VIII. IMMUNE (LYMPHOID) SYSTEM

INTRODUCTION

CN. Use green for D, the same colors for bone marrow (A) and thymus (B) used on Plate 83, and very light colors for H-L. (1) The structures depicting mucosal associated lymphoid tissue (E) are generalizations: more accurate representations can be seen on Plate 89. (2) The three lymphocyte types have identifying letters drawn into their nuclei. Color over the entire cell in all cases.

PRIMARY ORGANS:

BONE MARROW

THYMUS

The lymphoid system is the anatomical component of the immune system, and functions in defense against microorganisms entering the body as well as the destruction of cells or cell parts no longer recognizable as "self." Lymphoid tissues and organs are predominantly collections of lymphocytes and related cells (see below) often supported by a meshwork of reticular fibers and cells.

The red bone marrow and thymus are primary lymphoid organs. The bone marrow contains the precursors of all lymphocytes and disperses lymphocytes into the circulation. It consists largely of great varieties of blood cells in various stages of maturation, phagocytes, reticular cells and fibers, and fat cells. Some of the lymphocytes mature and undergo structural and biochemical revision (differentiation) in the bone marrow to become B lymphocytes. Some undifferentiated lymphocytes migrate via the blood to the thymus to become T lymphocytes before re-entering the circulation. Others become large lymphocytes, enter the circulation, and migrate to secondary lymphoid organs.

The thymus is located in the superior and anterior (inferior) mediastinum. It receives uncommitted lymphocytes from the bone marrow. The thymus is actively engaged in T lymphocyte proliferation and differentiation during embryonic and fetal life as well as the first decade of extrauterine life. The thymus begins to undergo degeneration (involution) after puberty.

SECONDARY ORGANS:

SPLFEN

LYMPH NODE

MUCOSAL ASSOCIATED LYMHOID TISSUE (MALT)

TONSILLI/ADENOID

APPENDIX

Secondary lymphoid organs are structures predominantly populated by lymphocytes that migrated from the primary lymphoid organs. The structural arrangement of these organs ranges from encapsulated, complex structures, like the spleen and lymph nodes, to a diffuse disposition of lymphocytes throughout the loose connective tissues (mucosal associated lymphoid tissue). These secondary organs are not a site for lymphocytic activation when challenged by antigens. The spleen processes incoming blood. Its lymphocytes and phagocytes react rapidly to the presence of microorganisms and aged red blood corpuscles. Lymph nodes screen lymph from incoming (afferent) lymphatic vessels, much in the same manner as the spleen processes blood. Diffuse and nodular masses of lymphoid tissue in the mucosal lining of open cavities constitute mucosal associated lymphoid tissue (MALT). Such tissue includes tonsils and adenoids situated close to the epithelial layer at portals of entry to certain open (nasal, oral, and pharyngeal) cavities. They are active in "marking" incoming microorganisms for subsequent destruction. Uncapsulated masses of lymphocytes and related cells occur in varying concentrations throughout the mucosa, forming distinct masses (diffuse lymphoid tissue). The vermiform appendix incorporates multiple lymphoid follicles in its mucosa. The density of these cell collections varies with the degree of immune responsiveness required.

CELLS:

B LYMPHOCYTE

PLASMA CELL

T LYMPHOCYTE

LARGE LYMPHOCYTE

PHAGOCYTE

Activated B lymphocytes (B, bone marrow-derived) differentiate along specific lines, one of which is the transformation into plasma cells. Both cells secrete protein molecules, called antibodies, into the tissue fluids. Antibodies interact with and enhance the destruction of elements that induced their activation and synthesis. Such elements are called antigens. The term antigen is restricted to those elements (molecules, cells, microorganisms) that induce activation of lymphocytes (immune response). T lymphocytes (T, thymus-derived) differentiate, upon stimulation by antigen, into one of a number of different activated cells, one of which stimulates and regulates specific and non-specific body defense operations (helper function; T H, cell).

