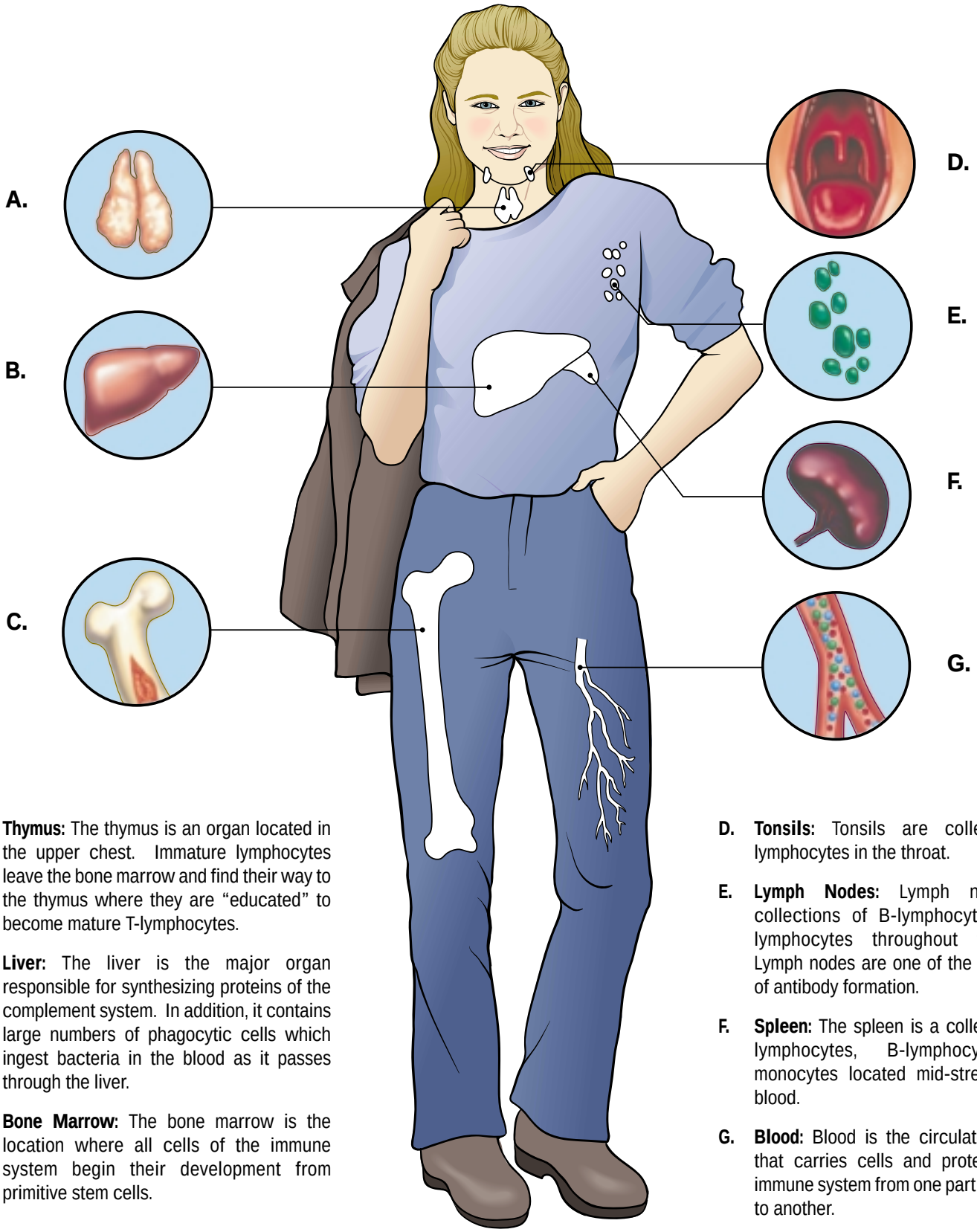
CHAPTER I

THE IMMUNE SYSTEM AND PRIMARY IMMUNE DEFICIENCY DISEASES

The immune system is composed of a variety of different cell types and proteins. Each component performs a special task aimed at recognizing and/or reacting against foreign material.

MAJOR ORGANS OF THE IMMUNE SYSTEM



A. Thymus: The thymus is an organ located in the upper chest. Immature lymphocytes leave the bone marrow and find their way to the thymus where they are "educated" to become mature T-lymphocytes.

