Although some macrophages migrate throughout the body, others reside permanently in body tissues, such as the brain, lungs, kidneys, liver, and connective tissues. The fixed macrophages that reside in the spleen, lymph nodes, and other tissues of the lymphatic system trap and filter out microorganisms and foreign invaders that enter the blood. Figure 1 shows the structures of the lymphatic system.

The appearance of foreign organisms in the body activates antimicrobial plasma proteins, often called complement proteins (Figure 2). There are about 20 known types of complement proteins. Under normal conditions, these proteins are present in the circulatory system in an inactive form. Marker proteins from invading microbes activate the complement proteins, which, in turn, serve as messengers. The proteins aggregate to initiate an attack on the cell membranes of fungal or bacterial cells. Some of the activated proteins trigger the formation of a protective coating around the invader, as shown in Figure 2(a). This coating seals the invading cell, immobilizing it. A second group punctures the cell membrane, as seen in Figure 2(b). Water enters the cell through the pore created by the protein, causing the cell to swell and burst. A third group of proteins attaches to the invader, as illustrated in Figure 2(c). The tiny microbes become less soluble and more susceptible to phagocytosis by leukocytes.

**Figure 1**
In the lymphatic system, pathogens, foreign cells and material, and debris from the body’s tissues are filtered out from the lymph (the fluid found outside capillaries), and the lymph is returned to the circulatory system.

**complement proteins** plasma proteins that help defend against invading microbes by tagging the microbe for phagocytosis, puncturing cell membranes, or triggering the formation of a mucous coating
Another specialized group of white blood cells, called lymphocytes, produces antibodies. Antibodies are protein molecules that protect the body from invaders. All cells have special markers located on their cell membranes. Normally, the immune system does not react to the body's own markers. However, intruding cells or foreign proteins activate the production of antibodies. The cell membrane of a bacterium and the outer coat of a virus contain many different antigens. The antigen (a term derived from antibody generator) may even be a toxin produced by moulds, bacteria, or algae. The toxin presents a danger to the cells of the body because it interferes with normal cell metabolism.

Two different types of lymphocytes are found in the immune system. The first is the T cell, which is produced in the bone marrow and is stored in a tiny organ called the thymus gland, from which the T cell receives its name. The T cell's mission is to seek out the intruder and signal the attack. Acting much like a sentry, some T cells identify the invader by its antigen markers (Figure 3), which are located on the cell membrane. Once the antigen is identified, another T cell passes this information on to the antibody-producing B cell.

B cells multiply and produce chemical weapons: the antibodies. Each B cell produces a single type of antibody, which is displayed along the cell membrane. Eventually, the B cells are released from the bone marrow and enter the circulatory system. Some B cells differentiate into super-antibody-producing cells called plasma cells. These plasma cells can produce as many as 2000 antibody molecules every second.

Antigen–Antibody Reactions
Antibodies are Y-shaped proteins engineered to target foreign invaders. Antibodies are specific; this means that an antibody produced against the influenza virus, for example, is not effective against HIV, the virus that causes AIDS. The tails of these Y-shaped proteins are very similar, regardless of the type of antibody. Variations only exist at the outer edge of each arm, the area in which the antibody combines with the antigen (Figure 4). Antigen markers found on the influenza virus are different from those found on HIV. Each antibody has a shape that is complementary to its specific antigen. Thus, the combining site of an antibody produced in response to the influenza virus will not complement HIV.

Many different antigen markers are located on the membrane of a virus or bacterium. Although different antibodies can attach to the invader, each antibody attaches only to its complementary marker. The attachment of antibodies to the antigens increases the size of the complex, making the antigen–antibody combination more conspicuous and, therefore, more easily engulfed and destroyed by the wandering macrophages.
How do antibodies prevent poisons or toxins from destroying cells? Specialized receptor sites are found on different cells, which may explain why some poisons affect the nervous system while others affect the digestive or circulatory system. The receptor site is designed to accommodate either a hormone or a specific nutrient. Toxins or poisons have a specialized geometry that allows them to become attached to the receptor sites on cell membranes. Unfortunately, the poison has a shape similar to a hormone or nutrient. Once attached, the poison is engulfed by the cell, which assumes that the poison is actually a needed substance. Antibodies interfere with the attachment of the toxins to the cell membranes’ receptor sites by binding with toxins, as shown in Figure 5.