Large, granular lymphocytes (natural killer or NK cells) destroy tumor cells or cells infected with virus. They can be activated by T lymphocytes to lyse target cells, as in graft rejection. Mononuclear phagocytes are cells that destroy phagocytosis antigen as well as particles that do not induce an immune response. They present antigen to lymphocytes (antigen-presenting cells) for identification and destruction.
White blood cells (WBCs, leukocytes) defend the body against foreign infections (bacteria, viruses). Most WBCs originate in the bone marrow from undifferentiated stem cells. Lymphocytes, which develop in the lymphatic organs (thymus, spleen, lymph nodes), and neutrophils, eosinophils, and basophils, are produced in the bone marrow.

**Granulocytes** are 60-70% of WBCs. They include neutrophils, eosinophils, and basophils. Neutrophils are the predominant type of granulocyte. They are phagocytic and involved in the innate immune response. Eosinophils are involved in allergic reactions and parasitic infections. Basophils are involved in allergic reactions and release histamine.

**Monocytes** are 3-8% of WBCs. They are larger than neutrophils and can migrate through tissue barriers. Monocytes can differentiate into macrophages, which are involved in phagocytosis and antigen presentation.

**Phagocytes** engulf bacteria and digest them within their lysosomes.

**Natural Immunity** is a non-specific response involving inflammation and phagocytosis.

1. **Tissue Damage**
2. **Microbes Enter Body**
3. **Mast Cells Release Histamine**
4. **Vasodilation**
5. **Protein Permeability**
6. **Fluid Swells Tissue**
7. **Diapedesis of Neutrophils**
8. **Phagocytosis of Microbes**
9. **Monocytes Follow**
10. **Death of Microbes**
11. **Pus Sac Develops**
12. **Tissue Repair**

After an injury (1), bacteria invade tissue space (2). Local mast cells release histamine (3), promoting vasodilation (4) and vascular permeability. Plasma proteins and fluids flow in (5), causing local edema (6). Fibroblasts and macrophages (7) begin phagocytosis (8). In severe infections, macrophages (9) transform into tissue macrophages and help engulf bacteria (10). A pus sac develops (11) and is either extruded or gradually cleared away during tissue repair (12).
TYPES AND GENERAL FUNCTIONS OF WHITE BLOOD CELLS. Although there are several types of white blood cells (WBCs, leukocytes) and they vary in morphology, they all share a common function: helping to defend the body against foreign microbial infections. On the basis of the presence or absence of specific granules in their cytoplasm, white blood cells are divided into granulocytes (those with granules, i.e., neutrophils, eosinophils, and basophils) and agranulocytes (those without granules, i.e., monocytes, macrophages, and lymphocytes). Functionally, white blood cells may be divided into two broad categories: (1) those that participate in nonspecific innate immune responses to infections and inflammations caused by tissue injury; and (2) those that take part in the acquired immune responses. Lymphocytes participate mainly in the second category; other white cells take part in the first.

Members of the family of granulocytes and agranulocytes originate in the bone marrow, where they are formed by the proliferative division of committed stem cells. Upon entry in the circulation, most of the WBCs participate in the inborn and nonspecific defensive reactions to invading infectious agents as well as in response to tissue injury and inflammation. The less numerous lymphocytes (they have no granules) originate from another line of stem cells that reside either in the bone marrow or in parts of the lymphatic system. Upon formation, the immature lymphocytes temporarily migrate into certain lymphatic organs (lymph nodes, thymus), where they differentiate and mature, becoming specialized to carry out their major function: defending the body against invading microorganisms through acquired immune reactions.

Various types of white blood cells are present in different proportions in the blood. Granulocytes are more numerous than agranulocytes. Among granulocytes, neutrophils are the most abundant cells; among the agranulocytes, lymphocytes outnumber the others.

NATURAL (NONSPECIFIC) IMMUNITY. To understand the functions of granulocytes and the phagocytic agranulocytes, we will consider their responses to tissue injury. Upon injury to the protective epithelial tissue covering the body, microbes (e.g., bacteria) enter the body, release their toxins, and create local infection. This stimulates the mast cells (which resemble the basophils but reside in tissues) to release their granules containing heparin and histamine within the tissue spaces. Nearby basophils may do the same in the blood. Heparin may prevent blood coagulation; histamine causes vasodilatation and increased permeability of the local blood vessels to blood proteins and blood cells. Blood proteins and fluids leak into the injured site, causing edema or swelling.

