Innate host defenses (chap 16)

- Host defenses are either innate (non specific) or adaptive (specific).
- Innate defenses considered the body's first line of defense, they act against any invading agent & they don't need previous exposure to the agent to act.
- Adaptive defenses considered the 2nd line of body's defense. They respond to certain molecules on or in the invading agent called Antigen.
- Innate defenses include:
  - Physical barrier: skin & mucus membrane
  - Chemical barrier: enzymes & antimicrobials secreted in saliva, stomach, mucus
  - Cellular defense: phagocytes (cells that engulf invading agent)
  - Inflammation
  - Fever
  - Molecular defense: compounds released that inhibit or destroy the microbe

A) Physical barrier

skin prevents the entry of m.o & toxic substances.

mucous covers some organs & body cavities & make it difficult to pathogens to enter.

Physical reflex like sneezing & coughing, flushes microbes to the outside.

Hair & mucus of respiratory system

Vomiting & diarrhea flush microbes & toxins from GIT, tears & saliva flush microbes from eyes & mouth.

B) Chemical barrier

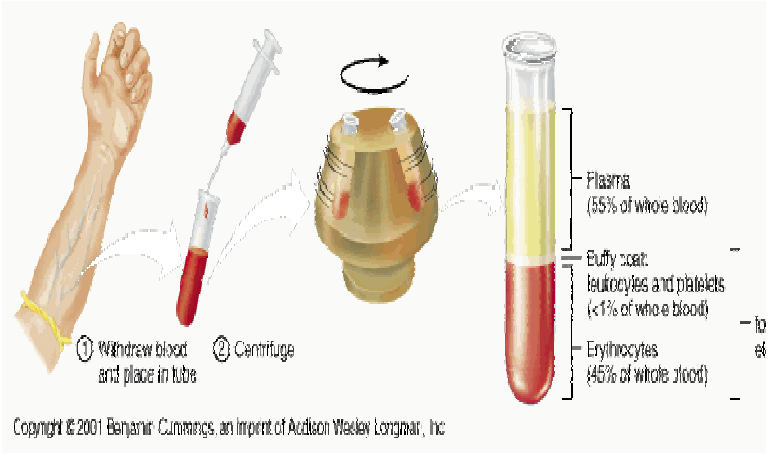
e.g sweat & sebum decrease pH of the skin; high salt content of sweat inhibits many microbes; very low pH of the stomach; Lysozyme enzyme in tears, mucous & saliva inhibits G+ve bacteria; presence of proteins that bind free iron & therefore inhibit bacterial growth like transferrin in blood & lactoferrin in saliva, mucus & milk. The low pH of stomach protects against GI microbes

C) Cellular defenses: rely on special cells found in blood & tissues.

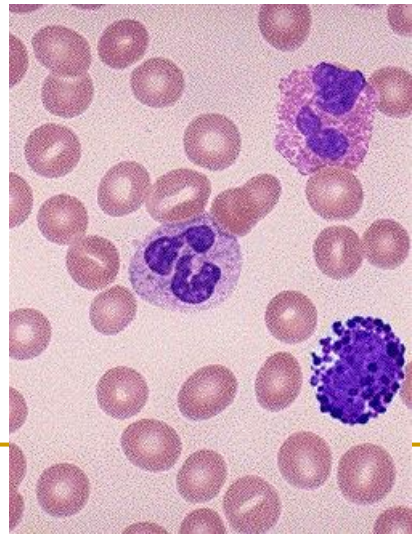
Blood: composed of plasma (60%) & formed elements (cells & cellular Fragments) (40%).

Formed element composed of

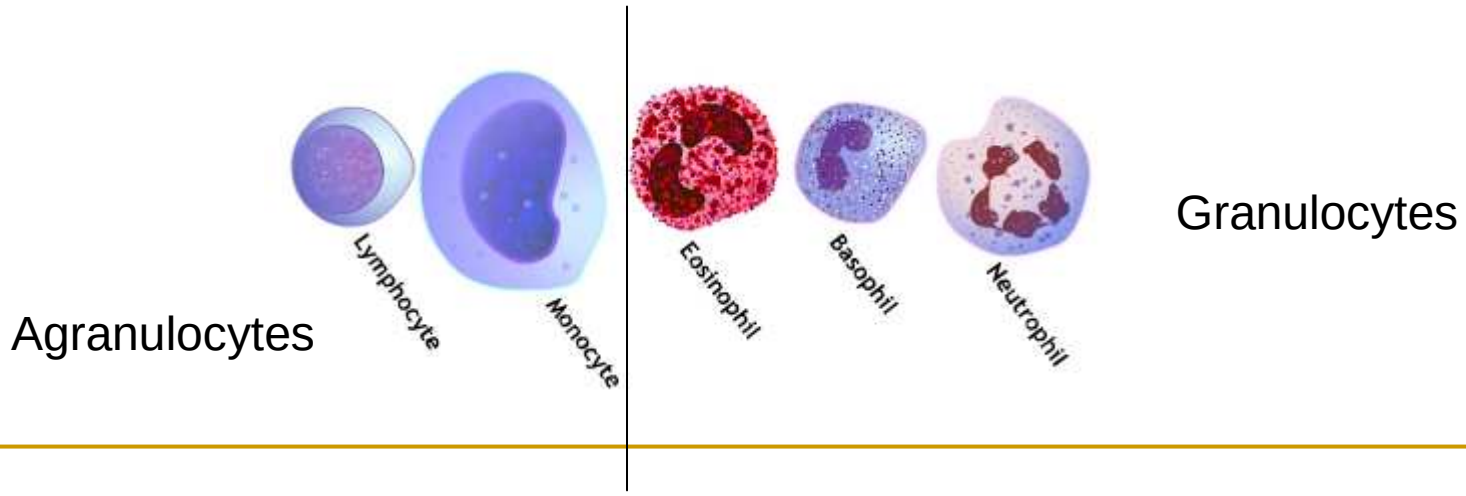
- erythrocytes (RBC) needed for O2 transport
- leukocytes (WBC) defensive cells
- platelets involved in blood clotting.



