Body Defenses

CHAPTER 43
THE BODY'S DEFENSES

Section A: Nonspecific Defenses Against Infection

1. The skin and mucus membranes provide first-line barriers to infection
2. Phagocytic cells, inflammation, and antimicrobial proteins function early in infection

Introduction

- An animal must defend itself against unwelcome intruders - the many potentially dangerous viruses, bacteria, and other pathogens it encounters in the air, in food, and in water.
- It must also deal with abnormal body cells, which, in some cases, may develop into cancer.

- Three cooperative lines of defense have evolved to counter these threats.
  - Two of these are nonspecific - that is, they do not distinguish one infectious agent from another.

Nonspecific defense mechanisms		Specific defense mechanisms (immune system)
First line of defense	Second line of defense	Third line of defense
• Skin • Mucous membranes • Secretions of skin and mucous membranes	• Phagocytic white blood cells • Antimicrobial proteins • The inflammatory response	• Lymphocytes • Antibodies

Fig. 43.1

- The first line of nonspecific defense is external, consisting of epithelial cells that cover and line our bodies and the secretions they produce.
- The second line of nonspecific defense is internal, involving phagocytic cells and antimicrobial proteins that indiscriminately attack invaders that penetrate the body's outer barriers.
- The third line of defense, the immune system, responds in a specific way to particular toxins, microorganisms, aberrant body cells, and other substances marked by foreign molecules.
  - Specific defensive proteins called antibodies are produced by lymphocytes.

- An invading microbe must penetrate the external barrier formed by the skin and mucous membranes, which cover the surface and line the openings of an animal's body.
- If it succeeds, the pathogen encounters the second line of nonspecific defense, interacting mechanisms that include phagocytosis, the inflammatory response, and antimicrobial proteins.

1. The skin and mucous membrane provide first-line barriers to infection

- Intact skin is a barrier that cannot normally be penetrated by bacteria or viruses, although even minute abrasions may allow their passage.
- Likewise, the mucous membranes that line the digestive, respiratory, and genitourinary tracts bar the entry of potentially harmful microbes.

- Beyond their role as a physical barrier, the skin and mucous membranes counter pathogens with chemical defenses.
  - In humans, for example, secretions from sebaceous and sweat glands give the skin a pH ranging from 3 to 5, which is acidic enough to prevent colonization by many microbes.
  - Microbial colonization is also inhibited by the washing action of saliva, tears, and mucous secretions that continually bathe the exposed epithelium.
  - All these secretions contain antimicrobial proteins.
    - One of these, the enzyme **lysozyme**, digests the cell walls of many bacteria, destroying them.

- *Mucus*, the viscous fluid secreted by cells of mucous membranes, also traps microbes and other particles that contact it.
  - In the trachea, ciliated epithelial cells sweep out mucus with its trapped microbes, preventing them from entering the lungs.

- Microbes present in food or water, or those in swallowed mucus, must contend with the highly acidic environment of the stomach.
  - The acid destroys many microbes before they can enter the intestinal tract.
  - One exception, the virus hepatitis A, can survive gastric acidity and gains access to the body via the digestive tract.

2. Phagocytic cells, inflammation, and antimicrobial proteins function early in infection

- Microbes that penetrate the first line of defense face the second line of defense, which depends mainly on **phagocytosis**, the ingestion of invading organisms by certain types of white cells.
- Phagocyte function is intimately associated with an effective inflammatory response and also with certain antimicrobial proteins.

- The phagocytic cells called **neutrophils** constitute about 60%-70% of all white blood cells (leukocytes).
  - Cells damaged by invading microbes release chemical signals that attract neutrophils from the blood.
  - The neutrophils enter the infected tissue, engulfing and destroying microbes there.
  - Neutrophils tend to self-destruct as they destroy foreign invaders, and their average life span is only a few days.

- **Monocytes**, about 5% of leukocytes, provide an even more effective phagocytic defense.
  - After a few hours in the blood, they migrate into tissues and develop into **macrophages**: large, long-lived phagocytes.
  - These cells extend long pseudopodia that can attach to polysaccharides on a microbe's surface, engulfing the microbe by phagocytosis, and fusing the resulting vacuole with a lysosome.

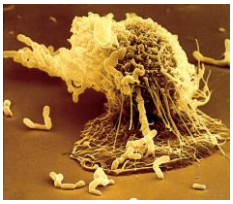


Fig. 43.3

- The lysosome has two ways of killing trapped microbes.
  - First, it can generate toxic forms of oxygen, such as superoxide anion and nitric oxide.
  - Second, lysosomal enzymes, including lysozyme, digest microbial components.

- There are microbes that have evolved mechanisms for evading phagocytic destruction.
  - Some bacteria have outer capsules to which a macrophage cannot attach.
  - Others, like *Mycobacterium tuberculosis*, are readily engulfed but are resistant to lysosomal destruction and can even reproduce inside a macrophage.
  - These microorganisms are a particular problem for both nonspecific and specific defenses of the body.

- Some macrophages migrate throughout the body, while others reside permanently in certain tissues, including the lung, liver, kidney, connective tissue, brain, and especially in lymph nodes and the spleen.

- The fixed macrophages in the spleen, lymph nodes, and other lymphatic tissues are particularly well located to contact infectious agents.
  - Interstitial fluid, perhaps containing pathogens, is taken up by lymphatic capillaries, and flows as lymph, eventually returning to the blood circulatory system.
  - Along the way, lymph must pass through numerous lymph nodes, where any pathogens present encounter macrophages and lymphocytes.
- Microorganisms, microbial fragments, and foreign molecules that enter the blood encounter macrophages when they become trapped in the netlike architecture of the spleen.

- **Eosinophils**, about 1.5% of all leukocytes, contribute to defense against large parasitic invaders, such as the blood fluke, *Schistosoma mansoni*.
  - Eosinophils position themselves against the external wall of a parasite and discharge destructive enzymes from cytoplasmic granules.

- **Natural killer** (**NK**) **cells** do not attack microorganisms directly but destroy virus-infected body cells.
  - They also attack abnormal body cells that could become cancerous.
  - NK cells mount an attack on the cell's membrane, causing the cell to lyse.

- Damage to tissue by a physical injury or by the entry of microorganisms triggers a localized **inflammatory response**.
  - Damaged cells or bacteria release chemical signals that cause nearby capillaries to dilate and become more permeable, leading to clot formation at the injury.
  - Increased local blood supply leads to the characteristic swelling, redness, and heat of inflammation.

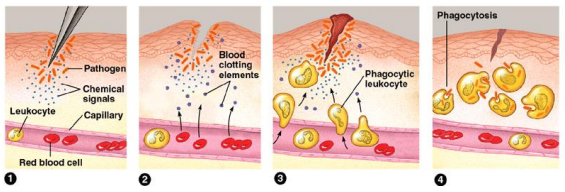


Fig. 43.5

- One of the chemical signals of the inflamatory response is **histamine**.
  - Histamine is released by circulating leucocytes called **basophils** and by **mast cells** in connective tissue.
  - Histamine triggers both dilation and increased permeability of nearby capillaries.
  - Leukocytes and damaged tissue cells also discharge *prostaglandins* and other substances that promote blood flow to the site of injury.

