The thymus is divided into lobules by connective tissue. The T lymphocytes mature in these lobules. The interior (medulla) of the lobule, which consists mostly of epithelial cells, stains lighter than the outer layer (cortex). The thymus gland produces thymic hormones, such as thymosin, that are thought to aid in maturation of T lymphocytes. Thymosin may also have other functions in immunity.

Red bone marrow is the site of origin for all types of blood cells, including the five types of white blood cells pictured in Figure 13.10. The marrow contains stem cells that are ever capable of dividing and producing cells that then differentiate into the various types of blood cells (see Fig. 13.14). In a child, most bones have red bone marrow, but in an adult it is present only in the bones of the skull, the sternum (breastbone), the ribs, the clavicle, the pelvic bones, and the vertebral column. The red bone marrow consists of a network of connective tissue fibers, called reticular fibers, which are produced by cells called reticular cells. These and the stem cells and their progeny are packed around thin-walled sinuses filled with venous blood. Differentiated blood cells enter the bloodstream at these sinuses.

Lymphoid organs have specific functions that assist immunity. Lymph is cleansed in lymph nodes; blood is cleansed in the spleen. All blood cells are made in red bone marrow. Most white blood cells mature in the red bone marrow, but T lymphocytes mature in the thymus.

14.2 Nonspecific Defenses

The **immune system** includes the cells and tissues that are responsible for immunity. **Immunity** is the body's ability to defend itself against infectious agents, foreign cells, and even abnormal body cells, such as cancer cells. Thereby, the internal environment has a better chance of remaining stable. Immunity includes nonspecific and specific defenses. The four types of nonspecific defenses—barriers to entry, the inflammatory reaction, natural killer cells, and protective proteins—are effective against many types of infectious agents.

Barriers to Entry

Skin and the mucous membranes lining the respiratory, digestive, and urinary tracts serve as mechanical barriers to entry by pathogens. Oil gland secretions contain chemicals that weaken or kill certain bacteria on the skin. The upper respiratory tract is lined by ciliated cells that sweep mucus and trapped particles up into the throat, where they can be swallowed or expectorated (coughed out). The stomach has an acidic pH, which inhibits the growth of or kills many types of bacteria. The various bacteria that normally reside in the intestine and other areas, such as the vagina, prevent pathogens from taking up residence.

Inflammatory Reaction

Whenever tissue is damaged, a series of events occurs that is known as the **inflammatory reaction.** The inflamed area has four outward signs: redness, heat, swelling, and pain. Figure 14.3 illustrates the participants in the inflammatory reaction. **Mast cells,** which occur in tissues, resemble basophils, one of the types of white cells found in the blood.

When an injury occurs, damaged tissue cells and mast cells release chemical mediators, such as **histamine** and **kinins,** which cause the capillaries to dilate and become more permeable. The enlarged capillaries cause the skin to redden, and the increased permeability allows proteins and fluids to escape into the tissues, resulting in swelling. The swollen area, as well as the kinins, stimulate free nerve endings, causing the sensation of pain.

Neutrophils and monocytes migrate to the site of injury. They are amoeboid and can change shape to squeeze through capillary walls and enter tissue fluid. Neutrophils, and also mast cells, phagocytize pathogens. The engulfed pathogens are destroyed by hydrolytic enzymes when the endocytic vesicle combines with a lysosome, one of the cellular organelles.

As they leave the blood and enter the tissues, monocytes differentiate into **macrophages,** large phagocytic cells that are able to devour a hundred pathogens and still survive. Some tissues, particularly connective tissue, have resident macrophages, which routinely act as scavengers, devouring old blood cells, bits of dead tissue, and other debris. Macrophages can also bring about an explosive increase in the number of leukocytes by liberating colony-stimulating factors, which pass by way of blood to the red bone marrow, where they stimulate the production and the release of white blood cells, primarily neutrophils. As the infection is being overcome, some neutrophils may die. These—along with dead cells, dead bacteria, and living white blood cells—form pus, a whitish material. Pus indicates that the body is trying to overcome the infection.