Leukocytes are divided to granulocytes & agranulocytes



- Granulocytes: have granular cytoplasm & irregular lobed nucleus. Distinguished by their nucleus & staining rxn.
  - Basophils (0.1% of total leukocytes), release histamine & responsible for allergic rxns.
  - Eosinophils: (1-5%), increase during allergies & worm infection, release defensive chemicals against worms, turn off allergic rxn
  - Neutrophils: (50-70%) Phagocytic cell, protect skin, blood & mucus membrane from infection.
  - Dendritic cells: phagocytic cell& plays a role in adaptive defense.
  - Mast cells: resident in tissues, release histamine & are very important in allergy



Agranulocytes: lack granules in cytoplasm & the nucleus is round. Includes Monocytes & lymphocytes.

Lymphocyte is important for adaptive response.

Neutrophils & monocytes are the major phagocytes in innate defense.

Phagocytes (eating cells): they engulf microbes & cell debris. They attack microbes at their portals of entry like wounds, mucus membrane or in blood & tissues.

Monocytes circulate in blood, some move to tissues where they change & mature into Macrophages (big eaters) that destroy microbes & other larger particles.

Macrophages are either fixed (fixed macrophages) in the tissue and accordingly have different names according to the tissue (kuppfer cells-liver, osteoclast-bones) or wander (wandering macrophages) that circulate in the blood & migrate into tissues towards foreign bodies.

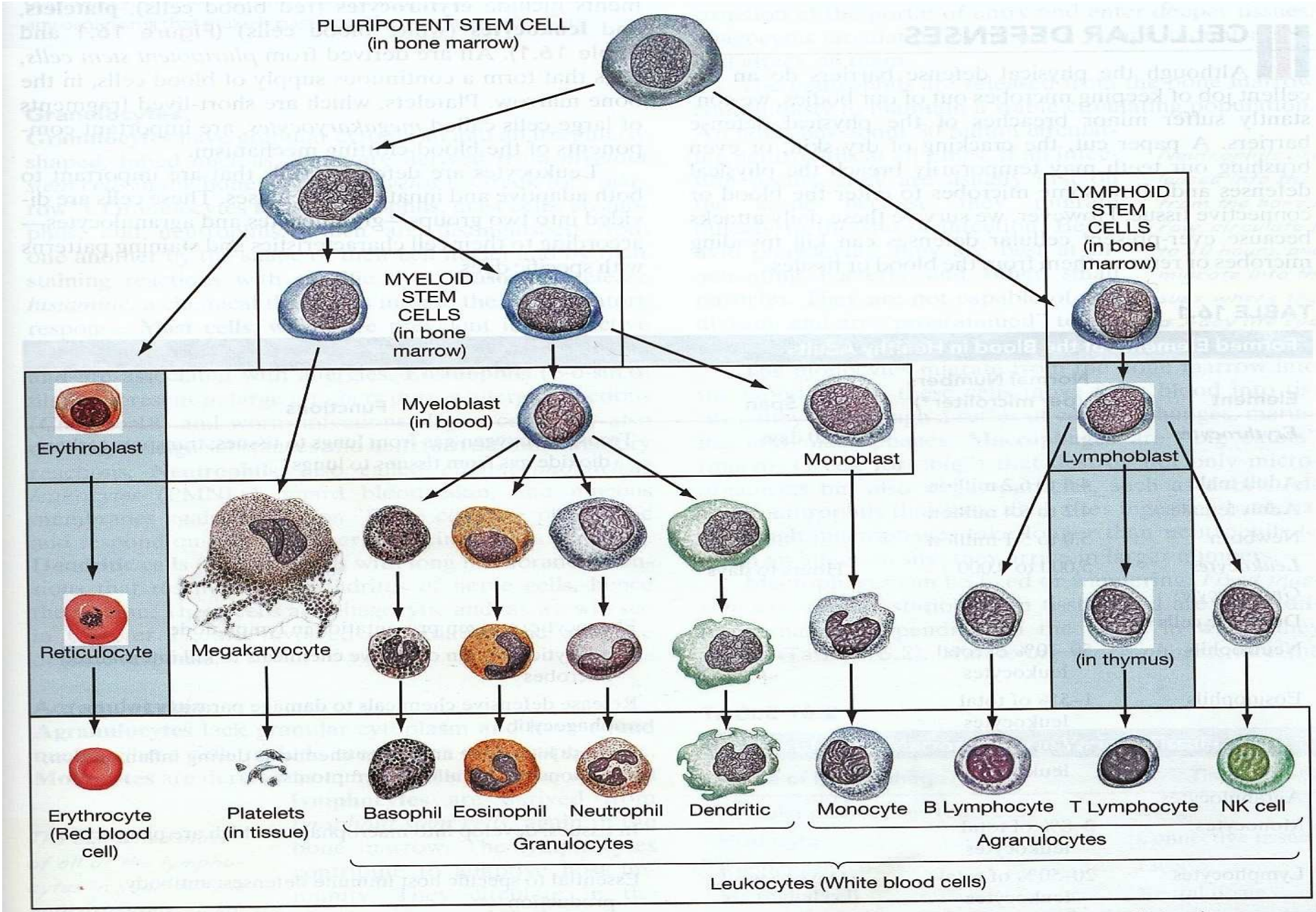


Figure 16.1 Formed (cellular) elements of the blood. These elements are derived from pluripotent stem cells (cells that form an endless supply of blood cells) in the bone marrow. The myeloid stem cells differentiate into several kinds of leukocytes, called granulocytes and agranulocytes. Lymphoid stem cells differentiate into B lymphocytes (B cells), T lymphocytes (T cells), and natural killer cells (NK cells).

