**BLOOD AND BODY FLUIDS**

**BODY FLUIDS**
- More than 2/3 of body weight.
- Significant in:
  - Homeostasis
  - Transport mechanism
  - Metabolic Reactions
  - Texture of Tissues,
  - Temperature regulation
- Made up of two compartments:
  - Intracellular Fluid (ICF) = 22 L (55%).
  - Extracellular Fluid (ECF) = 18 L (45%)
- Composed of organic and inorganic substances.

**Fluid Pathophysiology**
- **Dehydration** is excessive lost of water
  - Either mild, moderate or severe, or
  - Can be isotonic, hypertonic, & hypotonic
  - Caused by various factors with different symptoms and can be treated by oral rehydration Therapy (ORT)
- **Water Intoxication** is too much water.
  - Caused by imbalanced hemostasis due to various factors.
  - Have various signs and symptoms and can be treated by water restrictions and diuretics

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**Differences between ECF & ICF**

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**BLOOD**
- Connective Tissue in Fluid form
- Properties depend on color, volume, reaction & pH, specific gravity and viscosity.
- Composed of Blood Cells (erythrocytes, leukocytes, & thrombocytes) and plasma.

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**PLASMA PROTEINS**
- Plasma Proteins are:
  - Serum Albumin (4.7 g/dL)
  - Serum Globulin, (2.3 g/dL)
  - Fibrinogen (0.3 g/dL)
- Total Plasma Proteins = (7.3 g/dL)
- Albumin/Globulin (A/G) Ratio = 2.1
Properties of Plasma Proteins

- Molecular weights are:
  - Serum Albumin = 69 000
  - Serum Globulin = 156 000
  - Fibrinogen = 400 000
- Exert oncotic or colloidal pressure of 25 mm Hg.
- Specific gravity is 1.026.
- Have 1/6 Buffering action

Functions of Plasma Proteins

- Plasma proteins play important role in:
  - Coagulation of Blood
  - Defence Mechanism of the body
  - Transport Mechanism
  - Maintenance of Osmotic Pressure in the Blood.
  - Regulation of Acid-Base Balance
  - Viscosity of Blood
  - Erythrocyte Sedimentation Rate (ESR)
  - Suspension Stability of Red Blood Cell
  - Production of Trehpene Substances
  - Reserve Proteins

RED BLOOD CELLS (ERYTHROCYTES)

- Normal Value (4.5 million/cu mm in females and 5 million/cu mm in males)
- Normal Shape is biconcave
- Normal size is 7.7 um
- Normal structure has no nucleus and therefore no DNA and no mitochondrion
- Have Actin and Spectrin attached to Ankryin
- Lack of spectrin result in hereditary spherocytosis.

Properties of Erythrocytes

- RBCs pile up in Rouleaux Formation
- Specific gravity is 1.092 – 1.101
- Packed Cell Volume (PCV) or hematocrit value is 45 % (Blood) & 55% (plasma)
- Suspension Stability is uniform
- Lifespan is 120 days after which senile RBCs are destroyed by reticuloendothelial system
- Fate is the graveyard in the spleen

Functions of Red Blood Cells

- Major function of the transport of respiratory gases such as
  - Transport of Oxygen from the lungs to the tissues
  - Transport of Carbon Dioxide from the tissues to the lungs.
- Other functions include:
  - Buffering action in Blood, &
  - In Blood Group Determination

Variations in Number of Red Blood Cells

- Physiological Variations
  - Increase in RBCs Count (Polycythemia) can be due to Age, Sex, High Altitude, Muscle Exercise, Emotional Conditions, increased Environmental Temperature, & After Meals.
  - Decrease in RBCs Count can be due to High Barometric Pressures, During Sleep, and Pregnancy.
- Pathological Variations
  - Pathological Polycythemia
  - Primary Polycythemia – Polycythemias Vera
  - Secondary Polycythemia, &
  - Anemia
Variations in Size, Shape, & Structure of Red Blood Cells
- Variation in size of RBCs:
  - Microcytes – decrease in size
  - Macrocytes – increase in size
  - Anisocytosis – Cells without Uniform Size
- Variation in shape of RBCs can be due to:
  - Spherocytosis, elliptocytosis, sickle cell, & poikilocytosis.
- Variation in structure of RBCs:
  - Punctate Basophilism
  - Ring in RBC
  - Howell – Jolly Bodies

ERYTHROPOIESIS
- Process of origin, development, and maturation of RBCs
- In fetal life, it occurs in Mesoblastic, Hepatic, & Myeloid Stages
- In Newborn Babies, Children and Adults, RBCs are produced in the red bone marrow.

