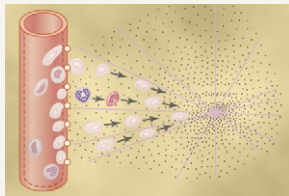


Resistance of the Body to Infection: I. Leukocytes, Granulocytes, the Monocyte-Macrophage System, and Inflammation



Our bodies are exposed continually to bacteria, viruses, fungi, and parasites, all of which occur normally and to varying degrees in the skin, the mouth, the respiratory passageways, the intestinal tract, the lining membranes of the eyes, and even the urinary tract. Many of these infectious agents are capable of causing serious abnormal physiologic function or even death if they invade the deeper

tissues. In addition, we are exposed intermittently to other highly infectious bacteria and viruses besides those that are normally present, and these can cause acute lethal diseases such as pneumonia, streptococcal infection, and typhoid fever.

Our bodies have a special system for combating the different infectious and toxic agents. This is comprised of blood leukocytes (white blood cells) and tissue cells derived from leukocytes. These cells work together in two ways to prevent disease: (1) by actually destroying invading bacteria or viruses by *phagocytosis*, and (2) by forming *antibodies* and *sensitized lymphocytes*, one or both of which may destroy or inactivate the invader. This chapter is concerned with the first of these methods, and Chapter 34 with the second.

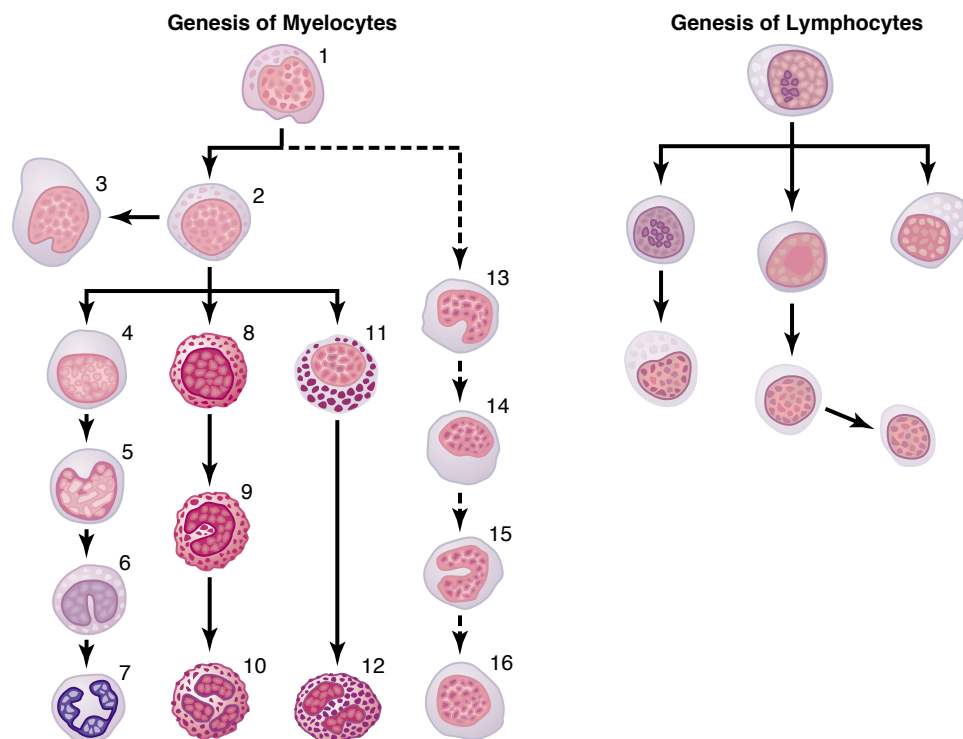
Leukocytes (White Blood Cells)

The leukocytes, also called *white blood cells*, are the *mobile units* of the body's protective system. They are formed partially in the bone marrow (*granulocytes* and *monocytes* and a few *lymphocytes*) and partially in the lymph tissue (*lymphocytes* and *plasma cells*). After formation, they are transported in the blood to different parts of the body where they are needed.

The real value of the white blood cells is that most of them are specifically transported to areas of serious infection and inflammation, thereby providing a rapid and potent defense against infectious agents. As we see later, the granulocytes and monocytes have a special ability to "seek out and destroy" a foreign invader.

General Characteristics of Leukocytes

Types of White Blood Cells. Six types of white blood cells are normally present in the blood. They are *polymorphonuclear neutrophils*, *polymorphonuclear eosinophils*, *polymorphonuclear basophils*, *monocytes*, *lymphocytes*, and, occasionally, *plasma cells*. In addition, there are large numbers of *platelets*, which are fragments of another type of cell similar to the white blood cells found in the bone marrow, the *megakaryocyte*. The first three types of cells, the polymorphonuclear cells, all have a granular appearance, as shown in cell numbers 7,

**Figure 33-1**

Genesis of white blood cells. The different cells of the myelocyte series are 1, myeloblast; 2, promyelocyte; 3, megakaryocyte; 4, neutrophil myelocyte; 5, young neutrophil metamyelocyte; 6, "band" neutrophil metamyelocyte; 7, polymorphonuclear neutrophil; 8, eosinophil myelocyte; 9, eosinophil metamyelocyte; 10, polymorphonuclear eosinophil; 11, basophil myelocyte; 12, polymorphonuclear basophil; 13–16, stages of monocyte formation.

10, and 12 in Figure 33-1, for which reason they are called *granulocytes*, or, in clinical terminology, "polys," because of the multiple nuclei.

The granulocytes and monocytes protect the body against invading organisms mainly by ingesting them—that is, by *phagocytosis*. The lymphocytes and plasma cells function mainly in connection with the immune system; this is discussed in Chapter 34. Finally, the function of platelets is specifically to activate the blood clotting mechanism, which is discussed in Chapter 36.

Concentrations of the Different White Blood Cells in the Blood.

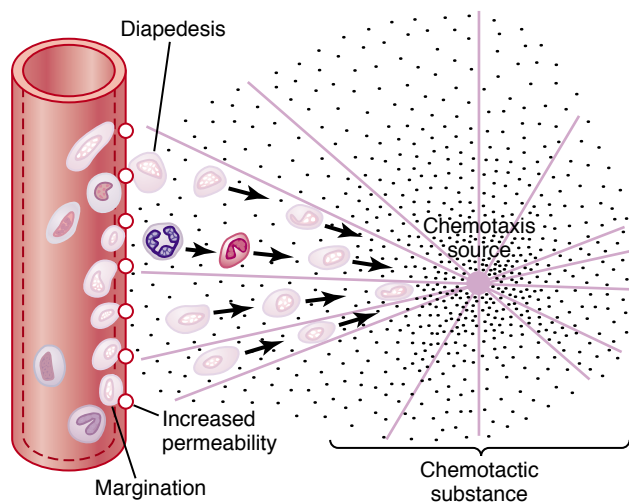
The adult human being has about 7000 white blood cells per *microliter* of blood (in comparison with 5 million red blood cells). Of the total white blood cells, the normal percentages of the different types are approximately the following:

Polymorphonuclear neutrophils	62.0%
Polymorphonuclear eosinophils	2.3%
Polymorphonuclear basophils	0.4%
Monocytes	5.3%
Lymphocytes	30.0%

The number of platelets, which are only cell fragments, in each microliter of blood is normally about 300,000.

Genesis of the White Blood Cells

Early differentiation of the pluripotential hematopoietic stem cell into the different types of committed stem cells is shown in Figure 32-2 in the previous

**Figure 33-2**

Movement of neutrophils by *diapedesis* through capillary pores and by *chemotaxis* toward an area of tissue damage.

chapter. Aside from those cells committed to form red blood cells, two major lineages of *white blood cells* are formed, the myelocytic and the lymphocytic lineages. The left side of Figure 33-1 shows the *myelocytic lineage*, beginning with the *myeloblast*; the right shows the *lymphocytic lineage*, beginning with the *lymphoblast*.

The granulocytes and monocytes are formed only in the bone marrow. Lymphocytes and plasma cells are produced mainly in the various lymphogenous tissues—especially the lymph glands, spleen, thymus, tonsils, and various pockets of lymphoid tissue

elsewhere in the body, such as in the bone marrow and in so-called Peyer's patches underneath the epithelium in the gut wall.

The white blood cells formed in the bone marrow are stored within the marrow until they are needed in the circulatory system. Then, when the need arises, various factors cause them to be released (these factors are discussed later). Normally, about three times as many white blood cells are stored in the marrow as circulate in the entire blood. This represents about a 6-day supply of these cells.

The lymphocytes are mostly stored in the various lymphoid tissues, except for a small number that are temporarily being transported in the blood.

As shown in Figure 33–1, megakaryocytes (cell 3) are also formed in the bone marrow. These megakaryocytes fragment in the bone marrow; the small fragments, known as *platelets* (or *thrombocytes*), then pass into the blood. They are very important in the initiation of blood clotting.

Life Span of the White Blood Cells

The life of the granulocytes after being released from the bone marrow is normally 4 to 8 hours circulating in the blood and another 4 to 5 days in tissues where they are needed. In times of serious tissue infection, this total life span is often shortened to only a few hours because the granulocytes proceed even more rapidly to the infected area, perform their functions, and, in the process, are themselves destroyed.

The monocytes also have a short transit time, 10 to 20 hours in the blood, before wandering through the capillary membranes into the tissues. Once in the tissues, they swell to much larger sizes to become *tissue macrophages*, and, in this form, can live for months unless destroyed while performing phagocytic functions. These tissue macrophages are the basis of the *tissue macrophage system*, discussed in greater detail later, which provides continuing defense against infection.

Lymphocytes enter the circulatory system continually, along with drainage of lymph from the lymph nodes and other lymphoid tissue. After a few hours, they pass out of the blood back into the tissues by diapedesis. Then, still later, they re-enter the lymph and return to the blood again and again; thus, there is continual circulation of lymphocytes through the body. The lymphocytes have life spans of weeks or months; this life span depends on the body's need for these cells.

The platelets in the blood are replaced about once every 10 days; in other words, about 30,000 platelets are formed each day for each microliter of blood.

Neutrophils and Macrophages Defend Against Infections

It is mainly the neutrophils and tissue macrophages that attack and destroy invading bacteria, viruses, and

other injurious agents. The neutrophils are mature cells that can attack and destroy bacteria even in the circulating blood. Conversely, the tissue macrophages begin life as blood monocytes, which are immature cells while still in the blood and have little ability to fight infectious agents at that time. However, once they enter the tissues, they begin to swell—sometimes increasing their diameters as much as fivefold—to as great as 60 to 80 micrometers, a size that can barely be seen with the naked eye. These cells are now called *macrophages*, and they are extremely capable of combating intratissue disease agents.

White Blood Cells Enter the Tissue Spaces by Diapedesis. Neutrophils and monocytes can squeeze through the pores of the blood capillaries by *diapedesis*. That is, even though a pore is much smaller than a cell, a small portion of the cell slides through the pore at a time; the portion sliding through is momentarily constricted to the size of the pore, as shown in Figure 33–2.

White Blood Cells Move Through Tissue Spaces by Ameboid Motion. Both neutrophils and macrophages can move through the tissues by ameboid motion, described in Chapter 2. Some cells move at velocities as great as 40 $\mu\text{m}/\text{min}$, a distance as great as their own length each minute.

White Blood Cells Are Attracted to Inflamed Tissue Areas by Chemotaxis. Many different chemical substances in the tissues cause both neutrophils and macrophages to move toward the source of the chemical. This phenomenon, shown in Figure 33–2, is known as *chemotaxis*. When a tissue becomes inflamed, at least a dozen different products are formed that can cause chemotaxis toward the inflamed area. They include (1) some of the bacterial or viral toxins, (2) degenerative products of the inflamed tissues themselves, (3) several reaction products of the “complement complex” (discussed in Chapter 34) activated in inflamed tissues, and (4) several reaction products caused by plasma clotting in the inflamed area, as well as other substances.