When a blood vessel ruptures, the blood forms a clot to seal the break. The chemical mediators (e.g., histamine and kinins) and antigens move through the tissue fluid and lymph to the lymph nodes. Now lymphocytes are activated to react to the threat of an infection. Sometimes inflammation persists, and the result is chronic inflammation that is often treated by administering anti-inflammatory agents such as aspirin, ibuprofen, or cortisone. These medications act against the chemical mediators released by the white blood cells in the area.

The inflammatory reaction is a "call to arms"—it marshals phagocytic white blood cells to the site of bacterial invasion and stimulates the immune system to react against a possible infection.

Visual Focus

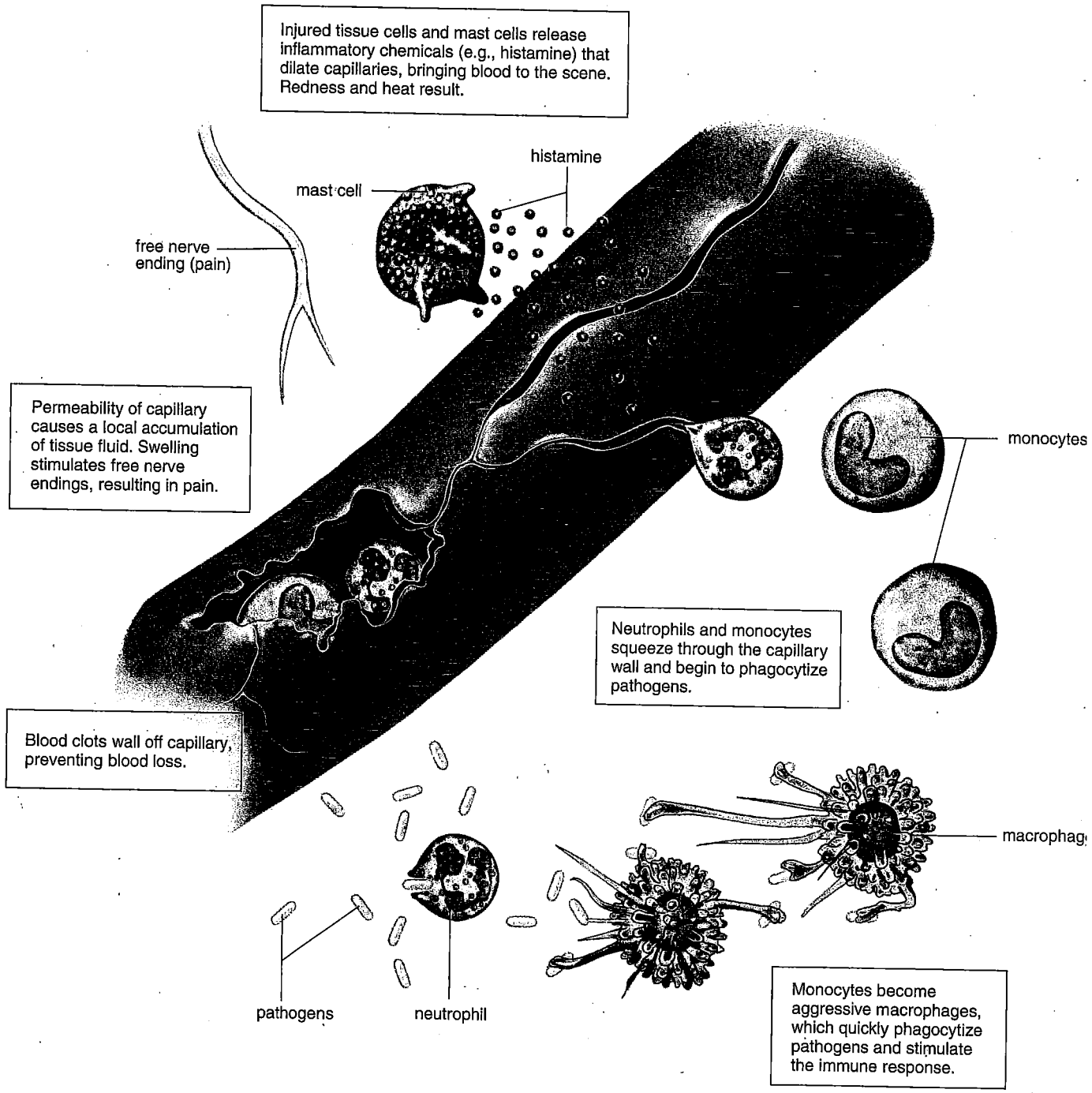


Figure 14.3 Inflammatory reaction.