- Enhanced blood flow and vessel permeability have several effects.
  - First, they aid in delivering clotting elements to the injured area.
    - Clotting marks the beginning of the repair process and helps block the spread of microbes elsewhere.
  - Second, this also enhances the migration of phagocytic cells from the blood into the injured tissues.
    - Phagocyte migration usually begins within an hour after injury.

- Chemotactic factor released by invading bacteria and injured tissues, and **chemokines** secreted by blood vessel endothelial cells and monocytes, attract phagocytes to the area.
  - Chemokines constitute a group of about 50 different proteins that bind to receptors on many types of leukocytes and induce numerous other changes central to inflammation.
    - For example, they induce the production of toxic forms of oxygen in phagocyte lysosomes and the release of histamine from basophils.

- Neutrophils are the first phagocytes to arrive at the point of assault, followed by macrophages that have developed from migrating monocytes.
  - Macrophages not only phagocytose pathogens and their products, but also clean up damaged tissue cells and the remains of neutrophils destroyed in the phagocytic process.
  - The pus that accumulates at the site of some infections consists mostly of dead phagocytic cells and the fluid and proteins that leaked from capillaries during the inflammatory response.
  - This pus is usually absorbed by the body within a few days.

- Severe tissue damage or infection may trigger a systemic (widespread) nonspecific response.
  - In a severe infection, such as meningitis or appendicitis, the number of leukocytes in the blood may increase severalfold within a few hours after the initial inflammatory events.
  - Fever, another systemic response to infection, can be triggered by toxins from pathogens or by **pyrogens** released by certain leukocytes.
  - This resets the body's thermostat and the higher temperature contributes to defense by inhibiting growth of some microbes, facilitating phagocytosis, and speeding up repair of tissues.

- Certain bacterial infections can induce an overwhelming systemic inflammatory response leading to a condition known as *septic shock*.
  - Characterized by high fever and low blood pressure, septic shock is the most common cause of death in U.S. critical care units.
  - Clearly, while local inflammation is an essential step toward healing, widespread inflammation can be devastating.

- A variety of proteins function in nonspecific defense either by attacking microbes directly or by impeding their reproduction.
  - In addition to lysozyme, other antimicrobial agents include about 20 serum proteins, known collectively as the **complement system**.
    - These carry out a cascade of steps that lead to lysis of microbes.
    - Some complement components work with chemokins to attract phagocytic cells to sites of infection.

- Another set of proteins that provide nonspecific defenses are the **interferons**, which are secreted by virus-infected cells.
  - While they do not seem to benefit the infected cell, these proteins diffuse to neighboring cells and induce them to produce other chemicals that inhibit viral reproduction.
  - Interferon limits cell-to-cell spread of viruses, helping to control viral infection.
  - Because they are nonspecific, interferons produced in response to one virus may confer short-term resistance to unrelated viruses.
  - One type of interferon activates phagocytes.

- To summarize the nonspecific defense systems, the first line of defense, the skin and mucous membranes, prevents most microbes from entering the body.
- The second line of defense uses phagocytes, natural killer cells, inflammation, and antimicrobial proteins to defend against microbes that have managed to enter the body.
- These two lines of defense are nonspecific in that they do not distinguish among pathogens.

CHAPTER 43
THE BODY'S DEFENSES

Section B: How Specific Immunity Arises

1. **Lymphocytes provide the specificity and diversity of the immune system**
2. **Antigens interact with specific lymphocytes, inducing immune responses and immunological memory**
3. **Lymphocyte development gives rise to an immune system that distinguishes self from nonself**

Introduction

- While microorganisms are under assault by phagocytic cells, the inflammatory response, and antimicrobial proteins, they inevitably encounter lymphocytes, the key cells of the immune system - the body's third line of defense.
- Lymphocytes generate efficient and selective immune responses that work throughout the body to eliminate particular invaders.
  - This includes pathogens, transplanted cells, and even cancer cells, which they detect as foreign.

1. Lymphocytes provide the specificity and diversity of the immune system

- The vertebrate body is populated by two main types of lymphocytes: **B lymphocytes** (**B cells**) and **T lymphocytes** (**T cells**).
  - Both types of lymphocytes circulate throughout the blood and lymph and are concentrated in the spleen, lymph nodes, and other lymphatic tissue.

- Because lymphocytes recognize and respond to particular microbes and foreign molecules, they are said to display *specificity*.
  - A foreign molecule that elicits a specific response by lymphocytes is called an **antigen**.
    - Antigens include molecules belonging to viruses, bacteria, fungi, protozoa, parasitic worms, and nonpathogens like pollen and transplanted tissue.
  - B cells and T cells specialize in different types of antigens, and they carry out different, but complementary, defensive actions.

- One way that an antigen elicits an immune response is by activating B cells to secrete proteins called **antibodies**.
  - Each antigen has a particular molecular shape and stimulates certain B cells to secrete antibodies that interact specifically with it.
  - In fact, B and T cells can distinguish among antigens with molecular shapes that are only slightly different, leading the immune system to target specific invaders.

- B and T cells recognize specific antigens through their plasma membrane-bound **antigen receptors**.
  - Antigen receptors on a B cell are transmembrane versions of antibodies and are often referred to as *membrane antibodies* (or membrane immunoglobins).
  - The antigen receptors on a T cell, called **T cell receptors**, are structurally related to membrane antibodies, but are never produced in a secreted form.
  - A single T or B lymphocyte bears about 100,000 receptors for antigen, all with exactly the same specificity.

- The particular structure of a lymphocyte's receptors is determined by genetic events that occur during its early development.
  - As an unspecialized cell differentiates into a B or T lymphocyte, segments of antibody genes or receptor genes are linked together by a type of genetic recombination, generating a single functional gene for each polypeptide of an antibody or receptor protein.
  - This process, which occurs before any contact with foreign antigens, creates an enormous variety of B and T cells in the body, each bearing antigen receptors of particular specificity.
  - This allows the immune system to respond to millions of antigens, and thus millions of potential pathogens.

2. Antigens interact with specific lymphocytes, inducing immune responses and immunological memory

- Although it encounters a large repertoire of B cells and T cells, a microorganism interacts only with lymphocytes bearing receptors specific for its various antigenic molecules.

- The "selection" of a lymphocyte by one of the microbe's antigens activates the lymphocyte, stimulating it to divide and differentiate, and eventually, producing two clones of cells.
  - One clone consists of a large number of **effector cells**, short-lived cells that combat the same antigen.
  - The other clone consists of **memory cells**, long-lived cells bearing receptors for the same antigen.