Phagocytosis (intracellular killing)

For a phagocyte to destroy a microbe it has to 1) find it, 2) adhere to it, 3) ingest it, 4) digest it.

1) Find

Phagocytes have receptors (toll-like receptors TLRs) that recognize certain molecules on the pathogen, e.g LPS, peptidoglycan, proteins, etc..

Phagocytes detect the release of specific chemicals from the pathogen or damaged tissues & therefore move toward these chemicals in a process called Chemotaxis.

Some bacteria interfere with chemotaxis & so escape phagocytosis

2) Adherence: Phagocytes bind to specific molecules on the surface of the pathogen. Some bacteria avoid adherence by having a capsule which make it difficult to adhere to phagocytes.

3) Ingestion: the cell membrane of the phagocyte forms extensions (pseudopodia) that surrounds the microbe then enclose it into a vacuole called phagosome.

4) Digestion:

The phagocyte has organelles (lysosomes) that contain digestive enzymes & proteins (defensins) that eat holes in microbe cell memb. These fuse with phagosome, release the enzymes & kill & break the microbe.

Macrophages also use O2 to produce H_2O_2, nitric oxide, hypochlorite that damage pathogen plasma membrane.

Some bacteria escape digestion, like

Yersinia pestis (plague) has capsule that resist digestion, it even multiply within macrophage.

Staphylococcus release toxins (leukocidin) that causes release of lysosomal enzymes inside the phagocyte & kills it