B. Liver: The liver is the major organ responsible for synthesizing proteins of the complement system. In addition, it contains large numbers of phagocytic cells which ingest bacteria in the blood as it passes through the liver.

C. Bone Marrow: The bone marrow is the location where all cells of the immune system begin their development from primitive stem cells.

D. Tonsils: Tonsils are collections of lymphocytes in the throat.

E. Lymph Nodes: Lymph nodes are collections of B-lymphocytes and T-lymphocytes throughout the body. Lymph nodes are one of the major sites of antibody formation.

F. Spleen: The spleen is a collection of T-lymphocytes, B-lymphocytes and monocytes located mid-stream in the blood.

G. Blood: Blood is the circulatory system that carries cells and proteins of the immune system from one part of the body to another.

COMPONENTS OF THE IMMUNE SYSTEM

The immune system is composed of a variety of different cell types and proteins. Each component performs a special task aimed at recognizing foreign material (antigens) and/or reacting against foreign material. For some components, recognition of the material as foreign to the body is their primary and only function. Other components function primarily to react against the foreign material. Still other components function to both recognize and react against foreign antigens. Since the functions of the immune system are so critical to survival, many of them can be performed by more than one component of the system. This redundancy acts as a back-up mechanism. Therefore, if one component of the whole system is missing or functioning poorly another component can partially take over at least some of its functions.

The major components of the immune system are:

B-lymphocytes
T-lymphocytes
Phagocytes
Complement

B-LYMPHOCYTES: B-lymphocytes (sometimes called B-cells) are specialized cells of the immune system whose major function is to produce antibodies (also called immunoglobulins or gammaglobulins). B-lymphocytes develop from primitive cells (stem cells) in the bone marrow (see Plate IV). When mature, B- lymphocytes can be found in the bone marrow, lymph nodes, spleen, some areas of the intestine, and to a lesser extent in the bloodstream.

When B-lymphocytes are stimulated by a foreign material (antigens), they respond by maturing into another cell type called plasma cells. Plasma cells are the mature cells that actually produce the antibodies. Antibodies, the major product of plasma cells, find their way into the bloodstream, tissues, respiratory secretions, intestinal secretions, and even tears. Antibodies are highly specialized serum protein molecules. For every foreign antigen, there are antibody molecules specifically designed for that antigen. Like a lock and key, there are antibody molecules that fit the poliovirus, others that are aimed specifically at the bacteria that causes diphtheria, and still others that match the measles virus. The variety of different antibody molecules is so extensive that B-lymphocytes have the ability to produce them against virtually all possible microorganisms in our environment. When antibody molecules recognize the microorganism as foreign, they physically attach to the microorganism and set off a complex chain of reactions involving other components of the immune system (see Plate II) that eventually destroy the microorganism. The chemical names for antibody proteins are “immunoglobulins” or “gammaglobulins”.

Antibodies vary from molecule to molecule with respect to which microorganisms they bind. They can also vary with respect to their specialized functions in the body (see Plate III). This kind of variation in specialized function is determined by the antibody’s chemical structure, which in turn determines the class of the antibody (or immunoglobulin). There are 4 major classes of antibodies or immunoglobulins:

Immunoglobulin G (IgG)
Immunoglobulin A (IgA)
Immunoglobulin M (IgM)
Immunoglobulin E (IgE)

Each immunoglobulin class has special chemical characteristics that provide it with specific advantages. For example,

NORMAL ANTI-BACTERIAL ACTION

In most instances, bacteria are destroyed by the cooperative efforts of phagocytic cells, Antibody and Complement.