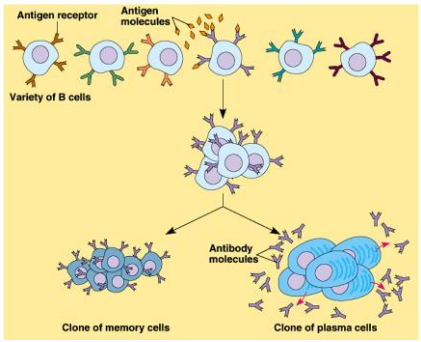


Fig. 43.6

- In this process of **clonal selection**, each antigen, by binding to specific receptors selectively, activates a tiny fraction of cells from the body's diverse pool of lymphocytes.
- This relatively small number of selected cells gives rise to clones of thousands of cells, all specific for and dedicated to eliminating that antigen.

- The selective proliferation and differentiation of lymphocytes that occur the first time the body is exposed to an antigen is the **primary immune response**.
  - About 10 to 17 days are required from the initial exposure for the maximum effector cell response.
  - During this period, selected B cells and T cells generate antibody-producing effector B cells, called **plasma cells**, and effector T cells, respectively.
  - While this response is developing, a stricken individual may become ill, but symptoms of the illness diminish and disappear as antibodies and effector T cells clear the antigen from the body.

- A second exposure to the same antigen at some later time elicits the **secondary immune response**.
  - This response is faster (only 2 to 7 days), of greater magnitude, and more prolonged.
  - In addition, the antibodies produced in the secondary response tend to have greater affinity for the antigen than those secreted in the primary response.

- Measures of antibody concentrations in the blood serum over time show the difference between primary and secondary immune responses.
  - The immune systems capacity to generate secondary immune responses is called *immunological memory*, based not only on effector cells, but also on clones of long-lived T and B memory cells.
    - These memory cells proliferate and differentiate rapidly when they later contact the same antigen.

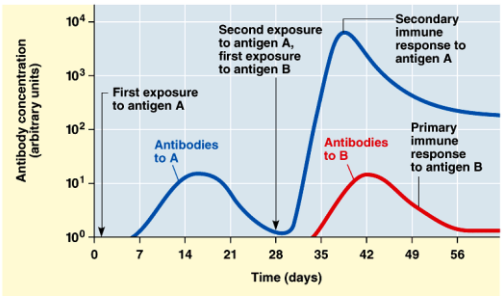


Fig. 43.7

3. Lymphocyte development gives rise to an immune system that distinguishes self from nonself

- Lymphocytes, like all blood cells, originate from pluripotent stem cells in the bone marrow or liver of a developing fetus.

- Early lymphocytes are all alike, but they later develop into T cells or B cells, depending on where they continue their maturation.
- Lymphocytes that migrate from the bone marrow to thymus develop into T cells.
- Lymphocytes that remain in the bone marrow and continue their maturation there become B cells.

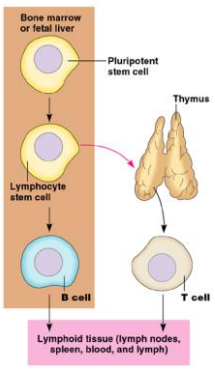


Fig. 43.8

- While B cells and T cells are maturing in the bone marrow and thymus, their antigen receptors are tested for potential self-reactivity.
  - For the most part, lymphocytes bearing receptors specific for molecules already present in the body are rendered nonfunctional or destroyed by apoptosis, leaving only lymphocytes that react to foreign molecules.
  - This *capacity to distinguish self from nonself* continues to develop as the cells migrate to lymphatic organs.
  - Thus, the body normally has no mature lymphocytes that react against self components, but failures of *self-tolerance* can lead to autoimmune diseases.

- Lymphocytes do not react to most self antigens, but T cells do have a crucial interaction with one important group of native molecules.
  - These are a collections of cell surface glycoproteins encoded by a family of genes called the **major histocompatibility complex** (**MHC**).
  - Two main classes of MHC molecules mark body cells as self.
    - **Class I MHC molecules** are found on almost all nucleated cells - that is, on almost every cell.
    - **Class II MHC molecules** are restricted to a few specialized cell types, including macrophages, B cells, activated T cells, and those inside the thymus.

- For a vertebrate species, there are numerous possible alleles for each class I and class II MHC gene, producing the most polymorphic proteins known.
  - As a result of the large number of different alleles in the human population, for example, most of us are heterozygous for every one of our MHC genes.
  - Moreover, it is unlikely that any two people, except identical twins, will have exactly the same set of MHC molecules.
  - The MHC provides a biochemical fingerprint virtually unique to each individual.

- MHC molecules vary from person to person because of their central role in the immune system.
  - Through **antigen presentation**, an MHC molecule cradles a fragment of an intracellular protein antigen in its hammocklike groove, carries it to the cell surface, and "presents" it to an antigen receptor on a T cell.
  - Thus T cells are alerted to an infectious agent after it has been internalized by a cell (through phagocytosis or receptor-mediated endocytosis), or after it has entered and replicated within a cell (through viral infection).

- There are two main types of T cells, and each responds to one class of MCH molecule.
  - **Cytotoxic T cells** (**T_C**) have antigen receptors that bind to protein fragments displayed by the body's class I MHC molecules.
  - **Helper T cells** (**T_H**) have receptors that bind to peptides displayed by the body's class II MCH molecules.

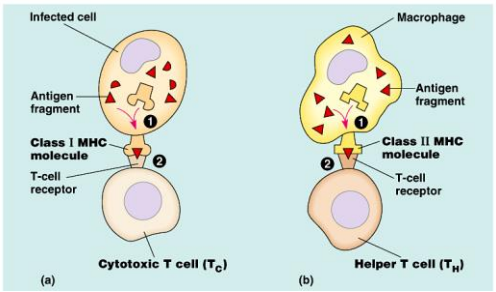


Fig. 43.9

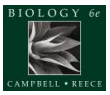
- Whether or not T cells respond to a pathogen, then, depends on the ability of MHC molecules to present a fragment to it.
  - Any one MHC molecule can present a variety of peptides that are structurally similar, and, because of the heterozygosity of our MHC genes, we each make two different MHC polypeptides per gene.
  - Chances are good that at least one of our MHC molecules will be able to present at least one fragment of a particular pathogen to our T cells - and generate an immune response against it.

- Class I MHC molecules, found in almost all cells, are poised to present fragments of proteins made by infecting microbes, usually viruses, to cytotoxic T cells.
  - Cytotoxic T cells respond by killing the infected cells.
  - Because all of our cells are vulnerable to infection by one or another virus, the wide distribution of class I MHC molecules is critical to our health.

- Class II MHC molecules are made by only a few cell types, chiefly macrophages and B cells.
  - These cells, called **antigen-presenting cells** (**APCs**) in this context, ingest bacteria and viruses and then destroy them.
  - Class II MHC molecules in these cells collect peptide remnants of this degradation and present them to helper T cells.
  - In response, the helper T cells send out chemical signals that incite other cell types to fight the pathogen.