Process of Erythropoiesis
- Uncommitted pluripotent hematopoietic Stem Cell
- Committed pluripotent hematopoietic Stem Cell
- Lymphoid Stem Cell
- Colony Forming Blastocyte
- Colony Forming Unit-E
- Colony Forming Unit-GM
- Colony Forming Unit-M
- Granulocytes
- Megakaryocyte
- Erythroblasts
- Neutrophils
- Basophils
- Eosinophils
- RBCs

Stages of Erythropoiesis
1. Proerythroblast
2. Early Normoblast
3. Intermediate Normoblast
4. Late Normoblast
5. Reticulocyte
6. Mature Erythrocyte

Factors Necessary for Erythropoiesis
- General Factors:
  - Erythropoietin
  - Thyroxine
  - Hemopoietic growth factors,
  - Vitamins
- Maturation factors, &
  - Vitamin B12 (Cyanocobalamin)
  - Intrinsic factor of Castle
  - Folic Acid
- Factors necessary for hemoglobin formation.

Hormonal Control of Erythropoiesis
- Erythropoietin stimulates the production of erythrocytes in the bone marrow.
- Erythropoietin synthesis is regulated by the concentration of oxygen in the blood.
**Adult males (15 g/dL) and in adult females (14 g/dL)**

**Functions of Hemoglobin**
- Transport of Gases
  - Transport of oxygen from the lungs to the tissues
  - Transport of carbon dioxide from tissues to the lungs
- Buffer Action

**Types of Hemoglobin**
- There are two types of:
  - Normal Hemoglobin - HbA
  - Fetal Hemoglobin - HbF
- Abnormal Hemoglobin are pathologic mutant forms of hemoglobin.
  - Hemoglobinopathies (HbS, HbC, HbE, HbM)
  - Hemoglobin in thalassemia and related disorders (HbG, H,I, Bart’s, Kenya, Lepore and Constant Spring)
- Abnormal hemoglobin derivatives
  - Carboxyhemoglobin (3-5%)
  - Methemoglobin (<3%)
  - Sulfhemoglobin (Traces-undetectable)

**Hemoglobin & Iron Metabolism**
- Normal Hemoglobin contents Varies Depending upon sex and age
- At Birth (25 g/dL). After 3 months (20 g/dL). After 1 year (17 g/dL). From puberty onward (14 - 16 g/dL).
- Adult males (15 g/dL) and in adult females (14 g/dL)

**Structure of Hemoglobin**
- Hemoglobin
- Porphyrin
- Globin

<table>
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<th>Mol. Weight</th>
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<tr>
<td>β-chain</td>
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**Synthesis of Hemoglobin**
- Sucinyl CoA + Glycine → ALA synthase
- ALA → α,δ-Aminolevulinic acid
- Fe²⁺ + Copropryrinogen IX → Copropryrinogen III
- Copropryrinogen III → Heme + Globin

**Cytochrome**
- Heme + Globin

**Cytoplasm**
- 2 Molecules of δ-Aminolevulinic acid
- Mitochondrion
Dietary iron is available as Heme and nonheme iron in A B

Normal Values of ESR

- Westergren’s method
  - In males: 3 to 7 mm in one hour
  - In females: 5 to 9 mm in one hour
  - In Infants: 0 to 2 mm in one hour

- Wintrobe’s method
  - In males: 0 to 9 mm in one hour
  - In females: 0 to 15 mm in one hour
  - In Infants: 0 to 3 mm in one hour

Variations of ESR

- Physiological Variation
  - Age, Sex, Menstruation, & Pregnancy
- Pathological Variation
  - ESR increases in diseases such as Tuberculosis. All types of anemia (except Sickle Cell anemia), malignant tumors, Rheumatoid arthritis, Rheumatic fever, & liver diseases.
  - ESR decreases in the disease such as: Allergic conditions, sickle cell anemia, Polycythemia, & Leukocytosis

Significance of Determination of ESR

Assessment of Pulmonary Tuberculosis, Rheumatoid arthritis, Polymyalgia rheumatica and Temporal arteritis

Factors affecting ESR

- Specific gravity, Rouleaux formation, increase in RBCs size, viscosity, & RBCs count

PACKED CELL VOLUME AND BLOOD INDICES

- Packed Cell Volume (PCV) is the proportion of blood occupied by RBCs expressed in percentage.
- Determined by measurement and autoanalyzer.
- PCV is useful in diagnosis of some diseases
- Normal values of PCV: in males (40-45%), & in females (38-42%)
- PCV increases in Polycythemia, Dehydration and Denge Shock Syndrome.
- PCV increases in Anemia, Cirrhosis of the liver, pregnancy, & hemorrhage.