As shown in Figure 33–2, chemotaxis depends on the concentration gradient of the chemotactic substance. The concentration is greatest near the source, which directs the unidirectional movement of the white cells. Chemotaxis is effective up to 100 micrometers away from an inflamed tissue. Therefore, because almost no tissue area is more than 50 micrometers away from a capillary, the chemotactic signal can easily move hordes of white cells from the capillaries into the inflamed area.

Phagocytosis

The most important function of the neutrophils and macrophages is *phagocytosis*, which means cellular ingestion of the offending agent. Phagocytes must be selective of the material that is phagocytized; otherwise, normal cells and structures of the body might be

ingested. Whether phagocytosis will occur depends especially on three selective procedures.

First, most natural structures in the tissues have smooth surfaces, which resist phagocytosis. But if the surface is rough, the likelihood of phagocytosis is increased.

Second, most natural substances of the body have protective protein coats that repel the phagocytes. Conversely, most dead tissues and foreign particles have no protective coats, which makes them subject to phagocytosis.

Third, the immune system of the body (described in detail in Chapter 34) develops *antibodies* against infectious agents such as bacteria. The antibodies then adhere to the bacterial membranes and thereby make the bacteria especially susceptible to phagocytosis. To do this, the antibody molecule also combines with the C3 product of the *complement cascade*, which is an additional part of the immune system discussed in the next chapter. The C3 molecules, in turn, attach to receptors on the phagocyte membrane, thus initiating phagocytosis. This selection and phagocytosis process is called *opsonization*.

Phagocytosis by Neutrophils. The neutrophils entering the tissues are already mature cells that can immediately begin phagocytosis. On approaching a particle to be phagocytized, the neutrophil first attaches itself to the particle and then projects pseudopodia in all directions around the particle. The pseudopodia meet one another on the opposite side and fuse. This creates an enclosed chamber that contains the phagocytized particle. Then the chamber invaginates to the inside of the cytoplasmic cavity and breaks away from the outer cell membrane to form a free-floating *phagocytic vesicle* (also called a *phagosome*) inside the cytoplasm. A single neutrophil can usually phagocytize 3 to 20 bacteria before the neutrophil itself becomes inactivated and dies.

Phagocytosis by Macrophages. Macrophages are the end-stage product of monocytes that enter the tissues from the blood. When activated by the immune system as described in Chapter 34, they are much more powerful phagocytes than neutrophils, often capable of phagocytizing as many as 100 bacteria. They also have the ability to engulf much larger particles, even whole red blood cells or, occasionally, malarial parasites, whereas neutrophils are not capable of phagocytizing particles much larger than bacteria. Also, after digesting particles, macrophages can extrude the residual products and often survive and function for many more months.

Once Phagocytized, Most Particles Are Digested by Intracellular Enzymes. Once a foreign particle has been phagocytized, lysosomes and other cytoplasmic granules in the neutrophil or macrophage immediately come in contact with the phagocytic vesicle, and their membranes fuse, thereby dumping many digestive enzymes and bactericidal agents into the vesicle. Thus, the phagocytic vesicle now becomes a *digestive vesicle*,

and digestion of the phagocytized particle begins immediately.

Both neutrophils and macrophages contain an abundance of lysosomes filled with *proteolytic enzymes* especially geared for digesting bacteria and other foreign protein matter. The lysosomes of macrophages (but not of neutrophils) also contain large amounts of *lipases*, which digest the thick lipid membranes possessed by some bacteria such as the tuberculosis bacillus.

Both Neutrophils and Macrophages Can Kill Bacteria. In addition to the digestion of ingested bacteria in phagosomes, neutrophils and macrophages contain *bactericidal agents* that kill most bacteria even when the lysosomal enzymes fail to digest them. This is especially important, because some bacteria have protective coats or other factors that prevent their destruction by digestive enzymes. Much of the killing effect results from several powerful *oxidizing agents* formed by enzymes in the membrane of the phagosome or by a special organelle called the *peroxisome*. These oxidizing agents include large quantities of *superoxide* (O_2^-), *hydrogen peroxide* (H_2O_2), and *hydroxyl ions* ($-OH^-$), all of which are lethal to most bacteria, even in small quantities. Also, one of the lysosomal enzymes, myeloperoxidase, catalyzes the reaction between H_2O_2 and chloride ions to form hypochlorite, which is exceedingly bactericidal.

Some bacteria, however, notably the tuberculosis bacillus, have coats that are resistant to lysosomal digestion and also secrete substances that partially resist the killing effects of the neutrophils and macrophages. These bacteria are responsible for many of the chronic diseases, an example of which is tuberculosis.

Monocyte-Macrophage Cell System (Reticuloendothelial System)

In the preceding paragraphs, we described the macrophages mainly as mobile cells that are capable of wandering through the tissues. However, after entering the tissues and becoming macrophages, another large portion of monocytes becomes attached to the tissues and remains attached for months or even years until they are called on to perform specific local protective functions. They have the same capabilities as the mobile macrophages to phagocytize large quantities of bacteria, viruses, necrotic tissue, or other foreign particles in the tissue. And, when appropriately stimulated, they can break away from their attachments and once again become mobile macrophages that respond to chemotaxis and all the other stimuli related to the inflammatory process. Thus, the body has a widespread “monocyte-macrophage system” in virtually all tissue areas.

The total combination of monocytes, mobile macrophages, fixed tissue macrophages, and a few

specialized endothelial cells in the bone marrow, spleen, and lymph nodes is called the *reticuloendothelial system*. However, all or almost all these cells originate from monocytic stem cells; therefore, the reticuloendothelial system is almost synonymous with the monocyte-macrophage system. Because the term *reticuloendothelial system* is much better known in medical literature than the term *monocyte-macrophage system*, it should be remembered as a generalized phagocytic system located in all tissues, especially in those tissue areas where large quantities of particles, toxins, and other unwanted substances must be destroyed.

Tissue Macrophages in the Skin and Subcutaneous Tissues (Histocytes). Although the skin is mainly impregnable to infectious agents, this is no longer true when the skin is broken. When infection begins in a subcutaneous tissue and local inflammation ensues, local tissue macrophages can divide in situ and form still more macrophages. Then they perform the usual functions of attacking and destroying the infectious agents, as described earlier.

Macrophages in the Lymph Nodes. Essentially no particulate matter that enters the tissues, such as bacteria, can be absorbed directly through the capillary membranes into the blood. Instead, if the particles are not destroyed locally in the tissues, they enter the lymph and flow to the lymph nodes located intermittently along the course of the lymph flow. The foreign particles are then trapped in these nodes in a meshwork of sinuses lined by *tissue macrophages*.

Figure 33–3 illustrates the general organization of the lymph node, showing lymph entering through the lymph node capsule by way of *afferent lymphatics*, then flowing through the *nodal medullary sinuses*, and finally passing out the *hilus* into *efferent lymphatics* that eventually empty into the venous blood.

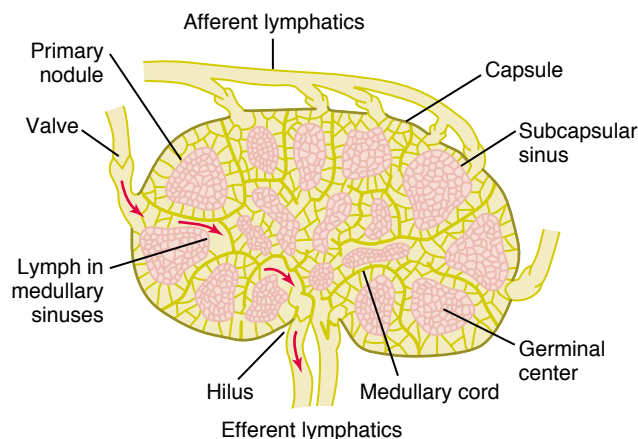


Figure 33–3

Functional diagram of a lymph node. (Redrawn from Ham AW: Histology, 6th ed. Philadelphia: JB Lippincott, 1969.) (Modified from Gartner LP, Hiatt JL: Color Textbook of Histology, 2nd ed. Philadelphia, WB Saunders, 2001.)

Large numbers of macrophages line the lymph sinuses, and if any particles enter the sinuses by way of the lymph, the macrophages phagocytize them and prevent general dissemination throughout the body.

Alveolar Macrophages in the Lungs. Another route by which invading organisms frequently enter the body is through the lungs. Large numbers of tissue macrophages are present as integral components of the alveolar walls. They can phagocytize particles that become entrapped in the alveoli. If the particles are digestible, the macrophages can also digest them and release the digestive products into the lymph. If the particle is not digestible, the macrophages often form a “giant cell” capsule around the particle until such time—if ever—that it can be slowly dissolved. Such capsules are frequently formed around tuberculosis bacilli, silica dust particles, and even carbon particles.

Macrophages (Kupffer Cells) in the Liver Sinusoids. Still another favorite route by which bacteria invade the body is through the gastrointestinal tract. Large numbers of bacteria from ingested food constantly pass through the gastrointestinal mucosa into the portal blood. Before this blood enters the general circulation, it passes through the sinusoids of the liver; these sinusoids are lined with tissue macrophages called *Kupffer cells*, shown in Figure 33–4. These cells form such an effective particulate filtration system that almost none of the bacteria from the gastrointestinal tract succeeds in passing from the portal blood into the general systemic circulation. Indeed, motion pictures of phagocytosis by Kupffer cells have demonstrated phagocytosis of a single bacterium in less than $\frac{1}{100}$ of a second.

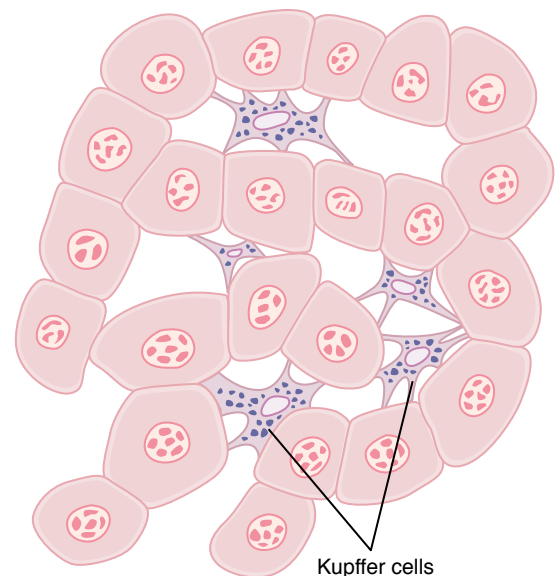


Figure 33–4

Kupffer cells lining the liver sinusoids, showing phagocytosis of India ink particles into the cytoplasm of the Kupffer cells. (Redrawn from Copenhagen WM, et al: Bailey's Textbook of Histology, 10th ed. Baltimore: Williams & Wilkins, 1971.)

Macrophages of the Spleen and Bone Marrow. If an invading organism succeeds in entering the general circulation, there are other lines of defense by the tissue macrophage system, especially by macrophages of the spleen and bone marrow. In both these tissues, macrophages have become entrapped by the reticular meshwork of the two organs, and when foreign particles come in contact with these macrophages, they are phagocytized.

The spleen is similar to the lymph nodes, except that blood, instead of lymph, flows through the tissue spaces of the spleen. Figure 33–5 shows a small peripheral segment of spleen tissue. Note that a small artery penetrates from the splenic capsule into the *splenic pulp* and terminates in small capillaries. The capillaries are highly porous, allowing whole blood to pass out of the capillaries into *cords of red pulp*. The blood then gradually *squeezes* through the trabecular meshwork of these cords and eventually returns to the circulation through the endothelial walls of the *venous sinuses*. The trabeculae of the red pulp are lined with vast numbers of macrophages, and the venous sinuses are also lined with macrophages. This peculiar passage of blood through the cords of the red pulp provides an exceptional means of phagocytizing unwanted debris in the blood, including especially old and abnormal red blood cells.