- MHC proteins also play a key role in the development of T-cell self-tolerance.
  - Developing T cells interact with other thymic cells, which have high levels of both class I and class II MHC molecules.
  - Only T cells bearing receptors with affinity for self MHC proteins reach maturity.
  - Developing T cells having receptors with affinity for class I MHC become cytotoxic T cells.
  - Those having receptors with affinity for class II MHC become helper T cells.

- To review, the immune responses of B and T lymphocytes exhibit four attributes that characterize the immune system as a whole: specificity, diversity, memory, and the ability to distinguish self from nonself.
- A critical component of the immune response is the MHC.
  - Proteins encoded by this gene complex display a combination of self (MHC molecule) and nonself (antigen fragment) that is recognized by specific T cells.



CHAPTER 43
THE BODY'S DEFENSES

Section C: Immune Responses

1. **Helper T lymphocytes function in both humoral and cell-mediated immunity: *an overview***
2. **In the cell-mediated response, cytotoxic T cells counter intracellular pathogens: *a closer look***
3. **In the humoral response: B cells make antibodies against extracellular pathogens: *a closer look***
4. **Invertebrates have a rudimentary immune system**

Introduction

- The immune system can mount two types of responses to antigens: a humoral response and a cell-mediated response.
  - **Humoral immunity** involves B cell activation and results from the production of antibodies that circulate in the blood plasma and lymph.
    - Circulating antibodies defend mainly against free bacteria, toxins, and viruses in the body fluids.
  - In **cell-mediated immunity**, T lymphocytes attack viruses and bacteria within infected cells and defend against fungi, protozoa, and parasitic worms.
    - They also attack "nonself" cancer and transplant cells.

- The humoral and cell-mediated immune responses are linked by cell-signaling interactions, especially via helper T cells.

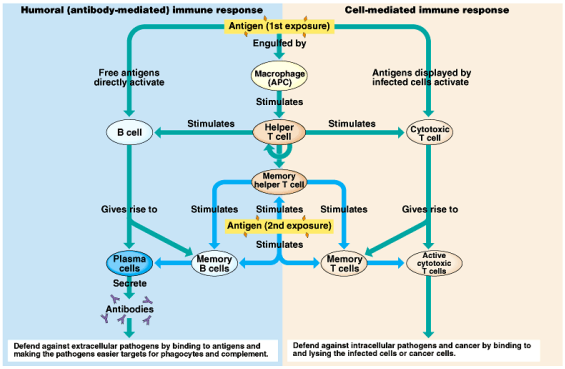


Fig. 43.10

1. Helper T lymphocytes function in both humoral and cell-mediated immunity: *an overview*

- Both types of immune responses are initiated by interactions between antigen-presenting cells (APCs) and helper T cells.
  - The APCs, including macrophages and some B cells, tell the immune system, via helper T cells, that a foreign antigen is in the body.
  - At the heart of the interactions between APCs and helper T cells are class II MHC molecules produced by the APCs, which bind to foreign antigens.

(1) An APC engulfs a bacterium and transports a fragment of it to the cell surface via a class II MHC molecule.

(2) A specific T_H cell is activated by binding to the MHC-antigen complex on the surface of the APC.
  - Both **CD4** proteins on the surface of the T_H cells and interleukin-1 secreted by the APC enhance activation.

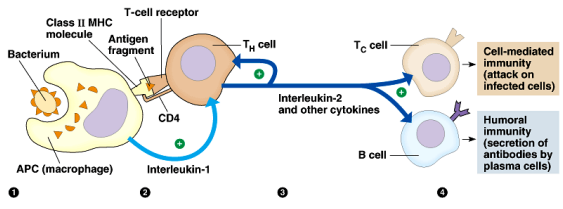


Fig. 43.11

- When a helper T cell is selected by specific contact with the class II MHC-antigen complex on an APC, the T_H cell proliferates and differentiates into a clone of activated helper T cells and memory helper T cells.
  - Activated helper T cells secrete several different **cytokines**, proteins or peptides that stimulate other lymphocytes.
  - For example, the cytokine **interleukin-2** (**IL-2**) helps B cells that have contacted antigen differentiate into antibody-secreting plasma cells.
    - IL-2 also helps cytotoxic T cells become active killers.

- The helper T cell itself is also subject to regulation by cytokines.
  - As a macrophages phagocytoses and presents antigen, the macrophage is stimulated to secrete a cytokine called **interleukin-1** (**IL-1**).
  - IL-1, plus the presented antigen, activates the helper T cell to produce IL-2 and other cytokines.
  - In a case of positive feedback, IL-2 secreted by the helper T cells stimulates that same cell to proliferate more rapidly and to become an even more active cytokine producer.
- Helper T cells modulate both humoral (B cell) and cell-mediated (cytotoxic T cell) immune responses.

2. In the cell-mediated response, cytotoxic T cells counter intracellular pathogens: *a closer look*

- Antigen-activated cytotoxic T lymphocytes kill cancers cells and cells infected by viruses and other intracellular pathogens.
- This is mediated through class I MHC molecules.
  - All nucleated cells continuously produce class I MHC molecules, which capture a small fragment of one of the other proteins synthesized by that cell and carries it to the surface.

- If the cell contains a replicating virus, class I MHC molecules expose foreign proteins that are synthesized in infected or abnormal cells to cytotoxic T cells.
  - This interaction is greatly enhanced by a T surface protein **CD8** which helps keep the cells together while the T_C cell is activated.

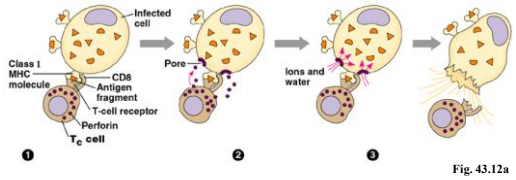


Fig. 43.12a

- A cytotoxic T cell is activated by specific contacts with class I MHC-antigen complexes on an infected cell and by IL-2 from a helper T cell.
  - The activated cytotoxic T cell differentiates into an active killer, which kills its target cell - the antigen-presenting cell - primarily by releasing **perforin**.
    - This protein forms pores into the target cell, which swells and eventually lyses.
  - The death of the infected cell not only deprives the pathogen of a place to reproduce, but it also exposes it to circulating antibodies, which mark it for disposal.
  - Once activated, the T_C cells kills other cells infected with the same pathogen.

- In the same way, T_C cells defend against malignant tumors.
  - Because tumor cells carry distinctive molecules not found on normal cells, they are identified as foreign by the immune system.
  - Class I MHC molecules on a tumor cell present fragments of **tumor antigens** to T_C cells.
  - Interestingly, certain cancers and viruses actively reduce the amount of class I MHC protein on affected cells so that they escape detection by T_C cells.
  - The body has a backup defense in the form of natural killer cells, part of the nonspecific defenses, which lyse virus-infected and cancer cells.