Gradually, the fluid in the swelling clots, trapping the bacteria and preventing their further penetration into the body.

At this time, the tissue macrophages, found permanently residing in many tissues like skin and lungs, attack the microbes and destroy them by phagocytosis. For this reason, the tissue macrophages are called the first line of defense. Phagocytosis consists of engulfing the microbes via the formation of the pseudopods followed by endocytosis of the phagocytic vesicle. Next, the endocytic vesicle is incorporated into the lysosomes of the phagocytes, where the microbe is digested by lysosomal enzymes. If infection persists, the neutrophils are attracted to the injury site. Indeed, a few hours after injury, the number of neutrophils increases by several fold in the blood and particularly near the infection site. The neutrophils squeeze through the spaces between the capillary endothelial cells by forming filopodia and displacing themselves (diapedesis). Once inside the injured site, the neutrophils begin to phagocytize the microbes in the same manner as the tissue macrophages. Neutrophils make up the second line of defense.

If the tissue macrophages and neutrophils do not adequately counter the infection, then the agranular monocytes move into the injury site in the same manner as the neutrophils. Monocytes are initially small and incapable of phagocytosis. Within an hour after leaving the blood, they enlarge, attaining a shape like the tissue macrophages. Then they begin to phagocytize the microbes and the dead neutrophils. Monocytes may in fact be the source of new tissue macrophages, which die after phagocytosis. The monocytes are called the third line of defense. Usually, these three lines of defense are sufficient to eliminate the source of infection.

During the course of these anti-infectious and inflammatory responses, the number of white cells (particularly the phagocytes) in the blood increases. This is caused by humoral factors released from the injured tissue and/or certain white cells. As a result, permeability of blood sinuses in the bone marrow increases, releasing fresh neutrophils and monocytes into the blood. The phagocytes find their way to the site of injury by chemotaxis or similar guiding mechanisms.

Gradually, the fibroblast cells of the connective tissue proliferate, sealing off the injured tissue to begin repair. A pus sac, containing fluid, dead cells, and dead microbes, forms. This pus is either extruded or gradually cleared off by the macrophages. If these nonspecific rapid natural defense reactions are not sufficient to eliminate the infection, the toxin intrusion in the blood activates other defensive responses such as the fever reaction and, more effectively, lymphocyte reactions, which lead to acquired immune responses (see plate 140).

CN: Use red for A, purple for J. Lightest colors for structures C-H. Dark colors for I, K, and N.
1. Color the various white blood cells at the top of the page, beginning with their origin in red bone marrow (A).
2. Color the nonspecific response to a microbe invasion, following the numbered titles. When coloring the second and third boxes, color in the background or larger structures before coloring the smaller ones, such as proteins (K) or microbes (I). Note that for number 3, color the tiny histamine molecules as well as the mast cell (E'). Color the numeral 6, but not the arrow representing the movement of fluid into the tissues.
3. Color the enlargement of phagocytosis and the macrophage action below it.
HIV-INFECTED IMMUNOSUPPRESSION

Effects of AIDS on:

T lymphocytes
Memory cells
Phagocytes
Inflammatory response
Antigens
Neurotransmitters
B lymphocytes
Memory cells
Plasma cells
Antibodies
Large lymphocytes
Mitotic regulation

At this time (early 1993), a catastrophic disease, called Acquired Immunodeficiency Syndrome (AIDS), is being experienced throughout the world, characterized by a marked reduction in functions of immune cells (immunosuppression). The disease is caused by an infection of phagocytes and lymphocytes with human immunodeficiency virus (HIV). The virus is transmitted from one person to another via body fluids, mainly blood and semen. Transmission is effected by male homosexual/bisexual activity (70%), intravenous drug use with shared, blood-contaminated syringes (17%), heterosexual intercourse with HIV-infected partners (4%), intravenous blood transfusions (2.5%), and transmission from infected mother to fetus by HIV transfer across placental membranes (7%).