1. PHAGOCYTIC CELL ENGAGES MICROBE

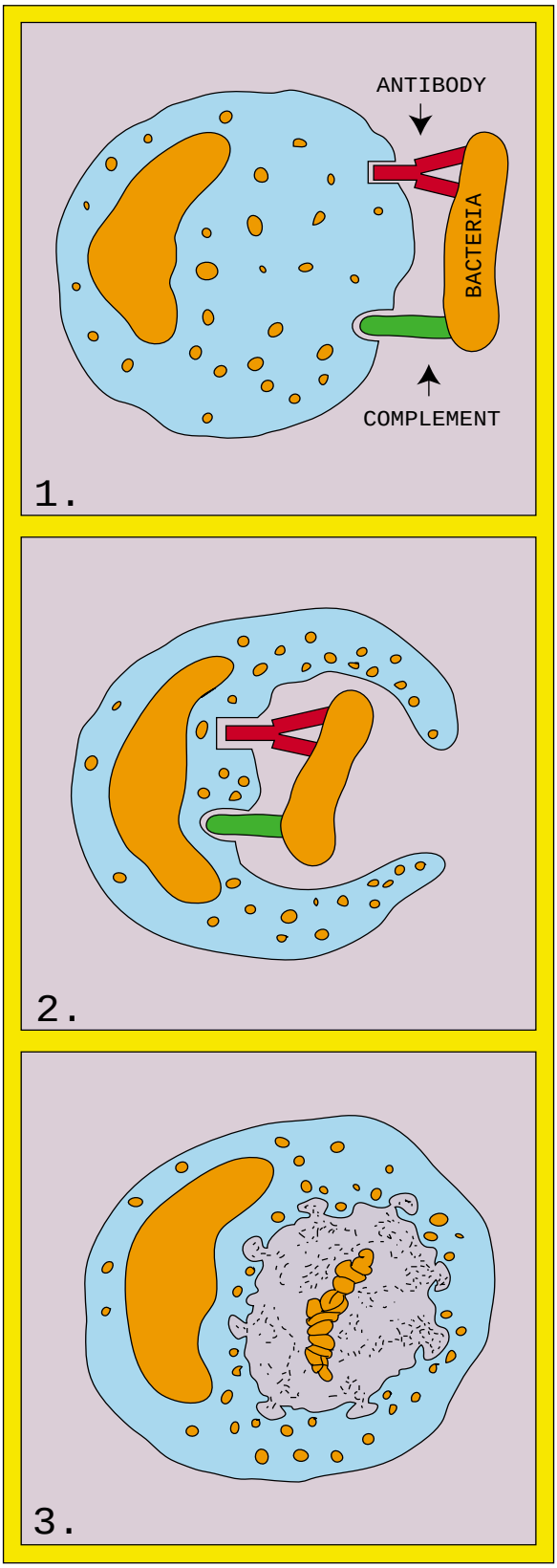
The microbe is coated with specific antibody and complement. The phagocytic cell then begins its attack on the microbe by attaching to the antibody and complement molecules.

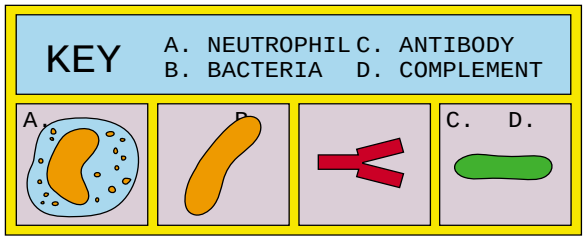
2. PHAGOCYTOSIS OF THE MICROBE

After attaching to the microbe, the phagocytic cell begins to ingest the microbe by extending itself around the microbe and engulfing it.

3. DESTRUCTION OF THE MICROBE

Once the microbe is ingested, bags of enzymes or chemicals are discharged into the vacuole where they kill the microbe.





antibodies in the IgG fraction are formed in large quantities, last for over a month and travel from the blood stream to the tissues easily. The IgG class is the only class of immunoglobulins which cross the placenta and pass immunity from the mother to the newborn.

Antibodies of the IgA fraction are produced near mucus membranes and find their way into secretions such as tears, bile, saliva, and mucus, where they protect against infection in the respiratory tract and intestines.

Antibodies of the IgM class are the first antibodies formed in response to infection. Therefore, they are important in protection during the early days of an infection.

Antibodies of the IgE class are responsible for allergic reactions.

Antibodies protect the host against infection in a number of different ways. For example, some microorganisms, such as viruses, must attach to body cells before they can cause an infection, but antibody bound to the surface of a virus can interfere with the virus's ability to attach to the host cell. In addition, antibody attached to the surface of some microorganisms can cause the activation of a group of proteins called the complement system that directly kills the bacteria or viruses. Antibody-coated bacteria are also much easier for phagocytic cells (see below) to ingest and kill than bacteria that are not coated with antibody. All of these actions of antibodies prevent microorganisms from successfully invading body tissues and causing serious infections.