3. In the humoral response, B cells make antibodies against extracellular pathogens: *a closer look*

- The humoral immune response is initiated when B cells bearing antigen receptors are selected by binding with specific antigens.
  - This is assisted by IL-2 and other cytokines secreted from helper T cells activated by the same antigen.
  - These B cells proliferate and differentiate into a clone of antibody-secreting plasma cells and a clone of memory B cells.

- Many antigens (primarily proteins), called **T-dependent antigens**, can trigger a humoral immune response by B cells only with the participation of helper T cells.

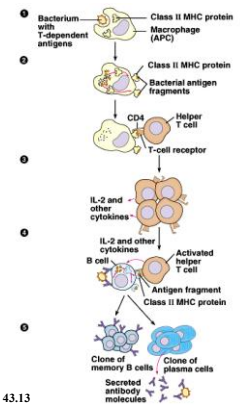


Fig. 43.13

- Other antigens, such as polysaccharides and proteins with many identical polypeptides, function as **T-independent antigens**.
  - These include the polysaccharides of many bacterial capsules and the proteins of the bacterial flagella.
  - These antigens bind simultaneously to a number of membrane antibodies on the B cell surface.
  - This stimulates the B cell to generate antibody-secreting plasma cells without the help of IL-2.
  - While this response is an important defense against many bacteria, it generates a weaker response than T-dependent antigens and generates no memory cells.

- Any given humoral response stimulates a variety of different B cells, each giving rise to a clone of thousands of plasma cells.
  - Each plasma cell is estimated to secrete about 2,000 antibody molecules per second over the cell's 4- to 5-day life span.

- Antigens that elicit a humoral immune response are typically the protein and polysaccharide surface components of microbes, incompatible transplanted tissues, or incompatible transfused cells.
  - In addition, for some humans, the proteins of foreign substances such as pollen or bee venom acts as antigens that induce an allergic, or hypersensitive humoral response.

- Antibodies constitute a group of globular serum proteins called **immunoglobins** (**Igs**).
  - A typical antibody molecule has two identical antigen-binding sites specific for the epitope that provokes its production.

- Neither the B cell receptor for antigen nor the secreted antibody actually binds to an entire antigen molecule.
  - An antibody interacts with a small, accessible portion of the antigen called a **epitope** or antigenic determinant.
  - A single antigen such as a bacterial surface protein usually has several effective epitopes, each capable of inducing the production of specific antibody.

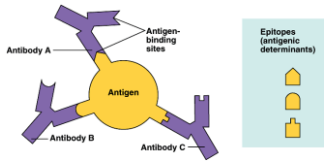


Fig. 43.14

- At the two tips of the Y-shaped antibody molecule are the variable regions (V) of the **heavy chains** and **light chains**.
  - The amino acid sequences in these regions vary extensively from antibody to antibody.
  - A heavy-chain V region and a light-chain V region together form the unique contours of an antibody's antigen-binding site.
  - Multiple noncovalent bonds form between the antigen-binding site and its epitope.

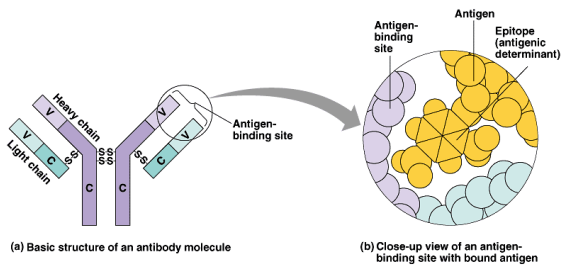


Fig. 43.15

- The power of antibody specificity and antigen-antibody binding has been applied in laboratory research, clinical diagnosis, and disease treatment.
  - Some antibody tools are *polyclonal*, the products of many different clones of B cells, each specific for a different epitope.
  - Others are *monoclonal*, prepared from a single clone of B cells grown in culture.
    - These cells produce **monoclonal antibodies**, specific for the same epitope on an antigen.
  - These have been used to tag specific molecules.
    - For example, toxin-linked antibodies search and destroy tumor cells.

- The tail of the Y-shaped antibody, formed by the constant regions (C) of the heavy chains, is responsible for the antibody's distribution in the body.
  - The heavy-chain constant regions also determine the mechanism by which it mediates antigen disposal.

- There are five major types of heavy-chain constant regions, determining the five major classes of antibodies.

Table 43.1 The Five Classes of Immunoglobulins

IgM (pentamer) 	IgMs are the first circulating antibodies to appear in response to an initial exposure to an antigen; their concentration in the blood then declines rapidly. Thus the presence of IgM usually indicates a current infection. IgM consists of five Y-shaped monomers arranged in a pentagonal structure. The numerous antigen-binding sites make it very effective in agglutinating antigens and in reactions involving complement. IgM is too large to cross the placenta and does not confer maternal immunity.
IgG (monomer) 	IgG is the most abundant of the circulating antibodies. It readily crosses the walls of blood vessels and enters tissue fluids. IgG also crosses the placenta and confers passive immunity on the fetus. IgG protects against bacteria, viruses, and toxins in the blood and lymph, and triggers action of the complement system.
IgA (dimer) 	IgA is produced by cells in mucous membranes. The main function of IgA is to prevent the attachment of viruses and bacteria to epithelial surfaces. IgA is also found in many body secretions, such as saliva, perspiration, and tears. Its presence in the first milk produced helps protect the infant from gastrointestinal infections.
IgD (monomer) 	IgD antibodies do not activate the complement system and cannot cross the placenta. They are mostly found on the surfaces of B cells, probably functioning as antigen receptors that help initiate the differentiation of B cells into plasma cells and memory B cells.
IgE (monomer) 	IgE molecules are slightly larger than IgG and represent only a small fraction of the antibodies in the blood. The tails attach to mast cells and basophils and, when triggered by an antigen, cause the cells to release histamine and other chemicals that cause an allergic reaction.

- The binding of antibodies to antigens to form antigen-antibody complexes is the basis of several antigen disposal mechanisms.

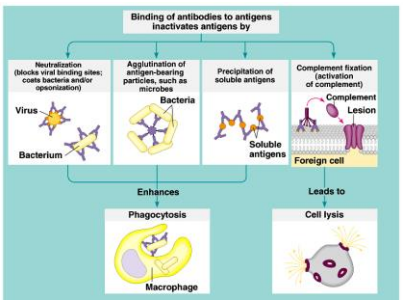


Fig. 43.16

- In **neutralization**, the antibody binds to and blocks the activity of the antigen.
  - For example, antibodies neutralize a virus by attaching to molecules that the virus uses to infect its host cell.
  - Similarly, antibodies may bind to the surface of a pathogenic bacterium.
  - These microbes, now coated by antibodies, are readily eliminated by phagocytosis.
    - In a process called **opsonization**, the bound antibodies enhance macrophage attachment to, and thus phagocytosis of, the microbes.

- Antibody-mediated **agglutination** of bacteria or viruses effectively neutralizes and opsonizes the microbes.
  - Agglutination is possible because each antibody molecule has at least two antigen-binding sites.
  - IgM can link together five or more viruses or bacteria.
  - These large complexes are readily phagocytosed by macrophages.
- In precipitation, the cross-linking of soluble antigen molecules - molecules dissolved in body fluids - forms immobile precipitates that are disposed of by phagocytosis.