Blood Indices

- Used for diagnosis of anemia
- The various blood indices are:
  1. Mean Corpuscular Volume (MCV) = 90 cu. μ
  2. Mean Corpuscular Hemoglobin (MCH) = 30 Pg
  3. Mean Corpuscular Hemoglobin Concentration (MCHC) = 30%, &
  4. Color Index (CI) = 1.0
ANEMIA

- Blood disorder due to reduction in:
  1. RBCs count
  2. Hemoglobin content, &
  3. Packed Cell Volume
This is because of:
  1. Decrease in RBCs production
  2. Increase RBCs destruction, &
  3. Excess blood loss from the body

Classification of Anemia

Anemia is classified by two methods

A. Morphological classification,
   1. Normocytic Normochromic anemia
   2. Macrocytic Normochromic anemia
   3. Macrocytic Hypochromic anemia &
   4. Microcytic Hypochromic anemia

B. Etiological classification
   1. Hemorrhagic anemia (Acute and Chronic)
   2. Hemolytic anemia (Extrinsic and Intrinsic, sickle cell anemia, Thalassemia)
   3. Nutrition deficiency anemia (Iron deficiency, Protein deficiency, Pernicious or Addison’s anemia, & Megaloblastic anemia).
   4. Aplastic anemia, &
   5. Anemia of chronic disease

Signs and Symptoms of Anemia

- Paleness of skin
- Increase heart rate and cardiac output
- Increase in rate and force of respiration
- In the GIT
- Increase in BMR
- Disturbed kidney function
- Affects female reproductive process, &
- Various neuromuscular symptoms

HEMOLYSIS AND FRAGILITY OF RED BLOOD CELLS

- Image of various cell types affected by hemolysis

- Image of red blood cells in various stages of hemolysis
Leukocytes (WBCs)

- Leukocytes, the only blood components that are complete cells:
  - Are less numerous than RBCs
  - Make up 1% of the total blood volume
  - Can leave capillaries via diapedesis
  - Move through tissue spaces
  - Leukocytosis – WBC count over 11,000 per cubic millimeter
  - Normal response to bacterial or viral invasion

Leukocyte Disorders: Leukemias

- Leukemia refers to cancerous conditions involving white blood cells
- Leukemias are named according to the abnormal white blood cells involved
  - Myelocytic leukemia – involves myeloblasts
  - Lymphocytic leukemia – involves lymphocytes
- Acute leukemia involves blast-type cells and primarily affects children
- Chronic leukemia is more prevalent in older people
**Leukemia**
- Immature white blood cells are found in the bloodstream in all leukemias
- Bone marrow becomes totally occupied with cancerous leukocytes
- The white blood cells produced, though numerous, are not functional
- Death is caused by internal hemorrhage and overwhelming infections
- Treatments include irradiation, antileukemic drugs, and bone marrow transplants

**Platelets**
- Platelets are fragments of megakaryocytes with a blue-staining outer region and a purple granular center
- The granules contain serotonin, Ca^{2+}, enzymes, ADP, and platelet-derived growth factor (PDGF)
- Platelets function in the clotting mechanism by forming a temporary plug that helps seal breaks in blood vessels

**Genesis of Platelets**
- The stem cell for platelets is the hemocytoblast
- The sequential developmental pathway is hemocytoblast, megakaryoblast, promegakaryocyte, megakaryocyte, and platelets

**Hemostasis**
- A series of reactions designed for stoppage of bleeding
- During hemostasis, three phases occur in rapid sequence:
  - Vascular spasms — immediate vasoconstriction in response to injury
  - Platelet plug formation
  - Coagulation (blood clotting)

**Platelet Plug Formation**
- Platelets do not stick to each other or to the endothelial lining of blood vessels
- Upon damage to a blood vessel, platelets:
  - Are stimulated by thromboxane A_{2}
  - Stick to exposed collagen fibers and form a platelet plug
  - Release serotonin and ADP, which attract still more platelets
- The platelet plug is limited to the immediate area of injury by PGI_{2}

**Coagulation**
- A set of reactions in which blood is transformed from a liquid to a gel
- Coagulation follows intrinsic and extrinsic pathways
Coagulation

- The final three steps of this series of reactions are:
  - Prothrombin activator is formed
  - Prothrombin is converted into thrombin
  - Thrombin catalyzes the joining of fibrinogen into a fibrin mesh