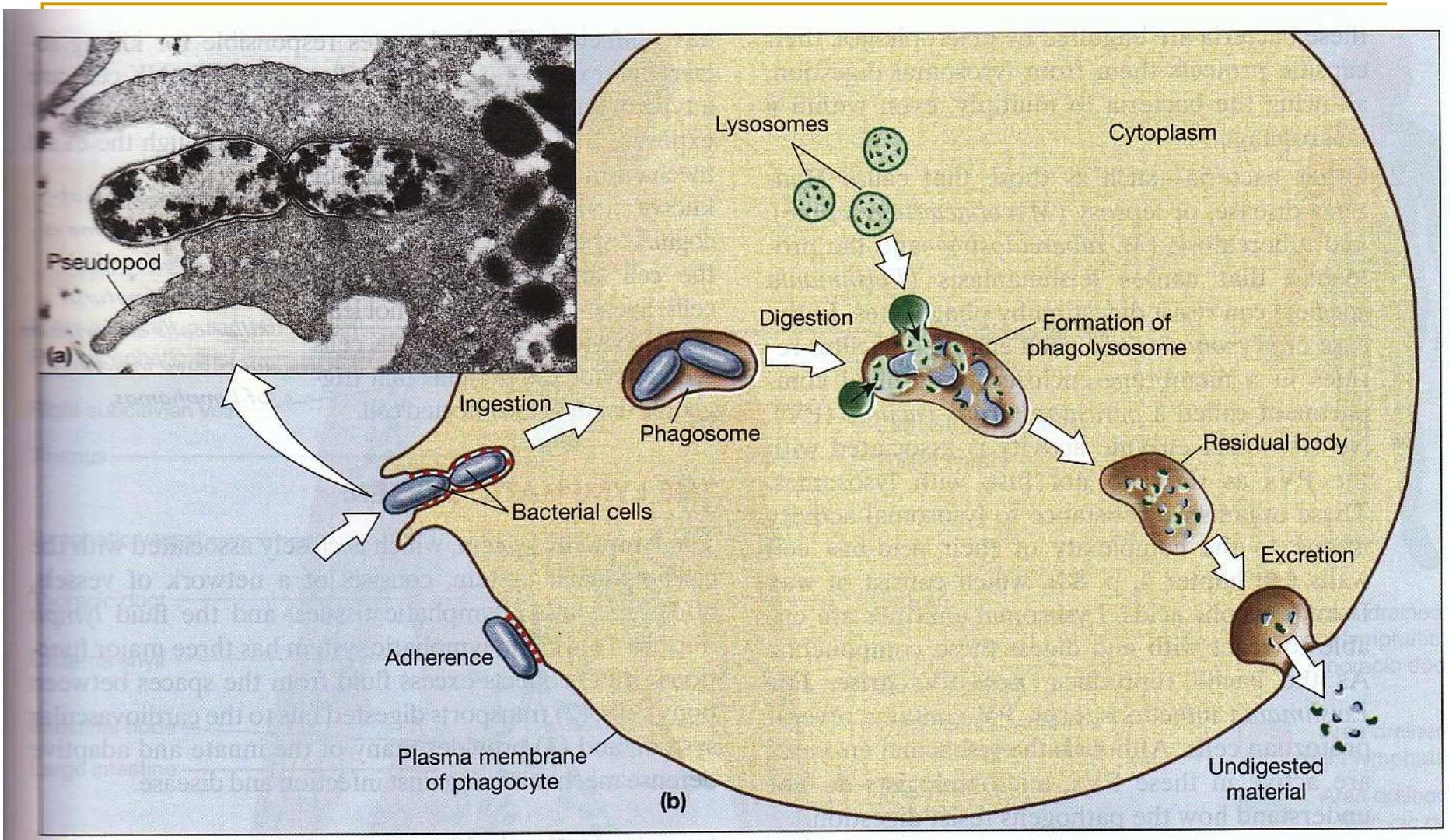


Figure 16.3 Phagocytosis of two bacterial cells by a neutrophil. **(a)** Extensions of cytoplasm, called pseudopodia, surround the bacteria. Fusion of the pseudopodia forms a cytoplasmic vacuole, called a phagosome, containing the bacteria (magnification unknown). *(Courtesy Dorothy F. Bainton, M.D., University of California at San Francisco)* **(b)** Phagocytes find their way to a site of infection by means of chemotaxis. Phagocytes, including macrophages and neutrophils, have proteins in their plasma membranes to which a bacterium adheres. The bacterium is then ingested into the cytoplasm of the phagocyte as a phagosome, which fuses with lysosomes to form a phagolysosome. The bacterium is digested, and any undigested material within the residual body is excreted from the cell.

Extracellular killing

- Is the killing & destruction of microbes without being ingested by defense cells, e.g worms (too large to be ingested) & viruses (they replicate inside cells).

- Eosinophils excrete toxic enzymes that damage worms. Once degraded, macrophages engulf the fragments

- Natural killer cells (NK, type of lymphocytes), kill intracellular viruses by triggering the death of infected cells before the virus multiply.

The lymphatic system

- It is a network of vessels, nodes & the fluid (lymph). It is closely associated to cardiovascular system.

- Function of the lymphatic system:
  - Collects excess fluid from tissues
  - Transport digested fats to cardiovascular system
  - Provides many of the innate & adaptive defenses

- Excess fluid between cells & blood proteins that leak from blood, drain into lymphatic capillaries, once there it is named lymph. Capillaries join to form vessels. Vessels pass through lymph nodes. Lymph is returned into venous blood through right & left lymphatic ducts. Lymph flow depends on skeletal muscle contraction as there is no pump (like in case of blood pump-*heart*). One way valves prevent lymph back flow

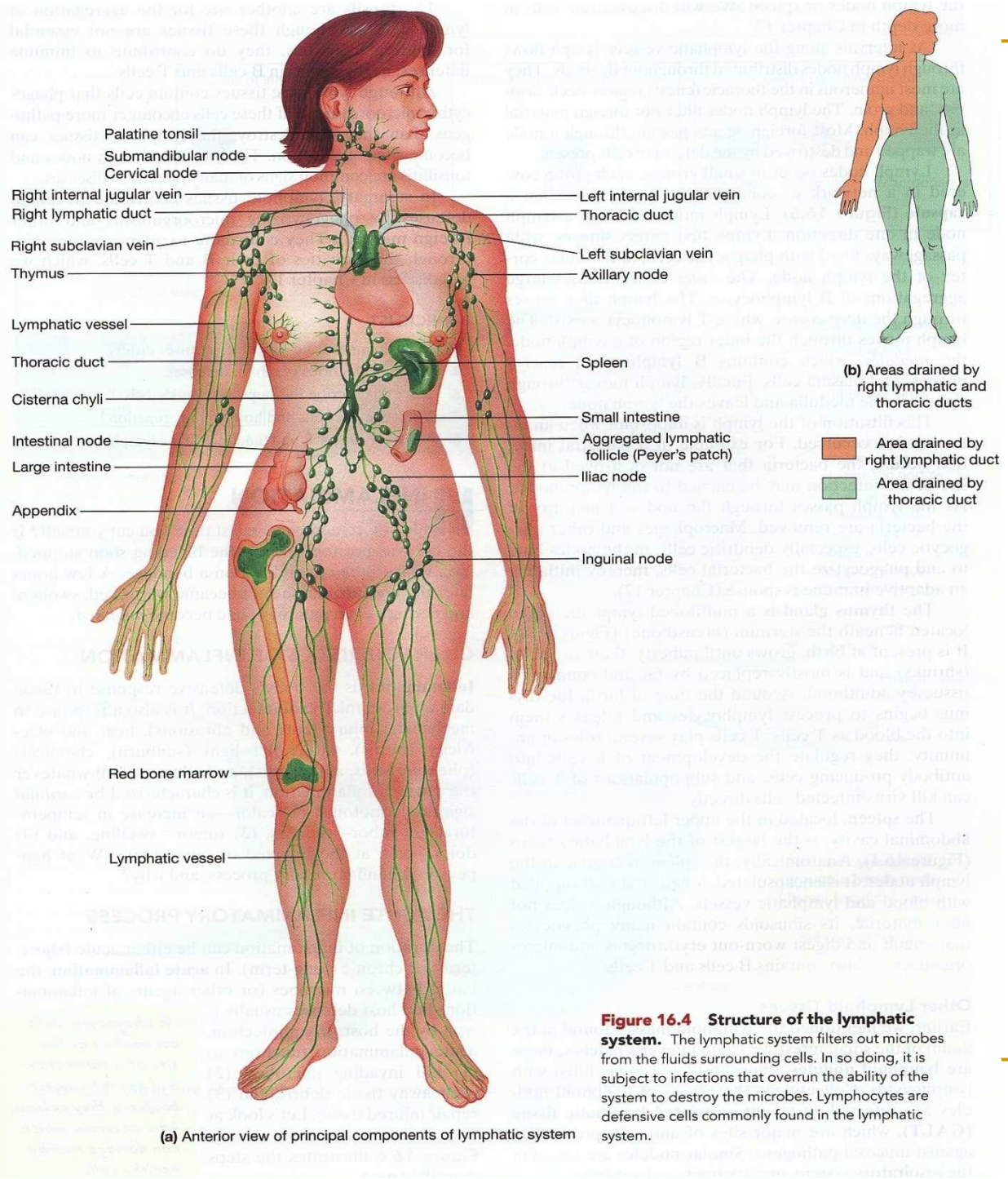


Figure 16.4 Structure of the lymphatic system. The lymphatic system filters out microbes from the fluids surrounding cells. In so doing, it is subject to infections that overrun the ability of the system to destroy the microbes. Lymphocytes are defensive cells commonly found in the lymphatic system.

