Innate Immunity: Nonspecific Defenses of the Host

Innate immunity		adaptive immunity
First line of defense	Second line of defense	Third line of defense
1- Intact skin. 2-Mucous membranes and their secretions. 3- Normal microbiota.	1-Phagocytes, such as neutrophils, dendritic cells and macrophages. 2- Inflammation. 3- Fever. 4-Antimicrobial substances	1-Specialized lymphocytes T cells and B cells. 2- Antibodies.

- Innate immunity involves defenses against any pathogen. regardless of species.
- adaptive immunity involves defenses against a specific pathogen.

The Concept of Immunity

Innate immunity refers to defenses that are present at birth. They are always present and available to provide rapid responses to protect us against disease. Innate immunity does not involve specific recognition of a microbe. Further, innate immunity does not have a memory response, that is, a more rapid and stronger immune reaction to the same microbe at a later date.

Adaptive immunity is based on a specific response to a specific microbe once a microbe has breached the innate immunity defenses. It adapts or adjusts to handle a particular microbe.

Unlike innate immunity, adaptive immunity is slower to respond, but it does have a memory component.

First line of defense

Physical Factors

1- The intact skin

is the human body's largest organ in terms of surface area and weight and is an extremely important component of the first line of defense. It consists of two distinct portions: the **dermis** and the **epidermis**. The top layer of epidermal cells is dead and contains a protective protein called **keratin**. The periodic shedding of the top layer helps remove microbes at the surface. In addition, the dryness of the skin is a major factor in inhibiting microbial growth on the skin.

2- Mucous membranes

line the entire gastrointestinal, respiratory, and genitourinary tracts. The epithelial layer of a mucous membrane secretes a fluid called mucus, a slightly viscous (thick) glycoprotein produced by **goblet cells** of a mucous membrane. Among other functions, mucus prevents the tracts from drying out.

One such mechanism that protects the eyes is the **lacrimal apparatus**, a group of structures that manufactures and drains away tears. The **lacrimal glands**, produce the tears and pass them under the upper eyelid.

Saliva: produced by the **salivary glands**, helps dilute the numbers of microorganisms and wash them from both the surface of the teeth and the mucous membrane of the mouth.

The mucous membrane of the nose also has mucus-coated hairs that filter inhaled air and trap microorganisms, dust, and pollutants. The cells of the mucous membrane of the lower respiratory tract are covered with **cilia**.

The cleansing of the **urethra** by the flow of urine is another physical factor that prevents microbial colonization in the genitourinary tract.

Vaginal secretions likewise move microorganisms out of the female body.

Peristalsis, defecation, and vomiting also expel microbes.

Peristalsis is a series of coordinated contractions that propel food along the gastrointestinal tract . Mass peristalsis of large intestinal contents into the rectum results in defecation. In response to microbial toxins, the muscles of the gastrointestinal tract contract vigorously, resulting in vomiting and/or diarrhea, which may also rid the body of microbes.

Chemical Factors

1- **Sebaceous** (oil) glands of the skin produce an oily substance called **sebum** that prevents hair from drying and becoming brittle.

One of the components of sebum is unsaturated fatty acids, which inhibit the growth of certain pathogenic bacteria and fungi. The low pH of the skin, between pH 3 and 5, is caused in part by the secretion of fatty acids and lactic acid. The skin's acidity probably discourages the growth of many other microorganisms.

2- **Sweat glands** of the skin produce **perspiration**, which helps maintain body temperature, eliminate certain wastes, and flush microorganisms from the surface of the skin. Perspiration also contains **lysozyme**, an enzyme capable of breaking down cell walls of gram-positive bacteria and, to a lesser extent, gram negative bacteria. Specifically, lysozyme breaks chemical bonds on peptidoglycan, which destroys the cell walls. Lysozyme is also found in **tears**, **saliva**, **nasal secretions, tissue fluids, and urine,** where it exhibits its antimicrobial activity.

Saliva also contains an antibody (immunoglobulin A) that prevents attachment of microbes so that they cannot penetrate mucous membranes.

3-Gastric juice is produced by the glands of the stomach. It is a mixture of hydrochloric acid, enzymes, and mucus. The very high acidity of gastric juice (pH 1.2-3.0) is sufficient to destroy bacteria and most bacterial toxins, except those of *Clostridium botulinum* and *Staphylococcus aureus*. However, many enteric pathogens are protected by food particles and can enter the intestines via the gastrointestinal tract. In contrast, the bacterium *Helicobacter pylori* neutralizes stomach acid, thereby allowing the bacterium to grow in the stomach.

4- **Vaginal secretions** play a role in antibacterial activity in two ways. Glycogen produced by vaginal epithelial cells is broken down into lactic acid by *Lactobacillus acidophilils.* This creates an acid pH (3-5) that inhibits microbes. **Urine**, in addition to containing lysozyme, has an acid pH (average 6) that inhibits microbes. Also, urine contains urea and other metabolic by-products, such as uric acid, hippuric acid, which inhibit microbes.

Normal Microbiota

several relationships between normal microbiota and host cells. Some of these relationships help prevent the overgrowth of pathogens and thus may be considered components of innate immunity.

- **antagonism**, the normal microbiota prevent pathogens from colonizing the host by competing with them for nutrients, by producing substances that are harmful to the pathogens, and by altering conditions that affect the survival of the pathogens, such as pH and oxygen availability. The presence of normal

microbiota in the vagina, for example, alters pH, thus preventing overpopulation by *Candida albicans*, a pathogenic yeast that causes vaginitis. In the large intestine, *E. coli* bacteria produce **bacteriocins** that inhibit the growth of *Salmonella* and *Shigella*.

- **commensalism**, one organism uses the body of a larger organism as its physical environment and may make use of the body to obtain nutrients. Thus in commensalism, one organism benefits while the other is unaffected. Most microbes that are part of the commensal microbiota are found on the skin and in the gastrointestinal tract. The majority of such microbes are bacteria that have highly specialized attachment mechanisms and precise environmental requirements for survival. Normally, such microbes are harmless, but they may cause disease if their environmental conditions change. These opportunistic pathogens include *E. coli, Staphylococcus aureus S. epidermids, Enterococcus faecalis,* and oral streptococci.

Question

- Describe the role of the skin and mucous membranes in innate immunity.
- Differentiate physical from chemical factors. and list five examples of each.
- Describe the role of normal microbiota in innate Immunity.
- Identify one physical factor and one chemical factor that prevent microbes from entering the body through skin and mucous membranes.
- Identify one physical factor and one chemical factor that prevent microbes from entering or colonizing the body through the eyes, digestive tract. and respiratory tract.
- Distinguish microbial antagonism from commensalism.

Second line of defense

When microbes penetrate the first line of defense, they encounter a second line of defense that includes defensive cells, such as

1-Phagocytic cells

2-Inflammation

3- Fever

4- Antimicrobial substances.

Before we look at the phagocytic cells, it will be helpful to first have an understanding of the cellular components of blood.

Leukocytes are divided into two main categories based on their appearance under a light microscope: **granulocytes** and **agranulocytes**.

1- Granulocytes: They are differentiated into three types of cells on the basis of how the granules stain: **neutrophils, basophils, and eosinophils**.

-**Neutrophils** are also commonly called polymorphonuclear leukocytes (PMNs), or polymorph.
Neutrophils, which are highly phagocytic and motile, are active in the initial stages of an infection. They have the ability to leave the blood, enter an infected tissue, and destroy microbes and foreign particles.

- **Basophils**: release substances, such as histamine, that are important in inflammation and allergic responses.

-**Eosinophils** are somewhat phagocytic and also have the ability to leave the blood. Their major function is to produce toxic proteins against certain parasites, such as helminths. Although eosinophils are physically too small to ingest and destroy helminths, they can attach to the outer surface of the parasites

and discharge peroxide ions that destroy them. Their number increases significantly during certain parasitic worm infections and hypersensitivity (allergy) reactions.

2- **Agranulocytes**: There are three different types of agranulocytes: **monocytes**, **dendritic cells**, and **lymphocytes**.

-**Monocytes** are not actively phagocytic until they leave circulating blood, enter body tissues, and mature into macrophages.

-**Dendritic cells** are especially abundant in the epidermis of the skin, mucous membranes, the thymus, and lymph nodes. The function of dendritic cells is to destroy microbes by phagocytosis and to initiate adaptive immunity responses.

-**Lymphocytes** include **natural killer cells**, **T cells**, and **B cells**. Natural killer (NK) cells are found in blood and in the spleen, lymph nodes, and red bone marrow. NK cells have the ability to kill a wide variety of infected body cells and certain tumor cells. NK cells attack any body cells that display abnormal or unusual plasma membrane proteins. The binding of NK cells to a target cell, such as an infected human cell, causes the release of vesicles containing toxic substances from NK cells. Some granules contain a protein called **perforin**, which inserts into the plasma membrane of the target cell and creates channels in the membrane. As a result, extracellular fluid flows into the target cell and the cell bursts, a process called **cytolysis**. Other granules of NK cells release granzymes, which are protein-digesting enzymes that induce the target cell to undergo apoptosis, or self-destruction.

T cells and B cells are not usually phagocytic but play a key role in adaptive immunity. They occur in lymphoid tissues of the lymphatic system and also circulate in blood.

The Lymphatic System

Lymphoid tissue contains large numbers of lymphocytes, including T cells, B cells, and phagocytic cells that participate in immune responses.
Lymph nodes are the sites of activation of T cells and B cells, which destroy microbes by immune responses.

Question…..

- Compare the structures and function of monocytes and neutrophils.
- Describe the six different types of white blood cells, and name a function for each type.

Phagocytes

Phagocytosis is the ingestion of a microorganism or other substances (such as debris) by a cell. The cells that perform this function are collectively called **phagocytes**, all of which are types of white blood cells or derivatives of white blood cells.

Actions of Phagocytic Cells

When an infection occurs, both **granulocytes** (especially **neutrophils**, but also **eosinophils** and **dendritic cells**) and **monocytes** migrate to the infected area. During this migration, monocytes leave the blood and migrate into tissues where they enlarge and develop into **macrophages**.

Some macrophages, called **fixed macrophages**, are resident in certain tissues and organs of the body.

Fixed macrophages are found in the liver (Kupffer's cells), lungs (alveolar macrophages), nervous system (microglial cells).

Other macrophages are motile and are called **free macrophages,** which roam the tissues and gather at sites of infection or inflammation.

The Mechanism of Phagocytosis

phagocytosis will divide into four main phases:

1- chemotaxis
2- adherence
3- ingestion
4- digestion

1- Chemotaxis

Chemotaxis is the chemical attraction of phagocytes to microorganisms. Among the chemotactic chemicals that attract phagocytes are microbial products, components of white blood cells and damaged tissue cells, cytokines_ released by other white blood cells, and peptides derived from complement.

2- Adherence

Adherence is the attachment of the phagocyte's plasma membrane to the surface of the microorganism or other foreign material. Adherence is facilitated by the attachment of pathogen-associated molecular patterns (PAMPs) of microbes to receptors, such as Toll –like receptors (TLRs), on the surface of phagocytes. The binding of PAMPs to TLRs not only initiates phagocytosis, but also induces the phagocyte to release specific cytokines that recruit additional phagocytes.

Microorganisms can be more readily phagocytized if they are first coated with certain serum proteins that promote attachment of the microorganisms to the phagocyte. This coating process is called **opsonization**. The proteins that act as **opsonins** include some components of the complement system and antibody molecules.

3-Ingestion

During this process, the plasma membrane of the phagocyte extends projections called pseudopods that engulf the microorganism. Once the microorganism is surrounded, the pseudopods meet and fuse, surrounding the microorganism with a sac called a **phagosome**, or phagocytic vesicle.

The membrane of a phagosome has enzymes that pump protons (H+) into the phagosome, reducing the pH to about 4. At this pH, hydrolytic enzymes arc activated.

4- Digestion

In this phase of phagocytosis, the phagosome pinches off from the plasma membrane and enters the cytoplasm. Within the cytoplasm, it contacts Lysosomes that contain digestive enzymes and bactericidal substance on contact, the phagosome and lysosome membranes fuse to form a single larger structure called a **phagolysosome**.

Intracellular killing:

Intracellular killing is done by two mechanisms:

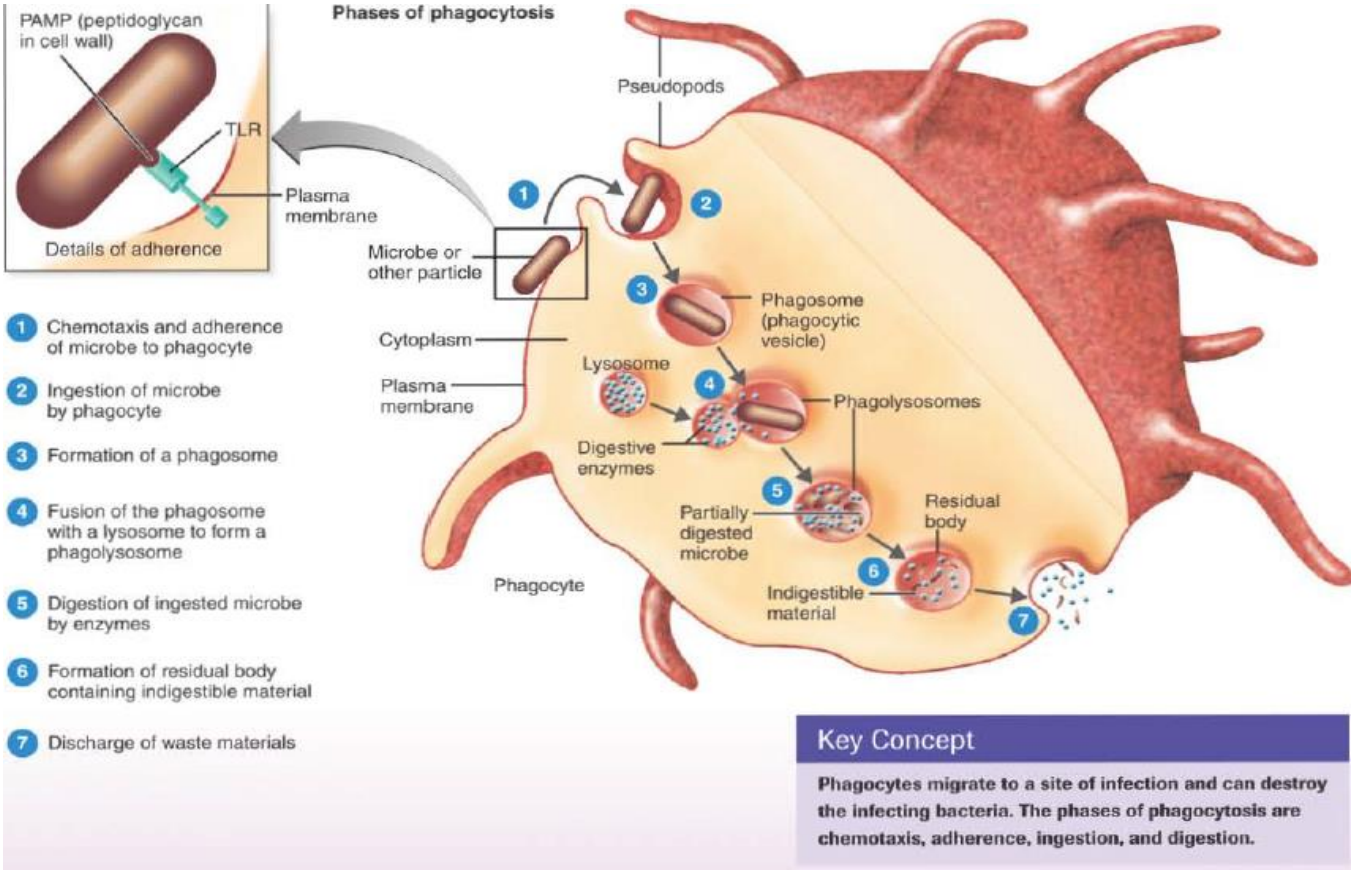
-Oxygen dependent mechanisms

Oxygen is converted to the following products which kill the microbe:

Lysosomes also contain enzymes that can produce toxic oxygen products such as superoxide radical (O^{2-}) , hydrogen peroxide (H_2O_2), nitric oxide (NO), singlet oxygen, and hydroxyl radical ($OH\cdot$)

-Non oxygen dependent mechanisms

The microbe is killed by many hydrolytic and proteolytic enzymes such as lysozyme which hydrolyzed peptidoglycan in bacterial cell walls. A variety of other enzymes, such as lipases, proteases, ribonuclease, and deoxy ribonuclease, hydrolyze other macromolecular components of microorganisms.



Microbial Evasion of Phagocytosis

The ability of a pathogen to cause disease is related to its ability to evade phagocytosis. Some bacteria have structures that inhibit adherence, such as the M protein and capsules.

- M protein of *Streptococcus pyogenes* inhibits the attachment of phagocytes to their surfaces and makes adherence more difficult.

-Organisms with large **capsules** include *Streptococcus pneumoniae* and *Haemophilus influenzae* type b. Heavily encapsulated microorganisms like these can be phagocytized only if the phagocyte traps the microorganism against a rough surface, such as a blood vessel, blood dot, or connective tissue fiber, from which the microbe cannot slide away.

Other microbes may be ingested but not killed. For example, *Staphylococcus* produces leucocidins that may kill phagocytes by causing the release of the phagocyte's own lysosomal enzymes into its cytoplasm. Streptolysin released by streptococci has a similar mechanism.
A number of intracellular pathogens secrete pore-forming toxins that lyse phagocyte cell membranes once inside the phagocyte. For example, *Trypanosoma cruzi* (the causative agent of American trypanosomiasis), and *Listeria monocytogenes* (the causative agent of listeriosis), produce membrane attack complexes that lyse phagolysosome membranes and release the microbes into the cytoplasm of the phagocyte, where they propagate.
Still other microbes have the ability to survive inside phagocytes. *Coxiella burnetii,* the causative agent of Q fever, actually requires the low pH inside a phagolysosome to replicate.