- During **complement fixation**, the antigen-antibody system activates the complement system, a complex of 20 different serum proteins.
  - In an infection, the first in a series of complement proteins is activated, triggering a cascade of activation steps, each component activating the next in the series.
  - Completion results in the lysis of many types of viruses and pathogenic cells.

- Lysis by complement can be achieved in two ways.
  - The *classical pathway* is triggered by antibodies bound to antigen and is therefore important in the humoral immune response.
  - The *alternative pathway* is triggered by substances that are naturally present on many bacteria, yeasts, viruses, and protozoan parasites.
    - It does not involve antibodies and thus is an important nonspecific defense.

- The classical pathway begins when IgM or IgG antibodies bind to a pathogen, such as a bacterium.
  - The first complement component links two bound antibodies and is activated, initiating the cascade.
  - Ultimately, complement proteins generate a **membrane attack complex** (**MAC**), which forms a pore in the bacterial membrane, resulting in cell lysis.

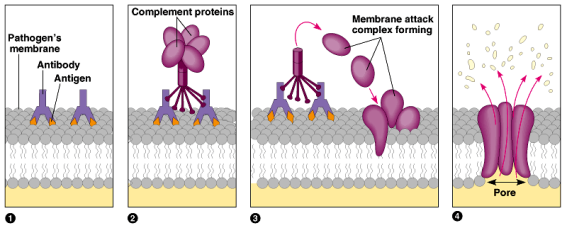


Fig. 43.17

- In both the classical and alternative pathways, many activated complement proteins contribute to inflammation.
  - Some trigger the release of histamine by binding to basophils and mast cells.
  - Several active complement proteins also attract phagocytes to the site.
  - One activated complement protein coats bacterial surfaces and stimulates phagocytosis, like an antibody.
  - During **immune adherence**, microbes coated with antibodies and complement adhere to blood vessel walls, making the pathogens easier prey for phagocytic cells circulating in the blood.

4. Invertebrates have a rudimentary immune system

- Invertebrate animals also exhibit highly effective mechanisms of host defense.
- The ability to make the distinction between self and nonself is seen in animals as ancient as sponges.
  - For example, if the cells of two sponges are mixed, the cells from each sponge will reaggregate, each excluding cells from the other individual.

- Invertebrates also dispose of what is not self, primarily by phagocytosis.
  - In sea stars, this is accomplished by amoeboid cells called *coelomocytes*.
- Furthermore, immunologists have begun to find cytokines in invertebrates.
  - For example, sea star coelomocytes produce interleukin-1 as they engulf foreign material.
    - This enhances the animal's defensive response by stimulating coelomocyte proliferation and attracting more coelomocytes to the area.

- Invertebrates depend on innate, nonspecific mechanisms of defense rather than acquired, antigen-specific mechanisms.
  - However, some invertebrates possess lymphocyte-like cells that produce antibody-like molecules.
  - For example, insects have a hemolymph protein, called *hemolin*, that binds to microbes and assists in their disposal.
    - Hemolin molecules, members of the immunoglobin superfamily and related to antibodies, do not exhibit diversity, but they are likely evolutionary precursors of vertebrate antibodies.

- By and large, invertebrates do not exhibit the hallmark of acquired immunity - immunological memory.
  - For example, sea star coelomocytes respond to a particular microbe with the same speed no matter how many times they have encountered that invader before.
  - However, earthworms do appear to have a kind of immunological memory.
    - When a portion of body wall from one worm is grafted onto another, the recipient rejects the initial graft in about two weeks, but a second graft from the same donor is rejected in just a few days.

CHAPTER 43
THE BODY'S DEFENSES

Section D: Immunity in Health and Disease

1. **Immunity can be achieved naturally or artificially**
2. **The immune system's capacity to distinguish self from nonself limits blood transfusion and tissue transplantation**
3. **Abnormal immune function can lead to disease**
4. **AIDS is an immunodeficiency disease caused by a virus**

1. Immunity can be achieved naturally or artificially

- Immunity conferred by recovering from an infectious disease such as chicken pox is called **active immunity** because it depends on the response of the infected person's own immune system.
  - Active immunity can be acquired naturally or artificially, by **immunization**, also known as **vaccination**.
  - Vaccines include inactivated toxins, killed microbes, parts of microbes, and viable but weakened microbes.
  - These no longer cause disease, but they can act as antigens, stimulating an immune response, and more important, immunological memory.

- A vaccinated person who encounters the actual pathogen will have the same quick secondary response based on memory cells as a person who has had the disease.
  - Routine immunization of infants and children has dramatically reduced the incidence of infectious diseases such as measles and whooping cough, and has led to the eradication of smallpox, a viral disease.
  - Unfortunately, not all infectious agents are easily managed by vaccination.
    - For example, although researchers are working intensively to develop a vaccine for HIV, they face many problems, such as antigenic variability.

- Antibodies can be transferred from one individual to another, providing **passive immunity**.
  - This occurs naturally when IgG antibodies of a pregnant woman cross the placenta to her fetus.
  - In addition, IgA antibodies are passed from mother to nursing infant in breast milk, especially in early secretions called colostrum.
  - Passive immunity persists as long as these antibodies last, a few weeks to a few months.
    - This protects the infant from infections until the baby's own immune system has matured.

- Passive immunity can be transferred artificially by injecting antibodies from an animal that is already immune to a disease into another animal.
  - This confers short-term, but immediate protection against that disease.
  - For example, a person bitten by a rabid animal may be injected with antibodies against rabies virus because rabies may progress rapidly, and the response to an active immunization could take too long to save the life of the victim.
    - Actually, most people infected with rabies virus are given both passive immunizations (the immediate fight) and active immunizations (longer term defense).

2. The immune system's capacity to distinguish self from nonself limits blood transfusion and tissue transplantation

- In addition to attacking pathogens, the immune system will also attack cells from other individuals.
  - For example, a skin graft from one person to a nonidentical individual will look healthy for a day or two, but it will then be destroyed by immune responses.
  - Interestingly, a pregnant woman does not reject the fetus as a foreign body, as apparently, the structure of the placenta is the key to this acceptance.

- One source of potential problems with blood transfusions is an immune reaction from individuals with incompatible blood types.
  - In the **ABO blood groups**, an individual with type A blood has A antigens on the surface of red blood cells.
    - This is not recognized as an antigen by the "owner," but it can be identified as foreign if placed in the body of another individual.
  - B antigens are found on type B red blood cells.
  - Both A and B antigens are found on type AB red blood cells.
  - Neither antigen is found on type O red blood cells.