Inflammation: Role of Neutrophils and Macrophages

Inflammation

When tissue injury occurs, whether caused by bacteria, trauma, chemicals, heat, or any other phenomenon, multiple substances are released by the injured tissues

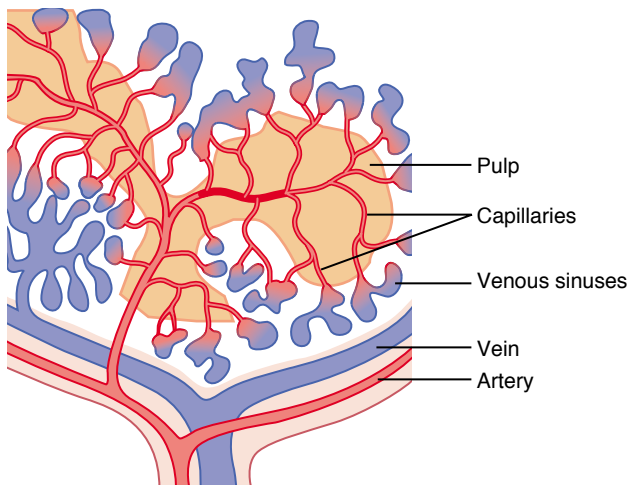


Figure 33–5

Functional structures of the spleen. (Modified from Bloom W, Fawcett DW: A Textbook of Histology, 10th ed. Philadelphia: WB Saunders, 1975.)

and cause dramatic secondary changes in the surrounding uninjured tissues. This entire complex of tissue changes is called *inflammation*.

Inflammation is characterized by (1) vasodilation of the local blood vessels, with consequent excess local blood flow; (2) increased permeability of the capillaries, allowing leakage of large quantities of fluid into the interstitial spaces; (3) often clotting of the fluid in the interstitial spaces because of excessive amounts of fibrinogen and other proteins leaking from the capillaries; (4) migration of large numbers of granulocytes and monocytes into the tissue; and (5) swelling of the tissue cells. Some of the many tissue products that cause these reactions are *histamine*, *bradykinin*, *serotonin*, *prostaglandins*, several different *reaction products of the complement system* (described in Chapter 34), *reaction products of the blood clotting system*, and multiple substances called *lymphokines* that are released by sensitized T cells (part of the immune system; also discussed in Chapter 34). Several of these substances strongly activate the macrophage system, and within a few hours, the macrophages begin to devour the destroyed tissues. But at times, the macrophages also further injure the still-living tissue cells.

“Walling-Off” Effect of Inflammation. One of the first results of inflammation is to “wall off” the area of injury from the remaining tissues. The tissue spaces and the lymphatics in the inflamed area are blocked by fibrinogen clots so that after a while, fluid barely flows through the spaces. This walling-off process delays the spread of bacteria or toxic products.

The intensity of the inflammatory process is usually proportional to the degree of tissue injury. For instance, when *staphylococci* invade tissues, they release extremely lethal cellular toxins. As a result, inflammation develops rapidly—indeed, much more rapidly than the staphylococci themselves can multiply and spread. Therefore, local staphylococcal infection is characteristically walled off rapidly and prevented from spreading through the body. Streptococci, in contrast, do not cause such intense local tissue destruction. Therefore, the walling-off process develops slowly over many hours, while many streptococci reproduce and migrate. As a result, streptococci often have a far greater tendency to spread through the body and cause death than do staphylococci, even though staphylococci are far more destructive to the tissues.

Macrophage and Neutrophil Responses During Inflammation

Tissue Macrophage Is a First Line of Defense Against Infection.

Within minutes after inflammation begins, the macrophages already present in the tissues, whether histiocytes in the subcutaneous tissues, alveolar macrophages in the lungs, microglia in the brain, or others, immediately begin their phagocytic actions.

When activated by the products of infection and inflammation, the first effect is rapid enlargement of each of these cells. Next, many of the previously sessile macrophages break loose from their attachments and become mobile, forming the first line of defense against infection during the first hour or so. The numbers of these early mobilized macrophages often are not great, but they are lifesaving.

Neutrophil Invasion of the Inflamed Area Is a Second Line of Defense. Within the first hour or so after inflammation begins, large numbers of neutrophils begin to invade the inflamed area from the blood. This is caused by products from the inflamed tissues that initiate the following reactions: (1) They alter the inside surface of the capillary endothelium, causing neutrophils to stick to the capillary walls in the inflamed area. This effect is called *margination* and is shown in Figure 33–2. (2) They cause the intercellular attachments between the endothelial cells of the capillaries and small venules to loosen, allowing openings large enough for neutrophils to pass by *diapedesis* directly from the blood into the tissue spaces. (3) Other products of inflammation then cause *chemotaxis* of the neutrophils toward the injured tissues, as explained earlier.

Thus, within several hours after tissue damage begins, the area becomes well supplied with neutrophils. Because the blood neutrophils are already mature cells, they are ready to immediately begin their scavenger functions for killing bacteria and removing foreign matter.

Acute Increase in Number of Neutrophils in the Blood—“Neutrophilia.” Also within a few hours after the onset of acute, severe inflammation, the number of neutrophils in the blood sometimes increases fourfold to fivefold—from a normal of 4000 to 5000 to 15,000 to 25,000 neutrophils per microliter. This is called *neutrophilia*, which means an increase in the number of neutrophils in the blood. Neutrophilia is caused by products of inflammation that enter the blood stream, are transported to the bone marrow, and there act on the stored neutrophils of the marrow to mobilize these into the circulating blood. This makes even more neutrophils available to the inflamed tissue area.

Second Macrophage Invasion into the Inflamed Tissue Is a Third Line of Defense. Along with the invasion of neutrophils, monocytes from the blood enter the inflamed tissue and enlarge to become macrophages. However, the number of monocytes in the circulating blood is low; also, the storage pool of monocytes in the bone marrow is much less than that of neutrophils. Therefore, the buildup of macrophages in the inflamed tissue area is much slower than that of neutrophils, requiring several days to become effective. Furthermore, even after invading the inflamed tissue, monocytes are still immature cells, requiring 8 hours or more to swell to much larger sizes and develop tremendous quantities of lysosomes; only then do they acquire the full capacity of *tissue macrophages* for phagocytosis. Yet, after several days to several weeks, the macrophages finally

come to dominate the phagocytic cells of the inflamed area because of greatly increased bone marrow production of new monocytes, as explained later.

As already pointed out, macrophages can phagocytize far more bacteria (about five times as many) and far larger particles, including even neutrophils themselves and large quantities of necrotic tissue, than can neutrophils. Also, the macrophages play an important role in initiating the development of antibodies, as we discuss in Chapter 34.

Increased Production of Granulocytes and Monocytes by the Bone Marrow Is a Fourth Line of Defense. The fourth line of defense is greatly increased production of both granulocytes and monocytes by the bone marrow. This results from stimulation of the granulocytic and monocytic progenitor cells of the marrow. However, it takes 3 to 4 days before newly formed granulocytes and monocytes reach the stage of leaving the bone marrow. If the stimulus from the inflamed tissue continues, the bone marrow can continue to produce these cells in tremendous quantities for months and even years, sometimes at a rate 20 to 50 times normal.

Feedback Control of the Macrophage and Neutrophil Responses

Although more than two dozen factors have been implicated in control of the macrophage response to inflammation, five of these are believed to play dominant roles. They are shown in Figure 33–6 and consist of (1) *tumor necrosis factor* (TNF), (2) *interleukin-1* (IL-1), (3) *granulocyte-macrophage colony-stimulating factor* (GM-CSF), (4) *granulocyte colony-stimulating factor* (G-CSF), and (5) *macrophage colony-stimulating factor* (M-CSF). These factors are formed by activated macrophage cells in the inflamed tissues and in smaller quantities by other inflamed tissue cells.

The cause of the increased production of granulocytes and monocytes by the bone marrow is mainly the three colony-stimulating factors, one of which, GM-CSF, stimulates both granulocyte and monocyte production; the other two, G-CSF and M-CSF, stimulate granulocyte and monocyte production, respectively. This combination of TNF, IL-1, and colony-stimulating factors provides a powerful feedback mechanism that begins with tissue inflammation and proceeds to formation of large numbers of defensive white blood cells that help remove the cause of the inflammation.

Formation of Pus

When neutrophils and macrophages engulf large numbers of bacteria and necrotic tissue, essentially all the neutrophils and many, if not most, of the macrophages eventually die. After several days, a cavity is often excavated in the inflamed tissues that contains varying portions of necrotic tissue, dead neutrophils, dead macrophages, and tissue fluid. This mixture is commonly known as *pus*. After the infection has been suppressed, the dead cells and necrotic tissue in the pus gradually autolyze over a period of days, and the end products are eventually absorbed

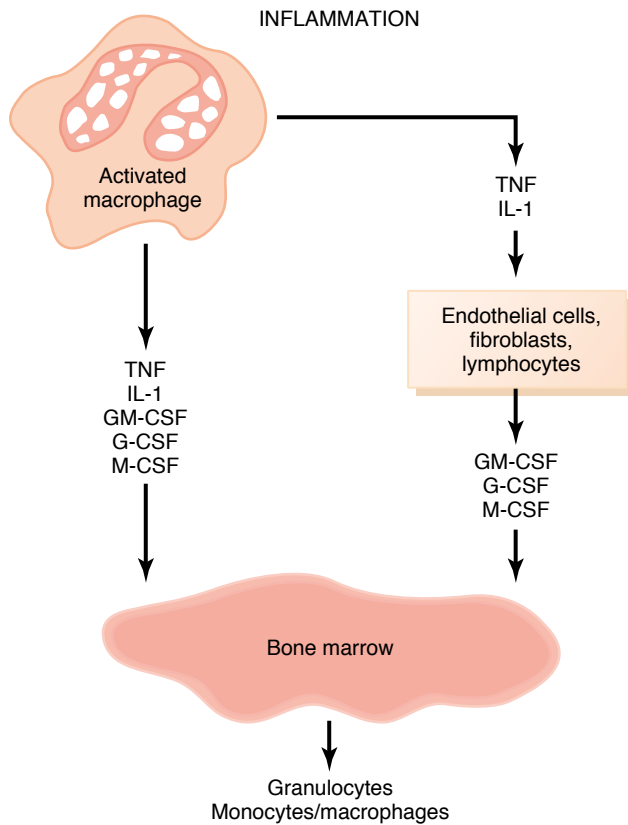


Figure 33-6

Control of bone marrow production of granulocytes and monocyte-macrophages in response to multiple growth factors released from activated macrophages in an inflamed tissue. G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-1, interleukin-1; M-CSF, monocyte colony-stimulating factor; TNF, tumor necrosis factor.

into the surrounding tissues and lymph until most of the evidence of tissue damage is gone.

Eosinophils

The eosinophils normally constitute about 2 per cent of all the blood leukocytes. Eosinophils are weak phagocytes, and they exhibit chemotaxis, but in comparison with the neutrophils, it is doubtful that the eosinophils are significant in protecting against the usual types of infection.

Eosinophils, however, are often produced in large numbers in people with parasitic infections, and they migrate in large numbers into tissues diseased by parasites. Although most parasites are too large to be phagocytized by eosinophils or any other phagocytic cells, eosinophils attach themselves to the parasites by way of special surface molecules and release substances that kill many of the parasites. For instance, one of the most widespread infections is *schistosomiasis*, a parasitic infection found in as many as one third of the population of some Third World countries; the parasite can invade any part of the body. Eosinophils attach themselves to the juvenile forms of the parasite

and kill many of them. They do so in several ways: (1) by releasing hydrolytic enzymes from their granules, which are modified lysosomes; (2) probably by also releasing highly reactive forms of oxygen that are especially lethal to parasites; and (3) by releasing from the granules a highly larvacidal polypeptide called *major basic protein*.