Listeria monocytogenes, Shigella (the causative agent of shigellosis), and *Rickettsia* (the causative agent of Rocky Mountain spotted fever and typhus) have the ability to escape from a phagosome before it fuses with a lysosome.

- Biofilms also play a role in evading phagocytes. Bacteria that are part of biofilms are much more resistant to phagocytosis because the phagocytes can not detach bacteria from the biofilm prior to phagocytosis.

Inflammation

Damage to the body's tissues triggers a local defensive response called inflammation, another component of the second line of defense. The damage can be caused by microbial infection, physical agents (such as heat, radiant energy, electricity, or sharp objects), or chemical agents (acids, bases, and gases). Inflammation is usually characterized by four signs and symptoms: **redness**, **pain**, **heat**, and **swelling**. Sometimes a fifth, loss of functions.

acute inflammation If the cause of an inflammation is removed in a relatively short period of time.

chronic inflammation. If the cause of an inflammation is difficult or impossible to remove, the inflammatory response is longer lasting but less intense. such as tuberculosis, caused by *M. tuberculosis.*

functions of inflammation:

(1) to destroy the injurious agent, if possible, and to remove it and its by-products from the body.

(2) if destruction is not possible, to limit the effects on the body by confining or walling off the injurious agent and its by products.

(3) to repair or replace tissue damaged by the injurious agent or its by-products.

During the early stages of inflammation, microbial structures, such as flagellin, lipopolysaccharides (LPS), and bacterial DNA stimulate the macrophages to produce cytokines, such as tumor necrosis factor alpha (α-TNF). In response to α-TNF in the blood, the liver synthesizes a group of proteins called **acute-**

phase proteins; other acute-phase proteins are present in the blood in an inactive form and are converted to an active form during inflammation. Acute-phase proteins induce both local and systemic responses and include proteins such as **C- reactive protein**, mannose-binding lectin and several specialized proteins such as fibrinogen for blood clotting and kinins for vasodilation.

Inflammation can be divide into three stages:

1-vasodilation and increased permeability of blood vessels,

2-phagocyte migration and phagocytosis,

3-tissue repair.

1-Vasodilation and Increased Permeability of Blood Vessels

- -The increase in permeability,which permits fluid to move from the blood into tissue spaces, is responsible for the **edema.**
- The release of histamine, kinins, prostaglandins and Leukotrienes causes vasodilation and increased permeability of blood vessels.
- Blood clots can form around an abscess to prevent dissemination of the infection.

2-Phagocyte Migration and Phagocytosis

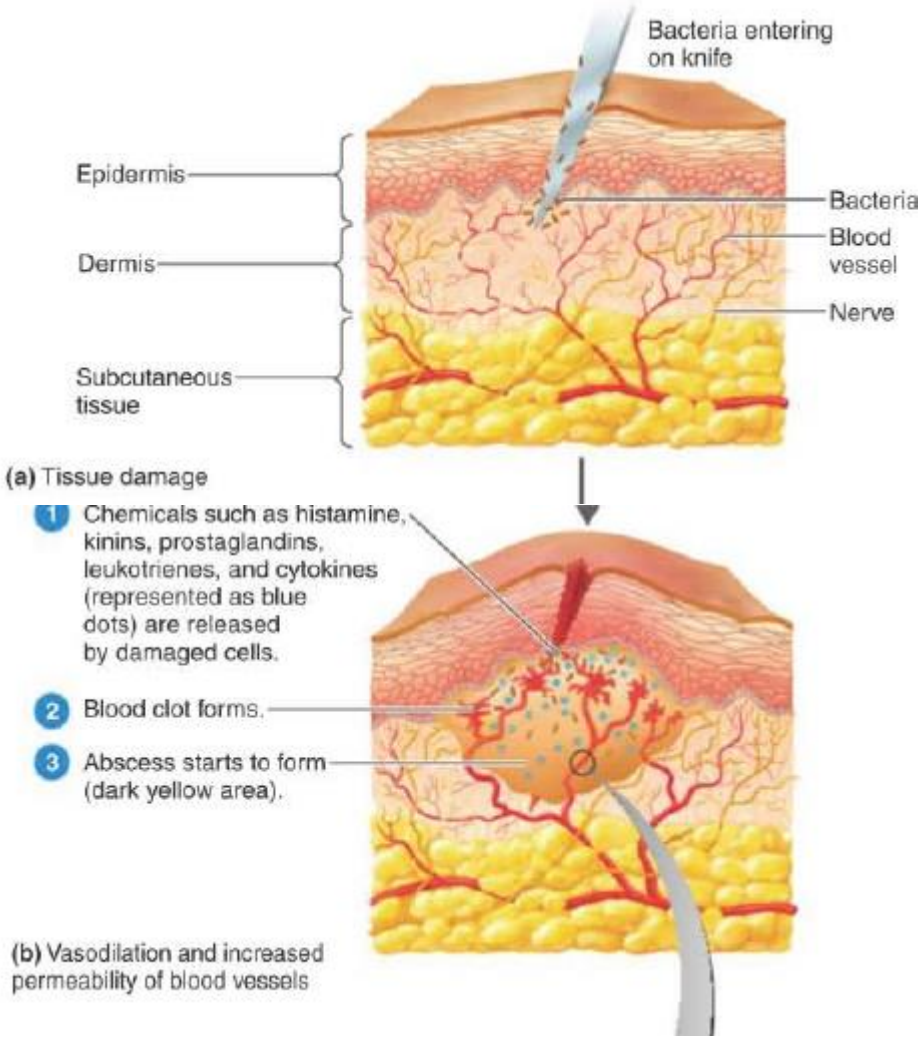
- Phagocytes have the ability to stick to the lining of the blood vessels (margination).
- They also have the ability to squeeze through blood vessels (diapedesis).
- Pus is the accumulation of damaged tissue and dead microbes, granulocytes, and macrophages.

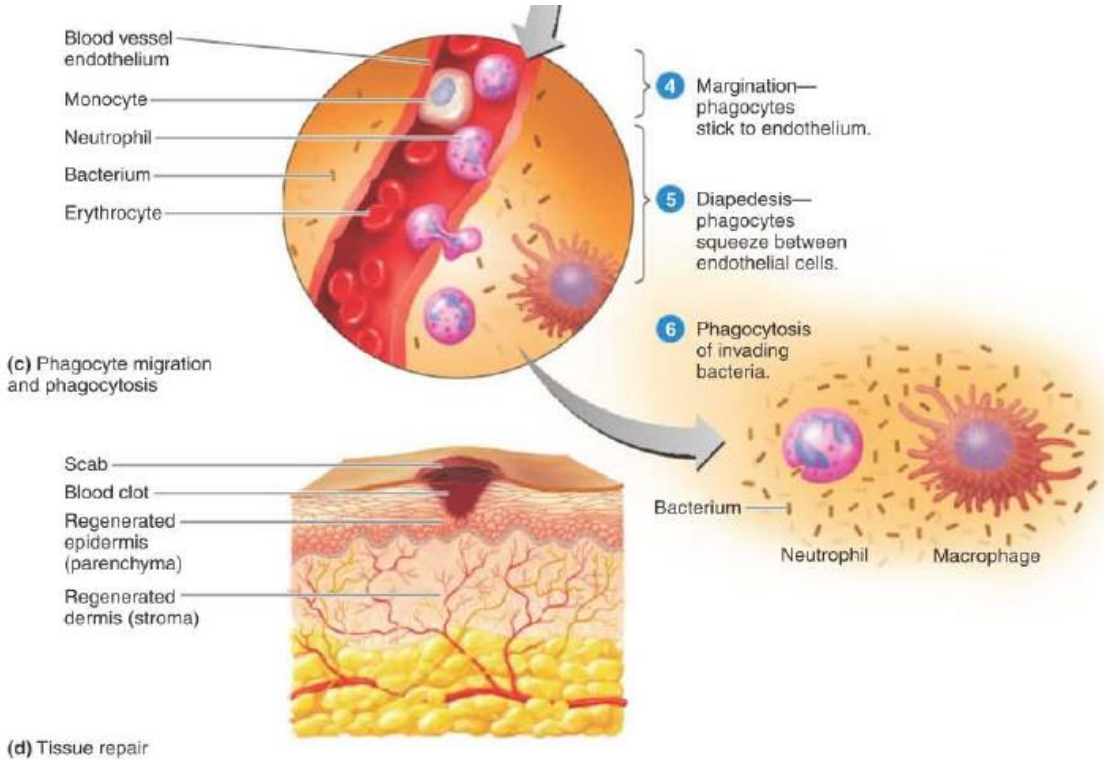
3-Tissue Repair

- A tissue is repaired when the stroma (supporting tissue) or parenchyma (functioning tissue) produces new cells.
- Stromal repair by fibroblasts produces scar tissue.

Some Questions

1- What purposes does inflammation serve?
2- What causes the redness, swelling, and pain associated with inflammation?
3- What is margination?

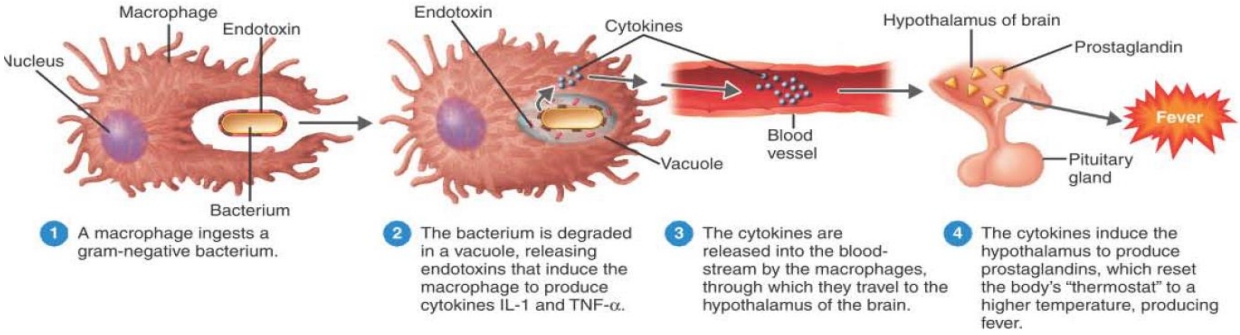

Bacteria entering on knife
Epidermis
Dermis
Subcutaneous tissue
Bacteria
Blood vessel
Nerve
(a) Tissue damage
1 Chemicals such as histamine, kinins, prostaglandins, leukotrienes, and cytokines (represented as blue dots) are released by damaged cells.
2 Blood clot forms.
3 Abscess starts to form (dark yellow area).
(b) Vasodilation and increased permeability of blood vessels



Fever

Inflammation is a local response of the body to injury. There are also systemic, or overall, responses; one of the most important is fever, an abnormally high body temperature, a third component of the second line of defense. The most frequent cause of fever is infection from bacteria (and their toxins) or viruses.

Body temperature is controlled by a part of the brain called the hypothalamus. The hypothalamus is sometimes called the body's thermostat, and it is normally set at 37°C . It is believed that certain substances affect the hypothalamus by setting it at a higher temperature. Recall that when phagocytes ingest gram-negative bacteria, the lipopolysaccharides (LPS) of the cell wall (endotoxins) are released, causing the phagocytes to release the cytokines interleukin- I (formerly called endogenous pyrogen), along with TNF- α. These cytokines cause the hypothalamus to release prostaglandins that reset the hypothalamic thermostat at a higher temperature, thereby causing fever.



Assume that the body is invaded by pathogens and that the thermostat setting is increased to 39°C. To adjust to the new thermostat setting, the body responds by constricting blood vessels, increasing the rate of metabolism, and shivering, all of which raise body temperature. Even though body temperature is

climbing higher than normal, the skin remains cold, and shivering occurs. This condition, called a **chill**, is a definite sign that body temperature is rising. When body temperature reaches the setting of the thermostat, the chill disappears. The body will continue to maintain its temperature at 39"C until the cytokines are eliminated. The thermostat is then reset to 37°C. As the infection subsides, heat-losing mechanisms such as vasodilation and sweating go into operation. The skin becomes warm, and the person begins to sweat. This phase of the fever, called the **crisis**, indicates that body temperature is falling. Interleukin-I helps step up the production of T cells. High body temperature intensifies the effect of antiviral interferons and increases production of **transferrins** that decrease the iron available to microbes. Also, because the high temperature speeds up the body's reactions, it may help body tissues repair themselves more quickly. Among the complications of fever are tachycardia (rapid heart rate), which may compromise older persons with cardiopulmonary disease; increased metabolic rate, which may produce acidosis; dehydration; electrolyte imbalances; seizures

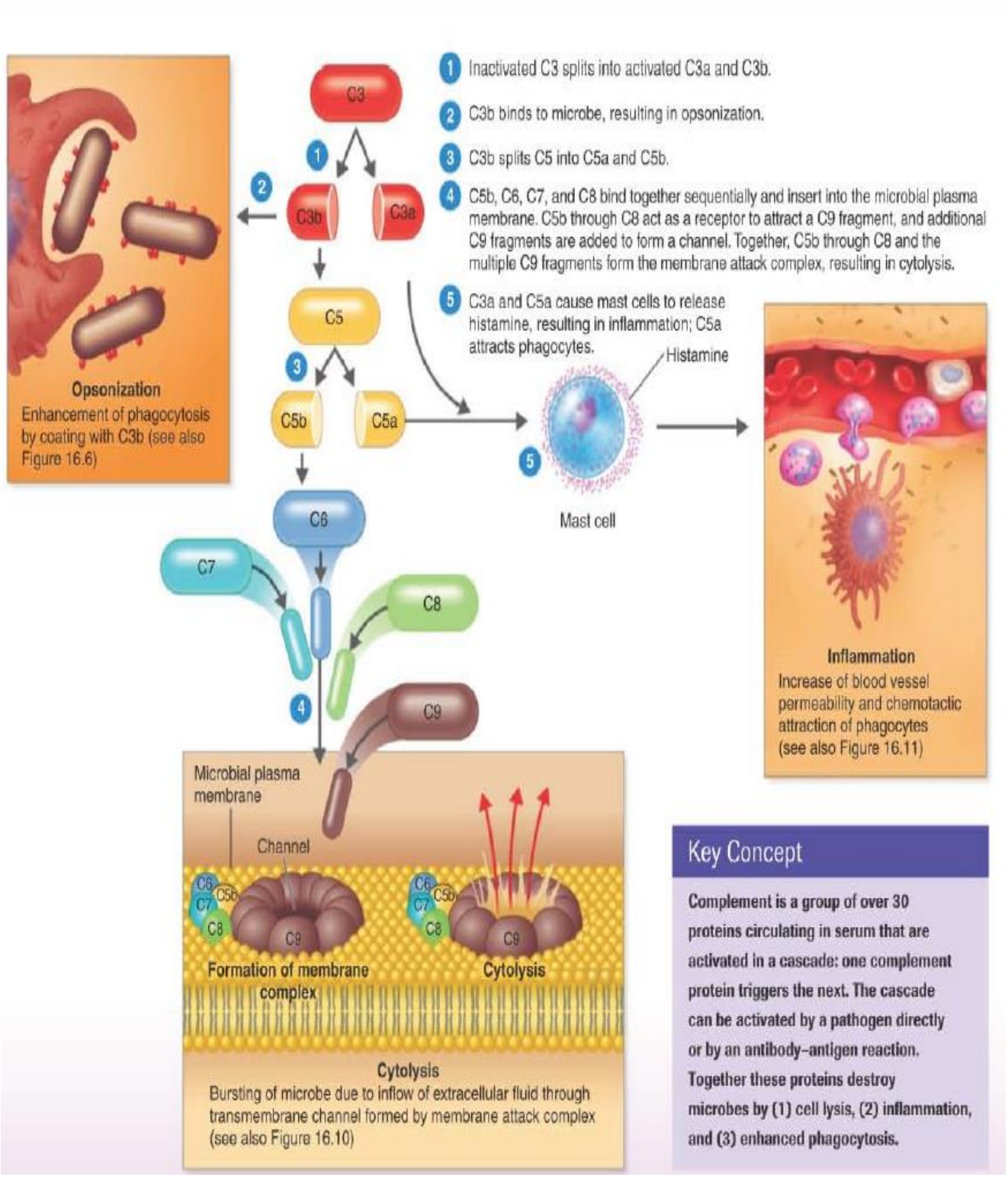
in young children; and delirium and coma. As a rule, death results if body temperature rises above 44 to 46"C.

Antimicrobial Substances

Among the most important of these are the proteins of the complement system: interferons, iron-binding proteins, and antimicrobial peptides.

1- The Complement System

The complement system is a defensive system consisting of over 30 proteins produced by the liver and found circulating in blood serum and within tissues throughout the body. The complement system is so-named because it "complements" the cells of the immune system in destroying microbes. The complement system is not adaptable and does not change over the course of a person's lifetime; for these reasons, it belongs to the innate immune system. However, it can be recruited and brought into action by the adaptive immune system. Together, proteins of the complement system destroy microbes by (I) cytolysis, (2) inflammation, and (3) phagocytosis and also prevent excessive damage to host tissues. Complement proteins are usually designated by an uppercase letter C and are inactive until they are split into fragments (products). The proteins are numbered Cl through C9, named for the order in which they were discovered. The fragments are activated proteins and are indicated by the lowercase letters a and b. For example, inactive complement protein C3 is split into two activated fragments, C3a and C3b. The activated fragments carry out the destructive actions of the Cl through C9 complement proteins. Complement proteins act in a cascade; that is, one reaction triggers another, which in turn triggers another, and so on.