- A person with type A blood already has antibodies to the B antigen, even if the person has never been exposed to type B blood.
  - These antibodies arise in response to bacteria (normal flora) that have epitopes very similar to blood group antigens.
  - Thus, an individual with type A blood does make antibodies to A-like bacterial epitopes - these are considered self - but that person does make antibodies to B-like bacterial epitopes.
  - If a person with type A blood receives a transfusion of type B blood, the preexisting anti-B antibodies will induce an immediate and devastating transfusion reaction.

- Because blood group antigens are polysaccharides, they induce T-independent responses, which elicit no memory cells.
  - Each response is like a primary response, and it generates IgM anti-blood-group antibodies, not IgG.
  - This is fortunate, because IgM antibodies do not cross the placenta where they may harm a developing fetus with a blood type different from its mother's.

- However, another blood group antigen, the **Rh factor**, can cause mother-fetus problems because antibodies produced to it are IgG.
  - This situation arises when a mother that is Rh-negative (lacks the Rh factor) has a fetus that is Rh-positive, having inherited the factor from the father.
  - If small amounts of fetal blood cross the placenta as may happen late in pregnancy or during delivery, the mother mounts a T-dependent humoral response against the Rh factor.
  - The danger occurs in subsequent Rh-positive pregnancies, when the mother's Rh-specific memory B cells produce IgG antibodies that can cross the placenta and destroy the red blood cells of the fetus.

- To prevent this, the mother is injected with anti-Rh antibodies after delivering her first Rh positive baby.
  - She is, in effect, passively immunized (artificially) to eliminate the Rh antigen before her own immune system responds and generates immunological memory against the Rh factor, endangering her future Rh-positive babies.

- The major histocompatibility complex (MHC) is responsible for stimulating the rejection of tissue grafts and organ transplants.
  - Because MHC creates a unique protein fingerprint for each individual, foreign MHC molecules are antigenic, inducing immune responses against the donated tissue or organ.
  - To minimize rejection, attempts are made to match MCH of tissue donor and recipient as closely as possible.
    - In the absence of identical twins, siblings usually provide the closest tissue-type match.

- In addition to MHC matching, various medicines are necessary to suppress the immune response to the transplant.
  - However, this strategy leaves the recipient more susceptible to infection and cancer during the course of treatment.
  - More selective drugs, which suppress helper T cell activation without crippling nonspecific defense or T-independent humoral responses, have greatly improved the success of organ transplants.

- In bone marrow transplants, it is the graft itself, rather than the host, that is the source of potential immune rejection.
  - Bone marrow transplants are used to treat leukemia and other cancers as well as various hematological diseases.
  - Prior to the transplant, the recipient is typically treated with irradiation to eliminate the recipient's immune system, leaving little chance of graft rejection.
  - However, the donated marrow, containing lymphocytes, may react against the recipient, producing **graft versus host reaction**, unless well matched.

3. Abnormal immune function can lead to disease

- Malfunctions of the immune system can produce effects ranging from the minor inconvenience of some allergies to the serious and often fatal consequences of certain autoimmune and immunodeficiency diseases.

- Allergies are hypersensitive (exaggerated) responses to certain environmental antigens, called allergens.
  - One hypothesis to explain the origin of allergies is that they are evolutionary remnants of the immune system's response to parasitic worms.
  - The humoral mechanism that combats worms is similar to the allergic response that causes such disorders as hay fever and allergic asthma.

- The most common allergies involve antibodies of the IgE class.
  - Hay fever, for example, occurs when plasma cells secrete IgE specific for pollen allergens.
  - Some IgE antibodies attach by their tails to mast cells present in connective tissue, without binding to the pollen.
  - Later, when pollen grains enter the body, they attach to the antigen-binding sites of mast cell-associated IgE, cross-linking adjacent antibody molecules.

- This event triggers the mast cell to *degranulate* - that is, to release histamines and other inflammatory agents from vesicles called granules.

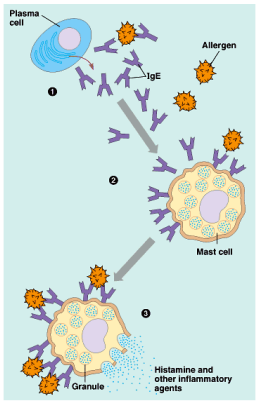


Fig. 43.18

- High levels of histamines cause dilation and increased permeability of small blood vessels.
  - These inflammatory events lead to typical allergy symptoms: sneezing, runny nose, tearing eyes, and smooth muscle contractions that can result in breathing difficulty.
  - Antihistamines diminish allergy symptoms by blocking receptors for histamine.

- Sometimes, an acute allergic response can result in **anaphylactic shock**, a life threatening reaction to injected or ingested allergens.
  - Anaphylactic shock results when widespread mast cell degranulation triggers abrupt dilation of peripheral blood vessels, causing a precipitous drop in blood pressure.
    - Death may occur within minutes.
  - Triggers of anaphylactic shock in susceptible individuals include bee venom, penicillin, or foods such as peanuts or fish.
  - Some hypersensitive individuals carry syringes with epinephrine, which counteracts this allergic response.

- Sometimes the immune system loses tolerance for self and turns against certain molecules of the body, causing one of many autoimmune diseases.
  - In *systemic lupus erythematosus* (*lupus*), the immune system generates antibodies against all sorts of self molecules, including histamines.
    - Lupus is characterized by skin rashes, fever, arthritis, and kidney dysfunction.
  - *Rheumatoid arthritis* leads to damage and painful inflammation of the cartilage and bone of joints.
  - In *insulin-dependent diabetes mellitus*, the insulin-producing beta cells of the pancreas are the targets of autoimmune cell-mediated responses.

- *Multiple sclerosis* (*MS*) is the most common chronic neurological disease in developed countries,
  - In MS, T cells reactive against myelin infiltrate the central nervous system and destroy the myelin of neurons.
  - People with MS experience a number of serious neurological abnormalities.

- The mechanisms that lead to autoimmunity are not fully understood.
  - It was thought that people with autoimmune diseases had self-reactive lymphocytes that escaped elimination during their development.
  - We now know that healthy people also have lymphocytes with the capacity to react against self, but these cells are inhibited from inducing an autoimmune reaction by several regulatory mechanisms.
  - So, autoimmune disease likely arises from some failure in immune regulation, perhaps linked with particular MHC alleles.

- In immunodeficiency diseases, the function of either the humoral or cell-mediated immune defense is compromised.
  - In *severe combined immunodeficiency* (*SCID*), both branches of the immune system fail to function.
  - For individuals with this disease, long-term survival requires a bone marrow transplant that will continue to supply functional lymphocytes.
  - Several gene therapy approaches are in clinical trials to attempt to reverse SCID, but results to this point have been equivocal.

- Immunodeficiency may also develop later in life.
  - For example, certain cancers suppress the immune system, especially Hodgkin's disease, which damages the lymphatic system.
  - AIDS is another acquired immune deficiency.