In a few areas of the world, another parasitic disease that causes eosinophilia is *trichinosis*. This results from invasion of the body's muscles by the *Trichinella* parasite ("pork worm") after a person eats undercooked infested pork.

Eosinophils also have a special propensity to collect in tissues in which allergic reactions occur, such as in the peribronchial tissues of the lungs in people with asthma and in the skin after allergic skin reactions. This is caused at least partly by the fact that many mast cells and basophils participate in allergic reactions, as we discuss in the next paragraph. The mast cells and basophils release an *eosinophil chemotactic factor* that causes eosinophils to migrate toward the inflamed allergic tissue. The eosinophils are believed to detoxify some of the inflammation-inducing substances released by the mast cells and basophils and probably also to phagocytize and destroy allergen-antibody complexes, thus preventing excess spread of the local inflammatory process.

Basophils

The basophils in the circulating blood are similar to the large tissue *mast cells* located immediately outside many of the capillaries in the body. Both mast cells and basophils liberate *heparin* into the blood, a substance that can prevent blood coagulation.

The mast cells and basophils also release *histamine*, as well as smaller quantities of *bradykinin* and *serotonin*. Indeed, it is mainly the mast cells in inflamed tissues that release these substances during inflammation.

The mast cells and basophils play an exceedingly important role in some types of allergic reactions because the type of antibody that causes allergic reactions, the immunoglobulin E (IgE) type (see Chapter 34), has a special propensity to become attached to mast cells and basophils. Then, when the specific antigen for the specific IgE antibody subsequently reacts with the antibody, the resulting attachment of antigen to antibody causes the mast cell or basophil to rupture and release exceedingly large quantities of *histamine*, *bradykinin*, *serotonin*, *heparin*, *slow-reacting substance of anaphylaxis*, and a number of *lysosomal enzymes*. These cause local vascular and tissue reactions that cause many, if not most, of the allergic manifestations. These reactions are discussed in greater detail in Chapter 34.

Leukopenia

A clinical condition known as *leukopenia* occasionally occurs in which the bone marrow produces very few

white blood cells, leaving the body unprotected against many bacteria and other agents that might invade the tissues.

Normally, the human body lives in symbiosis with many bacteria, because all the mucous membranes of the body are constantly exposed to large numbers of bacteria. The mouth almost always contains various spirochetal, pneumococcal, and streptococcal bacteria, and these same bacteria are present to a lesser extent in the entire respiratory tract. The distal gastrointestinal tract is especially loaded with colon bacilli. Furthermore, one can always find bacteria on the surfaces of the eyes, urethra, and vagina. Any decrease in the number of white blood cells immediately allows invasion of adjacent tissues by bacteria that are already present.

Within 2 days after the bone marrow stops producing white blood cells, ulcers may appear in the mouth and colon, or the person might develop some form of severe respiratory infection. Bacteria from the ulcers rapidly invade surrounding tissues and the blood. Without treatment, death often ensues in less than a week after acute total leukopenia begins.

Irradiation of the body by x-rays or gamma rays, or exposure to drugs and chemicals that contain benzene or anthracene nuclei, is likely to cause aplasia of the bone marrow. Indeed, some common drugs, such as chloramphenicol (an antibiotic), thiouracil (used to treat thyrotoxicosis), and even various barbiturate hypnotics, on very rare occasions cause leukopenia, thus setting off the entire infectious sequence of this malady.

After moderate irradiation injury to the bone marrow, some stem cells, myeloblasts, and hemocytoblasts may remain undestroyed in the marrow and are capable of regenerating the bone marrow, provided sufficient time is available. A patient properly treated with transfusions, plus antibiotics and other drugs to ward off infection, usually develops enough new bone marrow within weeks to months for blood cell concentrations to return to normal.

The Leukemias

Uncontrolled production of white blood cells can be caused by cancerous mutation of a myelogenous or lymphogenous cell. This causes *leukemia*, which is usually characterized by greatly increased numbers of abnormal white blood cells in the circulating blood.

Types of Leukemia. Leukemias are divided into two general types: *lymphocytic leukemias* and *myelogenous leukemias*. The lymphocytic leukemias are caused by cancerous production of lymphoid cells, usually beginning in a lymph node or other lymphocytic tissue and spreading to other areas of the body. The second type of leukemia, myelogenous leukemia, begins by cancerous production of young myelogenous cells in the bone marrow and then spreads throughout the body so that white blood cells are produced in many

extramedullary tissues—especially in the lymph nodes, spleen, and liver.

In myelogenous leukemia, the cancerous process occasionally produces partially differentiated cells, resulting in what might be called *neutrophilic leukemia*, *eosinophilic leukemia*, *basophilic leukemia*, or *monocytic leukemia*. More frequently, however, the leukemia cells are bizarre and undifferentiated and not identical to any of the normal white blood cells. Usually, the more undifferentiated the cell, the more *acute* is the leukemia, often leading to death within a few months if untreated. With some of the more differentiated cells, the process can be *chronic*, sometimes developing slowly over 10 to 20 years. Leukemic cells, especially the very undifferentiated cells, are usually nonfunctional for providing the normal protection against infection.

Effects of Leukemia on the Body

The first effect of leukemia is metastatic growth of leukemic cells in abnormal areas of the body. Leukemic cells from the bone marrow may reproduce so greatly that they invade the surrounding bone, causing pain and, eventually, a tendency for bones to fracture easily.

Almost all leukemias eventually spread to the spleen, lymph nodes, liver, and other vascular regions, regardless of whether the origin of the leukemia is in the bone marrow or the lymph nodes. Common effects in leukemia are the development of infection, severe anemia, and a bleeding tendency caused by thrombocytopenia (lack of platelets). These effects result mainly from displacement of the normal bone marrow and lymphoid cells by the nonfunctional leukemic cells.

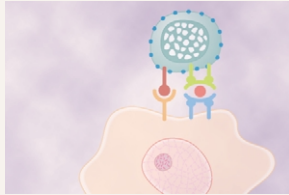
Finally, perhaps the most important effect of leukemia on the body is excessive use of metabolic substrates by the growing cancerous cells. The leukemic tissues reproduce new cells so rapidly that tremendous demands are made on the body reserves for foodstuffs, specific amino acids, and vitamins. Consequently, the energy of the patient is greatly depleted, and excessive utilization of amino acids by the leukemic cells causes especially rapid deterioration of the normal protein tissues of the body. Thus, while the leukemic tissues grow, other tissues become debilitated. After metabolic starvation has continued long enough, this alone is sufficient to cause death.

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Resistance of the Body to Infection: II. Immunity and Allergy



Innate Immunity

The human body has the ability to resist almost all types of organisms or toxins that tend to damage the tissues and organs. This capability is called *immunity*. Much of immunity is *acquired immunity* that does not develop until after the body is first attacked by a bacterium, virus, or toxin, often

requiring weeks or months to develop the immunity. An additional portion of immunity results from general processes, rather than from processes directed at specific disease organisms. This is called *innate immunity*. It includes the following:

1. Phagocytosis of bacteria and other invaders by white blood cells and cells of the tissue macrophage system, as described in Chapter 33.
2. Destruction of swallowed organisms by the acid secretions of the stomach and the digestive enzymes.
3. Resistance of the skin to invasion by organisms.
4. Presence in the blood of certain chemical compounds that attach to foreign organisms or toxins and destroy them. Some of these compounds are (1) *lysozyme*, a mucolytic polysaccharide that attacks bacteria and causes them to dissolve; (2) *basic polypeptides*, which react with and inactivate certain types of gram-positive bacteria; (3) the *complement complex* that is described later, a system of about 20 proteins that can be activated in various ways to destroy bacteria; and (4) *natural killer lymphocytes* that can recognize and destroy foreign cells, tumor cells, and even some infected cells.

This innate immunity makes the human body resistant to such diseases as some paralytic viral infections of animals, hog cholera, cattle plague, and distemper—a viral disease that kills a large percentage of dogs that become afflicted with it. Conversely, many lower animals are resistant or even immune to many human diseases, such as poliomyelitis, mumps, human cholera, measles, and syphilis, which are very damaging or even lethal to human beings.

Acquired (Adaptive) Immunity

In addition to its generalized innate immunity, the human body has the ability to develop extremely powerful specific immunity against individual invading agents such as lethal bacteria, viruses, toxins, and even foreign tissues from other animals. This is called *acquired or adaptive immunity*. Acquired immunity is caused by a special immune system that forms antibodies and/or activated lymphocytes that attack and destroy the specific invading organism or toxin. It is with this acquired immunity mechanism and some of its associated reactions—especially the allergies—that this chapter is concerned.

Acquired immunity can often bestow extreme protection. For instance, certain toxins, such as the paralytic botulinum toxin or the tetanizing toxin of tetanus, can be protected against in doses as high as 100,000 times the amount that would be lethal without immunity. This is the reason the treatment process known as *immunization* is so important in protecting human beings against

disease and against toxins, as explained in the course of this chapter.

Basic Types of Acquired Immunity

Two basic but closely allied types of acquired immunity occur in the body. In one of these the body develops circulating *antibodies*, which are globulin molecules in the blood plasma that are capable of attacking the invading agent. This type of immunity is called *humoral immunity* or *B-cell immunity* (because B lymphocytes produce the antibodies). The second type of acquired immunity is achieved through the formation of large numbers of *activated T lymphocytes* that are specifically crafted in the lymph nodes to destroy the foreign agent. This type of immunity is called *cell-mediated immunity* or *T-cell immunity* (because the activated lymphocytes are T lymphocytes). We shall see shortly that both the antibodies and the activated lymphocytes are formed in the lymphoid tissues of the body. Let us discuss the initiation of the immune process by *antigens*.

Both Types of Acquired Immunity Are Initiated by Antigens

Because acquired immunity does not develop until after invasion by a foreign organism or toxin, it is clear that the body must have some mechanism for recognizing this invasion. Each toxin or each type of organism almost always contains one or more specific chemical compounds in its makeup that are different from all other compounds. In general, these are proteins or large polysaccharides, and it is they that initiate the acquired immunity. These substances are called *antigens* (*antibody generations*).

For a substance to be antigenic, it usually must have a high molecular weight, 8000 or greater. Furthermore, the process of antigenicity usually depends on regularly recurring molecular groups, called *epitopes*, on the surface of the large molecule. This also explains why proteins and large polysaccharides are almost always antigenic, because both of these have this stereochemical characteristic.

Lymphocytes Are Responsible for Acquired Immunity

Acquired immunity is the product of the body's lymphocytes. In people who have a genetic lack of lymphocytes or whose lymphocytes have been destroyed by radiation or chemicals, no acquired immunity can develop. And within days after birth, such a person dies of fulminating bacterial infection unless treated by heroic measures. Therefore, it is clear that the lymphocytes are essential to survival of the human being.

The lymphocytes are located most extensively in the *lymph nodes*, but they are also found in special lymphoid tissues such as the *spleen*, *submucosal areas of*

the gastrointestinal tract, *thymus*, and *bone marrow*. The lymphoid tissue is distributed advantageously in the body to intercept invading organisms or toxins before they can spread too widely.

In most instances, the invading agent first enters the tissue fluids and then is carried by way of lymph vessels to the lymph node or other lymphoid tissue. For instance, the lymphoid tissue of the gastrointestinal walls is exposed immediately to antigens invading from the gut. The lymphoid tissue of the throat and pharynx (the tonsils and adenoids) is well located to intercept antigens that enter by way of the upper respiratory tract. The lymphoid tissue in the lymph nodes is exposed to antigens that invade the peripheral tissues of the body. And, finally, the lymphoid tissue of the spleen, thymus, and bone marrow plays the specific role of intercepting antigenic agents that have succeeded in reaching the circulating blood.

Two Types of Lymphocytes Promote “Cell-Mediated” Immunity or “Humoral” Immunity—the T and the B Lymphocytes.