Mast cells, which are related to basophils, a type of white blood cell, are involved in the inflammatory reaction. When a blood vessel is injured, mast cells release substances like histamine. Histamine dilates blood vessels and increases permeability so that tissue fluid leaks from the vessel. Swelling in the area stimulates pain receptors (free nerve endings). Neutrophils and monocytes which become macrophages squeeze through the capillary wall. These white blood cells begin to phagocytize pathogens (e.g., disease-causing viruses and bacteria), especially thos combined with antibodies. Blood clotting seals off the capillary, preventing blood loss.

Natural Killer Cells

Natural killer (NK) cells kill virus-infected cells and tumor cells by cell-to-cell contact. They are large, granular lymphocytes with no specificity and no memory. Their number is not increased by prior exposure to that kind of cell.

Protective Proteins

The **complement system,** often simply called complement, is a number of plasma proteins designated by the letter C and a subscript. A limited amount of activated complement protein is needed because a domino effect occurs: each activated protein in a series is capable of activating many other proteins.

Complement is activated when pathogens enter the body. It "complements" certain immune responses, which accounts for its name. For example, it is involved in and amplifies the inflammatory response because complement proteins attract phagocytes to the scene. Some complement proteins bind to the surface of pathogens already coated with antibodies, which ensures that the pathogens will be phagocytized by a neutrophil or macrophage.

Certain other complement proteins join to form a membrane attack complex that produces holes in the walls and plasma membranes of bacteria. Fluids and salts then enter the bacterial cell to the point that they burst (Fig. 14.4).

Interferon is a protein produced by virus-infected cells. Interferon binds to receptors of noninfected cells, causing them to prepare for possible attack by producing substances that interfere with viral replication. Interferon is specific to the species; therefore, only human interferon can be used in humans.

Immunity includes these nonspecific defenses: barriers to entry, the inflammatory reaction, natural killer cells, and protective proteins.

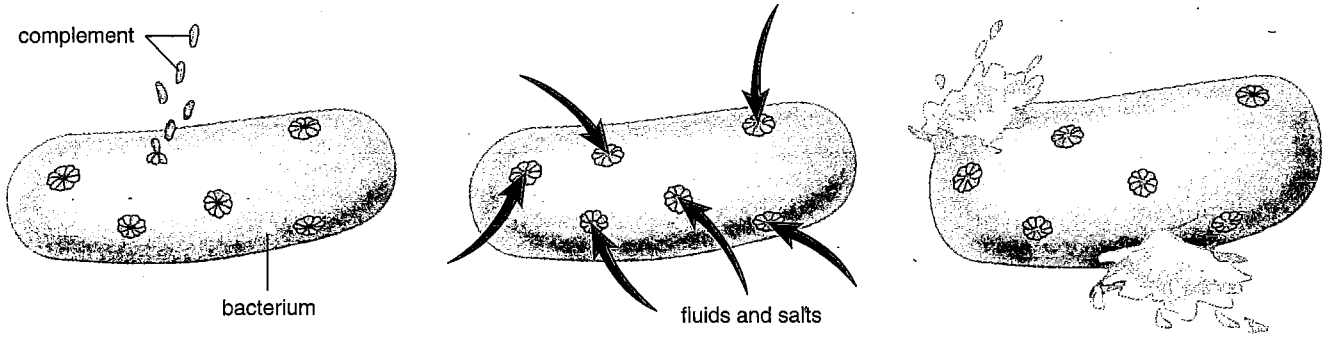
14.3 Specific Defenses

When nonspecific defenses have failed to prevent an infection, specific defenses come into play. An **antigen** is any foreign substance (often a protein or polysaccharide) that stimulates the immune system to react to it. Pathogens have antigens, but antigens can also be part of a foreign cell or a cancer cell. Because we do not ordinarily become immune to our own normal cells, it is said that the immune system is able to distinguish "self" from "nonself." Only in this way can the immune system aid, rather than counter, homeostasis.