**Chapter 16**

Blood

*Part C*

**Coagulation Phase 2: Pathway to Thrombin**

- Prothrombin activator catalyzes the transformation of prothrombin to the active enzyme thrombin

**Coagulation Phase 3: Common Pathway to the Fibrin Mesh**

- Thrombin catalyzes the polymerization of fibrinogen into fibrin
  - Insoluble fibrin strands form the structural basis of a clot
  - Fibrin causes plasma to become a gel-like trap
  - Fibrin in the presence of calcium ions activates factor XIII that:
    - Cross-links fibrin
    - Strengthens and stabilizes the clot

**Coagulation Phase 1: Two Pathways to Prothrombin Activator**

- May be initiated by either the intrinsic or extrinsic pathway
  - Triggered by tissue-damaging events
  - Involves a series of procoagulants
  - Each pathway cascades toward factor X
- Once factor X has been activated, it complexes with calcium ions, PF3, and factor V to form prothrombin activator
**Clot Retraction and Repair**

- Clot retraction – stabilization of the clot by squeezing serum from the fibrin strands
- Repair
  - Platelet-derived growth factor (PDGF) stimulates rebuilding of blood vessel wall
  - Fibroblasts form a connective tissue patch
  - Endothelial cells multiply and restore the endothelial lining

**Factors Limiting Clot Growth or Formation**

- Two homeostatic mechanisms prevent clots from becoming large
  - Swift removal of clotting factors
  - Inhibition of activated clotting factors

**Inhibition of Clotting Factors**

- Fibrin acts as an anticoagulant by binding thrombin and preventing its:
  - Positive feedback effects of coagulation
  - Ability to speed up the production of prothrombin activator via factor V
  - Acceleration of the intrinsic pathway by activating platelets
  - Thrombin not absorbed to fibrin is inactivated by antithrombin III
  - Heparin, another anticoagulant, also inhibits thrombin activity

**Factors Preventing Undesirable Clotting**

- Unnecessary clotting is prevented by the structural and molecular characteristics of endothelial cells lining the blood vessels
- Platelet adhesion is prevented by:
  - The smooth endothelial lining of blood vessels
  - Heparin and PG1, secreted by endothelial cells
  - Vitamin E quinone, a potent anticoagulant

**Hemostasis Disorders: Thromboembolic Disorders**

- Thrombus – a clot that develops and persist in an unbroken blood vessel
  - Thrombi can block circulation, resulting in tissue death
  - Coronary thrombosis – thrombus in blood vessel of the heart
  - Embolus – a thrombus freely floating in the blood stream
    - Pulmonary emboli can impair the ability of the body to obtain oxygen
    - Cerebral emboli can cause strokes

**Prevention of Undesirable Clots**

- Substances used to prevent undesirable clots include:
  - Aspirin – an antiprostaglandin that inhibits thromboxane A₂
  - Heparin – an anticoagulant used clinically for pre- and postoperative cardiac care
  - Warfarin – used for those prone to atrial fibrillation
  - Flavonoids – substances found in tea, red wine, and grape juice that have natural anticoagulant activity
**Hemostasis Disorders: Bleeding Disorders**

- Thrombocytopenia – condition where the number of circulating platelets is deficient
  - Patients show petechiae (small purple blotches on the skin) due to spontaneous, widespread hemorrhage
  - Caused by suppression or destruction of bone marrow (e.g., malignancy, radiation)
  - Platelet counts less than 50,000/mm³ is diagnostic for this condition
  - Treated with whole blood transfusions

- Hemophilia – hereditary bleeding disorders caused by lack of clotting factors
  - Hemophilia A – most common type (83% of all cases) due to a deficiency of factor VIII
  - Hemophilia B – results from a deficiency of factor IX
  - Hemophilia C – mild type, caused by a deficiency of factor XI
  - Symptoms include prolonged bleeding and painful and disabled joints
  - Treatment is with blood transfusions and the injection of missing factors

**Blood Transfusions**

- Transfusions are necessary:
  - When substantial blood loss occurs
  - In certain hemostasis disorders
  - Whole blood transfusions are used:
    - When blood loss is substantial
    - In treating thrombocytopenia
  - Packed red cells (cells with plasma removed) are used to treat anemia

**Human Blood Groups**

- RBC membranes have glycoprotein antigens on their external surfaces
  - These antigens are:
    - Unique to the individual
    - Recognized as foreign if transfused into another individual
    - Promoters of agglutination and are referred to as agglutinogens
  - Presence/absence of these antigens are used to classify blood groups