Key Concept

Complement is a group of over 30 proteins circulating in serum that are activated in a cascade: one complement protein triggers the next. The cascade can be activated by a pathogen directly or by an antibody–antigen reaction. Together these proteins destroy microbes by (1) cell lysis, (2) inflammation, and (3) enhanced phagocytosis.

Pathways of complement activation

1. Classical pathway.
2. Alternative pathway.
3. Lectin pathway.

The Classical Pathway

The classical pathway is initiated when antibodies bind to antigens (microbes) and occurs as follows:

1- Antibodies attach to antigens (for example, proteins or large polysaccharides on the surface of a bacterium or other cell), forming antigen- antibody complexes. The antigen-antibody complexes bind and activate Cl.

2- Next, activated Cl activates C2 and C4 by splitting them. C2 is split into fragments called C2a and C2b, and C4 is split into fragments called C4a and C4b.

3- C2a and C4b combine and together they activate C3 by splitting it into C3a and C3b. The C3 fragments then initiate cytolysis, inflammation, and opsonization

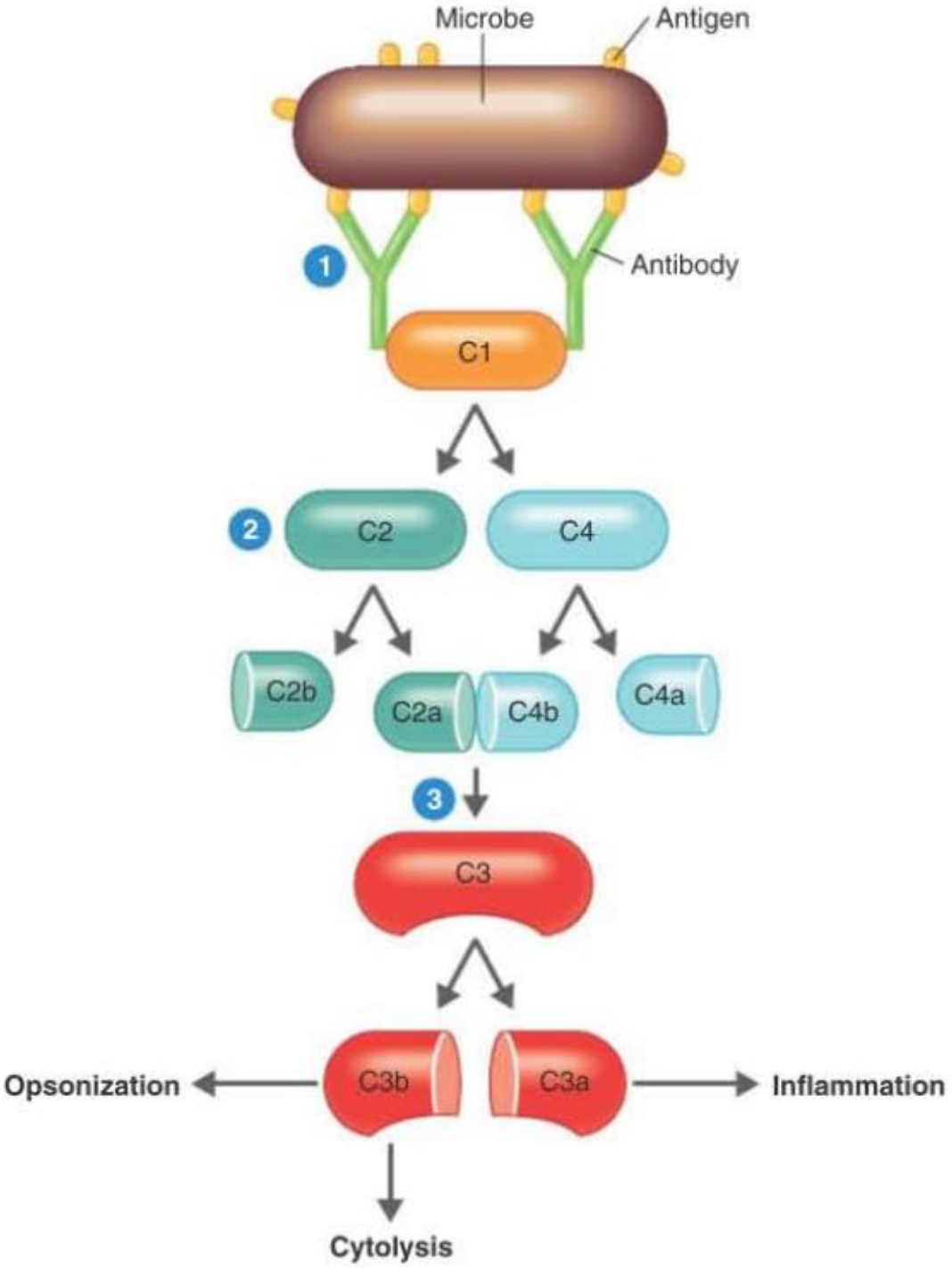
4- C3b binds to the surface of a microbe, and receptors on phagocytes attach to the C3b. Thus C3b enhances phagocytosis by coating a microbe, a process called **opsonization**, or immune adherence. Opsonization promotes attachment of a phagocyte to a microbe.

5- C3b also initiates a series of reactions that result in cytolysis. First, C3b splits C5 into C5b and C5a. Fragments C5b, C6, C7, and C8 bind together sequentially and insert into the plasma membrane of the invading cell. C5b through C8 act as a receptor that attracts a C9 fragment. Additional C9 fragments arc added

to form a transmembrane channel. Together, C5b through C8 and the multiple C9 fragments form the **membrane attack complex (MAC).**

6-The transmembrane channels (holes) of the MAC result in cytolysis, the bursting of the microbial cell due to the inflow of extracellular fluid through the channels.

7- C3a and C5a bind to mast cells and cause them to release histamine and other chemicals that increase blood vessel permeability during inflammations. C5a also functions as a very powerful chemotactic factor that attracts phagocytes to the site of an infection.

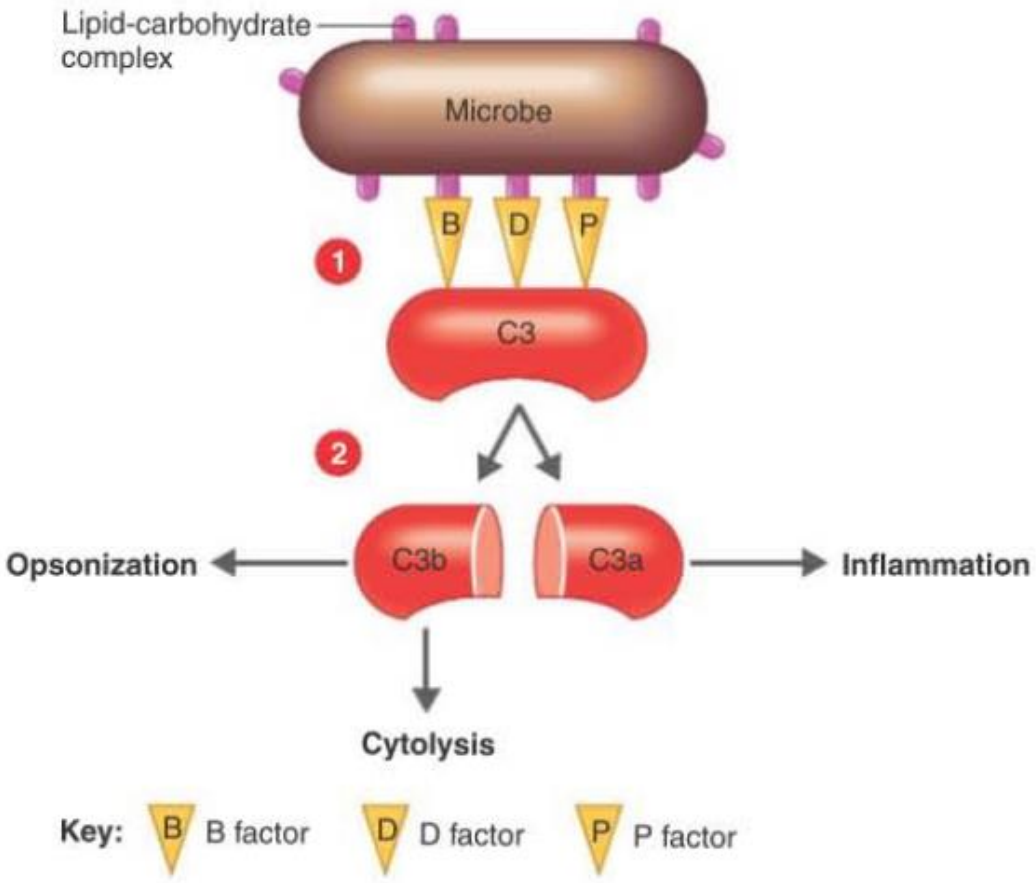


The Alternative Pathway

Unlike the classical pathway, the alternative pathway docs not involve antibodies. The alternative pathway is activated by contact between certain complement proteins and a pathogen.

1- C3 is constantly present in the blood . It combines with complement proteins called factor B, factor D, and factor P (properdin) on the surface of a pathogenic microbe. The complement proteins are attracted to microbial cell surface material (mostly lipid-carbohydrate complexes of certain bacteria and fungi).

2- Once the complement proteins combine and interact, C3 is split into fragments C3a and C3b. As in the classical pathway, C3a participates in inflammation, and C3b functions in cytolysis and opsonization.



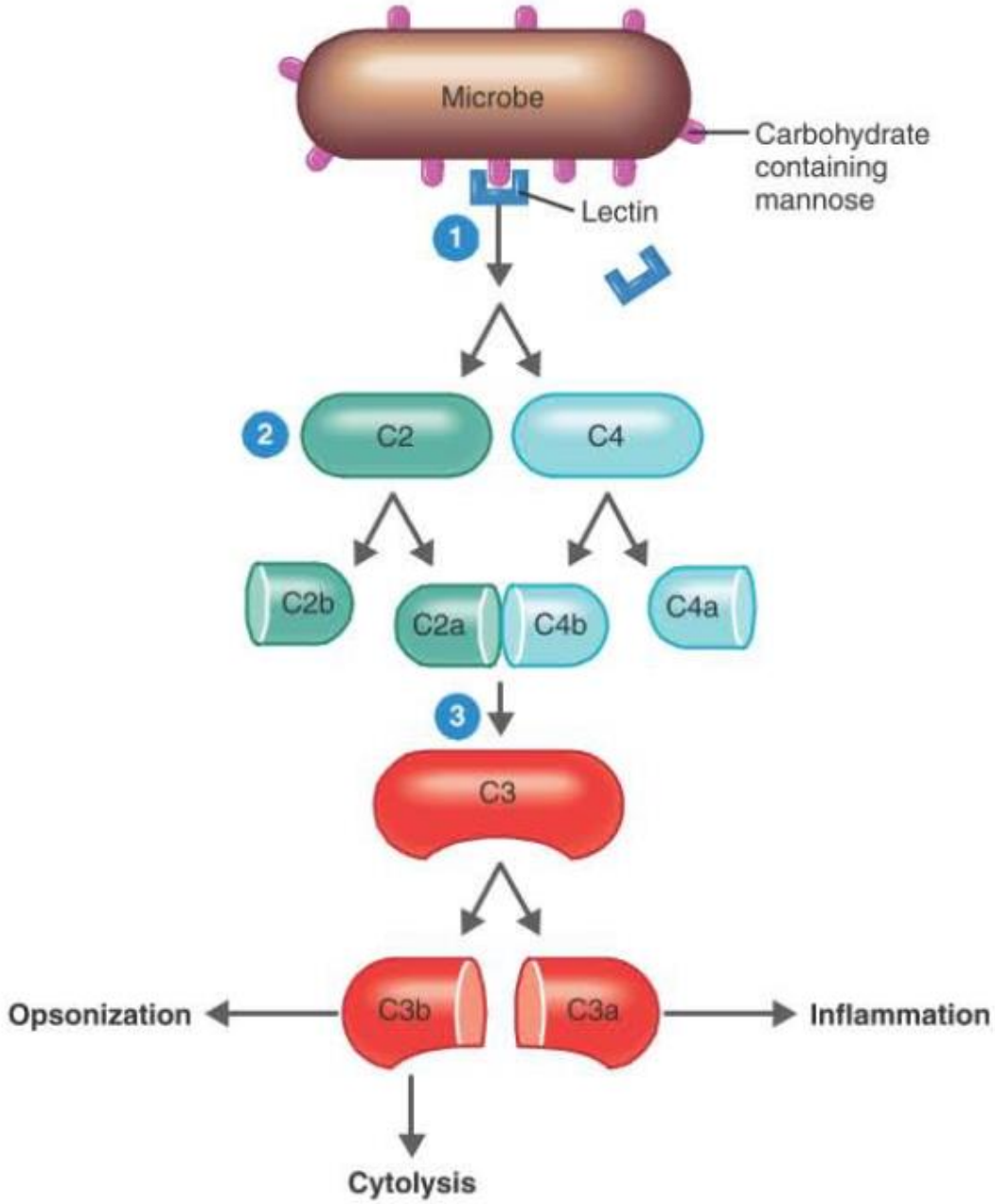
The Lectin Pathway

The lectin pathway is the most recently discovered mechanism for complement activation, When macrophages ingest bacteria, viruses, and other foreign matter by phagocytosis, they release cytokines that stimulate the liver to produce lectins. Proteins that bind to carbohydrates.

1- One such lectin, mannose-binding lectin (MBL), binds to the carbohydrate mannose. MBL binds to many pathogens because the MBL molecules recognize a distinctive pattern of carbohydrates that includes mannose, which is found in bacterial cell walls and on some viruses. As a result of binding, MBL functions as an opsonin to enhance phagocytosis and

2- activates C2 and C4;

3- C2a and C4b activate C3.


Microbe
Carbohydrate containing mannose
Lectin
1
2
C2
C4
C2b
C2a
C4b
C4a
3
C3
Opsonization
C3b
C3a
Inflammation
Cytolysis

Interferons

Interferons (IFNs) are a class of similar antiviral proteins produced by certain animal cells, such as lymphocytes and macrophages, after viral stimulation .

One of the principal functions of interferons is to interfere with viral multiplication.

Human interferons are of three principal types:

- alpha interferon (IFN -α),
- beta interferon (IFN - β),
- gamma iuterferoll (IFN-γ).

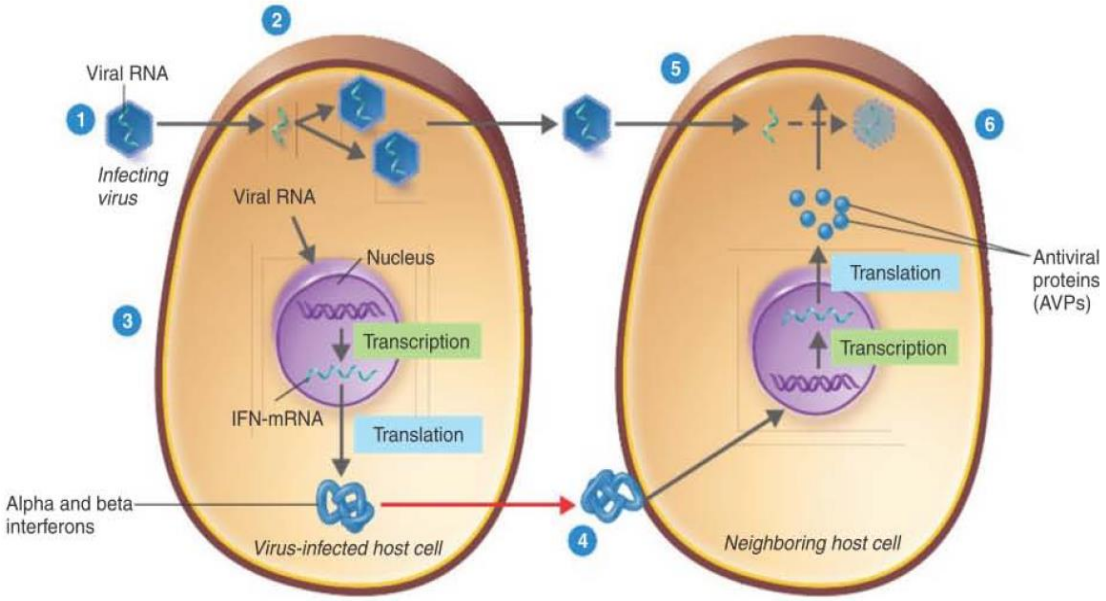
In the human body, interferons are produced by fibroblasts in connective tissue and by lymphocytes and other leukocytes. Each of the three types of interferons produced by these cells can have a slightly different effect on the body.

All interferons are small proteins, with molecular weights between 15,000 and 30,000. They are quite stable at low pH and are fairly resistant to heat.

Gamma interferon is produced by lymphocytes; it induces neutrophils and macrophages to kill bacteria. IFN- γ causes macrophages to produce nitric oxide that appears to kill bacteria as well as tumor cells by inhibiting ATP production.

Both IFN- α. and IFN- β are produced by virus-infected host cells only in very small quantities and diffuse to uninfected neighboring cells. They react with plasma or nuclear membrane receptors, inducing the uninfected cells to manufacture mRNA for the synthesis of antiviral proteins (AVPs). These proteins are enzymes that disrupt various stages of viral multiplication.