T-LYMPHOCYTES: T-lymphocytes (sometimes called T-cells) are another type of immune cell. T-lymphocytes do not produce antibody molecules. The specialized roles of T-lymphocytes are (1) to directly attack foreign antigens such as viruses, fungi, or transplanted tissues, and (2) to act as regulators of the immune system. T-lymphocytes develop from stem cells in the bone marrow. Early in fetal life, the immature cells migrate to the thymus, a specialized organ of the immune system in the chest. Within the thymus, immature lymphocytes develop into mature T-lymphocytes (the "T" stands for the thymus). The thymus is essential for this process, and T-lymphocytes cannot develop if the fetus does not have a thymus. Mature T-lymphocytes leave the thymus and populate other organs of the immune system, such as the spleen, lymph nodes, bone marrow, and blood. Each T-lymphocyte reacts with a specific antigen, just as each antibody molecule reacts with a specific antigen. In fact, T-lymphocytes have molecules on their surfaces that are similar to antibodies and recognize antigens. The variety of different T-lymphocytes is so extensive that the body has T-lymphocytes that can react against virtually any antigen.

T-lymphocytes also vary in their function. There are (1) "killer" or "effector" T-lymphocytes, (2) "helper" T-lymphocytes, and (3) "suppressor" T-lymphocytes. Each has a different role to play in the immune system. Killer, or effector, T-lymphocytes are the T-lymphocytes which perform the actual destruction of the invading microorganism. Killer T-lymphocytes protect the body from certain bacteria and viruses that have the ability to survive and even reproduce within the body's own cells. Killer T-lymphocytes also respond to foreign tissues in the body, such as a transplanted kidney. Killer T-lymphocytes migrate to the site of an infection or the transplanted tissues. Once there, the killer cell directly binds to its target and kills it.

Helper T-lymphocytes assist B-lym-

phocytes in producing antibody and assist killer T-lymphocytes in their attack on foreign substances. The helper T-lymphocyte "helps" or enhances the function of B-lymphocytes, causing them to produce more antibodies more quickly and switch from the production of IgM to IgG and IgA.

Suppressor T-lymphocytes suppress or turn off helper T-lymphocytes. Without suppressor cells, the immune system would keep working even after an infection had been cured and over react to the infection. Together, helper and suppressor T-lymphocytes act as the thermostat of the lymphocyte system to keep it turned on just enough - not too much and not too little.

PHAGOCYTES: Phagocytes are specialized cells of the immune system whose primary function is to ingest and kill microorganisms. These cells, like the others in the immune system, develop from primitive “stem” cells in the bone marrow. When mature, they migrate to all tissues of the body but are especially prominent in the bloodstream, spleen, liver, lymph nodes, and lungs.

There are several different types of phagocytic cells. Polymorphonuclear leukocytes (neutrophils or granulocytes) are found in the bloodstream and can migrate into sites of infection within a matter of minutes. It is this phagocytic cell that increases in number in the blood steam during infection and is in large part responsible for an elevated white blood cell count during infection. It also is the phagocytic cell that leaves the bloodstream and accumulates in the tissues during the first few hours of infection, and is responsible for the formation of “pus.”

Monocytes, another type of phagocytic cell, are also found circulating in the bloodstream. They also line the walls of blood vessels in organs like the liver and spleen. Here they capture microorganisms as they pass by in the blood. When monocytes leave the bloodstream and enter the tissues, they change shape and size and become macrophages.

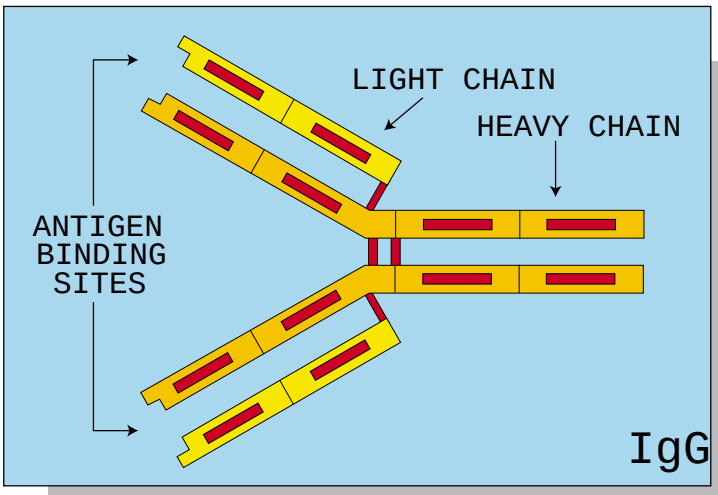
Phagocytic cells serve a number of critical functions in the body’s defense against infection. They have the ability to leave the bloodstream and move into the tissues to the site of infection. Once at the site of infection, they ingest the invading microorganisms. Ingestion of microorganisms by phagocytic cells is made easier when the microorganisms are coated with either antibody or complement or both. Once the phagocytic cell has engulfed or ingested the microorganism, it initiates a series of chemical reactions within the cell which result in the death of the microorganism.