- Lymphoid organs that are essential in body's defenses are: lymph nodes, spleen, thymus. Others less essential like lymphoid masses in intestines, respiratory system, urinary tract, tonsils.

- Lymphocytes circulate in blood, lymph & are dispersed in into lymphatic organs. Most lymphocytes are B lymphocytes (B cells) or T lymphocytes (T cells).

- B lymphocytes, originate & differentiate in bone marrow & migrate to lymph nodes & spleen.

- T cells, originate in bone marrow, migrate to the **T**hymus where they mature, then migrate to spleen & lymph nodes.

- Lymph nodes: occur in small groups, they contain B cells, T cells, dendritic cells & macrophages. Lymph passes through them in one direction, it is filtered & bacteria is phagocytized & destroyed.

- Thymus gland: present at birth, grows until puberty then atrophies gradually. It processes T lymphocytes & releases them in blood.

- Spleen: anatomically it is a large node, but does not filter lymph. It contains B & T cells & phagocytes. It digests old erythrocytes & microorganisms.

D) Inflammation

- It is the body's defensive mechanism to tissue damage whether it is caused by microbial infection, mechanical injury, UV light, electricity, chemicals or allergies.

- It is characterized by: hotness (increase in temp), redness, swelling, pain.

- Inflammation is either acute (short-term) or chronic (long-term). In acute inflammation, the host defenses won against microbe or inflammatory agent, in chronic inflammation, neither host nor inflammatory agent won.

- In infection, the inflammation acts to 1) kill microbe, 2) remove debris, 3) repair injured tissues

Steps involved in inflammation:

- Tissue is damaged & microbe enters the tissue.
- Basophils & mast cells release Histamine that causes vasodilation & increase permeability of blood capillaries. Vasodilation increases blood flow to damaged area resulting in redness & increase temp around the wound. Increased permeability will cause fluid to diffuse from capillaries to the injured cells resulting in swelling (edema).
- Blood brings clotting factors, nutrients & macrophages to the site of injury. Blood clotting occurs which stops bleeding & prevent microbes from spreading. Macrophages release cytokines (proteins that activates cells involved in inflammation) that attracts more phagocytes.
- Injured tissues also release bradykinin (small peptide) that stimulates pain receptors in the skin. Its action is intensified by prostaglandin.

- Inflamed tissues release cytokines that stimulate infiltration & production of leukocytes (leukocytosis).

- Phagocytes reach infected area & engulf microbes, many phagocytes die during this process.
- The infected site forms pus which is accumulation of dead macrophages, dead tissue & microbe debris. Some bacteria form pus because they release leukocidins that kill macrophages, viruses don't form pus.