- interferons are effective for only short periods
- they do not remain stable for long periods of time in the body.
- And when injected, interferons have side effects, such as nausea, fatigue, headache, vomiting, weight loss, and fever.
- High concentrations of interferons are toxic to the heart, liver, kidneys, and red bone marrow.
- They typically play a major role in infections that are acute and short term, such as colds and influenza.
- Another problem is that they have no effect on viral multiplication in cells already infected.
- Also, some viruses, such as adenoviruses (which cause respiratory infections), have resistance mechanisms that inhibit AVPs.
- Further, some viruses, such as the hepatitis B virus, do not induce the production of sufficient amounts of interferon in host cells following viral stimulation.



1. Viral RNA from an infecting virus enters the cell.
2. The infecting virus replicates into new viruses.
3. The infecting virus also induces the host cell to produce interferon mRNA (IFN-mRNA), which is translated into alpha and beta interferons.
4. Interferons released by the virus-infected host cell bind to plasma membrane or nuclear membrane receptors on uninfected neighboring host cells, inducing them to synthesize antiviral proteins (AVPs). These include oligoadenylate synthetase and protein kinase.
5. New viruses released by the virus-infected host cell infect neighboring host cells.
6. AVPs degrade viral mRNA and inhibit protein synthesis—and thus interfere with viral replication.

Antimicrobial Peptides

antimicrobial peptides (AMPs) may be one of the most important components of innate immunity. Antimicrobial peptides arc short peptides that consist of a chain of about 12 to 50 amino acids synthesized on ribosomes. The modes of action of AMPs include inhibiting cell wall synthesis; forming pores in the plasma membrane, resulting in lysis; and destroying DNA and RNA.

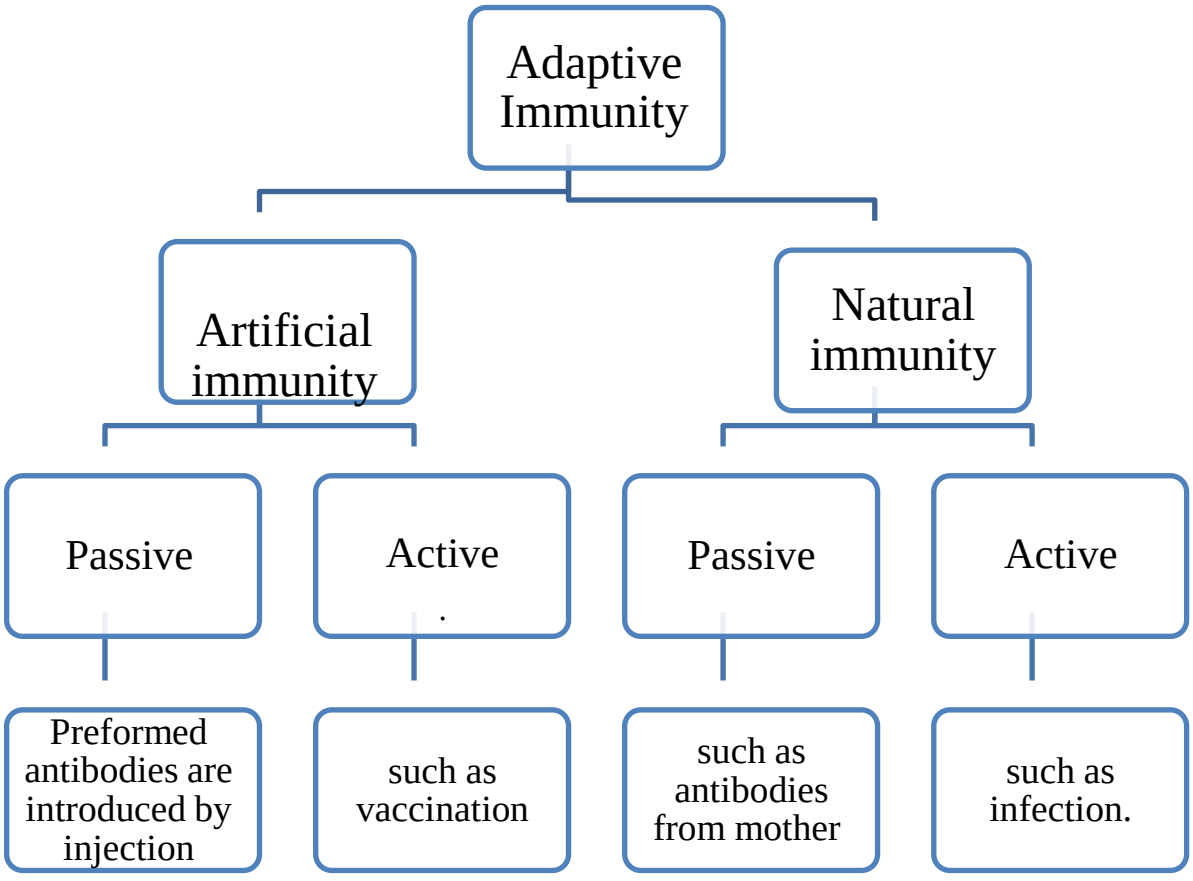
Among the AMPs produced by humans are dermcidin, produced by sweat glands; defensins and cathelicidirls, produced by neutrophils, macrophages, and epithelium; and thrombocidin, produced by platelets.

Adaptive Immunity: Specific Defenses of the Host

❖ Characters:

- Highly specific for the invading antigen.
- Can differentiate between self and non self antigens. The response occurs only to non self antigen.
- Diversity: responds to millions of different antigens.
- Immunological memory due to presence of memory cells.

❖ Types of acquired immunity:



❖ Mechanisms of acquired immunity:

- Humoral immunity:
  - ***Mediated by antibodies secreted from B lymphocytes.***
- Cell mediated immunity:
  - ***Mediated by T lymphocytes, NK cells and macrophages.***

Antigens and Antibodies

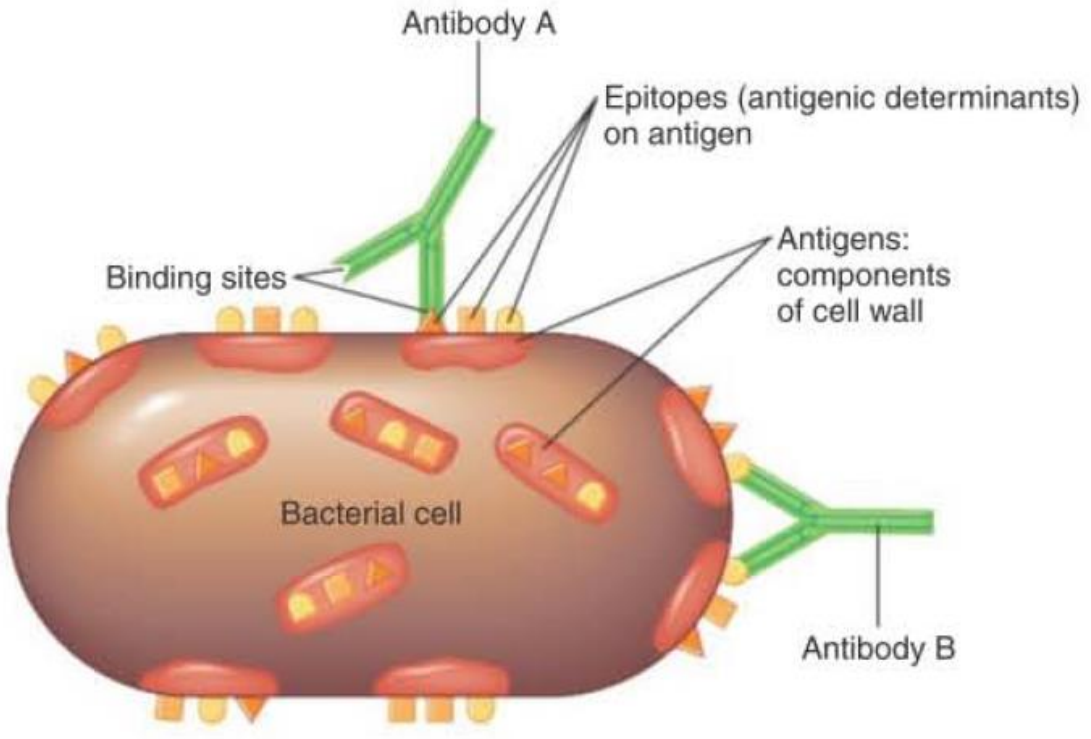
Antigens that cause a response are known as immunogens.

The Nature of Antigens

Most antigens are either proteins or large polysaccharides. Lipids and nucleic acids are usually antigenic only when combined with proteins and polysaccharides. Antigenic compounds are often components of invading microbes, such as capsules, cell walls, flagella, fimbriae, and toxins of bacteria; the coats of viruses; or the surfaces of other types of microbes.

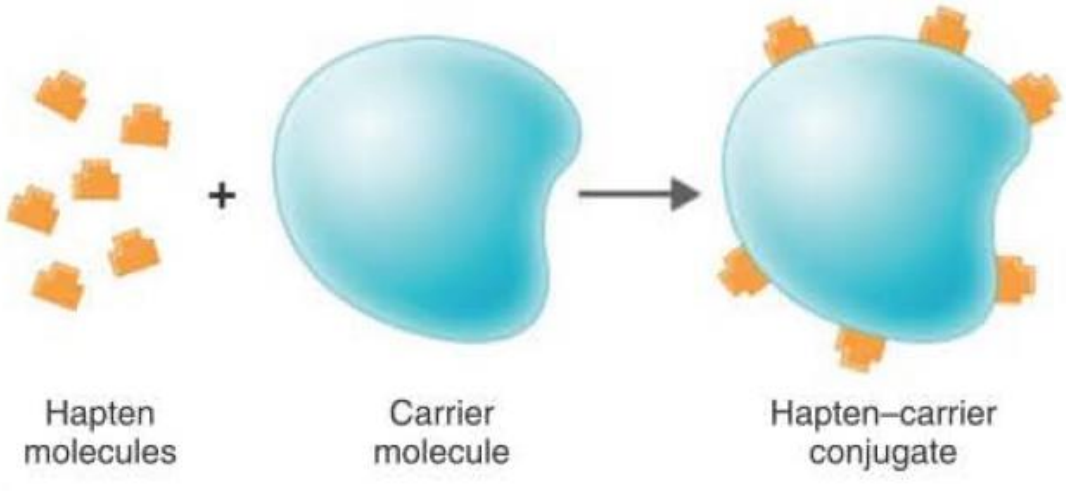
Non microbial antigens include pollen, egg white, blood cell surface molecules, serum proteins from other individuals or species, and surface molecules of transplanted tissues and organs.

Generally, antibodies recognize and interact with specific regions on antigens called **epitopes** or antigenic determinants (Figure below).



The nature of this interaction depends on the size, shape, and chemical structure of the binding site on the antibody molecule. Most antigens have a molecular weight of 10,000 or higher.

A foreign substance that has a low molecular weight is often not antigenic unless it is attached to a carrier molecule. These low molecular weight compounds are called **haptens**



Penicillin is a good example of a hapten. This drug is not antigenic by itself, but some people develop an allergic reaction to it. (Allergic reactions are a type of immune response). In these people, when penicillin combines with host proteins, the resulting combined molecule initiates an Immune response.

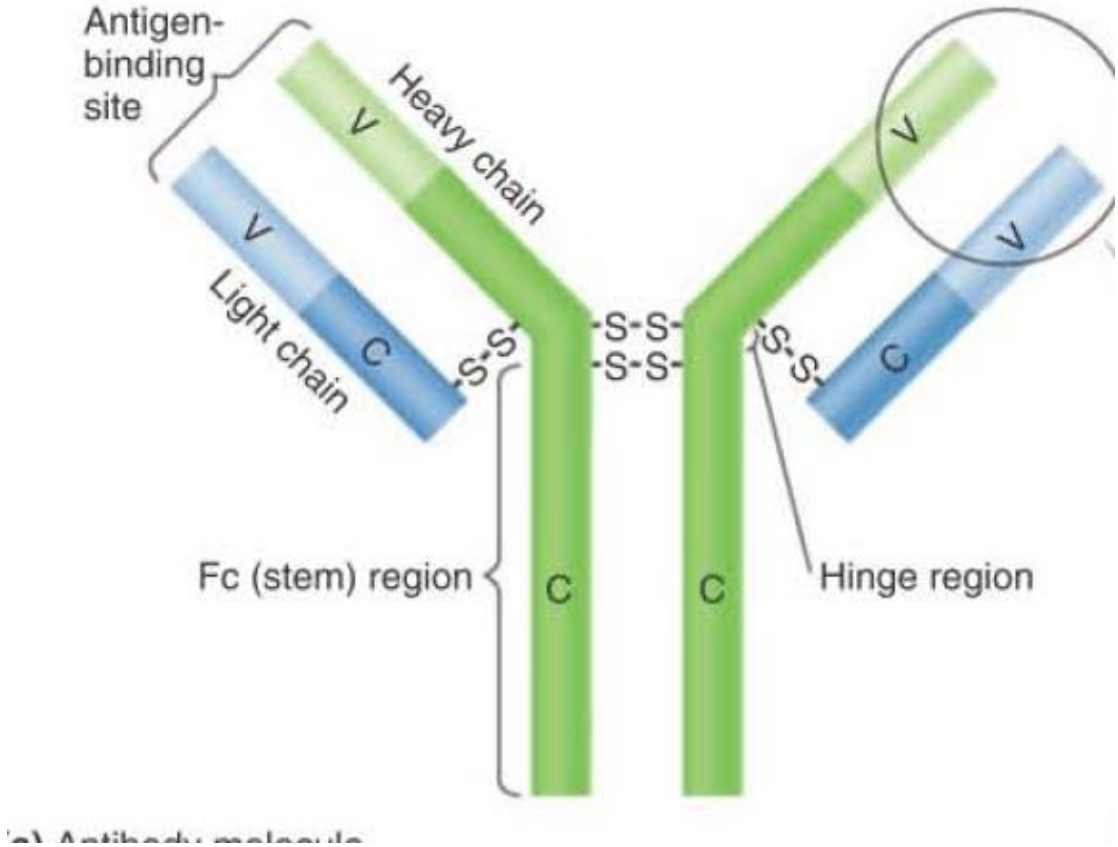
The Nature of Antibodies

Antibodies are globulin proteins therefore, we have come to use the term immunoglobulins (Ig) for antibodies. Globulin proteins arc relatively soluble. Antibodies are made in response to an antigen and can recognize and bind to the antigen.

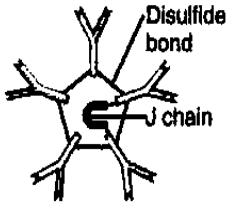
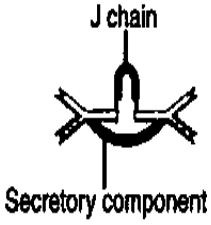
Each antibody has at least two identical sites that bind to epitopes. These sites are known as antigen-binding sites.

Antibody Structure

Because a bivalent antibody has the simplest molecular structure, it is called a monomer. A typical antibody monomer has four protein chains: two identical light chains and two identical heavy chain. The chains are joined by disulfide links and other bonds to form a Y-shaped molecule. The Y-shaped molecule is flexible and can assume a T shape (notice the hinge region in).



Immunoglobulin Classes

Characteristics	IgG	IgM	IgA	IgD	IgE
Structure					
Percentage of Total Serum	80%	5- 10%	10- 15%'	0.2%	0.002%
Location	Blood. lymph. intestine	Blood, lymph, B cell surface (as monomer)	Secretions (tears. saliva. mucus. intestine. milk). blood. lymph	B cell surface. blood, lymph	Bound to mast and basophil cells throughout body. blood
Half-life in Serum	23 days	5 days	6 days	3 days	2 days
Complement Fixation	yes	yes	No	No	No
placental Transfer	yes	No	No	No	No

Immunoglobulin Classes

IgG

- Functions are:
    1. The major immunoglobulin in secondary immune response.
    2. The only antibody that passes through the placenta because **placenta has receptors for its Fc portion.**
    3. Antitoxin & neutralize viruses
    4. **Complement fixation through its Fc portion.**
    5. **Opsonization of bacteria** by coating them and attaching them to macrophages **through its Fc portion.**

IgM

IgM antibodies generally remain in blood vessels without entering the surrounding tissues.

- Functions are:
    1. The major antibody in the primary immune response.
    2. The major **agglutinating** antibody.
    3. Complement fixation.
    4. Antigen receptor on the surface of B lymphocytes. **(It is attached to the cell surface through Fc portion).**
    5. It is the class of antibodies formed against ABO antigens.

IgA

- This class is found in both serum and mucosal surfaces.

- IgA present in the serum is called **serum IgA** and it is found in the **monomeric** form.
- IgA present at mucosal surfaces is called **secretory IgA.** It is found in the **dimeric** form.

1- The main function of secretory IgA is probably to prevent the attachment of microbial pathogens to mucosal surfaces. This is especially important in resistance to intestinal and respiratory pathogens.
2- Because IgA immunity is relatively short-lived, the length of immunity to many respiratory infections is correspondingly short.
3- IgA's presence in a mother's milk, especially the colostrum probably helps protect infants from gastrointestinal infections.

IgD

- It acts as antigen receptor on the surface of mature B lymphocytes. **(It is attached to the cell surface through Fc portion).**

has no well-defined function .

IgE

IgE molecules bind tightly by their Fc (stem) regions to receptors on mast cells and basophils.

1- When an antigen such as pollen cross-links with the IgE antibodies attached to a mast cell or basophil that cell releases histamine and other chemical mediators.
2- The concentration of IgE is greatly increased during some allergic reactions and parasitic infections, which is often diagnostically useful.

