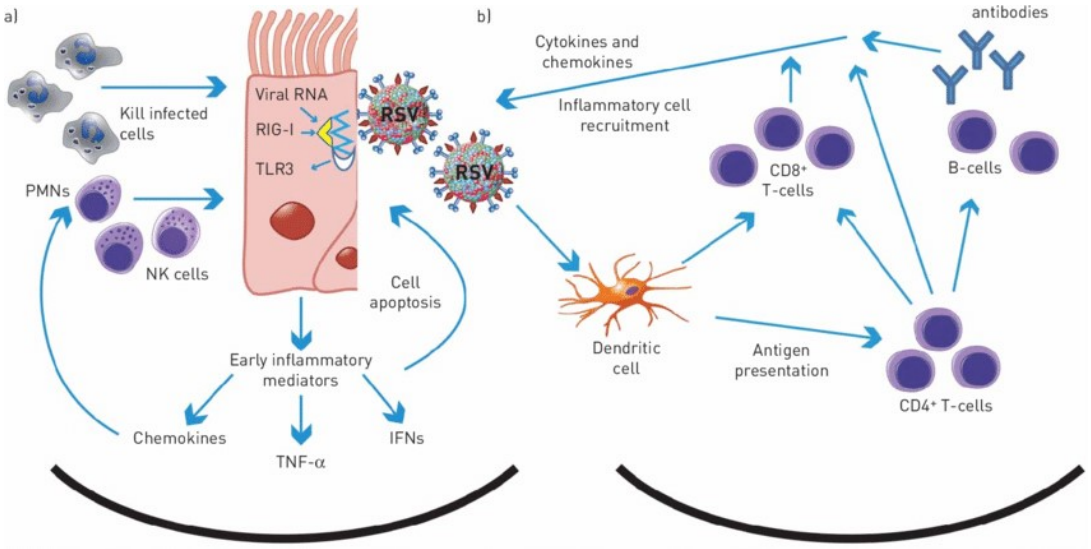
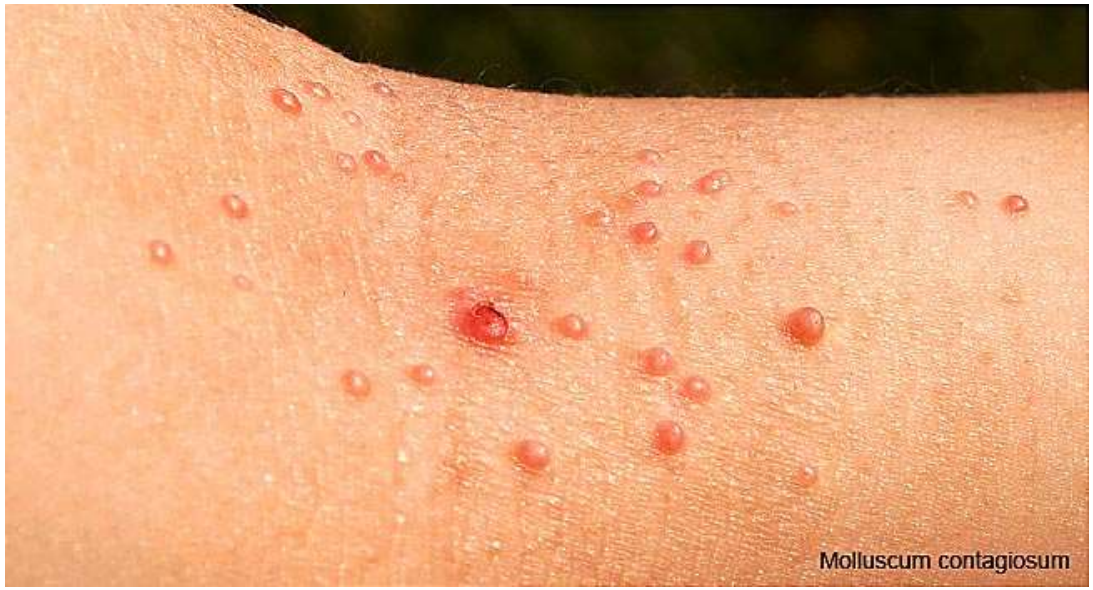
Inflammation

Cytopathic/cytoproliferative inflammation refers to inflammation in which the infected/injured cell is altered. The changes may include intranuclear/ cytoplasmic inclusions (cytomegalic inclusion disease, rabies [Negri body]); syncytia formation (respiratory syncytial virus and herpes virus); and apoptosis (Councilman body in viral hepatitis).



Inflammation

No inflammation. An inflammatory response to microbes cannot occur in severely Interleukin-1, inflammation mediation immunosuppressed individuals due to primary immunodeficiencies or acquired immunodeficient states (e.g., AIDS).



Inflammation

Questions

Inflammation

Inflammation

Inflammation

Inflammation

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