Lymphocytes are capable of recognizing an antigen because they have **antigen receptors**—plasma membrane receptor proteins whose shape allows them to combine with a specific antigen. It is often said that the receptor and the antigen fit together like a lock and a key. Because we encounter a million different antigens during our lifetime, we need a great diversity of lymphocytes to protect us against them. Remarkably, diversification occurs to such an extent during the maturation process that there is a lymphocyte type for any possible antigen.

Immunity usually lasts for some time. For example, once we recover from the measles, we usually do not get the illness a second time. Immunity is primarily the result of the action of the **B lymphocytes** and the **T lymphocytes.** B lymphocytes mature in the *b*one marrow,[2] and T lymphocytes mature in the *t*hymus gland. B lymphocytes, also called B cells, give rise to plasma cells, which produce **antibodies,** proteins shaped like the antigen receptor and capable of combining with and neutralizing a specific antigen. These antibodies are secreted into the blood, lymph, and other body fluids. In contrast, T lymphocytes, also called T cells, do not produce antibodies. Instead, certain T cells directly attack cells that bear nonself proteins. Other T cells regulate the immune response.

[2]Historically, the B stands for bursa of Fabricius, an organ in the chicken where these cells were first identified. As it turns out, however, the B can conveniently be thought of as referring to bone marrow.



Complement proteins form holes in the bacterial cell wall and membrane.

Holes allow fluids and salts to enter the bacterium.

Bacterium expands until it bursts.

Figure 14.4 Action of the complement system against a bacterium.
When complement proteins in the plasma are activated by an immune response, they form holes in bacterial cell walls and plasma membranes, allowing fluids and salts to enter until the cell eventually bursts.

B Cells and Antibody-Mediated Immunity

When a B cell in a lymph node or the spleen encounters a specific antigen, it is activated to divide many times. Most of the resulting cells are plasma cells. A **plasma cell** is a mature B cell that mass-produces antibodies against a specific antigen.

The **clonal selection theory** states that the antigen selects which lymphocyte will undergo clonal expansion and produce more lymphocytes bearing the same type of antigen receptor. Notice in Figure 14.5 that different types of antigen receptors are represented by color. The B cell with blue receptors undergoes clonal expansion because a specific antigen (red dots) is present and binds to its receptors. B cells are stimulated to divide and become plasma cells by helper T cell secretions called cytokines, as is discussed in the next section. Some members of the clone become memory cells, which are the means by which long-term immunity is possible. If the same antigen enters the system again, **memory B cells** quickly divide and give rise to more lymphocytes capable of quickly producing antibodies.

Once the threat of an infection has passed, the development of new plasma cells ceases, and those present undergo apoptosis. **Apoptosis** is a process of programmed cell death (PCD) involving a cascade of specific cellular events leading to the death and destruction of the cell. The methodology of PCD is still being worked out, but we know it is an essential physiological mechanism regulating the cell population within an organ system. PCD normally plays a central role in maintaining tissue homeostasis.

Defense by B cells is called **antibody-mediated immunity** because the various types of B cells produce antibodies. It is also called humoral immunity because these antibodies are present in blood and lymph. A humor is any fluid normally occurring in the body.

Characteristics of B Cells

- Antibody-mediated immunity against bacteria
- Produced and mature in bone marrow
- Reside in spleen and lymph nodes, circulate in blood and lymph
- Directly recognize antigen and then undergo clonal selection
- Clonal expansion produces antibody-secreting plasma cells as well as memory B cells