B Cells and Humoral Immunity

As we have seen, the humoral (antibody-mediated) response is carried out by antibodies. Antibodies are produced by a special group of lymphocytes called B cells.

Mechanism of antibody production:

Clonal selection:

- The immune system has a large pool of B lymphocytes.
- Each B cell carries on its surface a specific receptor **(IgM and IgD)** that recognize a specific antigen.
- When an antigen enters the body, only one B lymphocyte will proliferate to form a clone of antigen specific B lymphocytes.

❖ *Activation of B lymphocytes:*

- Mechanism of activation of B cells differ according to the type of antigen:

1- T cell-dependent antigen

An activated B cell undergoes clonal expansion, or proliferation. B cells usually require the assistance of a T helper cell (T_H) as shown in Figure (17-4)

T-dependent antigens are mainly **proteins**, such as those found on viruses, bacteria, foreign red blood cells, and haptens with their carrier molecules.

For antibodies to be produced in response to a T-dependent antigen, it is necessary that both B and T cells be activated and interact.

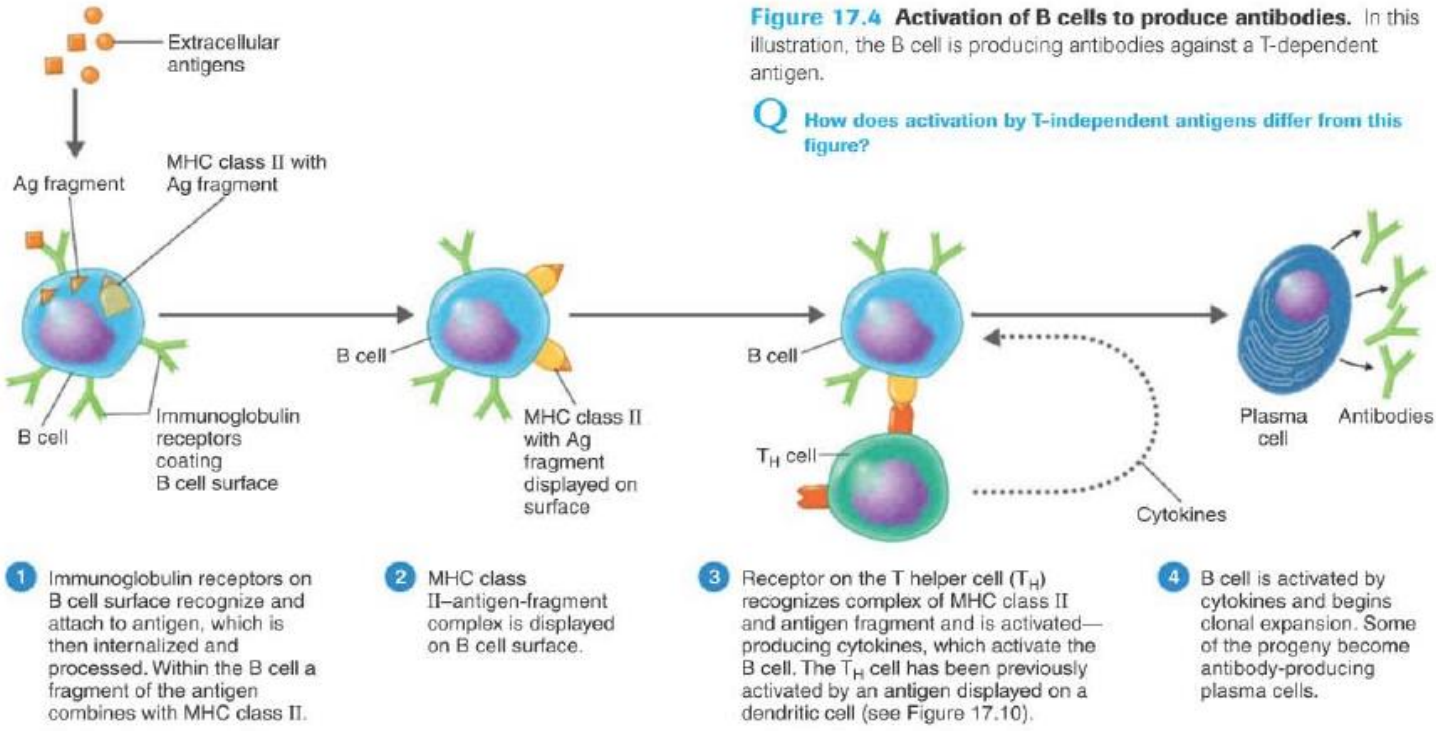


Figure 17.4 Activation of B cells to produce antibodies. In this illustration, the B cell is producing antibodies against a T-dependent antigen.

Q How does activation by T-independent antigens differ from this figure?

The process is initiated when the B cell contacts an antigen. It is important to note that the antigen contacts the surface immunoglobulins on the B cell and is enzymatically processed within the B cell and that fragments of it are combined with the major histocompatibility complex (MHC).

The MHC is a collection of genes that encode molecules of genetically diverse glycoproteins that are found on the plasma membranes of mammalian nucleated cells. in humans the MHC is also called the human leuckocyte antigen (HLA) system. The combination of the antigenic fragments and the MHC are then displayed on the B cell's surface for the receptors on the T helper cells to identify.

In this instance, the MHC is of class II, which is found only on the surface of antigen-presenting cells (APCs)-in this case, a B cell.

As shown in Figure 17.4, the T_H cell in contact with the antigenic fragment presented on the surface of the B cell

becomes activated and begins producing cytokines. These deliver a message that causes the activation of the B cell. An activated B cell proliferates into a large clone of cells, some of which will differentiate into

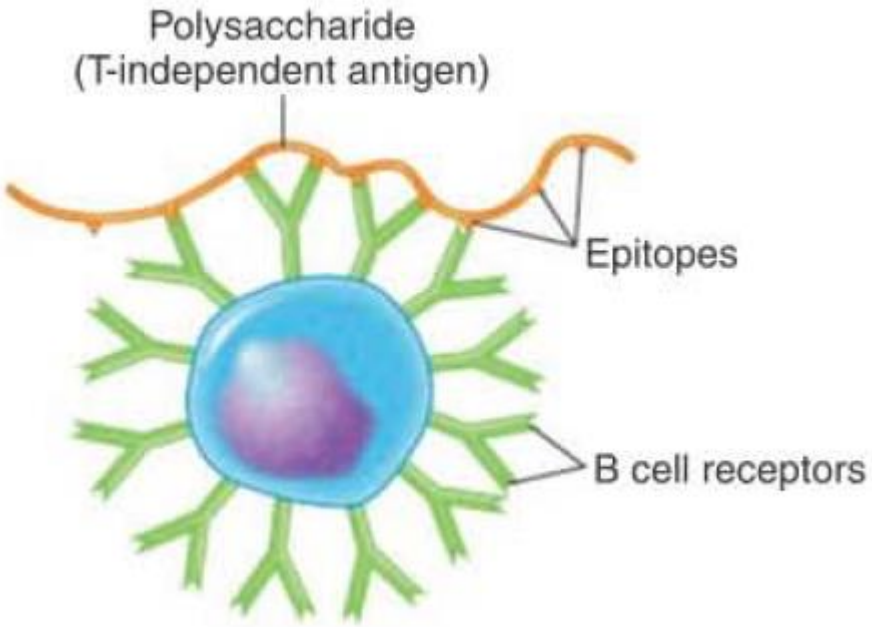
- ✓ **antibody-producing plasma cells.**
- ✓ Other clones of the activated B cell become **long-lived memory cells** that are responsible for the enhanced secondary response to an antigen.

2- T cell-independent antigens

- These antigens are characterized by repeating subunits such as are found in polysaccharides or lipopolysaccharides. Bacterial capsules are often good examples of T-independent antigens.
- These antigens interact with IgM receptor on B lymphocyte surface stimulating it directly to produce specific antibodies.

The repeating subunits, as shown in the following Figure can bind to multiple B cell receptors, which is probably why they do not require T cell assistance. T-independent antigens generally provoke a weaker immune response than do T-dependent antigens.

- ✓ This response is composed primarily of IgM, and no memory cells are generated.



Item	T cell dependent antigen	T cell independent antigen
Nature	Protein	Polysaccharide with repeated subunits of sugars
Memory cells	present	absent
Secondary immune response	occurs	Does not occur
Immunoglobulin class switch	Occurs (IgM is produced in primary immune response then IgG is produced in secondary immune response)	Does not occur (Only IgM is produced, no IgG is produced)

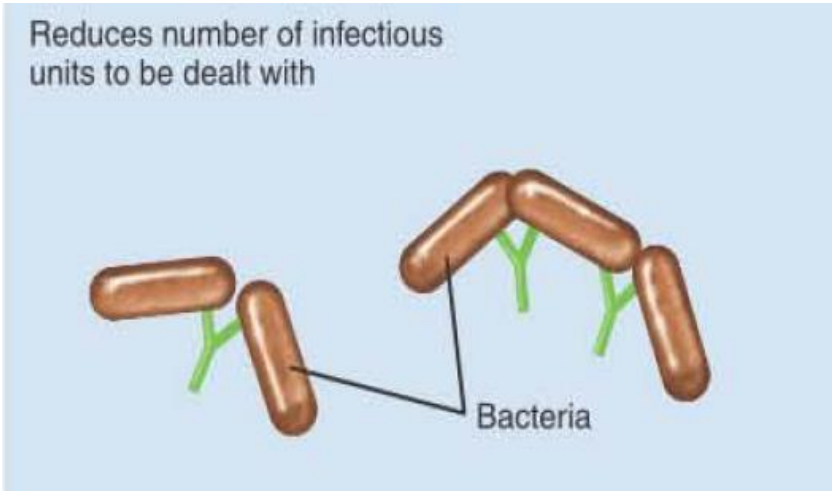
Antigen-Antibody Binding and Its Results

The strength of the bond between an antigen and an antibody is called **affinity**. In general, the closer the physical fit between antigen and antibody, the higher the affinity. Therefore, antibodies can be used to differentiate between the viruses of chickenpox and measles and between bacteria of different species.

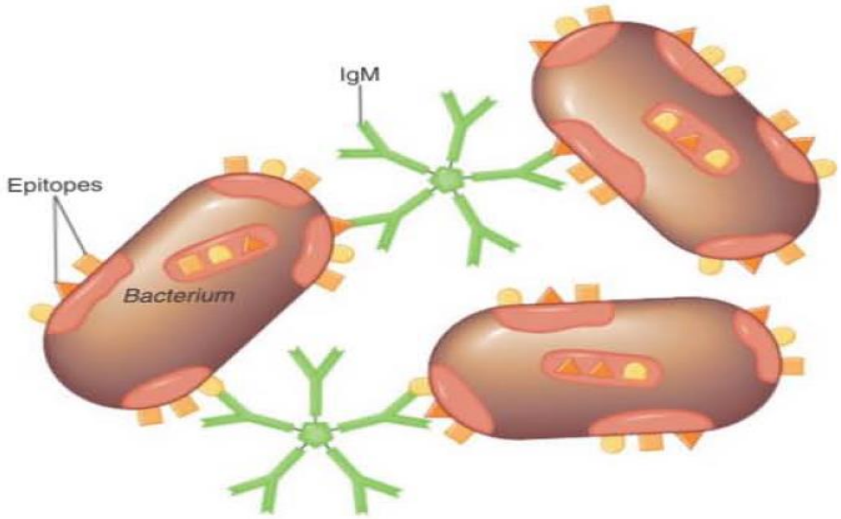
The antibody molecule itself is not damaging to the antigen. Foreign organisms and toxins are rendered harmless by only a few mechanisms: These are

1- Agglutination.
2- Opsonization.
3- Neutralization.
4- antibody-dependent cell-mediated cytotoxicity.
5- and the activation of complement leading to inflammation and cell lysis.

Agglutination, antibodies cause antigens to clump together. For example, the two antigen -binding sites of an IgG antibody can combine with epitopes on two different foreign cells, aggregating the cells into clumps that are more easily ingested by phagocytes.

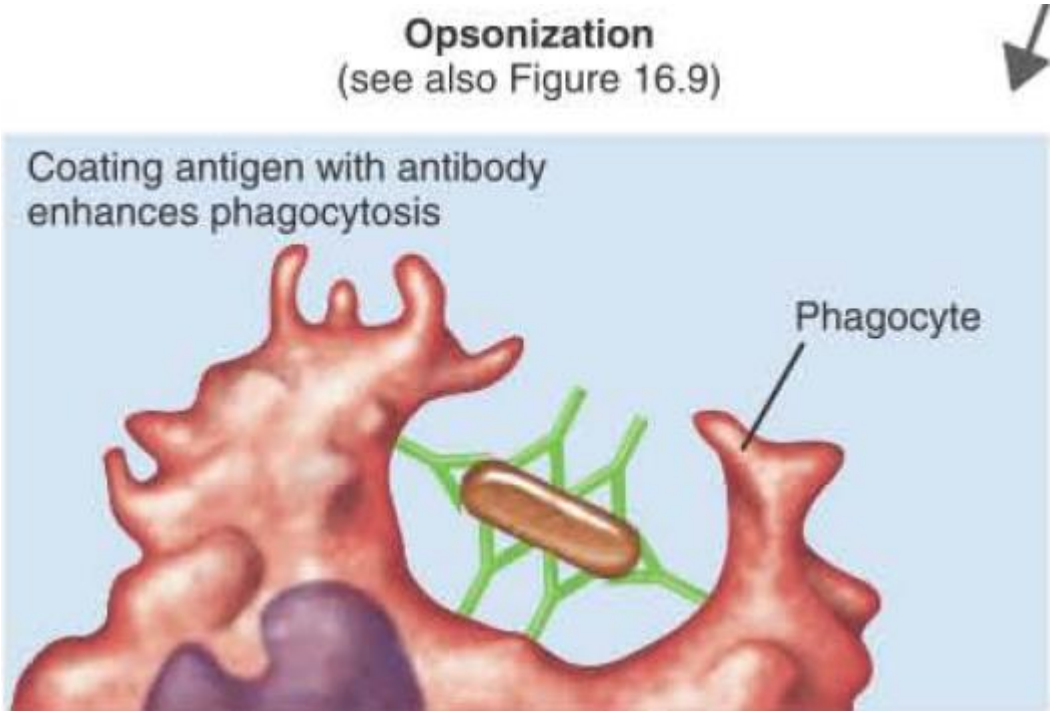


Because of its more numerous binding sites, IgM is more effective at cross-linking and aggregating particulate antigens



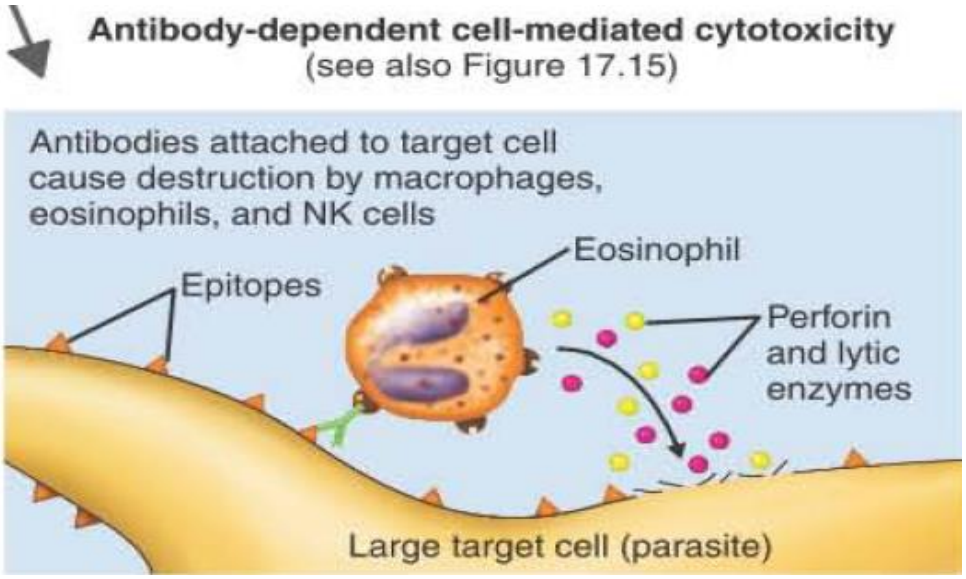
opsonization

the antigen, such as a bacterium, is coated with antibodies that enhance its ingestion and lysis by phagocytic cells.



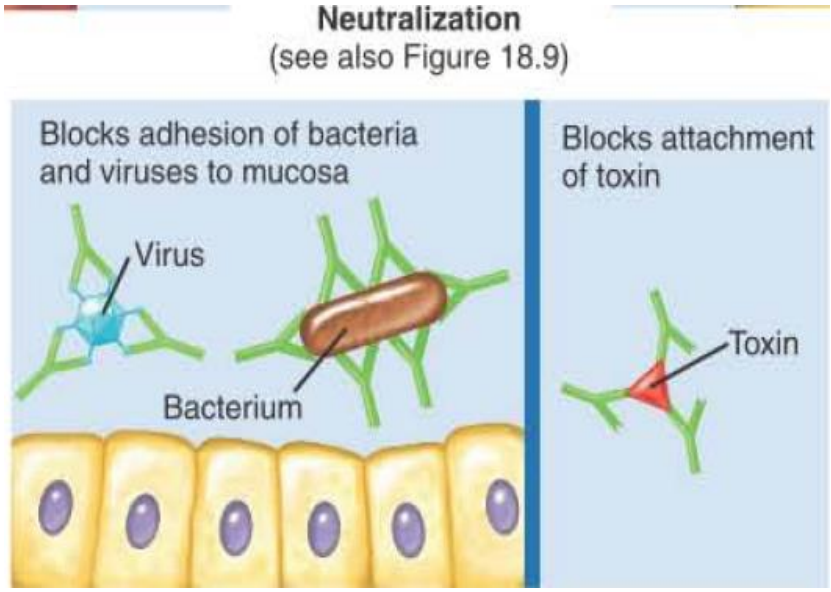
Antibody-dependent celI-mediated cytotoxicity

resembles opsonization in that the target organism becomes coated with antibodies; however, destruction of the target cell is by immune system cells that remain external to the target cell.