Although most lymphocytes in normal lymphoid tissue look alike when studied under the microscope, these cells are distinctly divided into two major populations. One of the populations, the T lymphocytes, is responsible for forming the activated lymphocytes that provide “cell-mediated” immunity, and the other population, the B lymphocytes, is responsible for forming antibodies that provide “humoral” immunity.

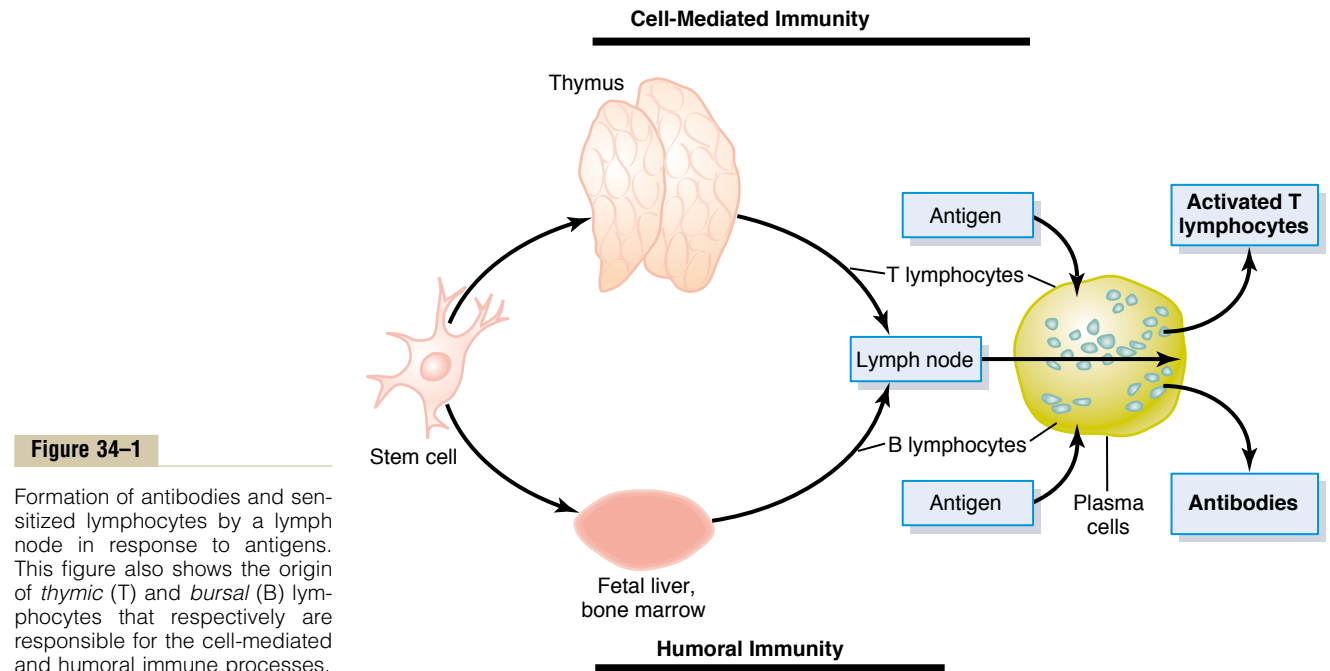
Both types of lymphocytes are derived originally in the embryo from *pluripotent hematopoietic stem cells* that form lymphocytes as one of their most important offspring as they differentiate. Almost all of the lymphocytes that are formed eventually end up in the lymphoid tissue, but before doing so, they are further differentiated or “preprocessed” in the following ways.

The lymphocytes that are destined to eventually form activated T lymphocytes first migrate to and are preprocessed in the *thymus* gland, and thus they are called “*T*” lymphocytes to designate the role of the thymus. They are responsible for cell-mediated immunity.

The other population of lymphocytes—the B lymphocytes that are destined to form antibodies—are preprocessed in the liver during midfetal life and in the bone marrow in late fetal life and after birth. This population of cells was first discovered in birds, which have a special preprocessing organ called the *bursa of Fabricius*. For this reason, these lymphocytes are called “*B*” lymphocytes to designate the role of the bursa, and they are responsible for humoral immunity. Figure 34–1 shows the two lymphocyte systems for the formation, respectively, of (1) the activated T lymphocytes and (2) the antibodies.

Preprocessing of the T and B Lymphocytes

Although all lymphocytes in the body originate from *lymphocyte-committed stem cells* of the embryo, these



stem cells themselves are incapable of forming directly either activated T lymphocytes or antibodies. Before they can do so, they must be further differentiated in appropriate processing areas as follows.

Thymus Gland Preprocesses the T Lymphocytes. The T lymphocytes, after origination in the bone marrow, first migrate to the thymus gland. Here they divide rapidly and at the same time develop extreme diversity for reacting against different specific antigens. That is, one thymic lymphocyte develops specific reactivity against one antigen. Then the next lymphocyte develops specificity against another antigen. This continues until there are thousands of different types of thymic lymphocytes with specific reactivities against many thousands of different antigens. These different types of preprocessed T lymphocytes now leave the thymus and spread by way of the blood throughout the body to lodge in lymphoid tissue everywhere.

The thymus also makes certain that any T lymphocytes leaving the thymus will not react against proteins or other antigens that are present in the body's own tissues; otherwise, the T lymphocytes would be lethal to the person's own body in only a few days. The thymus selects which T lymphocytes will be released by first mixing them with virtually all the specific "self-antigens" from the body's own tissues. If a T lymphocyte reacts, it is destroyed and phagocytized instead of being released. This happens to as many as 90 per cent of the cells. Thus, the only cells that are finally released are those that are nonreactive against the body's own antigens—they react only against antigens from an outside source, such as from a bacterium, a toxin, or even transplanted tissue from another person.

Most of the preprocessing of T lymphocytes in the thymus occurs shortly before birth of a baby and for a few months after birth. Beyond this period, removal of the thymus gland diminishes (but does not eliminate) the T-lymphocytic immune system. However, removal of the thymus several months before birth can prevent development of all cell-mediated immunity. Because this cellular type of immunity is mainly responsible for rejection of transplanted organs, such as hearts and kidneys, one can transplant organs with much less likelihood of rejection if the thymus is removed from an animal a reasonable time before its birth.

Liver and Bone Marrow Preprocess the B Lymphocytes. Much less is known about the details for preprocessing B lymphocytes than for preprocessing T lymphocytes. In the human being, B lymphocytes are known to be preprocessed in the liver during midfetal life and in the bone marrow during late fetal life and after birth.

B lymphocytes are different from T lymphocytes in two ways: First, instead of the whole cell developing reactivity against the antigen, as occurs for the T lymphocytes, the B lymphocytes actively secrete *antibodies* that are the reactive agents. These agents are large protein molecules that are capable of combining with and destroying the antigenic substance, which is explained elsewhere in this chapter and in Chapter 33. Second, the B lymphocytes have even greater diversity than the T lymphocytes, thus forming many millions of types of B-lymphocyte antibodies with different specific reactivities. After preprocessing, the B lymphocytes, like the T lymphocytes, migrate to lymphoid tissue throughout the body, where they lodge near but slightly removed from the T-lymphocyte areas.

T Lymphocytes and B-Lymphocyte Antibodies React Highly Specifically Against Specific Antigens—Role of Lymphocyte Clones

When specific antigens come in contact with T and B lymphocytes in the lymphoid tissue, certain of the T lymphocytes become activated to form activated T cells, and certain of the B lymphocytes become activated to form antibodies. The activated T cells and antibodies in turn react highly specifically against the particular types of antigens that initiated their development. The mechanism of this specificity is the following.

Millions of Specific Types of Lymphocytes Are Stored in the Lymphoid Tissue. Millions of different types of preformed B lymphocytes and preformed T lymphocytes that are capable of forming highly specific types of antibodies or T cells have been stored in the lymph tissue, as explained earlier. Each of these preformed lymphocytes is capable of forming only one type of antibody or one type of T cell with a single type of specificity. And only the specific type of antigen with which it can react can activate it. Once the specific lymphocyte is activated by its antigen, it reproduces wildly, forming tremendous numbers of duplicate lymphocytes. If it is a B lymphocyte, its progeny will eventually secrete the specific type of antibody that then circulates throughout the body. If it is a T lymphocyte, its progeny are specific sensitized T cells that are released into the lymph and then carried to the blood and circulated through all the tissue fluids and back into the lymph, sometimes circulating around and around in this circuit for months or years.

All the different lymphocytes that are capable of forming one specificity of antibody or T cell are called a *clone of lymphocytes*. That is, the lymphocytes in each clone are alike and are derived originally from one or a few early lymphocytes of its specific type.

Origin of the Many Clones of Lymphocytes

Only several hundred to a few thousand genes code for the millions of different types of antibodies and T lymphocytes. At first, it was a mystery how it was possible for so few genes to code for the millions of different specificities of antibody molecules or T cells that can be produced by the lymphoid tissue, especially when one considers that a single gene is usually necessary for the formation of each different type of protein. This mystery has now been solved.

The whole gene for forming each type of T cell or B cell is never present in the original stem cells from which the functional immune cells are formed. Instead, there are only “gene segments”—actually, hundreds of such segments—but not whole genes. During pre-processing of the respective T- and B-cell lymphocytes, these gene segments become mixed with one another

in random combinations, in this way finally forming whole genes.

Because there are several hundred types of gene segments, as well as millions of different combinations in which the segments can be arranged in single cells, one can understand the millions of different cell gene types that can occur. For each functional T or B lymphocyte that is finally formed, the gene structure codes for only a single antigen specificity. These mature cells then become the highly specific T and B cells that spread to and populate the lymphoid tissue.

Mechanism for Activating a Clone of Lymphocytes

Each clone of lymphocytes is responsive to only a single type of antigen (or to several similar antigens that have almost exactly the same stereochemical characteristics). The reason for this is the following: In the case of the B lymphocytes, each of these has on the surface of its cell membrane about 100,000 antibody molecules that will react highly specifically with only one specific type of antigen. Therefore, when the appropriate antigen comes along, it immediately attaches to the antibody in the cell membrane; this leads to the activation process, which we describe in more detail subsequently. In the case of the T lymphocytes, molecules similar to antibodies, called *surface receptor proteins* (or *T-cell markers*), are on the surface of the T-cell membrane, and these, too, are highly specific for one specified activating antigen.

Role of Macrophages in the Activation Process. Aside from the lymphocytes in lymphoid tissue, literally millions of macrophages are also present in the same tissue. These line the sinusoids of the lymph nodes, spleen, and other lymphoid tissue, and they lie in apposition to many of the lymph node lymphocytes. Most invading organisms are first phagocytized and partially digested by the macrophages, and the antigenic products are liberated into the macrophage cytosol. The macrophages then pass these antigens by cell-to-cell contact directly to the lymphocytes, thus leading to activation of the specified lymphocytic clones. The macrophages, in addition, secrete a special activating substance that promotes still further growth and reproduction of the specific lymphocytes. This substance is called *interleukin-1*.

Role of the T Cells in Activation of the B Lymphocytes. Most antigens activate both T lymphocytes and B lymphocytes at the same time. Some of the T cells that are formed, called *helper cells*, secrete specific substances (collectively called *lymphokines*) that activate the specific B lymphocytes. Indeed, without the aid of these helper T cells, the quantity of antibodies formed by the B lymphocytes is usually slight. We will discuss this cooperative relationship between helper T cells and B cells again after we have an opportunity to describe the mechanisms of the T-cell system of immunity.

Specific Attributes of the B-Lymphocyte System—Humoral Immunity and the Antibodies

Formation of Antibodies by Plasma Cells. Before exposure to a specific antigen, the clones of B lymphocytes remain dormant in the lymphoid tissue. On entry of a foreign antigen, macrophages in the lymphoid tissue phagocytize the antigen and then present it to adjacent B lymphocytes. In addition, the antigen is presented to T cells at the same time, and activated helper T cells are formed. These helper cells also contribute to extreme activation of the B lymphocytes, as we discuss more fully later.