Once in the body fluids, HIV surface molecules (glycoprotein or GP 120) attach to specific (CD4) receptors on the surface of the cell membranes of T lymphocytes and mononuclear phagocytes. Fusion of the virus to the cell and endocytosis of the virus (infection) usually follow. Infection then converts its genetic material (RNA) into DNA by means of an enzyme called reverse transcriptase attached to the viral RNA. This new viral DNA segment is then incorporated into the DNA of the host cell. This integrated DNA is called proviral DNA. It is capable of producing viral RNA which provides the "blueprint" (instructions) for the synthesis of viral proteins in the host cell, and the subsequent construction of intermediate virus (viral particles, virions). At any point prior to or after formation of the viral proteins, the production of pro-viral materials may be suspended (latency) or at least progression of the manifestations of the disease seems to slow. Two to ten years may pass during which the normal activities of daily living can be carried on without the symptoms/signs of life-threatening immunosuppression. When infected cells disburse the viral particles to other T cells or phagocytes, or when those infected cells cease responding to antigenic stimuli, the disease becomes activated (AIDS).

Immune function is initially suppressed due to the destruction of T lymphocytes by the infective process and the rapid depletion of cellular immunity (2-12), T memory cells decline in numbers, and related antigen memory is impaired (2), T cell-enhanced phagocytosis is diminished (3) and inflammatory responses are limited (4). Permitting an increase in antigen numbers and activity (5). Phagocytes of the brain and spinal cord (microglia) are particularly prone to HIV infection, resulting in defective neurotransmitter functions, memory loss and other neurologic deficits (encephalopathy) (6). B lymphocytes fail to proliferate in response to antigen (7) due to depleted T cell-related stimuli, sharply reducing their numbers and those of B memory cells (8), plasma cells (9) and antibodies (10). Large lymphocytes are reduced both in number and activity (11), disabling mitotic regulation (12) and permitting formation of neoplasms (cancer). The global effect of immunosuppression is the microorganism access to the unprotected body (opportunist infections). Many of these infections themselves are immunosuppressive. Early in the course of AIDS, it is not unusual to see the lymphoid cells respond rapidly to these infections with increased immune cell and antibody production; unfortunately, many of these activated cells are themselves infected. In summary, HIV infection leads to decreased numbers and functions of helper T cells and phagocytes which, in turn, adversely affect many aspects of acquired and natural immunity, resulting in infections, tumors, neurologic dysfunction, and wasting.
NATURAL IMMUNITY:

Anatomic Barrier:
Complement:
Phagocyte:
Inflammatory Response:

Immunity is an anatomic and physiologic state of security against disease. Natural immunity exists independent of any specific microorganismal interaction with a lymphocyte. Shortly before birth and following, one progressively acquires a specific immunity following each lymphocyte's encounter with antigen and resulting activation. Phagocytes participate in both natural and acquired immunity; lymphocytes participate in acquired immunity and enhance natural immunity.

Natural immunity operates indiscriminately against microorganisms and degenerated cells/cell parts. Anatomic barriers (1), such as skin, mucous membranes, physically resist microorganismal invasion. Phagocytes approach their prey from the blood (2) or connective tissues (3), engulf them (4, phagocytosis) and destroy them with lysosomal enzymes (5). Complement is the name given to several soluble proteins found in the body fluids which when activated attach to microorganisms, enhancing their phagocytosis. Tissue irritation, e.g., disruption by a splinter, induces an inflammatory response which involves both natural and acquired immunity.

ACQUIRED IMMUNITY:

Acquired immunity involves diverse but specific lymphocyte responses to the presence of antigen. A specific lymphocytic reaction to antigens (immune response) is characterized by the activation and proliferation of lymphocytes followed by the destruction of antigens. Two kinds of acquired immunity are possible based on lymphocyte types: humoral immunity and cellular immunity. Inherent in both kinds of immunity are: specificity and diversity of response, retention of cellular memory of antigen, and the ability to recognize self from non-self among the body's proteins.

HUMORAL IMMUNITY:

B Lymphocyte
Plasma Cell
Antibody

Humoral (fluid-related) immunity is characterized by B lymphocytes being activated by antigen (1), proliferating, forming memory (M) cells, secreting antibody (2), and forming plasma cells (3) which secrete antibody (4). Antibodies are complex proteins formed in response to a specific antigen and attached to it at the antigenic determinant site (5), facilitating phagocytosis.