- Healthy immune system function appears to depend on both the endocrine system and the nervous system.
  - For example, hormones secreted by the adrenal glands during stress affect the number of white blood cells and may suppress the immune system in other ways.
  - Similarly, some neurotransmitters secreted when we are relaxed and happy may enhance immunity.
  - Physiological evidence also points to an immune system-nervous system link based on the presence of neurotransmitter receptors on the surfaces of lymphocytes and a network of nerve fibers that penetrates deep into the thymus.

4. AIDS is an immunodeficiency disease caused by a virus

- In 1981, increased rates of two rare diseases, Kaposi's sarcoma, a cancer of the skin and blood vessels, and pneumonia caused by the protozoan *Pneumocystis carinii*, were the first signals to the medical community of a new threat to humans, later known as **acquired immunodeficiency syndrome**, or **AIDS**.
  - Both conditions were previously known to occur mainly in severely immunosuppressed individuals.
  - People with AIDS are susceptible to *opportunistic diseases*.

- In 1983, a retrovirus, now called **human immunodeficiency virus** (**HIV**), had been identified as the causative agent of AIDS.

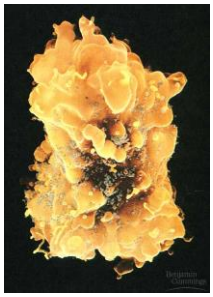


Fig. 43.19

- With the AIDS mortality close to 100%, HIV is the most lethal pathogen ever encountered.
  - Molecular studies reveal that the virus probably evolved from another HIV-like virus in chimpanzees in central Africa and appeared in humans sometimes between 1915 and 1940.
    - These first rare cases of infection and AIDS went unrecognized.

- There are two major strains of the virus, HIV-1 and HIV-2.
  - HIV-1 is the more widely distributed and more virulent.
- Both strains infect cells that bear CD4 molecules, especially helper T cells and class II MCH-bearing antigen-presenting cells, but also macrophages, some lymphocytes and some brain cells.
  - CD4 functions as the major receptor for the virus.

- The entry of the virus requires not only CD4 on the surface of the susceptible cells but also a second protein molecule, a *coreceptor*.
  - Two of the coreceptors that have been identified normally function as receptors for chemokines.
  - Some people who are innately resistant to HIV-1 owe their resistance to defective chemokine receptors which prevents HIV from binding and infecting cells.

- Once inside a cell, HIC RNA is reverse-transcribed, and the product DNA is integrated into the host genome.
  - In this provirus form, the viral genome directs the production of new virus particles.
  - Because a retrovirus exists as a provirus for the life of the infected cell, immune responses fail to eradicate it from the body.
  - Even more challenging for the immune responses are the frequent mutational changes that occur in each round of virus replication.
  - Indeed, most HIV particles produced in an infected person differ at least slightly from the original virus.

- In spite of these challenges, the immune system engages in a prolonged battle against HIV.

(1) The immune response diminishes the initial viral load, but HIV continues to replicate in lymphatic tissue.

(2) Viral load gradually rises as HIV is released from lymphatic tissue and helper T cell levels decrease.

(3) This results in extensive loss of humoral and cell-mediated immunity.

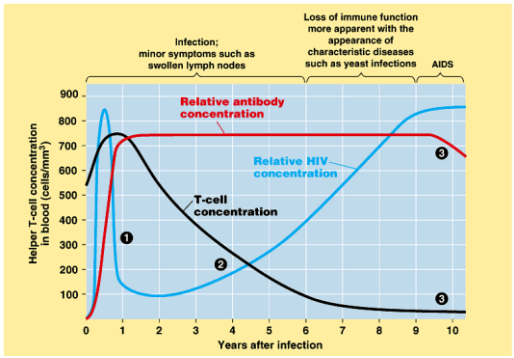


Fig. 43.20

- After an initial peak, virus levels in the blood fall as anti-HIV antibodies, produced 1 to 12 months after infection, rise.
  - A person who is *HIV-positive* is infected, having tested positive for the presence of antibodies to the virus.
  - The HIV antibody test has be used to screen all blood supplies in the U.S. since 1985.
    - However, this does not completely guarantee a safe blood supply because an infected individual may require several weeks or months before anti-HIV antibodies become detectable.

- After the early drop in HIV levels in the blood, the virus continues to be produced by cells in the lymph nodes, causing structural and functional damage.
  - In time, the concentration of HIV in the blood increases as a result of the breakdown of lymphatic tissue function, the release of virus from these tissues, and diminishing responses to the infection because of the depletion of helper T cells.

- The decline in helper T cells is primarily caused by direct mortality from HIV infection.
  - There is some evidence that some depletion of T cells is through inappropriately timed apoptosis.
  - The half-life of an actively infected helper T cell (one producing new copies of HIV) is less than 1.5 days.

- The time required for an HIV infection to progress from severe helper T cell depletion and AIDS varies greatly, but it currently averages about ten years.
  - During most of this time, the individual exhibits only moderate hints of illness, such as swollen lymph nodes and occasional fever.
  - Progress of the disease can be monitored by measuring changes in the level of T cells, although measures of viral load are a better indicator of disease prognosis and of the effectiveness of anti-HIV treatment.

- At this time, HIV infection cannot be cured, and the progression to AIDS cannot be prevented.
- New, expensive drug therapies can slow this progression.
  - These drugs slow viral replication by inhibiting DNA synthesis, reverse transcriptase, and protease.
    - Protease inhibitors prevents a key step in the synthesis of HIV proteins.
  - Combinations of these drugs decrease viral load and therefore allow the number of helper T cells to rise.
  - Other drugs treat the myriad of opportunistic diseases as they develop.

- Transmission of HIV requires the transfer of body fluids containing infected cells, such as semen or blood, from person to person.
  - Unprotected sex (that is, without a condom) among male homosexuals and transmission via nonsterile needles (typically among intravenous drug users) account for most of the AIDS cases reported thus far in the United States and Europe.
  - However, transmission of HIV among heterosexuals is rapidly increasing as a result of unprotected sex with infected partners.
  - In Africa and Asia, transmission has been primarily by heterosexual sex, especially where there is a high incidence of genital lesions from other diseases.

- HIV is not transmitted by casual contact.
  - So far, only one case of HIV transmission by kissing has been reported, and both individuals had bleeding gums.
  - Transmission of HIV from mother to child can occur during fetal development or during nursing.
  - HIV screening has virtually eliminated blood transfusions as a route of transmission in developed countries.

- As of 2000 the Joint United Nations Program on AIDS estimates that 30 to 40 million people worldwide are living with HIV or HIV/AIDS.
  - Of these, approximately 70% reside in sub-Saharan Africa.
  - The number of people with AIDS is expected to grow by nearly 20% per year.

- The best approach for slowing the spread of HIV is to educate people about the practices that transmit the disease, such as using nonsterile needles and having sex without a condom.
  - Although condoms do not completely eliminate the risk of transmitting HIV (or other similar transmitted viruses, such as the hepatitis B virus), they do reduce it.
  - Any individual who has sex - vaginal, oral, or anal - with a partner who had unprotected sex with another person during the past two decades risks exposure to HIV.