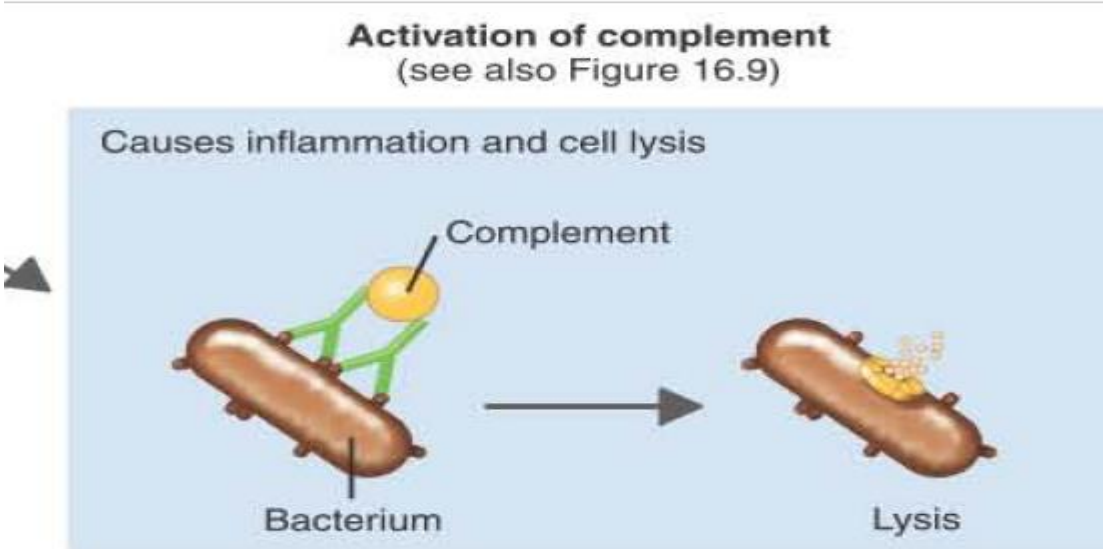
Neutralization

IgG antibodies inactivate microbes by blocking their attachment to host cells, and they neutralize toxins in a similar manner



activation of the complement system

For example, inflammation is caused by infection or tissue injury. One aspect of inflammation is that it will often cause microbes in the inflamed area to become coated with certain proteins. This, in turn, leads to the attachment to the microbe of an antibody-complement complex. This complex lyses the microbe, which then attracts phagocytes and other defensive immune system cells to the area.



T Cells and Cellular Immunity

Humoral antibodies are effective against pathogens such as viruses and bacteria that are circulating freely, where the antibodies can contact them. Intracellular antigens, such as a virus within an infected cell, are not exposed to circulating antibodies. Some bacteria and parasites can also invade and live within cells. T cells probably evolved in response to this aspect of pathogenicity. They are also the way in which the immune system recognizes cells that are nonself, especially cancer cells. Like B cells, each T cell is specific for only a certain antigen. T cells have TCRs. T cells develop from stem cells in the fed bone marrow (Figure 17.8).

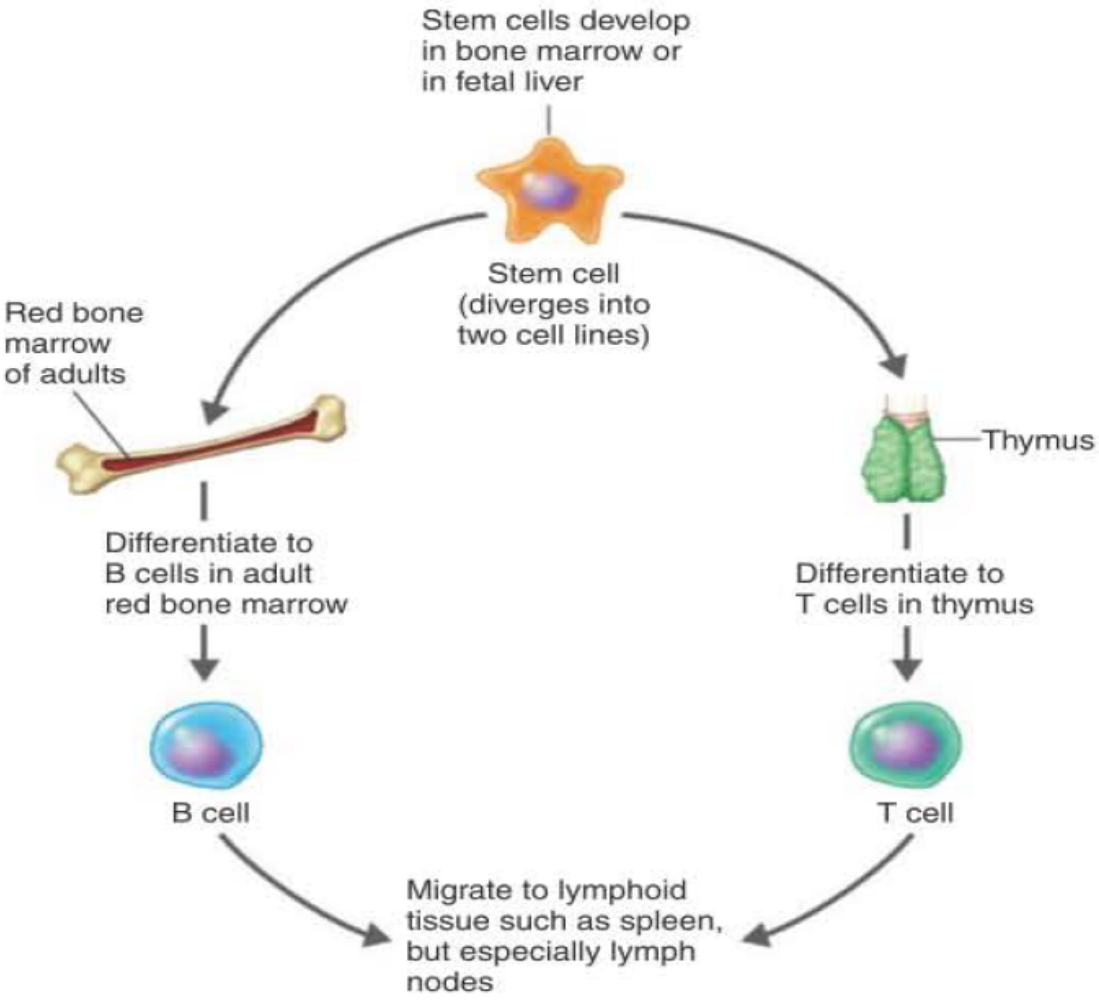


Figure 17.8 Differentiation of T cells and B cells. Both B cells and

The recognition of antigens by a T cell requires that they be first processed by specialized antigen-presenting cells (APCs). This resembles the situation previously discussed in humoral immunity in which a B cell served as the APC (see Figure 17.4). After processing, an antigenic fragment is presented on the APC surface together with a molecule of the MHC. they include activated macrophages and, most important, dendritic cells.

The body's ability to make new T cells decreases with age, beginning in late adolescence. Eventually, the T-cell producing thymus becomes less active, and red bone marrow produces fewer B cells. As a result, the immune system is relatively weak

in older adults. However, sufficient long-lived T and B memory cells survive to make immunization of older adults effective for such diseases as influenza and pneumococcal pneumonia.

T Cells and Cellular Immunity

Classes of T Cells

There are classes of T cells that have different functions, rather like the classes of immunoglobulins. For example, T helper cells cooperate with B cells in the production of antibodies.

- T helper cells are an important part of humoral immunity.

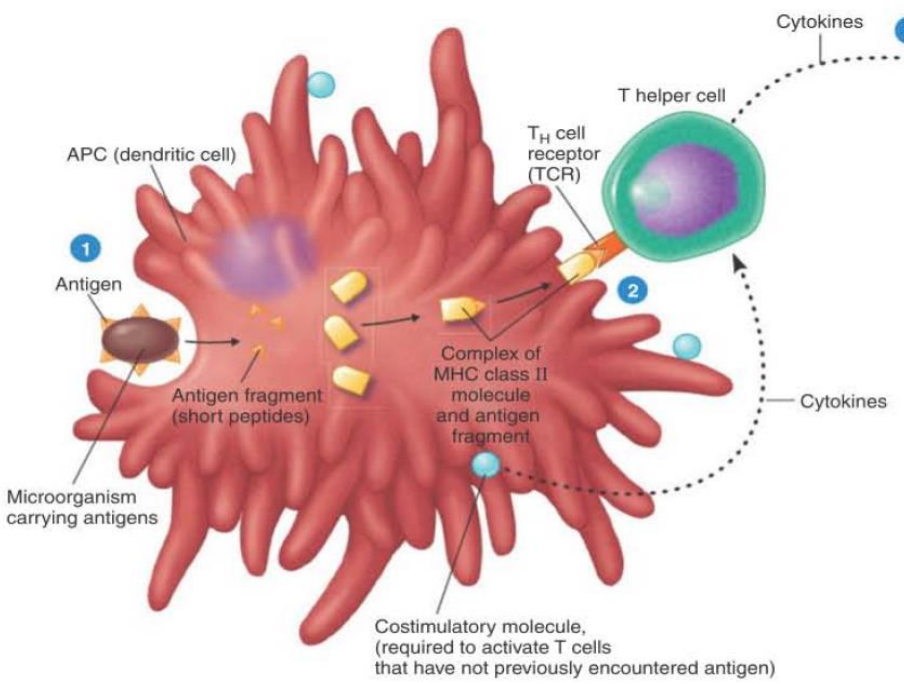
- T helper are an even more essential element of cellular immunity.

Primarily, the two populations of T cells that concern us here are T helper cells (T_H cells) and T cytotoxic cells (Tc).

A Tc cell can differentiate into an effector cell called a cytotoxic T lymphocyte (CTL).

T cells are also classified by certain glycoproteins on their surface called clusters of differentiation. or CD. These are membrane molecules that arc especially important for adhesion to receptors. The CDs of greatest interest are CD4 and CD8.

T_H cells are classified as CD4+, which bind to MHC class II molecules on B cells and APCs (Figures 17.10). Tc cells are classified as CD8+, which bind to MHC class I molecules

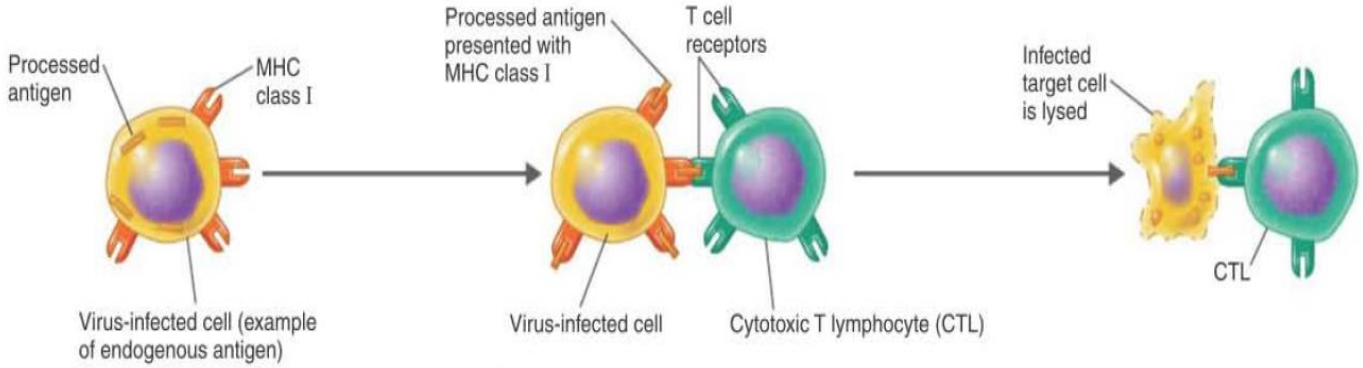


1 An APC encounters and ingests a microorganism. The antigen is enzymatically processed into short peptides, which combine with MHC class II molecules and are displayed on the surface of the APC.

2 A receptor (TCR) on the surface of the $CD4^+$ T helper cell (T_H cell) binds to the MHC–antigen complex. If this includes a Toll-like receptor, the APC is stimulated to secrete a costimulatory molecule. These two signals activate the T_H cell, which produces cytokines.

3 The cytokines cause the T_H cell to proliferate and to develop its effector functions.

Figure 17.11 Killing of virus-infected target cell by cytotoxic T lymphocyte.



1 A normal cell will not trigger a response by a cytotoxic T lymphocyte (CTL), but a virus-infected cell (shown here) or a cancer cell produces abnormal endogenous antigens.

2 The abnormal antigen is presented on the cell surface in association with MHC class I molecules. $CD8^+$ T cells with receptors for the antigen are transformed into CTLs.

3 The CTL induces destruction of the virus-infected cell by apoptosis.

Figure 17.11 Killing of virus-infected target cell by cytotoxic T lymphocyte.

T Helper Cells ($CD4^+$ T Cells)

Macrophages, when functioning as APCs, also are important in adaptive cellular immunity. T_H cells can recognize an antigen presented on the surface of a macrophage and activate the macrophage, making it more effective in both phagocytosis and in antigen presentation.

Even more important as APCs are dendritic cells. Dendritic cells arc especially important in the activation of $CD4^+$ T cells and in developing their effector functions (Figure 17.10).

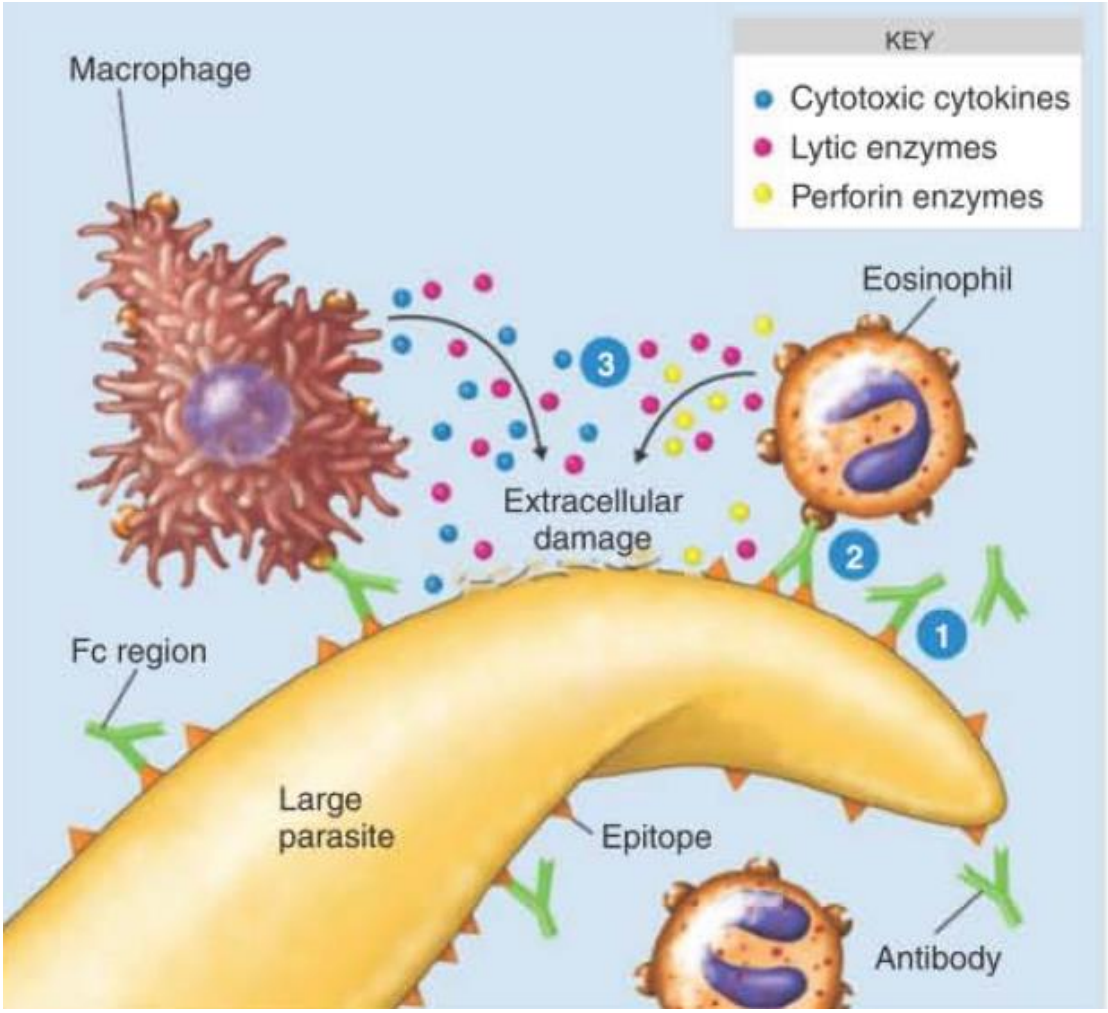
For a CD4 + T cell to become activated, its TCR recognizes an antigen that has been processed and is presented as fragments held in a complex with proteins of MHC class II on the surface of the APC. The activated T_H cell begins to proliferate at the rate of two to three cell cycles a day and to secrete cytokines, which are essential for its effector functions. The proliferating T_H cell differentiates into populations of T_H1 and T_H2 cells; it also forms a population of memory cells.