Those B lymphocytes specific for the antigen immediately enlarge and take on the appearance of *lymphoblasts*. Some of the lymphoblasts further differentiate to form *plasmablasts*, which are precursors of *plasma cells*. In the plasmablasts, the cytoplasm expands and the rough endoplasmic reticulum vastly proliferates. The plasmablasts then begin to divide at a rate of about once every 10 hours for about nine divisions, giving in 4 days a total population of about 500 cells for each original plasmablast. The mature plasma cell then produces gamma globulin antibodies at an extremely rapid rate—about 2000 molecules per second for each plasma cell. In turn, the antibodies are secreted into the lymph and carried to the circulating blood. This process continues for several days or weeks until finally exhaustion and death of the plasma cells occur.

Formation of “Memory” Cells—Difference Between Primary Response and Secondary Response. A few of the lymphoblasts formed by activation of a clone of B lymphocytes do not go on to form plasma cells but instead form moderate numbers of new B lymphocytes similar to those of the original clone. In other words, the B-cell population of the specifically activated clone becomes greatly enhanced, and the new B lymphocytes are added to the original lymphocytes of the same clone. They also circulate throughout the body to populate all the lymphoid tissue; immunologically, however, they remain dormant until activated once again by a new quantity of the same antigen. These lymphocytes are called *memory cells*. Subsequent exposure to the same antigen will cause a much more rapid and much more potent antibody response this second time around, because there are many more memory cells than there were original B lymphocytes of the specific clone.

Figure 34–2 shows the differences between the *primary response* for forming antibodies that occurs on first exposure to a specific antigen and the *secondary response* that occurs after second exposure to the same antigen. Note the 1-week delay in the appearance of the primary response, its weak potency, and its short life. The secondary response, by contrast, begins rapidly after exposure to the antigen (often within hours), is far more potent, and forms antibodies for many months rather than for only a few weeks. The

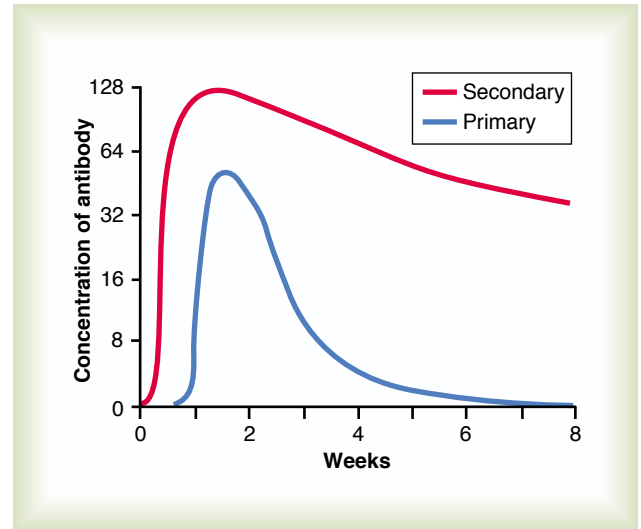


Figure 34–2

Time course of the antibody response in the circulating blood to a *primary* injection of antigen and to a *secondary* injection several months later.

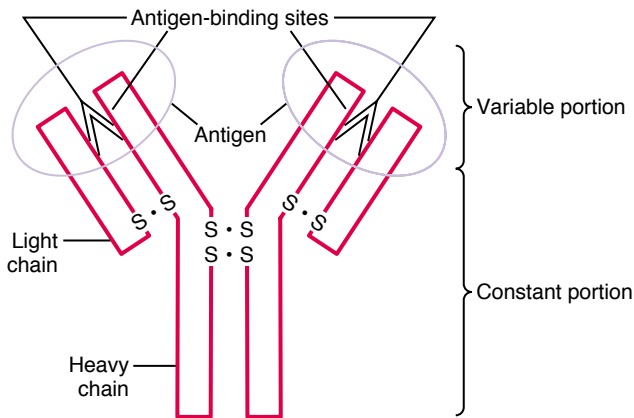
increased potency and duration of the secondary response explain why *immunization* is usually accomplished by injecting antigen in multiple doses with periods of several weeks or several months between injections.

Nature of the Antibodies

The antibodies are gamma globulins called *immunoglobulins* (abbreviated as *Ig*), and they have molecular weights between 160,000 and 970,000. They usually constitute about 20 per cent of all the plasma proteins.

All the immunoglobulins are composed of combinations of *light* and *heavy polypeptide chains*. Most are a combination of two light and two heavy chains, as shown in Figure 34–3. However, some of the immunoglobulins have combinations of as many as 10 heavy and 10 light chains, which gives rise to high-molecular-weight immunoglobulins. Yet, in all immunoglobulins, each heavy chain is paralleled by a light chain at one of its ends, thus forming a heavy-light pair, and there are always at least 2 and as many as 10 such pairs in each immunoglobulin molecule.

Figure 34–3 shows by the circled area a designated end of each light and heavy chain, called the *variable portion*; the remainder of each chain is called the *constant portion*. The variable portion is different for each specificity of antibody, and it is this portion that attaches specifically to a particular type of antigen. The constant portion of the antibody determines other properties of the antibody, establishing such factors as diffusivity of the antibody in the tissues, adherence of the antibody to specific structures within the tissues, attachment to the *complement complex*, the ease with which the antibodies pass through membranes, and other biological properties of the antibody.

**Figure 34-3**

Structure of the typical IgG antibody, showing it to be composed of two heavy polypeptide chains and two light polypeptide chains. The antigen binds at two different sites on the variable portions of the chains.

Specificity of Antibodies. Each antibody is specific for a particular antigen; this is caused by its unique structural organization of amino acids in the variable portions of both the light and heavy chains. The amino acid organization has a different steric shape for each antigen specificity, so that when an antigen comes in contact with it, multiple prosthetic groups of the antigen fit as a mirror image with those of the antibody, thus allowing rapid and tight bonding between the antibody and the antigen. When the antibody is highly specific, there are so many bonding sites that the antibody-antigen coupling is exceedingly strong, held together by (1) hydrophobic bonding, (2) hydrogen bonding, (3) ionic attractions, and (4) van der Waals forces. It also obeys the thermodynamic mass action law.

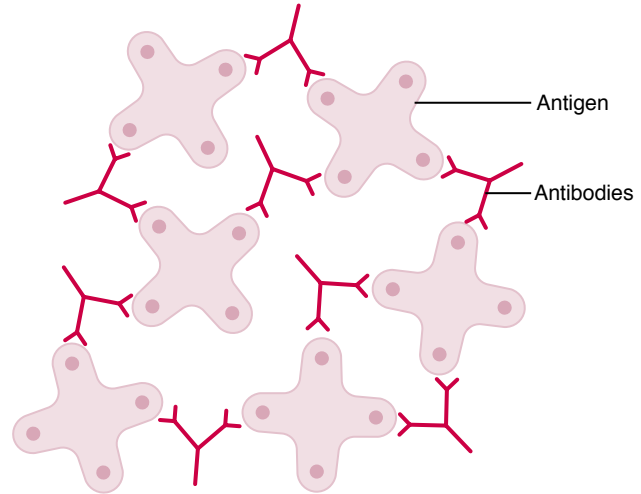
$$K_a = \frac{\text{Concentration of bound antibody-antigen}}{\text{Concentration of antibody} \times \text{Concentration of antigen}}$$

K_a is called the *affinity constant* and is a measure of how tightly the antibody binds with the antigen.

Note, especially, in Figure 34-3 that there are two variable sites on the illustrated antibody for attachment of antigens, making this type of antibody *bivalent*. A small proportion of the antibodies, which consist of combinations of up to 10 light and 10 heavy chains, have as many as 10 *binding* sites.

Classes of Antibodies. There are five general classes of antibodies, respectively named *IgM*, *IgG*, *IgA*, *IgD*, and *IgE*. Ig stands for immunoglobulin, and the other five respective letters designate the respective classes.

For the purpose of our present limited discussion, two of these classes of antibodies are of particular importance: IgG, which is a bivalent antibody and constitutes about 75 per cent of the antibodies of the normal person, and IgE, which constitutes only a small percentage of the antibodies but is especially involved

**Figure 34-4**

Binding of antigen molecules to one another by bivalent antibodies.

in allergy. The IgM class is also interesting because a large share of the antibodies formed during the primary response are of this type. These antibodies have 10 binding sites that make them exceedingly effective in protecting the body against invaders, even though there are not many IgM antibodies.

Mechanisms of Action of Antibodies

Antibodies act mainly in two ways to protect the body against invading agents: (1) by direct attack on the invader and (2) by activation of the “complement system” that then has multiple means of its own for destroying the invader.

Direct Action of Antibodies on Invading Agents. Figure 34-4 shows antibodies (designated by the red Y-shaped bars) reacting with antigens (designated by the shaded objects). Because of the bivalent nature of the antibodies and the multiple antigen sites on most invading agents, the antibodies can inactivate the invading agent in one of several ways, as follows:

1. *Agglutination*, in which multiple large particles with antigens on their surfaces, such as bacteria or red cells, are bound together into a clump
2. *Precipitation*, in which the molecular complex of soluble antigen (such as tetanus toxin) and antibody becomes so large that it is rendered insoluble and precipitates
3. *Neutralization*, in which the antibodies cover the toxic sites of the antigenic agent
4. *Lysis*, in which some potent antibodies are occasionally capable of directly attacking membranes of cellular agents and thereby cause rupture of the agent

These direct actions of antibodies attacking the antigenic invaders often are not strong enough to play a major role in protecting the body against the invader. Most of the protection comes through the *amplifying* effects of the complement system described next.

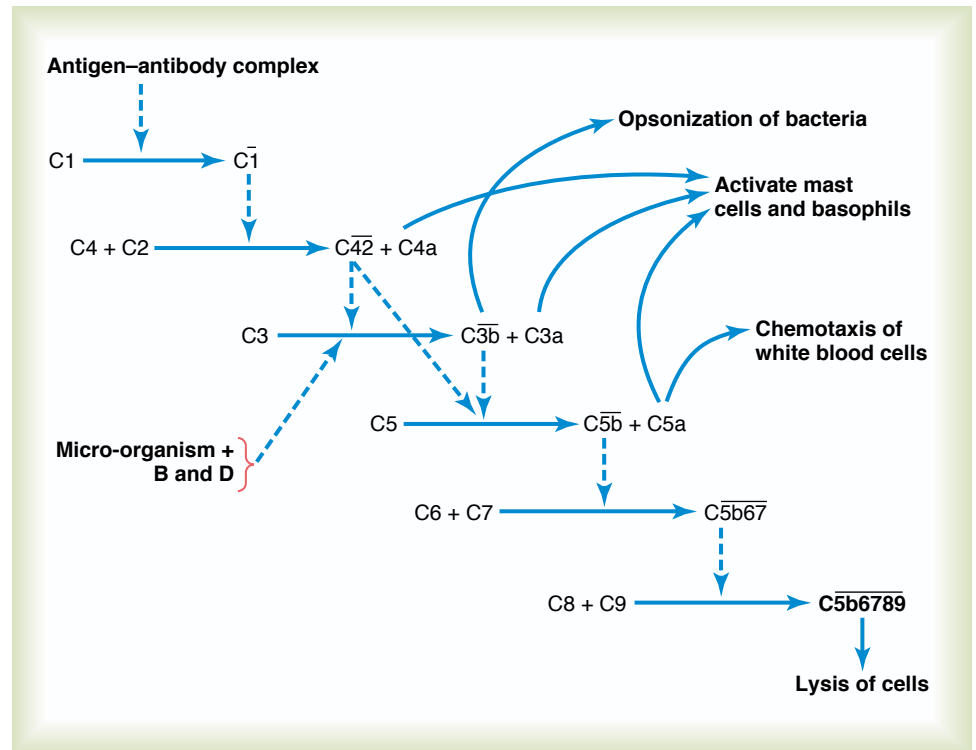


Figure 34-5

Cascade of reactions during activation of the classic pathway of complement. (Modified from Alexander JW, Good RA: Fundamentals of Clinical Immunology. Philadelphia: WB Saunders, 1977.)