COMPLEMENT: The complement system is composed of 18 serum proteins, which function in an ordered and integrated fashion to defend against infection and produce inflammation. Some proteins in the complement system are produced in the liver, while certain phagocytic cells, the macrophages, produce others.

The complement components must be converted from inactive forms to activated forms in order to perform their protective functions. In some instances, microorganisms must first combine with antibody in order to activate complement. In other cases, the microorganisms can activate complement without the need for antibody. As mentioned above, one of the proteins of the complement system coats microorganisms to make them more easily ingested by phagocytic cells. Other components of complement act to send out chemical signals to attract phagocytic cells to the sites of infection.

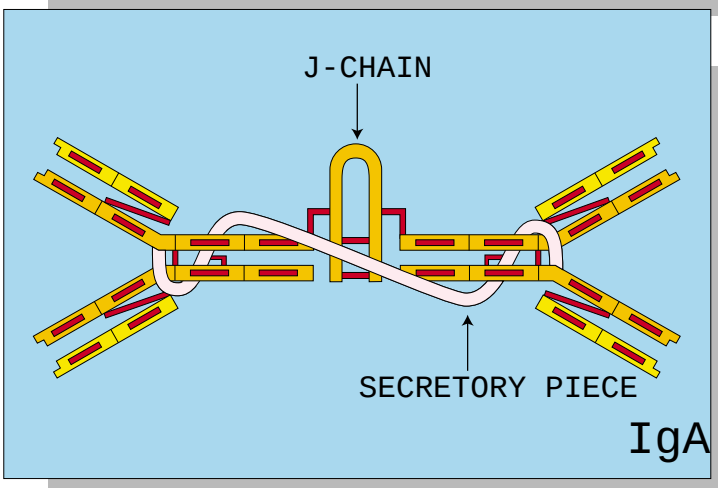
IMMUNOGLOBULIN STRUCTURE

Each class or type of immunoglobulin shares properties in common with the others. They all have antigen binding sites which combine specifically with the foreign antigen.



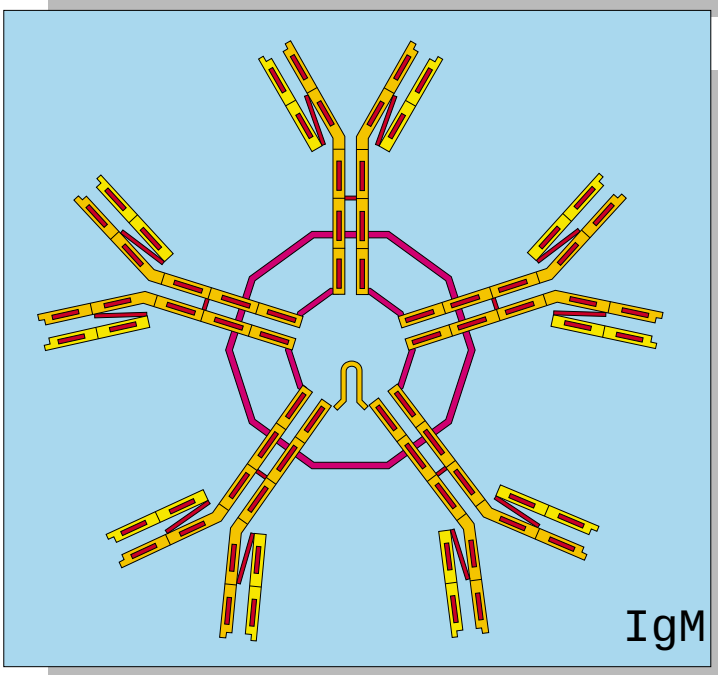
IgG

IgG is the major immunoglobulin class in the body and is found in the blood stream as well as in tissues.



SECRETORY IgA

Secretory IgA is composed of two IgA molecules joined by a J-chain and attached to a secretory piece. These modifications allow the secretory IgA to be secreted into mucus, intestinal juices and tears where it protects those areas from infection.