**Blood Groups**

- Humans have 30 varieties of naturally occurring RBC antigens
  - The antigens of the ABO and Rh blood groups cause vigorous transfusion reactions when they are improperly transfused
  - Other blood groups (M, N, Duffy, Kell, and Lewis) are mainly used for legalities
ABO Blood Groups

- The ABO blood groups consists of:
  - Two antigens (A and B) on the surface of the RBCs
  - Two antibodies in the plasma (anti-A and anti-B)
- An individual with ABO blood may have various types of antigens and spontaneously preformed antibodies
- Agglutinogens and their corresponding antibodies cannot be mixed without serious hemolytic reactions

Rh Blood Groups

- There are eight different Rh agglutinogens, three of which (C, D, and E) are common
- Presence of the Rh agglutinogens on RBCs is indicated as Rh⁺
- Anti-Rh antibodies are not spontaneously formed in Rh⁻ individuals
- However, if an Rh⁻ individual receives Rh⁺ blood, anti-Rh antibodies form
- A second exposure to Rh⁺ blood will result in a typical transfusion reaction

Hemolytic Disease of the Newborn

- Hemolytic disease of the newborn – Rh⁺ antibodies of a sensitized Rh⁻ mother cross the placenta and attack and destroy the RBCs of an Rh⁺ baby
- Rh⁻ mother become sensitized when Rh⁺ blood (from a previous pregnancy of an Rh⁺ baby or a Rh⁺ transfusion) causes her body to synthesize Rh⁺ antibodies
- The drug RhGAM can prevent the Rh⁻ mother from becoming sensitized
- Treatment of hemolytic disease of the newborn involves pre-birth transfusions and exchange transfusions after birth

Transfusion Reactions

- Transfusion reactions occur when mismatched blood is infused
- Donor’s cells are attacked by the recipient’s plasma agglutinins causing:
  - Diminished oxygen-carrying capacity
  - Clumped cells that impede blood flow
  - Ruptured RBCs that release free hemoglobin into the bloodstream
- Circulating hemoglobin precipitates in the kidneys and causes renal failure

Blood Typing

- When serum containing anti-A or anti-B agglutinins is added to blood, agglutination will occur between the agglutinin and the corresponding agglutinogens
- Positive reactions indicate agglutination

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Plasma Volume Expander

- When shock is imminent from low blood volume, volume must be replaced
- Plasma or plasma expanders can be administered
- Plasma expanders:
  - Have osmotic properties that directly increase fluid volume
  - Are used when plasma is not available
  - Examples: purified human serum albumin, plasminate and dextran
- Isotonic saline can also be used to replace lost blood volume.

Diagnostic Blood Tests

- Laboratory examination of blood can assess an individual’s state of health
- Microscopic examination:
  - Variations in size and shape of RBCs — predictions of anemias
  - Type and number of WBCs — diagnostic of various diseases
- Chemical analysis can provide a comprehensive picture of one’s general health status in relation to normal values

Lymphatic System: Overview

- Consists of two semi-independent parts
  - A meandering network of lymphatic vessels
  - Lymphoid tissues and organs scattered throughout the body
- Returns interstitial fluid and leaked plasma proteins back to the blood
- Lymph — interstitial fluid once it has entered lymphatic vessels

Lymphatic Vessels

- A one-way system in which lymph flows toward the heart
- Lymph vessels include:
  - Microscopic, permeable, blind-ended capillaries
  - Lymphatic collecting vessels
  - Trunks and ducts
Lymphatic Capillaries

- Similar to blood capillaries, with modifications
  - Remarkably permeable
  - Loosely joined endothelial minivalves
  - Withstand interstitial pressure and remain open
  - The minivalves function as one-way gates that:
    - Allow interstitial fluid to enter lymph capillaries
    - Do not allow lymph to escape from the capillaries

Lymphatic Trunks

- Lymphatic trunks are formed by the union of the largest collecting ducts
- Major trunks include:
  - Paired lumbar, bronchomediastinal, subclavian, and jugular trunks
  - A single intestinal trunk
  - Lymph is delivered into one of two large ducts
  - Right lymphatic duct – drains the right upper arm and the right side of the head and thorax
  - Thoracic duct – arises from the cisterna chyli and drains the rest of the body

Lymphatic Collecting Vessels

- Have the same three tunics as veins
- Have thinner walls, with more internal valves
- Anastomose more frequently
- Collecting vessels in the skin travel with superficial veins
- Deep vessels travel with arteries
- Nutrients are supplied from branching vasa vasorum
Lymphatic Transport