Complement System for Antibody Action

“Complement” is a collective term that describes a system of about 20 proteins, many of which are enzyme precursors. The principal actors in this system are 11 proteins designated C1 through C9, B, and D, shown in Figure 34-5. All these are present normally among the plasma proteins in the blood as well as among the proteins that leak out of the capillaries into the tissue spaces. The enzyme precursors are normally inactive, but they can be activated mainly by the so-called *classic pathway*.

Classic Pathway. The classic pathway is initiated by an antigen-antibody reaction. That is, when an antibody binds with an antigen, a specific reactive site on the “constant” portion of the antibody becomes uncovered, or “activated,” and this in turn binds directly with the C1 molecule of the complement system, setting into motion a “cascade” of sequential reactions, shown in Figure 34-5, beginning with activation of the proenzyme C1 itself. The C1 enzymes that are formed then *activate successively increasing quantities of enzymes* in the later stages of the system, so that from a small beginning, an extremely large “amplified” reaction occurs. Multiple end products are formed, as shown to the right in the figure, and several of these cause important effects that help to prevent damage to the body’s tissues caused by the invading organism or toxin. Among the more important effects are the following:

1. **Opsonization and phagocytosis.** One of the products of the complement cascade, C3b, strongly activates phagocytosis by both neutrophils and macrophages, causing these cells

to engulf the bacteria to which the antigen-antibody complexes are attached. This process is called *opsonization*. It often enhances the number of bacteria that can be destroyed by many hundredfold.

2. **Lysis.** One of the most important of all the products of the complement cascade is the *lytic complex*, which is a combination of multiple complement factors and designated C5b6789. This has a direct effect of rupturing the cell membranes of bacteria or other invading organisms.
3. **Agglutination.** The complement products also change the surfaces of the invading organisms, causing them to adhere to one another, thus promoting agglutination.
4. **Neutralization of viruses.** The complement enzymes and other complement products can attack the structures of some viruses and thereby render them nonvirulent.
5. **Chemotaxis.** Fragment C5a initiates chemotaxis of neutrophils and macrophages, thus causing large numbers of these phagocytes to migrate into the tissue area adjacent to the antigenic agent.
6. **Activation of mast cells and basophils.** Fragments C3a, C4a, and C5a activate mast cells and basophils, causing them to release histamine, heparin, and several other substances into the local fluids. These substances in turn cause increased local blood flow, increased leakage of fluid and plasma protein into the tissue, and other local tissue reactions that help inactivate or immobilize the antigenic agent. The same factors play a major role in inflammation (which was

discussed in Chapter 33) and in allergy, as we discuss later.

7. **Inflammatory effects.** In addition to inflammatory effects caused by activation of the mast cells and basophils, several other complement products contribute to local inflammation. These products cause (1) the already increased blood flow to increase still further, (2) the capillary leakage of proteins to be increased, and (3) the interstitial fluid proteins to coagulate in the tissue spaces, thus preventing movement of the invading organism through the tissues.

Special Attributes of the T-Lymphocyte System—Activated T Cells and Cell-Mediated Immunity

Release of Activated T Cells from Lymphoid Tissue and Formation of Memory Cells. On exposure to the proper antigen, as presented by adjacent macrophages, the T lymphocytes of a specific lymphocyte clone proliferate and release large numbers of activated, specifically reacting T cells in ways that parallel antibody release by activated B cells. The principal difference is that instead of releasing antibodies, whole activated T cells are formed and released into the lymph. These then pass into the circulation and are distributed throughout the body, passing through the capillary walls into the tissue spaces, back into the lymph and blood once again, and circulating again and again throughout the body, sometimes lasting for months or even years.

Also, *T-lymphocyte memory cells* are formed in the same way that B memory cells are formed in the antibody system. That is, when a clone of T lymphocytes is activated by an antigen, many of the newly formed lymphocytes are preserved in the lymphoid tissue to become additional T lymphocytes of that specific clone; in fact, these memory cells even spread throughout the lymphoid tissue of the entire body. Therefore, on subsequent exposure to the same antigen anywhere in the body, release of activated T cells occurs far more rapidly and much more powerfully than had occurred during first exposure.

Antigen-Presenting Cells, MHC Proteins, and Antigen Receptors on the T Lymphocytes. T-cell responses are extremely antigen specific, like the antibody responses of B cells, and are at least as important as antibodies in defending against infection. In fact, acquired immune responses usually require assistance from T cells to begin the process, and T cells play a major role in actually helping to eliminate invading pathogens.

Although B lymphocytes recognize intact antigens, T lymphocytes respond to antigens only when they are bound to specific molecules called *MHC proteins* on the surface of *antigen-presenting cells* in the lymphoid tissues (Figure 34–6). The three major types of antigen-presenting cells are *macrophages*, *B lymphocytes*, and *dendritic cells*. The dendritic cells, the most potent of the antigen-presenting cells, are located throughout the body, and their only known function is

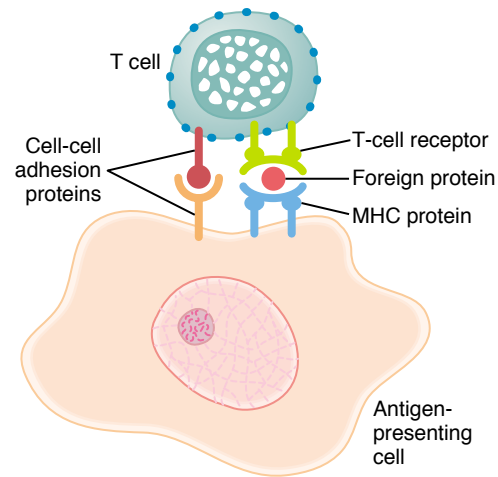


Figure 34–6

Activation of T cells requires interaction of T-cell receptors with an antigen (foreign protein) that is transported to the surface of the antigen-presenting cell by a major histocompatibility complex (MHC) protein. Cell-to-cell adhesion proteins enable the T cell to bind to the antigen-presenting cell long enough to become activated.

to present antigens to T cells. Interaction of *cell adhesion proteins* is critical in permitting the T cells to bind to antigen-presenting cells long enough to become activated.

The MHC proteins are encoded by a large group of genes called the *major histocompatibility complex (MHC)*. The MHC proteins bind peptide fragments of antigen proteins that are degraded inside antigen-presenting cells and then transport them to the cell surface. There are two types of MHC proteins: (1) *MHC I proteins*, which present antigens to *cytotoxic T cells*, and (2) *MHC II proteins*, which present antigens to *T helper cells*. The specific functions of cytotoxic and helper T cells are discussed later.

The antigens on the surface of antigen-presenting cells bind with *receptor molecules* on the surfaces of T cells in the same way that they bind with plasma protein antibodies. These receptor molecules are composed of a variable unit similar to the variable portion of the humoral antibody, but its stem section is firmly bound to the cell membrane of the T lymphocyte. There are as many as 100,000 receptor sites on a single T cell.

Several Types of T Cells and Their Different Functions

It has become clear that there are multiple types of T cells. They are classified into three major groups: (1) *helper T cells*, (2) *cytotoxic T cells*, and (3) *suppressor T cells*. The functions of each of these are distinct.

Helper T Cells—Their Role in Overall Regulation of Immunity

The helper T cells are by far the most numerous of the T cells, usually constituting more than three quarters

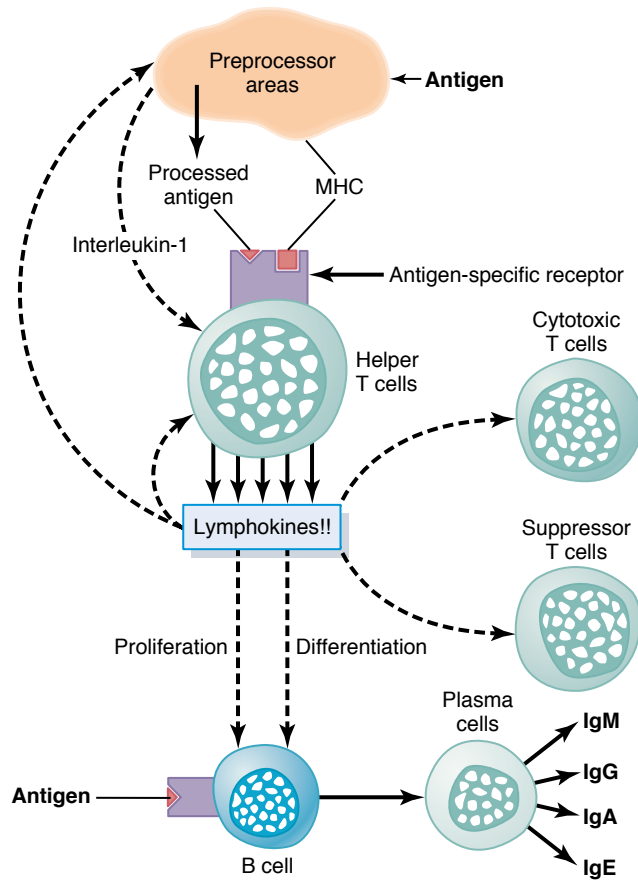


Figure 34-7

Regulation of the immune system, emphasizing a pivotal role of the *helper T cells*. MHC, major histocompatibility complex.

of all of them. As their name implies, they *help* in the functions of the immune system, and they do so in many ways. In fact, they serve as the major regulator of virtually all immune functions, as shown in Figure 34-7. They do this by forming a series of protein mediators, called *lymphokines*, that act on other cells of the immune system as well as on bone marrow cells. Among the important lymphokines secreted by the helper T cells are the following:

- Interleukin-2
- Interleukin-3
- Interleukin-4
- Interleukin-5
- Interleukin-6
- Granulocyte-monocyte colony-stimulating factor
- Interferon- γ

Specific Regulatory Functions of the Lymphokines. In the absence of the lymphokines from the helper T cells, the remainder of the immune system is almost paralyzed. In fact, it is the helper T cells that are inactivated or destroyed by the *acquired immunodeficiency syndrome (AIDS) virus*, which leaves the body almost totally unprotected against infectious disease, therefore leading to the now well-known debilitating and

lethal effects of AIDS. Some of the specific regulatory functions are the following.

Stimulation of Growth and Proliferation of Cytotoxic T Cells and Suppressor T Cells. In the absence of helper T cells, the clones for producing cytotoxic T cells and suppressor T cells are activated only slightly by most antigens. The lymphokine *interleukin-2* has an especially strong stimulatory effect in causing growth and proliferation of both cytotoxic and suppressor T cells. In addition, several of the other lymphokines have less potent effects.

Stimulation of B-Cell Growth and Differentiation to Form Plasma Cells and Antibodies. The direct actions of antigen to cause B-cell growth, proliferation, formation of plasma cells, and secretion of antibodies are also slight without the “help” of the helper T cells. Almost all the interleukins participate in the B-cell response, but especially interleukins 4, 5, and 6. In fact, these three interleukins have such potent effects on the B cells that they have been called *B-cell stimulating factors* or *B-cell growth factors*.

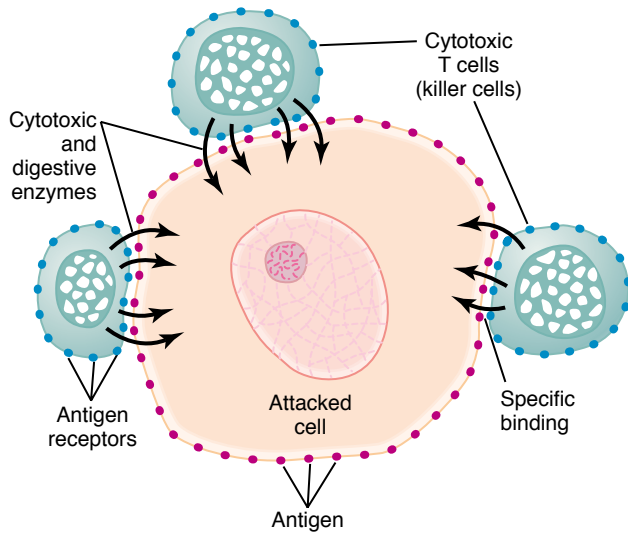
Activation of the Macrophage System. The lymphokines also affect the macrophages. First, they slow or stop the migration of the macrophages after they have been chemotactically attracted into the inflamed tissue area, thus causing great accumulation of macrophages. Second, they activate the macrophages to cause far more efficient phagocytosis, allowing them to attack and destroy increasing numbers of invading bacteria or other tissue-destroying agents.