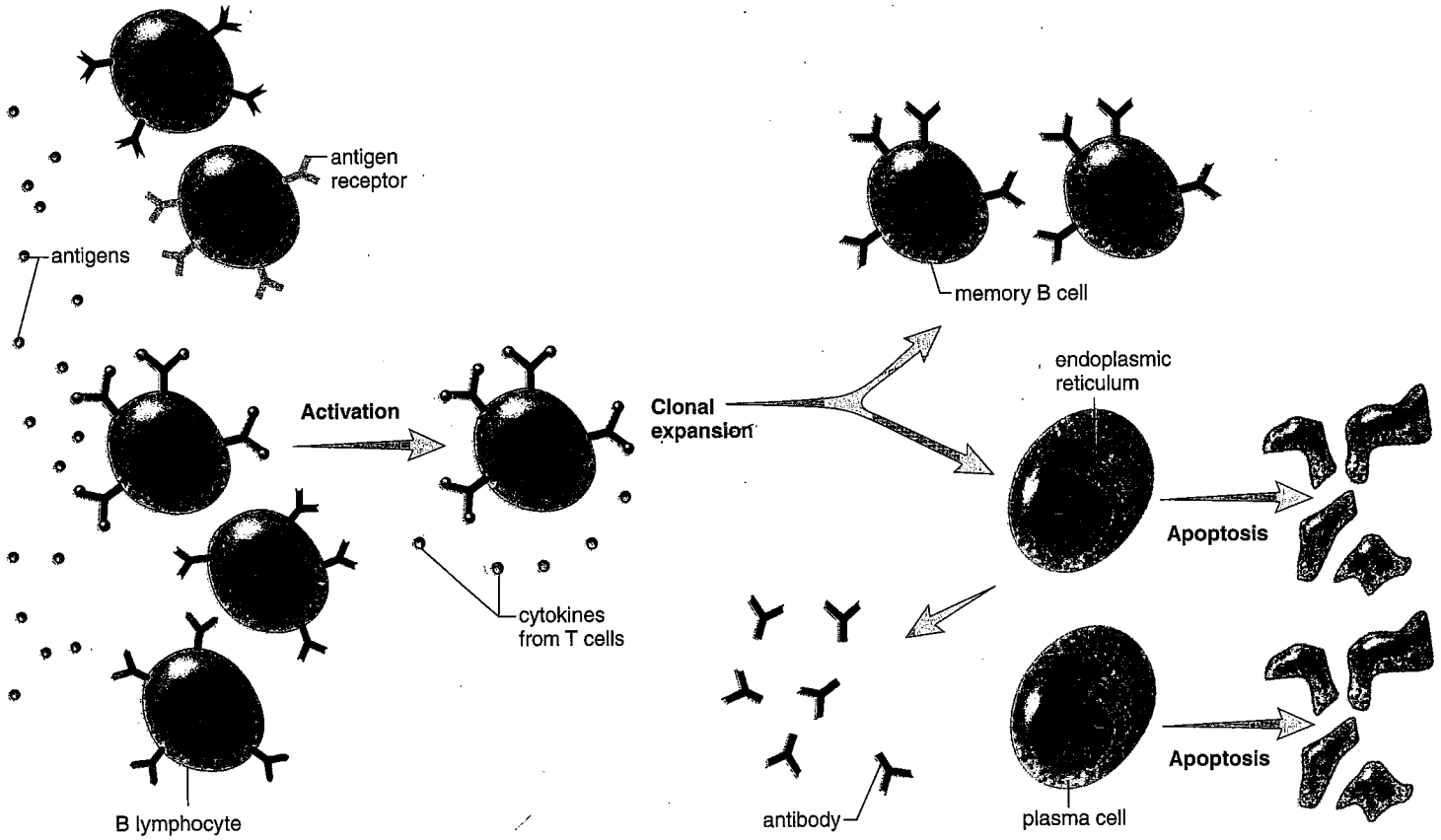


Figure 14.5 Clonal selection theory as it applies to B cells.
Each type B cell bears a specific antigen receptor (note different colors). When an antigen (red dots) combines with the antigen receptors in blue, that B cell is stimulated by cytokines, and it undergoes clonal expansion. The result is many plasma cells, which produce specific antibodies against this antigen and memory B cells which immediately recognize this antigen in the future. After the infection passes, plasma cells undergo apoptosis.