CELLULAR IMMUNITY:

T Lymphocyte
Helper cell (Th)
Cytolytic cell (Tc)

Cellular immunity is characterized by T lymphocytes being activated by antigens attached to antigen presenting cells (phagocytes, 1). Activated T cells differentiate into helper T lymphocytes (Th) and cytolytic T lymphocytes (Tc, CTL). Helper T lymphocytes (2) enhance humoral immunity by activating B cells, augment the inflammatory response, activate phagocytes with stimulating factors (lymphokines), and form memory (M) cells. Cytolytic T lymphocytes (3) bind to and destroy infected cells, and form memory cells. Memory cells recognize specific structural characteristics of the antigens encountered ("memory") and facilitate rapid immune responses on subsequent exposure to those antigens.
ACQUIRED IMMUNITY: SPECIFIC ANTIBODY RESPONSE

MICROBE ANTIGEN, B-LYMPHOCYTE, AG-RECEPTOR, PLASMA CELL, CLONE

ANTIBODY, BLOOD CIRCULATION, MEMORY CELL

Antigens (AGs) are protein or polysaccharide substances on the surface of microbes or foreign cells entering the body (1). In the lymph nodes, AGs are detected by receptors on B-lymphocytes (BCs) (2). Each BC is genetically programmed to respond to one particular AG. Sensitized BCs transform into plasma cells (PCs) (3). PCs divide, forming a clone (4). The clone produces antibody (AB) (5), rapidly and profusely. Each AB is specific for an AG. The AB circulates in the lymph and blood, attaching to and deactivating AG (6). AB can inactivate AG either directly—or indirectly by activating the complement system (7), a cascade of enzyme reactions in the plasma that will facilitate direct actions of AB as well as promote chemotaxis and inflammatory responses, causing lysis or phagocytosis of AG cells.

During sensitization, some PCs transform to memory cells (MCs). These remain dormant in the lymph nodes. Upon further exposure to the AG, MCs will evoke a pronounced, exaggerated response (AB production) that will rapidly deactivate AGs. The MC response is the basis of immunization and vaccination practices.

ACQUIRED IMMUNITY: CELL-MEDIATED RESPONSE

TISSUE PIECE, T-LYMPHOCYTE, SENSITIZED T-CELL, KILLER T-CELL, AG-RECEPTOR, LYSOSOME, HELPER T-CELL, LYMPHOKINES, SUPPRESSOR T-CELL

The AG on slow-acting bacteria (tuberculosis), fungi, cancer cells, and cells of transplanted tissue (1) sensitize another type of lymphocyte, i.e., T-cells (TC) (2). Sensitized TCs proliferate (3), forming several subtypes. Killer (Cytotoxic) TCs (4) contain AB-like molecules (receptors), enabling them to bind with AG on foreign cells. After attachment, TCs swell, producing lysosomes, which will be injected into the antigenic cell (5), causing its death (e.g., rejection of transplant). Another TC type, the helper TC (6), enhances AB production by BC (7). Helper TCs may also produce lymphokines, strong AB-like substances (8). The suppressor TC (9) opposes the action of the helper TC, homeostatically regulating immune responses.
In contrast to phagocytes, the lymphocytes participate in a more complicated type of immune response that develops slowly and specifically against particular foreign substances (antigens). This response is expressed only after exposure to the antigen (hence the term acquired immunity), although the ability to respond to specific types of antigen is genetically programmed. There are two categories of acquired immune responses, each mediated by a different family of lymphocytes: humoral- or antibody-mediated and cell-mediated.

ANTIBODY-MEDIATED RESPONSE: FUNCTIONS OF B-LYMPHOCYTES. Let us assume that a certain bacteria penetrates the blood after an injury. The bacterial wall contains proteins or polysaccharides, which are foreign to the body and considered harmful. These substances are called antigens, and their presence is sensed by special receptor molecules located on the surface of a certain types of circulating lymphocytes called the B-lymphocytes. (The "B" comes from Bursa of Fabricus, an avian lymph organ generating these cells; the source of B-cells in the human body is probably the bone marrow.) Each type of B-lymphocyte contains only one kind of antigenic receptor and can respond to only one type of antigen.