Feedback Stimulatory Effect on the Helper Cells Themselves. Some of the lymphokines, especially interleukin-2, have a direct positive feedback effect in stimulating activation of the helper T cells themselves. This acts as an amplifier by further enhancing the helper cell response as well as the entire immune response to an invading antigen.

Cytotoxic T Cells

The cytotoxic T cell is a direct-attack cell that is capable of killing micro-organisms and, at times, even some of the body’s own cells. For this reason, these cells are called *killer cells*. The receptor proteins on the surfaces of the cytotoxic cells cause them to bind tightly to those organisms or cells that contain the appropriate binding-specific antigen. Then, they kill the attacked cell in the manner shown in Figure 34-8. After binding, the cytotoxic T cell secretes *hole-forming proteins*, called *perforins*, that literally punch round holes in the membrane of the attacked cell. Then fluid flows rapidly into the cell from the interstitial space. In addition, the cytotoxic T cell releases cytotoxic substances directly into the attacked cell. Almost immediately, the attacked cell becomes greatly swollen, and it usually dissolves shortly thereafter.

Especially important, these cytotoxic killer cells can pull away from the victim cells after they have punched holes and delivered cytotoxic substances and

**Figure 34-8**

Direct destruction of an invading cell by sensitized lymphocytes (cytotoxic T cells).

then move on to kill more cells. Indeed, some of these cells persist for months in the tissues.

Some of the cytotoxic T cells are especially lethal to tissue cells that have been invaded by viruses because many virus particles become entrapped in the membranes of the tissue cells and attract T cells in response to the viral antigenicity. The cytotoxic cells also play an important role in destroying cancer cells, heart transplant cells, or other types of cells that are foreign to the person's own body.

Suppressor T Cells

Much less is known about the suppressor T cells than about the others, but they are capable of suppressing the functions of both cytotoxic and helper T cells. It is believed that these suppressor functions serve the purpose of preventing the cytotoxic cells from causing excessive immune reactions that might be damaging to the body's own tissues. For this reason, the suppressor cells are classified, along with the helper T cells, as *regulatory T cells*. It is probable that the suppressor T-cell system plays an important role in limiting the ability of the immune system to attack a person's own body tissues, called *immune tolerance*, as we discuss in the next section.

Tolerance of the Acquired Immunity System to One's Own Tissues—Role of Preprocessing in the Thymus and Bone Marrow

If a person should become immune to his or her own tissues, the process of acquired immunity would destroy the individual's own body. The immune mechanism normally "recognizes" a person's own tissues

as being distinctive from bacteria or viruses, and the person's immunity system forms few antibodies or activated T cells against his or her own antigens.

Most Tolerance Results from Clone Selection During Preprocessing. It is believed that most tolerance develops during preprocessing of T lymphocytes in the thymus and of B lymphocytes in the bone marrow. The reason for this belief is that injecting a strong antigen into a fetus while the lymphocytes are being preprocessed in these two areas prevents development of clones of lymphocytes in the lymphoid tissue that are specific for the injected antigen. Experiments have shown that specific immature lymphocytes in the thymus, when exposed to a strong antigen, become lymphoblastic, proliferate considerably, and then combine with the stimulating antigen—an effect that is believed to cause the cells themselves to be destroyed by the thymic epithelial cells before they can migrate to and colonize the total body lymphoid tissue.

It is believed that during the preprocessing of lymphocytes in the thymus and bone marrow, all or most of those clones of lymphocytes that are specific to damage the body's own tissues are self-destroyed because of their continual exposure to the body's antigens.

Failure of the Tolerance Mechanism Causes Autoimmune Diseases. Sometimes people lose their immune tolerance of their own tissues. This occurs to a greater extent the older a person becomes. It usually occurs after destruction of some of the body's own tissues, which releases considerable quantities of "self-antigens" that circulate in the body and presumably cause acquired immunity in the form of either activated T cells or antibodies.

Several specific diseases that result from autoimmunity include (1) *rheumatic fever*, in which the body becomes immunized against tissues in the joints and heart, especially the heart valves, after exposure to a specific type of streptococcal toxin that has an epitope in its molecular structure similar to the structure of some of the body's own self-antigens; (2) one type of *glomerulonephritis*, in which the person becomes immunized against the basement membranes of glomeruli; (3) *myasthenia gravis*, in which immunity develops against the acetylcholine receptor proteins of the neuromuscular junction, causing paralysis; and (4) *lupus erythematosus*, in which the person becomes immunized against many different body tissues at the same time, a disease that causes extensive damage and often rapid death.

Immunization by Injection of Antigens

Immunization has been used for many years to produce acquired immunity against specific diseases. A person can be immunized by injecting dead organisms that are no longer capable of causing disease but that still have some of their chemical antigens. This type of immunization is used to protect against typhoid fever,

whooping cough, diphtheria, and many other types of bacterial diseases.

Immunity can be achieved against toxins that have been treated with chemicals so that their toxic nature has been destroyed even though their antigens for causing immunity are still intact. This procedure is used in immunizing against tetanus, botulism, and other similar toxic diseases.

And, finally, a person can be immunized by being infected with live organisms that have been “attenuated.” That is, these organisms either have been grown in special culture media or have been passed through a series of animals until they have mutated enough that they will not cause disease but do still carry specific antigens required for immunization. This procedure is used to protect against poliomyelitis, yellow fever, measles, smallpox, and many other viral diseases.

Passive Immunity

Thus far, all the acquired immunity we have discussed has been *active immunity*. That is, the person’s own body develops either antibodies or activated T cells in response to invasion of the body by a foreign antigen. However, temporary immunity can be achieved in a person without injecting any antigen. This is done by infusing antibodies, activated T cells, or both obtained from the blood of someone else or from some other animal that has been actively immunized against the antigen.

Antibodies last in the body of the recipient for 2 to 3 weeks, and during that time, the person is protected against the invading disease. Activated T cells last for a few weeks if transfused from another person but only for a few hours to a few days if transfused from an animal. Such transfusion of antibodies or T lymphocytes to confer immunity is called *passive immunity*.

ALLERGY AND HYPERSENSITIVITY

An important undesirable side effect of immunity is the development, under some conditions, of *allergy* or other types of *immune hypersensitivity*. There are several types of allergy and other hypersensitivities, some of which occur only in people who have a specific allergic tendency.

Allergy Caused by Activated T Cells: Delayed-Reaction Allergy

Delayed-reaction allergy is caused by activated T cells and not by antibodies. In the case of poison ivy, the toxin of poison ivy in itself does not cause much harm to the tissues. However, on repeated exposure, it does cause the formation of activated helper and cytotoxic T cells. Then, after subsequent exposure to the poison ivy toxin, within a day or so, the activated T cells

diffuse from the circulating blood in large numbers into the skin to respond to the poison ivy toxin. And, at the same time, these T cells elicit a cell-mediated type of immune reaction. Remembering that this type of immunity can cause release of many toxic substances from the activated T cells as well as extensive invasion of the tissues by macrophages along with their subsequent effects, one can well understand that the eventual result of some delayed-reaction allergies can be serious tissue damage. The damage normally occurs in the tissue area where the instigating antigen is present, such as in the skin in the case of poison ivy, or in the lungs to cause lung edema or asthmatic attacks in the case of some airborne antigens.

Allergies in the “Allergic” Person, Who Has Excess IgE Antibodies

Some people have an “allergic” tendency. Their allergies are called *atopic allergies* because they are caused by a nonordinary response of the immune system. The allergic tendency is genetically passed from parent to child and is characterized by the presence of large quantities of IgE *antibodies* in the blood. These antibodies are called *reagins* or *sensitizing antibodies* to distinguish them from the more common IgG antibodies. When an *allergen* (defined as an antigen that reacts specifically with a specific type of IgE reagin antibody) enters the body, an allergen-reagin reaction takes place, and a subsequent allergic reaction occurs.

A special characteristic of the IgE antibodies (the reagins) is a strong propensity to attach to mast cells and basophils. Indeed, a single mast cell or basophil can bind as many as half a million molecules of IgE antibodies. Then, when an antigen (an allergen) that has multiple binding sites binds with several IgE antibodies that are already attached to a mast cell or basophil, this causes immediate change in the membrane of the mast cell or basophil, perhaps resulting from a physical effect of the antibody molecules to contort the cell membrane. At any rate, many of the mast cells and basophils rupture; others release special agents immediately or shortly thereafter, including *histamine*, *protease*, *slow-reacting substance of anaphylaxis* (which is a mixture of toxic leukotrienes), *eosinophil chemotactic substance*, *neutrophil chemotactic substance*, *heparin*, and *platelet activating factors*. These substances cause such effects as dilation of the local blood vessels; attraction of eosinophils and neutrophils to the reactive site; increased permeability of the capillaries with loss of fluid into the tissues; and contraction of local smooth muscle cells. Therefore, several different tissue responses can occur, depending on the type of tissue in which the allergen-reagin reaction occurs. Among the different types of allergic reactions caused in this manner are the following.

Anaphylaxis. When a specific allergen is injected directly into the circulation, the allergen can react with basophils of the blood and mast cells in the tissues

located immediately outside the small blood vessels if the basophils and mast cells have been sensitized by attachment of IgE reagents. Therefore, a widespread allergic reaction occurs throughout the vascular system and closely associated tissues. This is called *anaphylaxis*. *Histamine* is released into the circulation and causes body-wide vasodilation as well as increased permeability of the capillaries with resultant marked loss of plasma from the circulation. An occasional person who experiences this reaction dies of circulatory shock within a few minutes unless treated with epinephrine to oppose the effects of the histamine.

Also released from the activated basophils and mast cells is a mixture of leukotrienes called *slow-reacting substance of anaphylaxis*. These leukotrienes can cause spasm of the smooth muscle of the bronchioles, eliciting an asthma-like attack, sometimes causing death by suffocation.

Urticaria. Urticaria results from antigen entering specific skin areas and causing localized anaphylactoid reactions. *Histamine* released locally causes (1) vasodilation that induces an immediate *red flare* and (2) increased local permeability of the capillaries that leads to local circumscribed areas of swelling of the skin within another few minutes. The swellings are commonly called *hives*. Administration of antihistamine drugs to a person before exposure will prevent the hives.

Hay Fever. In hay fever, the allergen-reagin reaction occurs in the nose. *Histamine* released in response to the reaction causes local intranasal vascular dilation, with resultant increased capillary pressure as well as increased capillary permeability. Both these effects cause rapid fluid leakage into the nasal cavities and into associated deeper tissues of the nose; and the nasal linings become swollen and secretory. Here again, use of antihistamine drugs can prevent this swelling reaction. But other products of the allergen-reagin reaction can still cause irritation of the nose, eliciting the typical sneezing syndrome.

Asthma. Asthma often occurs in the “allergic” type of person. In such a person, the allergen-reagin reaction occurs in the bronchioles of the lungs. Here, an important product released from the mast cells is believed to be the *slow-reacting substance of anaphylaxis*, which causes spasm of the bronchiolar smooth muscle. Consequently, the person has difficulty breathing until the reactive products of the allergic reaction have been removed. Administration of antihistaminics has less effect on the course of asthma because histamine does

not appear to be the major factor eliciting the asthmatic reaction.

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