Viruses also use receptor sites as entry ports. The virus injects its hereditary material into the cell, but most often leaves the outer protein coat in the entry port. Because of this outer coat, different viruses come to rest in distinct locations. For example, the outer coat of the cold virus has a geometry that enables it to attach to lung cells. HIV attaches to the receptor sites of the T cell. Once attached, the T cell engulfs the virus, creating another problem for the immune system. Antibody production requires a blueprint of the invader, but the protein coat of the virus hides inside the very cells assigned as sentries for invading antigens. Does this provide a clue as to why the body experiences difficulty defeating HIV (Figure 6)?

Antibodies that attach themselves to the invading viruses alter their shape, thereby preventing access to the entry ports. Misshapen viruses float around the body, unable to find an appropriate entry port. Occasionally, the outer coat of the invader will change shape because of mutations. The mutated microbes may still gain access to the receptor site but are not tied up by the antibody.
How the Body Recognizes Harmful Antigens

Figure 7 illustrates how the body recognizes harmful antigens. The T cells scout the body in search of foreign invaders that pose a threat to your survival. The macrophages attack the invaders and engulf them. As mentioned earlier, the antigen markers are not destroyed with the invader but are pushed toward the cell membrane of the macrophage. Pressing the antigens into its cell membrane, the macrophage couples with the T cells, also referred to as helper T cells. The T cells read the antigen’s shape and release a chemical messenger called lymphokine. The lymphokine causes the B cells to divide into identical cells called clones. Later, a second message is sent from the helper T cells to the B cells, triggering the production of antibodies. Each B cell produces a specific type of antibody. By the time the B cells enter the circulatory system, many antibodies are attached to their cell membranes.

The helper T cells activate an additional defender, the killer T cells. As the name suggests, these lymphocytes carry out search-and-destroy missions. Once activated, the killer T cells puncture the cell membrane of the intruder, which may be a fungus, protozoan parasite, or bacterium. Viruses, however, are much more insidious, because they hide within the familiar confines of the host cell. Here, the true value of the killer T cells is demonstrated. Once the viral coat is found attached to the cell’s membrane, the T cell attacks the infected cell. By destroying the infected body cell, the killer T cell prevents the virus from reproducing.

**Figure 7**
The body recognizes harmful antigens.

1. **Antigen marker**
   - **Invading bacterium**

2. **Macrophage engulfs the bacterium and pushes antigen markers to outer membrane of macrophage.**

3. **Helper T cell**
   - **Identifies the antigen present on the cell membrane of the macrophage.**

4. **B cell**
   - **Antibodies**
   - **Helper T cell**
   - **Antigen marker**
   - **Helper T cells**
     - T cells with receptors that bind to fragments of antigens
   - **Lymphokine**
     - Protein produced by the T cells that acts as a chemical messenger between other T cells and B cells
   - **Killer T cells**
     - T cells that puncture the cell membranes of cells infected with foreign invaders, killing the cells and the invaders, and which destroy body cells that have become infected by a virus

5. **Antibodies attach to the antigens.**
Killer T cells also destroy mutated cells (Figure 8). This is an extremely important process because some of the altered cells may be cancerous. Many experts believe that everyone develops cancerous cells, but, in most cases, the T cells eliminate the problem before a tumour forms. Whether or not you develop cancer depends on the success of your killer T cells. Killer T cells may also account for the body’s rejection of organ transplants. Antigen markers on the cell membranes of the donor will be different from those of the recipient. Once the foreign markers of the transplanted tissue are recognized, their killer T cells initiate an assault. Immunosuppressant drugs, such as cyclosporin, can slow the killer T cells. Unfortunately, slowing the killer T cells can result in a new set of complications. Individuals who receive these drugs become susceptible to bacterial infections. One of the leading causes of death for an organ transplant patient is pneumonia.