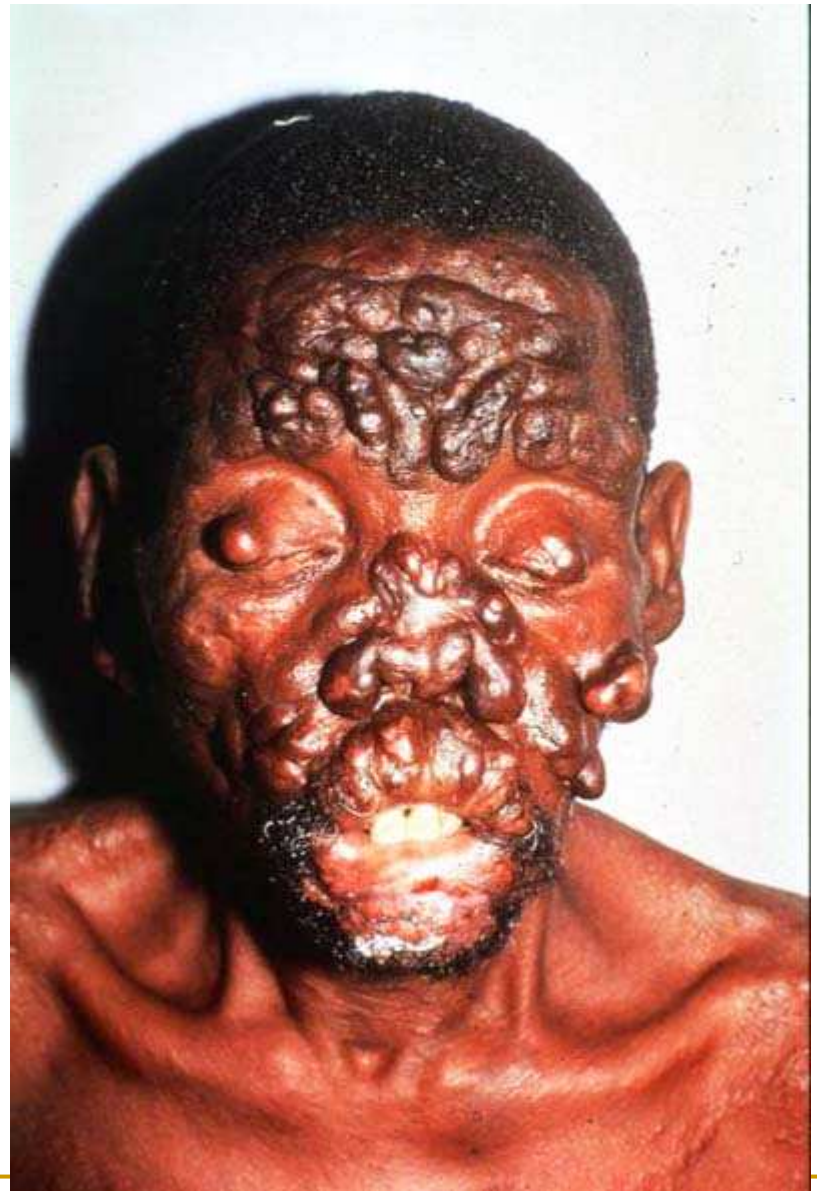
Repair & regeneration

- Dead cells & debris are removed, blood clot dissolves & Fibroblasts (connective tissue) replaces the destroyed tissue.
- Fibers & fibroblast replaces the muscle & nerve tissues that cannot be regenerated.
- New epidermis replaces the destroyed one.
- Healing is more rapid in young than elderly as it depends on cell division & blood circulation, also healing is affected by nutrition.

- Chronic inflammation:

Neither the agent of inflammation nor the host defense wins the battle.

since the causative agent not destroyed, a granuloma is formed. Granuloma is a pocket of tissues that surrounds & walls off the causative agent. Composed of epithelial cells, macrophages, collagen fibers & lymphocytes. e.g leproma (leprosy or Hansen's disease), tubercles (TB).



Leprosy

E) Fever

- A rise in body temp above 37.8ºC when measured orally (normal range 36.1-37.5ºC). At 43C death results.
- Body temp is regulated by hypothalamus.

- Fever is caused by pyrogens. Exogenous pyrogens that includes endotoxins & some exotoxins are released by pathogens, these cause release of endogenous pyrogens from macrophages that in turn act on hypothalamus to reset its thermostat at higher temp.

- Benefits of fever:
  - High body temp is above the optimum temp for pathogens growth
  - Some microbial enzymes & toxins are inactivated
  - Fever improves immune response by enhancing chemical rxns
  - enhances Phagocytosis &increase the production of antiviral interferon

- Increase breakdown of lysosomes, causing death to infected cells & the pathogen inside them
- Makes the patient feels ill & so to get rest which will spare energy to fight the infection

When to use antipyretics then??? For high fever & to patients with disorders that will be affected by increase heart rate, electrolyte imbalance. High fever causes convulsions to children.

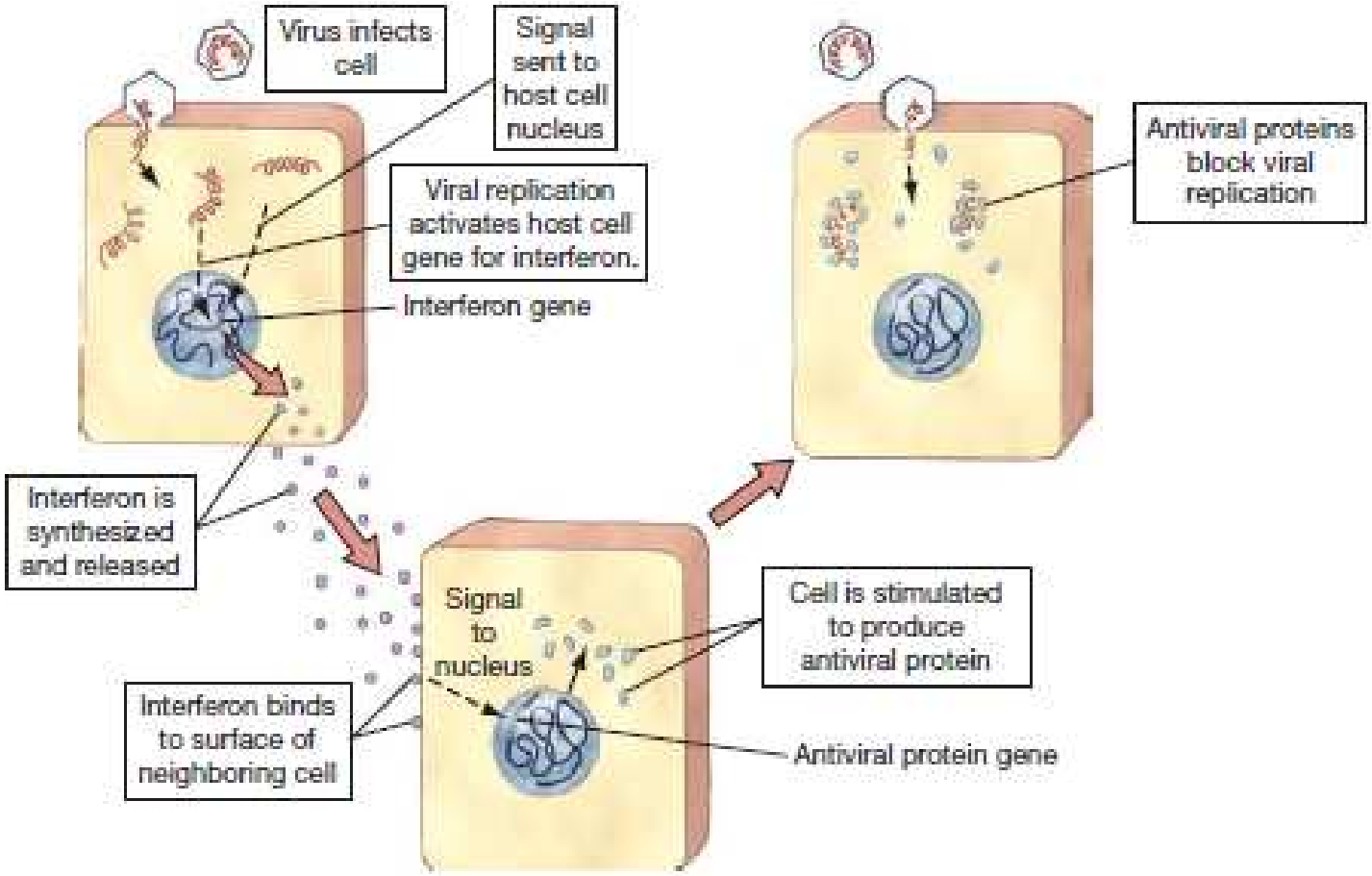
F) Molecular defenses (interferons & complement)