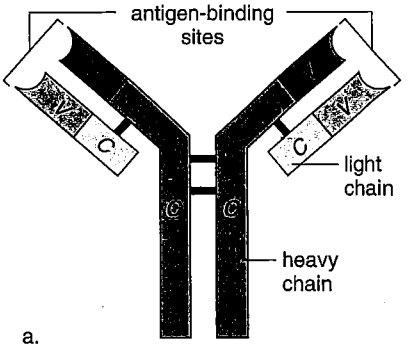
Structure of IgG

The most common type of antibody is IgG, a Y-shaped protein molecule with two arms. Each arm has a "heavy" (long) polypeptide chain and a "light" (short) polypeptide chain. These chains have constant regions, where the sequence of amino acids is set, and variable regions, where the sequence of amino acids varies between antibodies (Fig. 14.6). The constant regions are not identical among all the antibodies. Instead, they are almost the same within different classes of antibodies. The variable regions form an antigen-binding site, and their shape is specific to a particular antigen. The antigen combines with the antibody at the antigen-binding site in a lock-and-key manner.

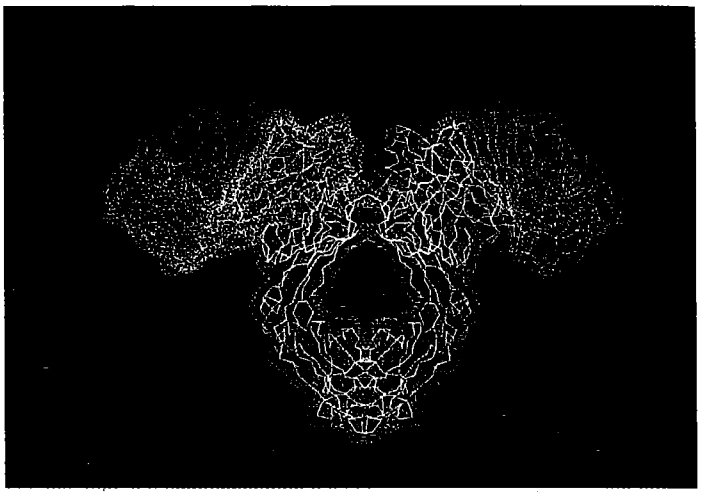
The antigen-antibody reaction can take several forms, but quite often the reaction produces complexes of antigens combined with antibodies. Such antigen-antibody complexes, sometimes called immune complexes, mark the antigens for destruction. For example, an antigen-antibody complex may be engulfed by neutrophils or macrophages, or it may activate complement. Complement makes pathogens more susceptible to phagocytosis, as discussed previously.

Other Types of Antibodies

There are five different classes of circulating antibody proteins or **immunoglobulins (Igs)** (Table 14.1). IgG antibodies are the major type in blood, and lesser amounts are also found in lymph and tissue fluid. IgG antibodies bind to pathogens and their toxins. IgM antibodies are pentamers, meaning that they contain five of the Y-shaped structures shown in Figure 14.6*a*. These antibodies appear in blood soon after an infection begins and disappear before it is over. They are good activators of the complement system. IgA antibodies are monomers or dimers containing two Y-shaped structures. They are the main type of antibody found in bodily secretions. They bind to pathogens before they reach the bloodstream. The main function of IgD molecules seems to be to serve as antigen receptors on immature B cells. IgE antibodies, which are responsible for immediate allergic responses, are discussed on page 274 and in the Health Focus on page 275.



a.



b.

Figure 14.6 Structure of the most common antibody (IgG). **a.** An IgG antibody contains two heavy (long) polypeptide chains and two light (short) chains arranged so there are two variable regions, where a particular antigen is capable of binding with an antibody (*V* = variable region, *C* = constant region). **b.** Computer model of an antibody molecule. The antigen combines with the two side branches.

An antigen combines with an antibody at the antigen-binding site in a lock-and-key manner. The reaction can produce antigen-antibody complexes, which contain several molecules of antibody and antigen.

Table 14.1 Antibodies

Class	Presence	Function
IgG	Main antibody type in circulation	Binds to pathogens, activates complement, and enhances phagocytosis
IgM	Antibody type found in circulation; largest antibody	Activates complement; clumps cells
IgA	Main antibody type in secretions such as saliva and milk	Prevents pathogens from attaching to epithelial cells in digestive and respiratory tract
IgD	Antibody type found on surface of immature B cells	Presence signifies readiness of B cell
IgE	Antibody type found as antigen receptors on basophils in blood and on mast cells in tissues	Responsible for immediate allergic response and protection against certain parasitic worms