- The lymphatic system lacks an organ that acts as a pump
- Vessels are low pressure conduits
- Uses the same methods as veins to propel lymph
  - Pulsations of nearby arteries
  - Contraction of smooth muscle in the walls of the lymphatics

Lymphoid Cells

- Lymphocytes are the main cells involved in the immune response
- The two main varieties are T cells and B cells

Lymphocytes

- T cells and B cells protect the body against antigens
- Antigen — anything the body perceives as foreign
  - Bacteria and their toxins, and viruses
  - Mismatched RBCs or cancer cells
- T cells
  - Manage the immune response
  - Attack and destroy foreign cells
- B cells
  - Produce plasma cells, which secrete antibodies
  - Antibodies immobilize antigens

Other Lymphoid Cells

- Macrophages — phagocytize foreign substances and help activate T cells
- Dendritic cells — spiny-looking cells with functions similar to macrophages
- Reticular cells — fibroblast-like cells that produce a stroma, or network, that supports other cell types in lymphoid organs

Lymphoid Tissue

- Diffuse lymphatic tissue — scattered reticular tissue elements in every body organ
- Larger collections appear in the lamina propria of mucous membranes and lymphoid organs
- Lymphatic follicles (nodules) — solid, spherical bodies consisting of tightly packed reticular elements and cells
  - Have a germinatal center composed of dendritic cells and B cells
  - Found in isolation and as part of larger lymphoid organs

Lymphoid Organs

- Lymphoid organs — discrete, encapsulated collections of diffuse lymphoid tissue and follicles
- Examples include the lymph nodes, spleen, and thymus

- tonsils (in oropharyngeal region)
- thymus (in thoracic region active during youth)
- spleen (curves around left side of abdomen)
- pos. nodes (in abdomen)
Lymph Nodes
- Nodes are imbedded in connective tissue and clustered along lymphatic vessels.
- Aggregations of these nodes occur near the body surface in inguinal, axillary, and cervical regions of the body.
- Their two basic functions are:
  - Filtration – macrophages destroy microorganisms and debris.
  - Immune system activation – monitor for antigens and mount an attack against them.

Structure of a Lymph Node
- Nodes are bean shaped and surrounded by a fibrous capsule.
- Trabeculae extended inward from the capsule and divide the node into compartments.
- Nodes have two histologically distinct regions: a cortex and a medulla.

Structure of a Lymph Node
- The cortex contains follicles with germinal centers, heavy with dividing B cells.
- Dendritic cells nearly encapsulate the follicles.
- The deep cortex houses T cells in transit.
- T cells circulate continuously among the blood, lymph nodes, and lymphatic stream.

Structure of a Lymph Node
- Medullary cords extend from the cortex and contain B cells, T cells, and plasma cells.
- Throughout the node are lymph sinuses crisscrossed by reticular fibers.
- Macrophages reside on these fibers and phagocytize foreign matter.

Circulation in the Lymph Nodes
- Lymph enters via a number of afferent lymphatic vessels.
- It then enters a large subcapsular sinus and travels into a number of smaller sinuses.
- It meanders through these sinuses and exits the node at the hilus via efferent vessels.
- Because there are fewer efferent vessels, lymph stagnates somewhat in the node.
  - This allows lymphocytes and macrophages time to carry out their protective functions.

Homeostatic Imbalances of the Lymph Nodes
- If lymph nodes are overwhelmed by large numbers of antigen:
  - They become inflamed and tender to the touch.
    - Such nodes are called buboes (or erroneously, swollen glands).
  - Nodes can also become secondary cancer sites.
    - Such nodes are swollen, but are not painful.
      - This distinguishes cancerous nodes from infected ones.
Other Lymphoid Organs

- The spleen, thymus gland, and tonsils
- Peyer’s patches and bits of lymphatic tissue scattered in connective tissue
- All are composed of reticular connective tissue and all help protect the body
- Only lymph nodes filter lymph

Spleen

- Largest lymphoid organ, located on the left side of the abdominal cavity beneath the diaphragm
- It extends to curl around the anterior aspect of the stomach
- It is served by the splenic artery and vein, which enter and exit at the hilus
- Functions
  - Site of lymphocyte proliferation
  - Immune surveillance and response
  - Cleanses the blood

Additional Spleen Functions

- Stores breakdown products of RBCs
  - Spleen macrophages salvage and store iron for later use by bone marrow
- Site of fetal erythrocyte production (normally ceases after birth)
- Stores blood platelets