Once the battle against foreign invaders has been won, another T cell, the suppressor T cell, signals the immune system to shut down. Communication between the helper T cells and the suppressor T cells ensures that the body maintains adequate numbers of antibodies to contain the invading antigen. Most of the B cells and T cells will die off within a few days after the battle, but a small contingent will remain long after to guard the site. Phagocytes survey the area, cleaning up the debris left from dead and injured cells. Tissues begin the work of repair and replacement.

The Immune System’s Memory

The native population of Hawaii was nearly annihilated by measles in the late 18th and early 19th centuries after British explorer James Cook and his sailors unwittingly introduced the disease when they arrived at the Hawaiian Islands. In North America, the native population was decimated by epidemics of smallpox. Because neither group had been exposed to these viruses before, they had no antibodies to fight infection.

At this time, Europeans and Asians, unlike the native populations of Hawaii and North America, had long been exposed to many different types of viruses and were better able to produce antibodies to fight them. Europeans and Asians were among the first to domesticate and live in close proximity to animals, so many diseases had been transmitted via animals to humans. The diseases were easily transmitted among humans because of overcrowding in cities and poor sanitation conditions. The diseases killed those who were susceptible; those who were resistant to disease lived on and conferred their resistance to future generations.

As mentioned earlier, the helper T cells must read a blueprint of the invader before B cells produce antibodies. This blueprint is stored even after the invader is destroyed so that subsequent infections can be destroyed before the microbe gains a foothold. Immunity is based on maintaining an adequate number of antibodies.

It is believed that a memory B cell is generated during the infection. Like helper T cells, the memory B cells hold an imprint of the antigen or antigens that characterize the invader. Most T cells and B cells produced to fight the infection die off within a few days; however, the memory B cells remain. The memory B cells identify the enemy and quickly mobilize antibody-producing B cells. Invading pathogens are defeated before they become established. As long as the memory B cell survives, the individual is immune. That is why a person does not usually catch chickenpox more than once.
Matching Tissues for Organ Transplant
The main challenge with any tissue or organ transplant is the immune response of the recipient—that is, the immune system’s ability to distinguish between “self” and “non-self.” The donor organ is often identified as a foreign invader by distinctive protein markers on its cell membrane. The distinctive marker (known as major histocompatibility complex, or MHC) is a protein fingerprint unique to each individual. The recipient makes antibodies designed to destroy the foreign invader.

Kidney transplants can be used as an example. Living donor kidneys account for about 15% of all kidney transplants. Because humans are born with two kidneys, the donor is able to give one kidney without significant effects on quality of life. A single kidney can carry out the filtering and osmoregulatory functions of the body. To reduce rejections, attempts are made to match MHC of the tissues of donors and recipients as closely as possible. For living donor transplants, physicians usually look to close relatives because the MHC is genetically controlled. The better the match, the greater the chances of long-term success.

Kidney transplants from recently deceased donors account for the vast majority of transplants. However, the need for organs far surpasses supply (Figure 9). Again, as with living donors, close matching is essential. Not every donor kidney is appropriate for a specific recipient. To help reduce the rejection factor, even for close matches, immunosuppressant drugs can be given. However, a drug that minimizes the fight against foreign tissues will also reduce the immune system’s ability to fight off invading viruses and bacteria. These drugs place patients at risk of infections.

One of the most promising breakthroughs in organ transplant research comes from a research team working at Ontario’s London Health Sciences Centre. The research team has come up with an antibody that targets and disarms immune cells responsible for organ rejection while leaving the remainder of the immune system untouched. Early work suggests that the antibody reprograms the immune system to accept transplanted organs.

Stem Cell Research
The answer for replacing damaged tissues may lie in stem cell research, not transplantation. Stem cells are cells that can differentiate and develop into a variety of different tissues such as epithelial tissue, muscle tissue, or nerve tissue. Intestinal stem cells reline the gut; stem cells of the skin replace cells that are continuously sloughed off; and stem cells give rise to a wide range of blood cells that protect against foreign invaders and identify human cells that have mutated, such as cancer cells. Stem cells are pluripotent cells that can give rise to different types of body cells.