- ## Interferons

- According to structure & function, interferons are divided into type I (includes α,β)& type II (γ).

- Interferons INF(α,β) : proteins that are released by cells after being infected by viruses. γ interferons are released by non-infected NK & lymphocytes that are sensitive to specific antigens (cancer, virus, bacteria). Interferons cause uninfected cells to produce antiviral proteins (AVPs) that interferes with the virus replication. AVPs are enzymes that prevent the cells from producing viral nucleic acids & capsid proteins. Therefore they slow the spread of the virus.

- AVPs are specially effective against RNA viruses


Virus infects cell
Signal sent to host cell nucleus
Viral replication activates host cell gene for interferon.
Interferon gene
Interferon is synthesized and released
Interferon binds to surface of neighboring cell
Signal to nucleus
Cell is stimulated to produce antiviral protein
Antiviral protein gene
Antiviral proteins block viral replication

- INF–γ also, enhances the activity of NK cells, macrophages & lymphocytes, the cells needed to attack microbes & tumors, also helps macrophages to rid themselves from bacterial infection (e.g *M.tuberculosis* inside macrophage).

- They are species specific, i.e interferon produced by certain animal can not be used for human, only for that animal species.

Therapeutic value of interferons:

Since interferons are produced in minute amounts by cells, recombinant interferon (rINF) is produced in a cheaper way& more abundant quantities.

- Interferons stimulate adaptive immune defenses, therefore are used for some viral infections (e.g Hepatitis C) & several types of cancers

- Have side effects: fever, nausea, fatigue, vomiting, weight loss & high doses may cause toxicity to heart, kidneys & liver.

Complement system

- It is a set of large regulatory proteins that are important in the non specific host defense. These proteins are named, C1, C2, C3, C4..etc, 20 serum proteins are identified so far
- Produced by liver & circulate in plasma in inactive form
- It acts once a microbe is detected, much earlier than the adaptive immune response.

- Functions of the complement system:
  - Enhance phagocytosis by phagocytes
  - Lyse bacteria & enveloped viruses directly
  - Generate peptide fragments that regulate inflammation & immune response.

- Complement system acts in cascade, i.e a series of rxns where the next rxn produces more product than the previous (amplify some effects).

- Complement system acts in 2 pathways; the classical pathway & the alternative pathway.

- Classical pathway: in this pathway the complement is activated when antibodies bind to antigens (microbe).

- Alternative pathway: complement is activated by pathogen surface i.e when polysaccharides on the surface of microbe interact with complement proteins (activated earlier than classical pathway).

- Both pathways will result in activating the complement leading to :opsonization, inflammation & membrane attack complex.