Structure of the Spleen

- Surrounded by a fibrous capsule, it has trabeculae that extend inward and contains lymphocytes, macrophages, and huge numbers of erythrocytes
- Two distinct areas of the spleen are:
  - White pulp – area containing mostly lymphocytes suspended on reticular fibers and involved in immune functions
  - Red pulp – remaining splenic tissue concerned with disposing of worn-out RBCs and bloodborne pathogens

Thymus

- A bilobed organ that secretes hormones (thymosin and thymopoietin) that cause T lymphocytes to become immunocompetent
- The size of the thymus varies with age
  - In infants, it is found in the inferior neck and extends into the mediastinum, where it partially overlies the heart
  - It increases in size and is most active during childhood
  - It stops growing during adolescence and then gradually atrophies
Internal Anatomy of the Thymus

- Thymic lobes contain an outer cortex and inner medulla
- The cortex contains densely packed lymphocytes and scattered macrophages
- The medulla contains fewer lymphocytes and thymic (Hassall’s) corpuscles

Thymus

- The thymus differs from other lymphoid organs in important ways
  - It functions strictly in T lymphocyte maturation
  - It does not directly fight antigens
- The stroma of the thymus consists of star-shaped epithelial cells (not reticular fibers)
- These star-shaped thymocytes secret thymosins and thymopoietins that stimulate lymphocytes to become immunocompetent

Tonsils

- Simplest lymphoid organs; form a ring of lymphatic tissue around the pharynx
- Location of the tonsils
  - Palatine tonsils – either side of the posterior end of the oral cavity
  - Lingual tonsil – lies at the base of the tongue
  - Pharyngeal tonsil – posterior wall of the nasopharynx
  - Tubal tonsils – surround the openings of the auditory tubes into the pharynx

Tonsils

- Lymphoid tissue of tonsils contains follicles with germinal centers
- Tonsil masses are not fully encapsulated
- Epithelial tissue overlying tonsil masses invaginates, forming blind-ended crypts
- Crypts trap and destroy bacteria and particulate matter

Aggregates of Lymphoid Follicles

- Peyer’s patches – isolated clusters of lymphoid tissue, similar to tonsils
  - Found in the wall of the distal portion of the small intestine
  - Similar structures are found in the appendix
- Peyer’s patches and the appendix:
  - Destroy bacteria, preventing them from breaching the intestinal wall
  - Generate “memory” lymphocytes for long-term immunity

MALT

- MALT – mucosa-associated lymphatic tissue, composed of:
  - Peyer’s patches, tonsils, and the appendix (digestive tract)
  - Lymphoid nodules in the wall of the bronchi (respiratory tract)
- MALT protects the digestive and respiratory systems from foreign matter
Chapter 20
The Immune System: Innate and Adaptive Body Defenses

Part A

Immunity: Two Intrinsic Defense Systems

- Innate (nonspecific) system responds quickly and consists of:
  - First line of defense – intact skin and mucosae prevent entry of microorganisms
  - Second line of defense – antimicrobial proteins, phagocytes, and other cells
    - Inhibit invaders spread throughout the body
    - Inflammation is its hallmark and most important mechanism

- Adaptive (specific) defense system
  - Third line of defense – mounts attack against particular foreign substances
  - Takes longer to react than the innate system
  - Works in conjunction with the innate system

Surface Barriers

- Skin, mucous membranes, and their secretions make up the first line of defense
- Keratin in the skin:
  - Presents a formidable physical barrier to most microorganisms
  - Resistant to weak acids and bases, bacterial enzymes, and toxins
- Mucosae provide similar mechanical barriers

Epithelial Chemical Barriers

- Epithelial membranes produce protective chemicals that destroy microorganisms
  - Skin acidity (pH of 3 to 5) inhibits bacterial growth
  - Sebum contains chemicals toxic to bacteria
  - Stomach mucosae secrete concentrated HCl and protein-digesting enzymes
  - Saliva and lacrimal fluid contain lysozyme
  - Mucus traps microorganisms that enter the digestive and respiratory systems

Respiratory Tract Mucosae

- Mucus-coated hairs in the nose trap inhaled particles
- Mucosa of the upper respiratory tract is ciliated
  - Cilia sweep dust- and bacteria-laden mucus away from lower respiratory passages
Internal Defenses: Cells and Chemicals

- The body uses nonspecific cellular and chemical devices to protect itself
  - Phagocytes and natural killer (NK) cells
  - Antimicrobial proteins in blood and tissue fluid
  - Inflammatory response enlists macrophages, mast cells, WBCs, and chemicals
- Harmful substances are identified by surface carbohydrates unique to infectious organisms