The function of T_H1 cells:

1- The cytokines produced by T_H1 cells, especially IFN -γ, activate mostly those cells related to important elements of cellular immunity.
2- They also stimulate the production of antibodies that promote phagocytosis and are especially effective in enhancing the activity of complement, such as opsonization and inflammation.

The function of T_H2 cells:

1- T_H2 also produce cytokines that are associated primarily with the production of antibodies, especially IgE, that are important in allergic reactions.
2- They are also important in the activation of the eosinophils that defend against infections by extracellular parasites such as helminths.



T Cytotoxic Cells (CD8+ T cells)

T cytotoxic cells, despite their name, are not capable of attacking any target cell as they emerge from the thymus; rather, they are precursors to CTLs, which do have this capability.

This differentiation requires sequential, and complex, activation of the precursor Tc by an antigen processed by a dendritic cell and interaction with a T_H cell and costimulatory signals. The resulting CTL is an effector cell that has the ability to recognize and kill target cells that are considered nonself.

Primarily, these target cells are **self cells** that have been altered by infection with a pathogen, especially viruses. On their surface they carry fragments of endogenous antigens that are generally synthesized within the cell and are mostly of viral or parasitic origin. Other important target cells are tumor cells and transplanted foreign tissue. Rather than reacting with antigenic fragments presented by an APC in complex with MHC class II molecules, the CD8+ T cell recognizes endogenous antigens on the target cell 's surface that are in combination with an MHC class I molecule. MHC class I molecules are found on nucleated cells; therefore, a CTL can attack almost any cell of the host that has been altered. In its attack, a CTL attaches to the target cell and releases a pore-forming protein, **perforin**.

T Regulatory Cells

T regulatory cells (T_{reg}) formerly called T suppressor cells, make up about 5- 10% of the T cell population. They are a subset of the CD4+ T helper cells and are distinguished by carrying an additional CD25 molecule.

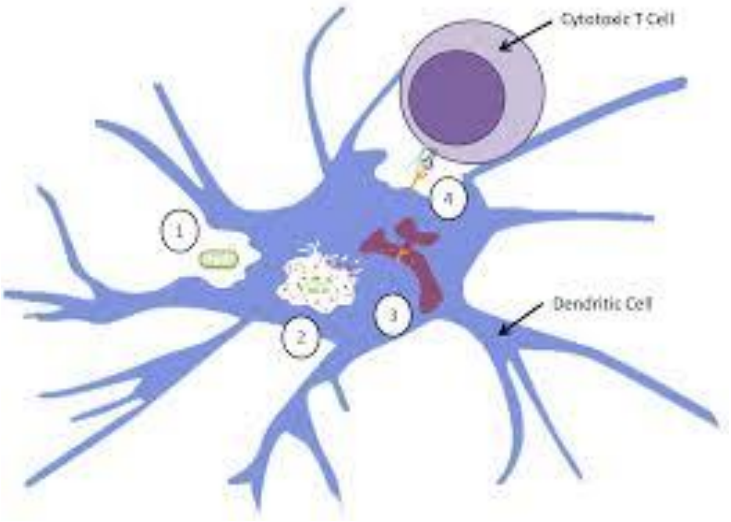
Their primary function is to combat autoimmunity by suppressing T cells that escape deletion in the thymus without the necessary "education" to avoid reacting against the body's self. They are also useful in protecting, from the immune system, the intestinal bacteria required for digestion and other useful functions. Similarly, in pregnancy they may play a role in protecting the fetus from rejection as **nonself**.

Antigen-Presenting Cells (APCs)

Although B cells are a form of antigen -presenting cell (APC) that we have already discussed with humoral immunity, we will now consider other APCs associated with cellular immunity. These APC's are the dendritic cells and the activated macrophages.

Dendritic Cells

Dendritic cells (DCs) are characterized by long extensions called dendrites because they resemble the dendrites of nerve cells.



They were first identified in anatomical studies of the skin by Langerhans in 1868, and the dendritic cells in the skin and genital tract are still called Langerhans cells, or Langerhans DC.

This represents only one of at least four populations of DCs named for their derivation or location. Other populations are found in the lymph nodes, spleen, thymus, blood, and various tissues, except the brain.

Dendritic cells are the principal APCs to induce immune responses by T cells.

Macrophages

Macrophages (from the Greek for large eaters) are cells usually found in a resting state. They are important for innate immunity and for ridding the body of worn out blood cells and other debris, such as cellular remnants from apoptosis. Their phagocytic capabilities are greatly increased when they are stimulated to become activated macrophages. This activation can be initiated by ingestion of antigenic material.

Other stimuli, such as cytokines produced by an activated helper T cell, can further enhance their capabilities. Once activated, macrophages are more effective as phagocytes and as APCs. Activated macrophages are important factors in the control of cancer cells and such intracellular pathogens as the tubercle bacillus and virus-infected cells.

After taking up an antigen, APCs tend to migrate to lymph nodes or other lymphoid centers on the mucosa, where they present the antigen to T cells located there. T cells carrying receptors that are capable of binding with any specific antigen are present in relatively limited numbers.

Extracellular Killing by the Immune System

We have seen how the action of a cytotoxic T lymphocyte CTL can lead to the destruction of a target cell. A component of the innate immune system that has not yet been discussed can also destroy certain virus-infected cells and tumor cells. These are granular leukocytes (10-15% of circulating lymphocytes) called natural killer (NK) cells. They can also attack parasites, which are normally much larger than bacteria, in contrast to CTLs, NK cells are not immunologically specific; that is, they do not need to be stimulated by an antigen. NK cells cause pores to form in the target cell, which leads to either lysis or apoptosis.

The functions of NK cells and the other principal cells involved in cellular immunity are briefly summarized in Table 17.2.

Cell	Function
T Helper (T_H1) Cell	Activates cells related to cell-mediated immunity: macrophages, T_c cells, and natural killer cells
T Helper (T_H2) Cell	Stimulates production of eosinophils, IgM, and IgE
Cytotoxic T Lymphocyte (CTL)	Destroys target cells on contact; generated from T cytotoxic (T_c) cell
T Regulatory (T_{reg}) cell	Regulates immune response and helps maintain tolerance
Activated Macrophage	Enhanced phagocytic activity; attacks cancer cells
Natural Killer (NK) Cell	Attacks and destroys target cells; participates in antibody-dependent cell-mediated cytotoxicity

Cytokines: Chemical Messengers of Immune Cells

The immune response requires complex interactions between different cells. The communication required for this is mediated by chemical messengers called **cytokines** These are soluble proteins or glycoproteins that are produced by practically all cells of the immune system in response to a stimulus. Many cytokines-there are probably more than 200-have common names that reflect their functions known at the time of their discovery; some are now known to have multiple functions . A cytokine acts only on a cell that has a receptor for it.

Cytokines that serve as communicators between leukocytes (white blood cell s) are now known as **interleukins** (between leukocytes). such as IL- l, and so on, by an international committee.

A family of small cytokines that induces the migration of leukocytes into areas of infection or tissue damage is called **chemokines**, from chemotaxis. They are especially important in inflammation. Certain chemokine receptors are important for infection by HIV.

Another family of cytokines is the **interferons**, originally named for one of their functions, protecting cells from viral infection, such as IFN-α, and so on. A number of these arc available as commercial products in treating disease conditions such as hepatitis and some cancers. A very important cytokine family is that of **tumor necrosis factor**, such as TNF-α, and so on. TNF was originally named because tumor cells were observed to be one of its targets. These cytokines are a strong factor in inflammatory reactions of auto immune diseases such as rheumatoid arthritis. Monoclonal antibodies that block the action of TNF are an available therapy for some of these conditions.

A family of cytokines, **hematopoietic cytokines**, function in controlling the pathways by which stem cells develop into different red or white blood cells. Some of these are interleukins with designations such as IL-3, and so on.

Immunological Memory

The intensity of the antibody-mediated humoral response can be reflected by the antibody titer, the relative amount of antibody in the serum. After the initial contact with an antigen, the exposed person's serum contains no detectable antibodies for 4 to 7 days. Then there is a slow rise in antibody titer: first, IgM class antibodies are produced, followed by IgG peaking in about 10 to 17 days, after which antibody titer gradually declines. This pattern is characteristic of a primary response to an antigen. The antibody-mediated immune responses of the host intensify after a second exposure to an antigen. This secondary response is also called the memory (or anamnestic) response. As shown in Figure 17.16 this response is comparatively more rapid, reaching a peak in only 2 to 7 days, lasts many days, and is considerably greater in magnitude. Some activated B cells do not become antibody-producing plasma cells but persist as long-lived but non proliferating memory cells. Years, or even decades later, if these cells are stimulated by the same antigen, they very rapidly differentiate into antibody-producing plasma cells. A similar response occurs with T cells, which, is necessary for establishing the lifelong memory for distinguishing self from non self.

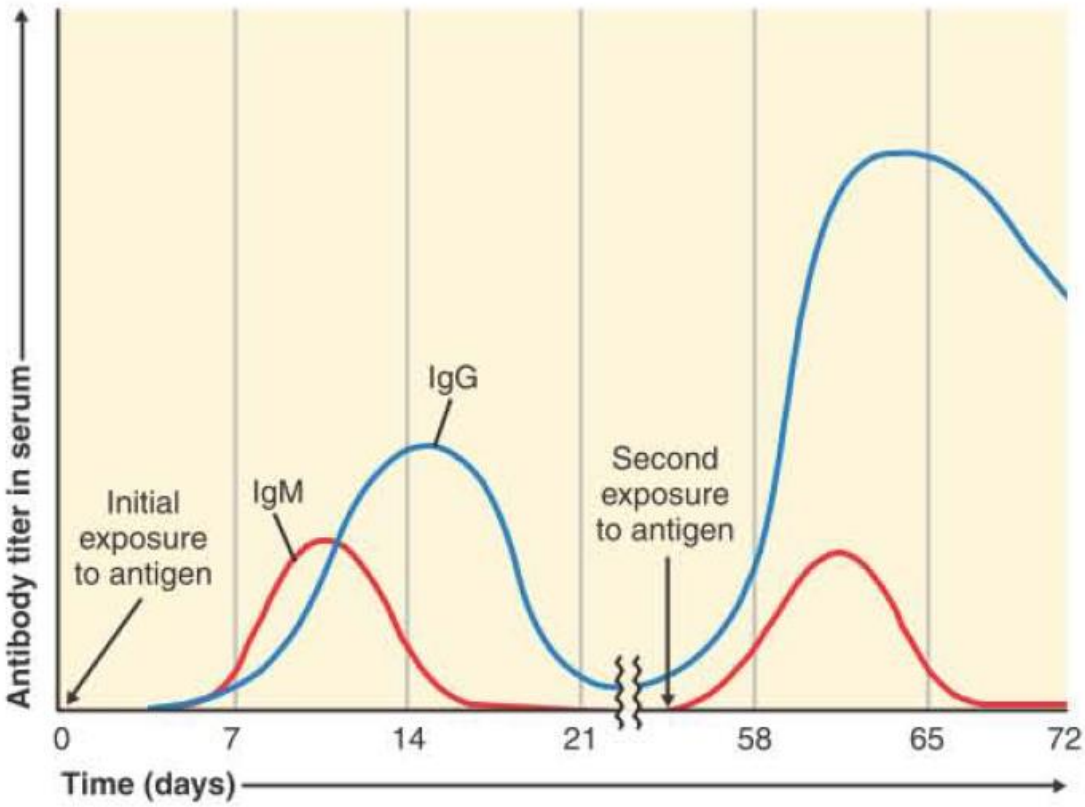


Figure 17.16 The primary and secondary immune responses to an antigen.

Disorders Associated with the Immune System

Hypersensitivity

The term hypersensitivity refers to an antigenic response beyond that which is considered normal; the term allergy is more familiar and is essentially synonymous. Hypersensitivity responses occur in individuals who have been sensitized by previous exposure to an antigen, which in this context is sometimes called an allergen. When an individual who was previously sensitized is exposed to that antigen again, his or her immune system reacts to it in a damaging manner. The four principal types of hypersensitivity reactions, are :

1- Type I anaphylactic.

2- Type II cytotoxic

3- Type III immune complex, and

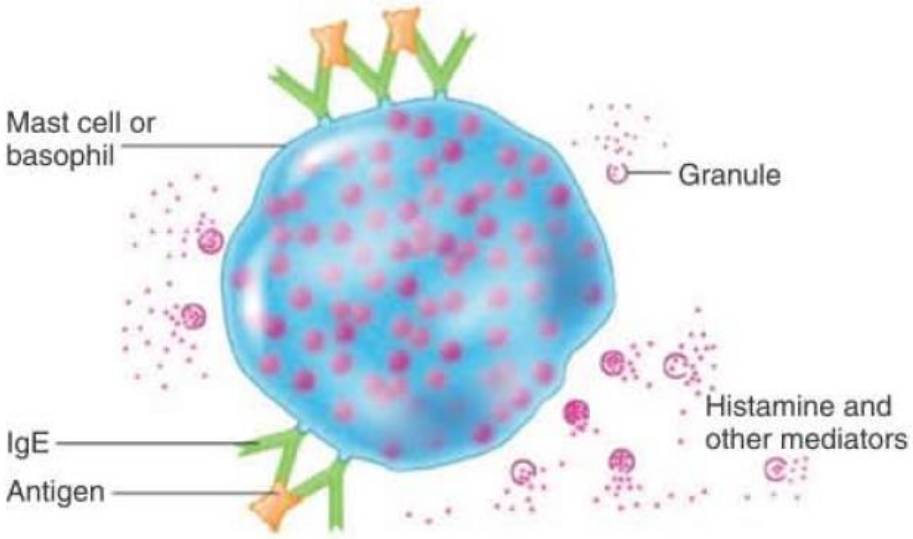
4-Type IV cell-mediated (or delayed -type) reactions.

Type I (Anaphylactic) Reactions

Type I, or anaphylactic, reactions often occur within 2 to 30 minutes after a person sensitized to an antigen is reexposed to that antigen. Anaphylaxis means "the opposite of protected," from the prefix *ana-*, meaning against, and the Greek *phylaxis*, meaning protection. Anaphylaxis is an inclusive term for the reactions caused when certain antigens combine with IgE antibodies. Anaphylactic responses can be systemic reactions, which produce shock and breathing difficulties and are sometimes fatal, or localized reactions, which include common allergic conditions such as hay fever, asthma, and hives (slightly raised, often itchy and reddened areas of the skin). The IgE antibodies produced in response to an antigen, such as insect venom or plant pollen, bind to

the surfaces of cells such as mast cells and basophils. These two cell types are similar in morphology and in their contribution to allergic reactions. **Mast cells** are especially prevalent in the connective tissue of the skin and respiratory tract and in surrounding blood vessels. **Basophils** circulate in the bloodstream, where they constitute fewer than 1 % of the leukocytes. Both are filled with granules containing a variety of chemicals called mediators.

Mast cells and basophils can have as many as 500,000 sites for IgE attachment. The Fc (stem) region of an IgE antibody can attach to one of these specific receptor sites on such a cell, leaving two antigen-binding sites free. Of course, the attached IgE monomers will not all be specific for the same antigen. But when an antigen such as plant pollen encounters two adjacent antibodies of the same appropriate specificity, it can bind to one antigen-binding site on each antibody, bridging the space between them. This bridge triggers the mast cell or basophil to undergo degranulation, which releases the granules inside these cells and also the mediators they contain. These mediators cause the unpleasant and damaging effects of an allergic reaction . The best-known mediator is **histamine**. The release of histamine increases the permeability and distension of blood capillaries, resulting in edema (swelling) and erythema (redness). Other effects include increased mucus secretion (a runny nose, for example) and smooth muscle contraction, which in the respiratory bronchi results in breathing difficulty.



(a) IgE antibodies, produced in response to an antigen, coat mast cells and basophils. When an antigen bridges the gap between two adjacent antibody molecules of the same specificity, the cell undergoes degranulation and releases histamine and other mediators.

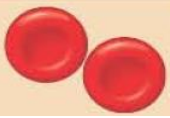
Other mediators include **leukotrienes** of various types and **prostaglandins**. Collectively, all these mediators serve as chemotactic agents that, in a few hours, attract neutrophils and eosinophils to the site of the degranulated cell. They then activate various factors that cause inflammatory symptoms, such as distension of the capillaries, swelling, increased secretion of mucus, and involuntary contractions of smooth muscles.

Type II (Cytotoxic) Reactions

Type II (cytotoxic) reactions generally involve the activation of complement by the combination of IgG or IgM antibodies with an antigenic cell. This activation stimulates complement to lyse the affected cell, which might be either a foreign cell or a host cell that carries a foreign antigenic determinant (such as a drug) on its surface. Additional cellular damage may be caused within 5 to 8 hours by the action of macrophages and other cells that attack antibody-coated cells. The most familiar cytotoxic hypersensitivity reactions are transfusion reactions, in

which red blood cells are destroyed as a result of reacting with circulating antibodies. These involve blood group systems that include the ABO and Rh antigens.

A person's ABO blood type depends on the presence or absence of carbohydrate antigens located on the cell membranes of red blood cells (RBCs). Cells of blood type O lack both A and B antigens. The table below shows that the plasma of individuals with a given blood type, such as A, have antibodies against the alternative blood type, anti-B antibody. These antibodies are presumed to arise in response to microorganism and ingested foodstuffs that have antigenic determinants very similar to blood group antigens. Individuals with type AB cells have plasma with no antibodies to either A or B antigens. Type O individuals have antibodies against both A and B antigens.