IgM

IgM is composed of five immunoglobulin molecules attached to each other. It is formed very early in infection and activates complement very easily.

When the entire system is assembled on the surface of some microorganisms, a complex is created which can puncture the microorganism and cause it to burst.

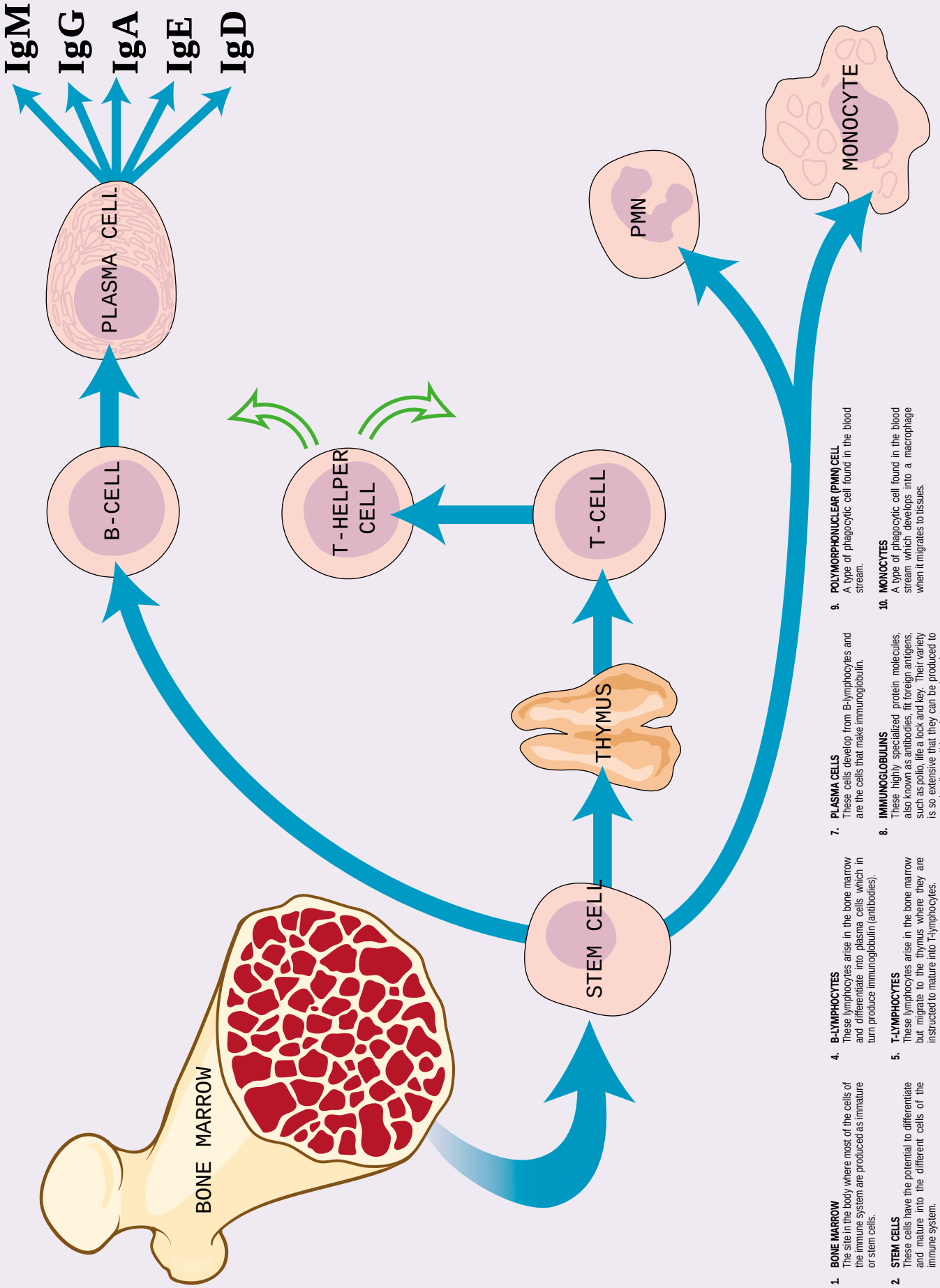
THE IMMUNE SYSTEM AND PRIMARY IMMUNODEFICIENCY DISEASES

When part of the immune system is either absent or its function is hampered, an immune deficiency disease may result. An immune deficiency disease may be caused either by an intrinsic (inborn) defect in the cells of the immune system or an extrinsic environmental factor or agent may damage the immune system. In the former case, the immune deficiency disease is a primary immune deficiency disease. When the damage is caused by an extrinsic force, such as an environmental factor or agent, it is called a secondary immune deficiency disease. For example, AIDS is a secondary immune deficiency disease caused by the HIV virus. Secondary immune deficiencies can also be caused by irradiation, chemotherapy, malnutrition, and burns. The secondary immune deficiencies are not discussed in this book.