In the lymph nodes, the intruding antigen is sensed by the B-cells, which become sensitized and transform to a larger secretory type of cell called the plasma cell. The plasma cell then proliferates, forming a clone, and all the cells in the clone synthesize a specific protein molecule called the antibody, which is secreted to the plasma. Upon encountering the antigen, the antibodies bind with the antigen molecules and deactivate them. This whole process takes from days to weeks to develop.

After the antigens are deactivated, the antibodies usually diminish in number. However, upon second exposure to the same antigen, the body's antibody production is often more rapid and more intense, as though the immune system has "learned" to deal with this particular antigen more efficiently. This enhanced response is due to a particular type of plasma cell called the memory cell. B-cells produce memory cells upon their first exposure to the antigen. Memory cells learn how to produce the antibody but do not do so at first. Instead, they rest until the second exposure to the same antigen, whereupon they become activated rapidly and form numerous clones to produce large amounts of the antibody. The memory cells are involved in immunization by vaccination. Here the body is intentionally exposed to a small amount of dead or transformed antigen (e.g., dead smallpox virus) in order to sensitize the immune system and form memory cells. When the body is exposed to the same antigen later (e.g., during a real smallpox infection), antibody production will be quick and intense.

BIOCHEMISTRY OF THE ANTIBODY-ANTIGEN REACTION. All the antibodies produced against the many different antigens are protein molecules (immunoglobulins, Ig) possessing both common and diverse features. Each antibody is roughly Y-shaped, consisting of heavy chains and two light chains. The heavy chains provide the constant part of the antibody, which is the same in all antibodies; the light chains, located in the arms of the Y (attached to the heavy chains), constitute the variable and functionally significant part of the molecule. Thus, each antibody has two sites, one on each of the variable arm, for interaction with the antigen. Antibodies can deactivate antigens by direct combination, causing precipitation (agglutination) or by masking the active sites of the antigens. Antibodies can also achieve the same goals indirectly by activating the complement system, which consists of a series of enzymes arranged to catalyze a cascade of chemical events. The combination of a single antibody molecule with the antigen activates this cascade, which rapidly mobilizes millions of enzymes that quickly lyse the microorganism to which the antigen is attached or cause agglutination and similar defensive reactions.

CELL-MEDIATED IMMUNITY: FUNCTIONS OF T-LYMPHOCYTES. Another family of lymphocytes known as T-lymphocytes ("T" for thymus) participates in acquired immune responses by directly attacking and destroying foreign cells. T-cells responses are involved in defense against the slow-acting bacteria such as tuberculosis and against fungal infections. T-cells are also involved in rejecting transplanted organs and eliminating cancer cells in the body.

When a tissue from one organism is transplanted into another organism (even of the same species), the antigenic substances in the transplant sensitize certain T-cells within the host's lymph nodes. The sensitized T-cells proliferate, transforming into a family of T-cells. The most important of these is the cytotoxic or killer T-cell. This cell contains on its surface antibody like substances (antigen receptors) that recognize and bind with the surface antigens of foreign cells (the transplant). Next the killer T-cell infuses lysosomal enzymes into the foreign cell, causing its lysis and death. In general, T-cell-mediated immunity is based upon the differentiation (recognition) of self antigens normally present in the host's body cells from nonself antigens present in the foreign cells and cancer cells. This ability to differentiate the self from nonself is acquired early in life (fetal-neonatal periods) when the precursor cells of T-cells migrate into the thymus gland and inhabit this lymphatic organ for a while. Thymus removal in early life, but not in adulthood, causes severe T-cell-mediated immune deficiency. Indeed, the adult thymus becomes fatty and atrophic. T-cell number is greatly deficient in victims of AIDS (Acquired Immune Deficiency Syndrome).

CN: Use the same colors as on the previous page for microbe/antigen (A). Use red for blood circulation (H), though the portion shown in the box in the upper left corner is actually a capillary site that normally receives purple colors (as on the previous page). The lymph node (C) receives the same color as lymphocyte on the previous page, but the B- and T-lymphocyte cells on this page will receive two different colors.

1. Start with the upper panel and follow the numbered sequence, beginning in the upper left rectangle. Color the lymph production and storage sites in the body. Color the diagrammatic material on antibodies and the complement system. When coloring the immunization chart, note that the memory cell (G), shown in the large lymph node at the top of the plate, is responsible for the increase in antibodies.