Blood Group	Erythrocyte or Red Blood Cell Antigens	Illustration	Plasma Antibodies	Blood That Can Be Received
AB	A and B		Neither anti-A nor anti-B antibodies	A, B, AB, O
B	B		Anti-A	B, O
A	A		Anti-B	A, O
O	Neither A nor B		Anti-A and Anti-B	O

The Rh Blood Group System

The roughly 85% of the population whose cells possess this antigen are called Rh +; those lacking this RBC antigen (about 15%) are Rh - . Antibodies that react with the Rh antigen do not occur naturally in the serum of Rh - individuals, but exposure to this antigen can sensitize their immune systems to produce anti-Rh antibodies.

Blood Transfusions and Rh Incompatibility If blood from an Rh + donor is given to an Rh - recipient, the donor's RBCs stimulate the production of anti-Rh ant ibodies in the recipient. If the recipient then receives Rh + RBCs in a subsequent transfusion, a rapid, serious hemolytic reaction will develop.

Hemolytic Disease of the Newbom Blood transfusions are not the only way in which an Rh - person can become sensitized to Rh + blood. When an Rh - woman and an Rh + man produce a child, there is a 50% chance that the child will be Rh +

Drug-Induced Cytotoxic Reactions

Blood platelets (thrombocytes) are minute cell-like bodies that are destroyed by drug-induced cytotoxic reactions in the disease called thrombocytopenic purpura. The drug molecules are usually hapten because they are too small to be antigenic by themselves; but, in the situation illustrated in Figure 19.5, a platelet has become coated with molecules of a drug and the combination is antigenic. Both antibody and complement are needed for lysis of the platelet. Because platelets are necessary for blood dotting, their loss results in hemorrhages that appear on the skin as purple spots (purpura).

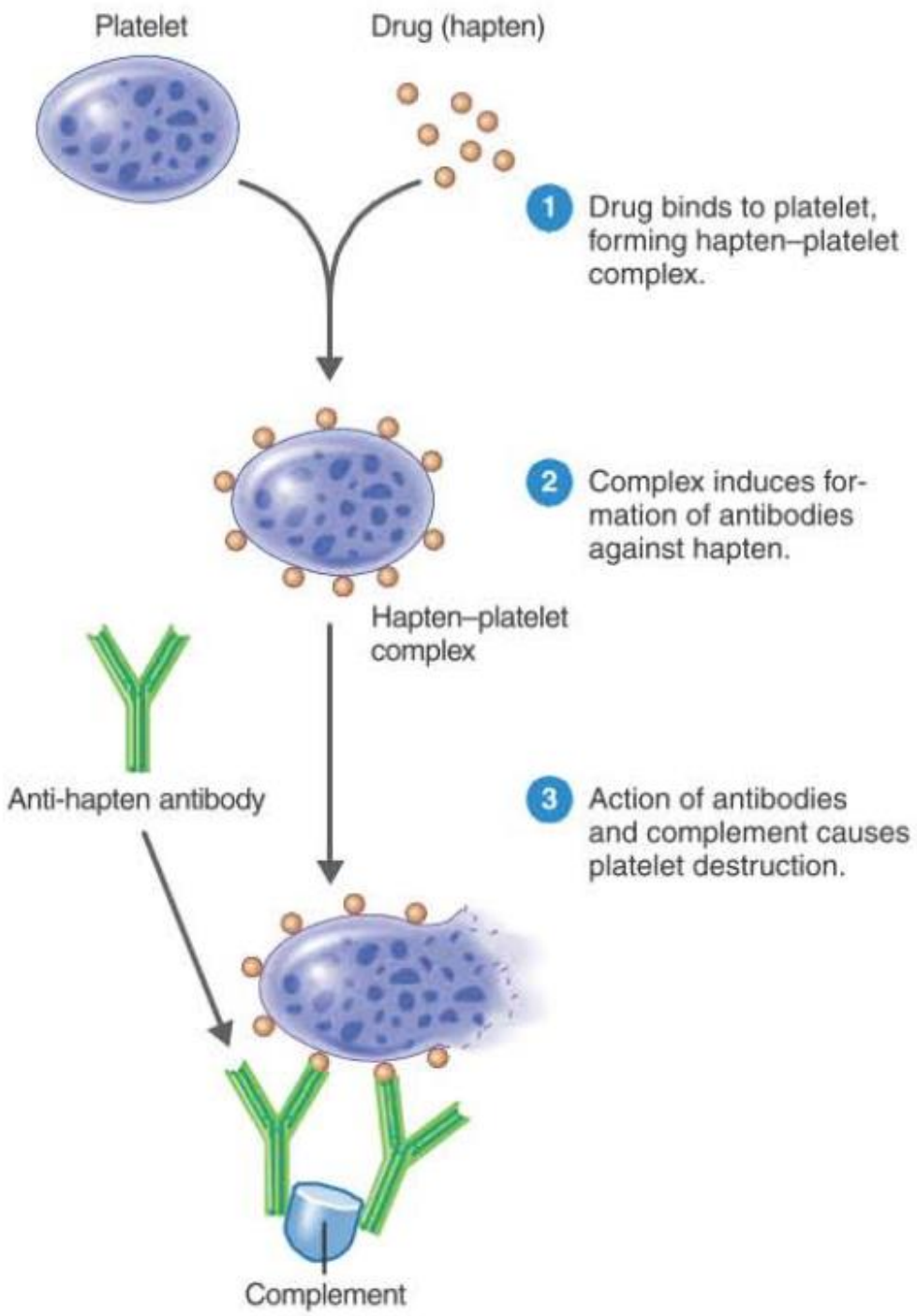


Figure 19.5 Drug-induced thrombocytopenic purpura.
Molecules of a drug such as quinine accumulate on the surface of a platelet and stimulate an immune response that destroys the platelet.

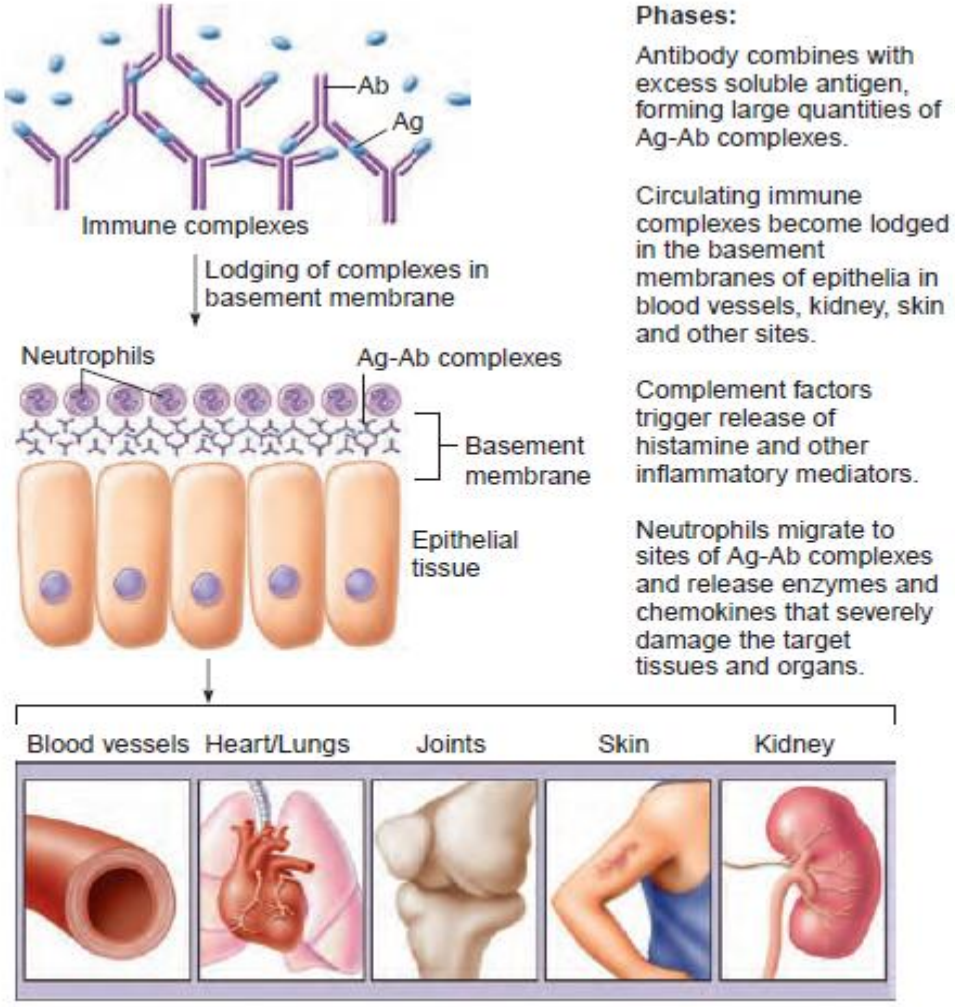
Type III (Immune Complex) Reactions

Type III hypersensitivity involves the reaction of soluble antigen with antibody and the deposition of the resulting complexes in basement membranes of epithelial tissue. It is similar to type II, because it involves the production of IgG and IgM antibodies after repeated exposure to antigens and the activation of complement.

Type III differs from type II because its antigens are not attached to the surface of a cell. The interaction of these antigens with antibodies produces free-floating complexes that can be deposited in the tissues, causing an immune complex reaction or disease. This category includes therapy-related disorders (serum sickness and the Arthus reaction) and a number of autoimmune diseases (such as glomerulonephritis and lupus erythematosus).

Mechanisms of Immune Complex Diseases

After initial exposure to a profuse amount of antigen, the immune system produces large quantities of antibodies that circulate in the fluid compartments. When this antigen enters the system a second time, it reacts with the antibodies to form antigen-antibody complexes. These complexes summon various inflammatory components such as complement and neutrophils, which would ordinarily eliminate Ab-Ag complexes as part of the normal immune response. In an immune complex disease, however, these complexes are so abundant that they deposit in the basement membranes of epithelial tissues and become inaccessible. In response to these events, neutrophils release lysosomal granules that digest tissues and cause a destructive inflammatory condition. The symptoms of type III hypersensitivities are due in great measure to this pathologic state.



Major organs where immune complexes are deposited

Types of Immune Complex Disease

During the early tests of immunotherapy using animals, hypersensitivity reactions to serum and vaccines were common. In addition to anaphylaxis, two syndromes, the Arthus reaction and serum sickness, were identified. These syndromes are associated with certain types of passive immunization (especially with animal serum). Serum sickness and the Arthus reaction are like anaphylaxis in requiring sensitization and preformed antibodies. Characteristics that set them apart from anaphylaxis are (1) they depend upon IgG, IgM, or IgA (precipitating antibodies) rather than IgE; (2) they require large doses of antigen (not a minuscule dose as in anaphylaxis); and (3) their symptoms are delayed (a few hours to days). The Arthus reaction and serum sickness differ from

each other in some important ways. The Arthus reaction is a localized dermal injury due to inflamed blood vessels in the vicinity of any injected antigen. Serum sickness is a systemic injury initiated by antigen antibody complexes that circulate in the blood and settle into membranes at various sites.

The Arthus Reaction

The Arthus reaction is usually an acute response to a second injection of vaccines (boosters) or drugs at the same site as the first injection. In a few hours, the area becomes red, hot to the touch, swollen, and very painful. These symptoms are mainly due to the destruction of tissues in and around the blood vessels and the release of histamine from mast cells and basophils. Although the reaction is usually self-limiting and rapidly cleared, intravascular blood clotting can occasionally cause necrosis and loss of tissue.

Serum Sickness

Serum sickness was named for a condition that appeared in soldiers after repeated injections of horse serum to treat tetanus. It can also be caused by injections of animal hormones and drugs. The immune complexes enter the circulation; are carried throughout the body; and are eventually deposited in blood vessels of the kidney, heart, skin, and joints. The condition can become chronic, causing symptoms such as enlarged lymph nodes, rashes, painful joints, swelling, fever, and renal dysfunction.

Homework

1- Contrast type II and type III hypersensitivities with respect to type of antigen, antibody, and manifestations of disease.

2- Explain what occurs in immune complex disease and give examples.

Type IV (Delayed Cell-Mediated) Reactions

up to this point we have discussed humoral immune responses involving IgE, IgG, or IgM. Type IV reactions involve cell-mediated immune responses and are caused mainly by T cells. Instead of occurring within a few minutes or hours after a sensitized individual is again exposed to an antigen, these **delayed cell-mediated reactions**, (or **delayed hypersensitivity)** are not apparent for a day or more. A major factor in the delay is the time required for the participating T cells and macrophages to migrate to and accumulate near the foreign antigens. Transplant rejection is most commonly mediated by cytotoxic T lymphocytes .

Causes of Delayed Cell-Mediated Reactions

Sensitization for delayed hypersensitivity reactions occurs when certain foreign antigens, particularly those that bind to tissue cells, are phagocytized by macrophages and then presented to receptors on the T-cell surface. Contact between the antigenic determinant sites and the appropriate T cell causes the T cell to proliferate into mature differentiated T cells and memory cells. When a person sensitized in this way is reexposed to the same antigen, a delayed hypersensitivity reaction might result.

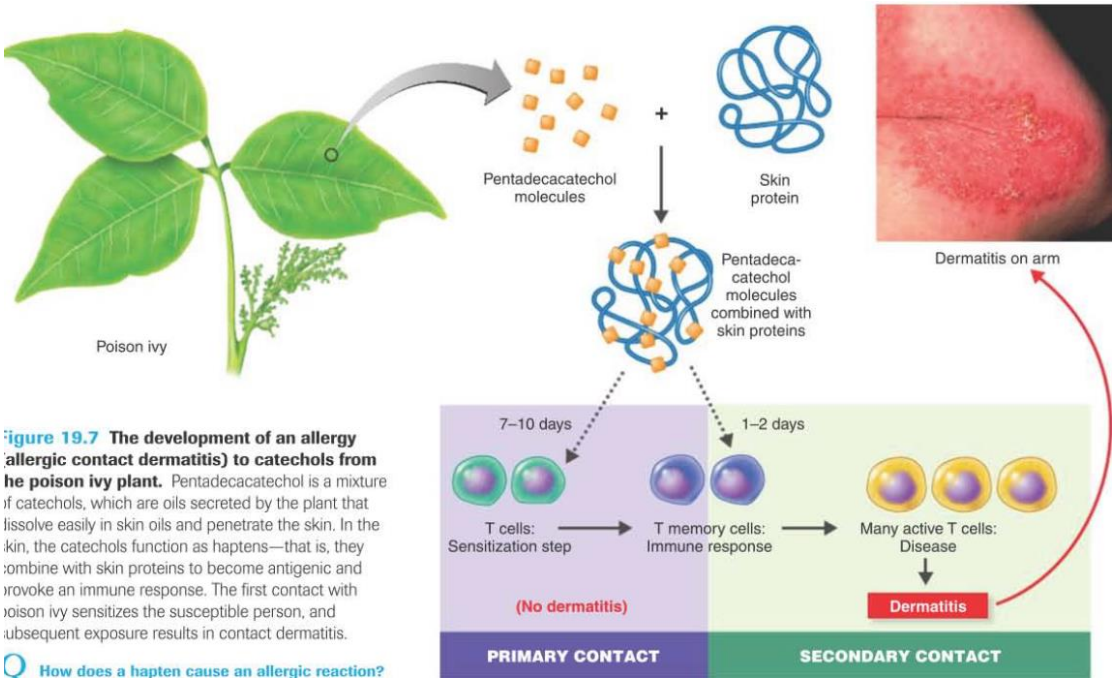
Memory cells from the initial exposure activate T cells, which release destructive cytokines in their interaction with the target antigen. In addition, some cytokines contribute to the inflammatory reaction to the foreign antigen by attracting macrophages to the site and activating them.

Delayed Cell-Mediated Hypersensitivity

Reactions of the Skin

We have seen that hypersensitivity symptoms are frequently displayed on the skin . One delayed hypersensitivity reaction that involves the skin is the familiar skin test for tuberculosis. Because Mycobacterium tuberculosis is often located within macrophages, this organism can stimulate a delayed cell - mediated immune response. As a screening test, protein components of the bacteria are injected into the skin. If the recipient has (or has had) a previous infection by tuberculosis bacteria, an inflammatory reaction to the injection of these antigens will appear on the skin in I to 2 days; this interval is typical of delayed hypersensitivity

reactions. **Allergic contact dermatitis**, another common manifestation of delayed cell -mediated hypersensitivity, is usually caused by haptens that combine with proteins (particularly the amino acid lysine) in the skin of some people to produce an immune response. Reactions to poison ivy (Figure 19.7), cosmetics, and the metals in jewelry (especially nickel) are familiar examples of these allergies.



igure 19.7 The development of an allergy allergic contact dermatitis) to catechols from he poison ivy plant. Pentadecacatechol is a mixture f catechols, which are oils secreted by the plant that lissolve easily in skin oils and penetrate the skin. In the kin, the catechols function as haptens—that is, they ombine with skin proteins to become antigenic and rovoke an immune response. The first contact with oison ivy sensitizes the susceptible person, and ubsequent exposure results in contact dermatitis.

How does a hapten cause an allergic reaction?

T-Cell-Mediated Recognition of Foreign MHC Receptors

Host Rejection of Graft When certain T cells of a host recognize foreign class I MHC markers on the surface of grafted cells, they release interleukin-2 as part of a general immune mobilization. The effect is to expand the helper and cytotoxic T cells specific to the antigens displayed by the donated cells. The cytotoxic cells bind to the grafted tissue and secrete lymphokines that begin the rejection process within 2 weeks of transplantation. Late in this process, antibodies formed against the graft tissue contribute to immune damage. A final blow is the destruction of the vascular supply, promoting death of the grafted tissue.