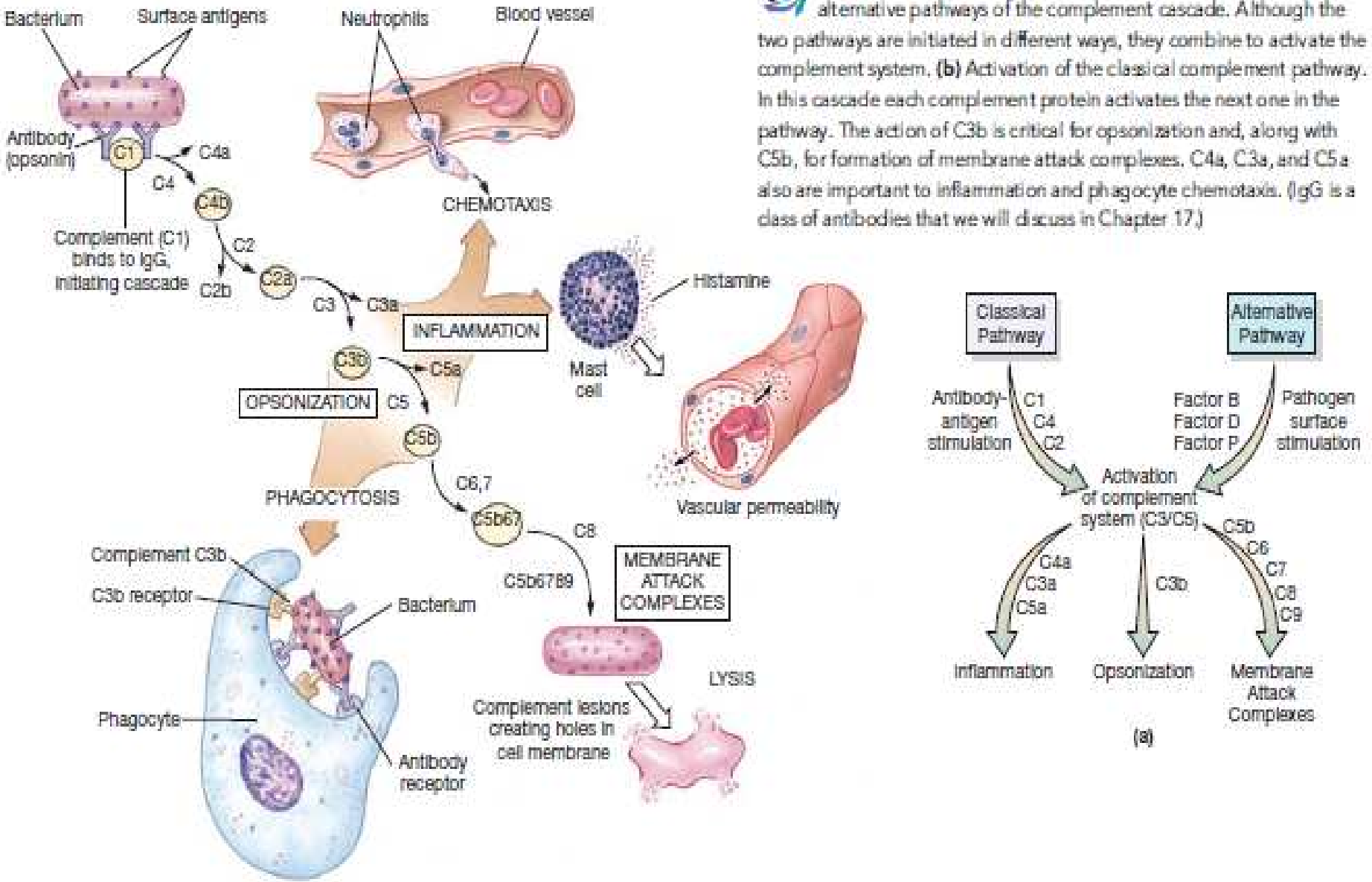


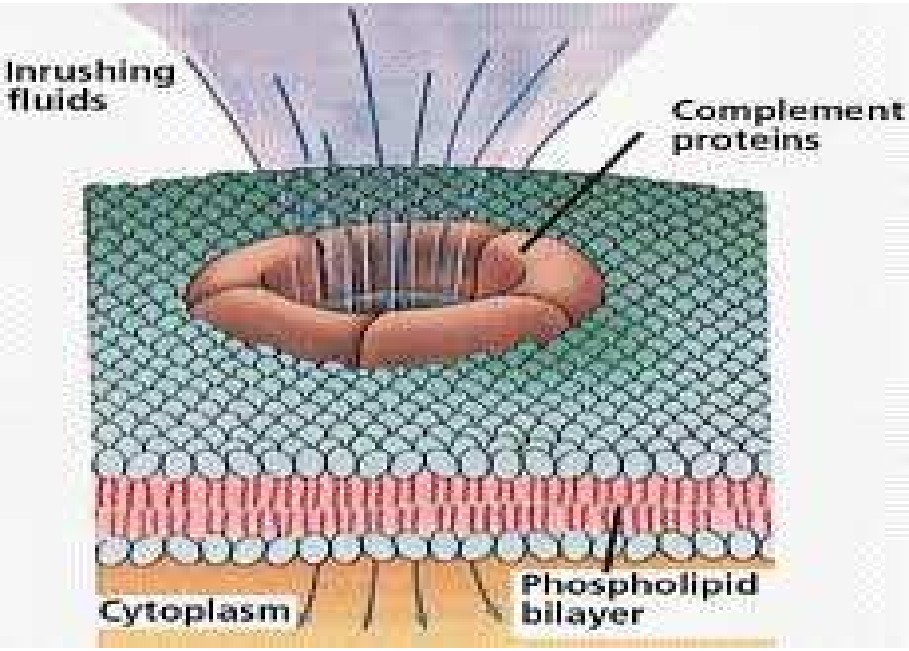
Figure 16.8 The complement system. (a) Classical and alternative pathways of the complement cascade. Although the two pathways are initiated in different ways, they combine to activate the complement system. (b) Activation of the classical complement pathway. In this cascade each complement protein activates the next one in the pathway. The action of C3b is critical for opsonization and, along with C5b, for formation of membrane attack complexes. C4a, C3a, and C5a also are important to inflammation and phagocyte chemotaxis. (IgG is a class of antibodies that we will discuss in Chapter 17.)

- Opsonization (immune adherence): special antibodies (opsonin) bind to the surface of microbe. Certain C proteins bind to these antibodies which activates the cascade. This will lead to binding of C3b protein to the surface of microbe. Phagocytes recognize this protein (C3b) & phagocytosis is stimulated.

- Inflammation: some of the products (C proteins) of the cascade stimulate chemotaxis & thus phagocytosis. Also they bind to mast cells & basophils causing the release of Histamine.

- Membrane Attack Complexes (MAC): C3b triggers complement cascade resulting in formation of hydrophobic protein complexes that are inserted into the microbe cell membrane causing lesions in cells. These complexes extend through the membrane & form a pore (MAC) which causes cell contents to leak out (lysis). This process called immune cytolysis. Host cell membrane has proteins that protect against MAC lysis

- Impaired activity of complement: absence of one or more of complement proteins will reduce the patient's resistance to infections especially bacterial infections. Such deficiencies could be acquired or congenital.


Inrushing fluids
Complement proteins
Cytoplasm
Phospholipid bilayer