In 1998, James Thomson, a researcher at the University of Wisconsin, demonstrated that human stem cells could transform into a variety of cells, such as bone marrow, brain tissue, muscle, skin, pancreas, liver, or practically any human tissue. If it were possible to regulate the differentiation of human stem cells, the cells could replace destroyed islet cells that produce insulin, repair damaged cartilage, or repair cardiac tissue that has been destroyed by heart disease.

Dr. Freda Miller and colleagues at the Montreal Neurological Institute (MNI) have discovered multipotent stem cells in adult skin. These skin cells can be directed to become neurons or even muscle cells. The MNI researchers expect that new findings will confirm the versatility of adult skin stem cells.

Organ Donation in Canada
Canada’s organ donation rate is among the lowest of all the developed countries—more than 3000 Canadians are waiting for an organ transplant. One organ donor can donate numerous organs and tissues including lungs, heart, liver, kidneys, pancreas, bowel, eye tissue, skin, heart valves, bone, tendons, veins, and ligaments. You can indicate your wish to become an organ donor on your health-care card or your driver’s license. Discuss this decision with family so your wishes are known.

\textbf{DID YOU KNOW?}

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\textbf{pluripotent cells} cells that are capable of differentiating into a number of different specialized cells, such as neurons or muscle cells
Take a Stand: The Future of Stem Cell Research

Chapter 10

The greatest challenge of organ transplants is to trick the recipient’s immune system into accepting the new organ. Finding someone with a close tissue match to donate an organ can be extremely difficult. What if the person who needs a transplant could use his or her own stem cells to repair the damaged organ?

Consider this scenario: Twenty-four people suffering from the same degenerative brain disorder participate in a research project. Scientists inject immature neurons (glial cells) into the patients’ brains in the hope that the degenerative effects of the disorder can be reversed by replacing the damaged nerve cells. The glial cells were obtained by culturing the patients’ own bone marrow stem cells (stromal cells) with retinoic acid and growth factor, and subjecting them to other conditions that induced them to differentiate into glial cells. After two years, 13 patients show signs of improvement, 7 show no beneficial effects, 2 show accelerated degeneration of brain tissue, 1 experiences an unexplained immune-like reaction, and 1 develops a glioma (a form of brain cancer).

Statement

Governments should redirect some funding from organ transplant research to autologous (i.e., originating from the same individual) stem cell research.

EXPLORÉ an issue

The Immune Response

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Function</th>
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<tbody>
<tr>
<td>lymphocytes</td>
<td>produce antibodies</td>
</tr>
<tr>
<td>helper T cells</td>
<td>act as sentries to identify foreign invading substances</td>
</tr>
<tr>
<td>B cells</td>
<td>produce antibodies</td>
</tr>
<tr>
<td>killer T cells</td>
<td>puncture cell membranes of infected cells, thereby killing the cell</td>
</tr>
<tr>
<td>suppressor T cells</td>
<td>turn off the immune system</td>
</tr>
<tr>
<td>memory T cells</td>
<td>retain information about the geometry of the antigen</td>
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</tbody>
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Section 10.2 Questions

Understanding Concepts
1. Define and contrast these terms: antigen, antibody; T cell lymphocytes, B cell lymphocytes; macrophages, lymphocytes.
2. Explain how B cell, helper T cell, and killer T cell lymphocytes provide immunity.
3. How do antibodies defeat antigens? Describe four contributions that antibodies make to the immune system.
4. How do memory B cells provide continuing immunity?

Making Connections
5. A research group has begun testing on a potential cure for type 1 diabetes, an inherited disease caused by the destruction of the insulin-producing cells in the pancreas by one’s own immune system. An immunosuppressant drug is administered twice daily to a test group of 150 people.
   (a) Why can the immunosuppressant drug prevent diabetes?
   (b) Researchers found that the drug wasn’t effective once symptoms for diabetes were expressed in test subjects. What conclusions can you draw about this?
   (c) Explain why researchers are working on a test to identify antibodies that destroy insulin-producing cells.
   (d) List three important research questions that remain to be answered.