The Primary Immunodeficiency Diseases are a group of disorders caused by basic defects in immune function that are intrinsic to, or inherent in, the cells and tissues of the immune system. There are nearly 100 primary immune deficiency diseases. Some are relatively common, while others are relatively rare. Although there are some that affect a single cell or protein of the immune system, others may affect more than one component of the immune system. Although primary immune deficiency diseases may differ from one another in many ways, they share one important feature. They all result from a defect in one of the functions of the normal immune system.

The primary immune deficiencies result from defects in T-lymphocytes, B-lymphocytes, phagocytic cells or the complement system. Most of them are inherited diseases and may run in families, such as X-linked agammaglobulinemia (XLA) or Severe Combined Immunodeficiency (SCID). Other primary immune deficiencies, such as Common Variable Immunodeficiency (CVID) and Selective IgA Deficiency do not appear to be inherited in a clear cut or predictable fashion. In these disorders the cause is unknown but the interaction of genetic and environmental factors may play a role in their causation.

Because one of the most important functions of the normal immune system is to protect us against infection, patients with primary immune deficiency diseases commonly have an increased susceptibility to infection. This increased susceptibility to infection may include too many infections, infections that are difficult to clear up, or unusually severe infections. The infections may be located in the sinuses (sinusitis), the bronchi (bronchitis), the lung (pneumonia) or the intestinal tract (infectious diarrhea). Another function of the immune system is to discriminate between the individual ("self") and foreign material (“non-self”), such as microorganisms, pollen or even a transplanted kidney from another individual. In some immune deficiency diseases, the immune system is unable to discriminate between "self" and (non-self). Therefore, in addition to an increased susceptibility to infection, patients with immune deficiencies may have autoimmune diseases



1. **BONE MARROW**
The site in the body where most of the cells of the immune system are produced as immature or stem cells.

2. **STEM CELLS**
These cells have the potential to differentiate and mature into the different cells of the immune system.

3. **THYMUS**
An organ located in the chest which instructs immature lymphocytes to become mature T-lymphocytes.

4. **B-LYMPHOCYTES**
These lymphocytes arise in the bone marrow and differentiate into plasma cells which in turn produce immunoglobulin (antibodies).

5. **T-LYMPHOCYTES**
These lymphocytes arise in the bone marrow but migrate to the thymus where they are instructed to mature into T-lymphocytes.

6. **T-HELPER LYMPHOCYTES**
These specialized lymphocytes "help" other T-lymphocytes and B-lymphocytes to perform their functions.

7. **PLASMA CELLS**
These cells develop from B-lymphocytes and are the cells that make immunoglobulin.

8. **IMMUNOGLOBULINS**
These highly specialized protein molecules, also known as antibodies, fit foreign antigens, such as polio, life a lock and key. Their variety is so extensive that they can be produced to match all possible microorganisms in our environment.

9. **POLYMORPHONUCLEAR (PMN) CELL**
A type of phagocytic cell found in the blood stream.

10. **MONOCYTES**
A type of phagocytic cell found in the blood stream which develops into a macrophage when it migrates to tissues.

in which their immune system attacks their own cells or tissues as if they were foreign or "non-self".

Primary immune deficiency diseases can occur in individuals of any age. The original descriptions of these diseases were in children, but as medical experience has grown many adolescents and adults have been diagnosed with primary immune deficiency diseases. This is in part due to the fact that some of the disorders, such as Common Variable Immunodeficiency Disease and Selective IgA Deficiency, may have their initial clinical presentation in adult life. But it is also due to the fact that effective therapy exists for nearly all of the disorders and patients diagnosed in infancy and childhood now reach adult life as productive members of society.

Finally, the primary immune deficiency diseases were originally felt to be very rare. However, they are more common than originally thought. In fact, Selective IgA deficiency, occurs as often as 1/500 individuals, translating into 500,000 patients in the United States alone.