Phagocytes

- Macrophages are the chief phagocytic cells
- Free macrophages wander throughout a region in search of cellular debris
- Kupffer cells (liver) and microglia (brain) are fixed macrophages
- Neutrophils become phagocytic when encountering infectious material
- Eosinophils are weakly phagocytic against parasitic worms
- Mast cells bind and ingest a wide range of bacteria

Mechanism of Phagocytosis

- Microbes adhere to the phagocyte
- Pseudopods engulf the particle (antigen) into a phagosome
- Phagosomes fuse with a lysosome to form a phagolysosome
- Microbes in the phagolysosome are enzymatically digested
- Indigestible and residual material is removed by exocytosis

Natural Killer (NK) Cells

- Cells that can lyse and kill cancer cells and virus-infected cells
- Natural killer cells:
  - Are a small, distinct group of large granular lymphocytes
  - React nonspecifically and eliminate cancerous and virus-infected cells
  - Kill their target cells by releasing cytolytic chemicals
  - Secrete potent chemicals that enhance the inflammatory response

Inflammation: Tissue Response to Injury

- The inflammatory response is triggered whenever body tissues are injured
  - Prevents the spread of damaging agents to nearby tissues
  - Disposes of cell debris and pathogens
  - Sets the stage for repair processes
- The four cardinal signs of acute inflammation are redness, heat, swelling, and pain
Inflammatory Response

- Begins with a flood of inflammatory chemicals released into the extracellular fluid
- Inflammatory mediators:
  - Include kinins, prostaglandins (PGs), complement, and cytokines
  - Are released by injured tissue, phagocytes, lymphocytes, and mast cells
  - Cause local small blood vessels to dilate, resulting in hyperemia

Inflammatory Response: Vascular Permeability

- Chemicals liberated by the inflammatory response increase the permeability of local capillaries
- Exudate (fluid containing proteins, clotting factors, and antibodies):
  - Seeps into tissue spaces causing local edema (swelling)
  - The edema contributes to the sensation of pain

Inflammatory Response: Edema

- The surge of protein-rich fluids into tissue spaces (edema):
  - Helps to dilute harmful substances
  - Brings in large quantities of oxygen and nutrients needed for repair
  - Allows entry of clotting proteins, which prevent the spread of bacteria

Inflammatory Response: Phagocytic Mobilization

- Occurs in four main phases:
  - Leukocytosis – neutrophils are released from the bone marrow in response to leukocytosis-inducing factors released by injured cells
  - Margination – neutrophils cling to the walls of capillaries in the injured area
  - Diapedesis – neutrophils squeeze through capillary walls and begin phagocytosis
  - Chemotaxis – inflammatory chemicals attract neutrophils to the injury site

Flowchart of Events in Inflammation
Antimicrobial Proteins

- Enhance the innate defenses by:
  - Attacking microorganisms directly
  - Hindering microorganisms’ ability to reproduce
- The most important antimicrobial proteins are:
  - Interferon
  - Complement proteins

Interferon (IFN)

- Genes that synthesize IFN are activated when a host cell is invaded by a virus
- Interferon molecules leave the infected cell and enter neighboring cells

Interferon Family

- Interferons are a family of related proteins each with slightly different physiological effects
  - Lymphocytes secrete gamma (γ) interferon, but most other WBCs secrete alpha (α) interferon
  - Fibroblasts secrete beta (β) interferon
  - Interferons also activate macrophages and mobilize NK cells
- FDA-approved alpha IFN is used:
  - As an antiviral drug against hepatitis C virus
  - To treat genital warts caused by a herpes virus

Complement

- 20 or so proteins that circulate in the blood in an inactive form
- Proteins include C1 through C9, factors B, D, and P, and regulatory proteins
- Provides a major mechanism for destroying foreign substances in the body
- Amplifies all aspects of the inflammatory response
- Kills bacteria and certain other cell types (our cells are immune to complement)
- Enhances the effectiveness of both nonspecific and specific defenses

Complement Pathways

- Complement can be activated by two pathways: classical and alternative
  - Classical pathway is linked to the immune system
  - Depends upon the binding of antibodies to invading organisms
  - Subsequent binding of C1 to the antigen-antibody complexes (complement fixation)
- Alternative pathway is triggered by interaction among factors B, D, and P, and polysaccharide molecules present on microorganisms
Complement Pathways
- Each pathway involves a cascade in which complement proteins are activated in an orderly sequence and where each step catalyzes the next.
- Both pathways converge on C3, which cleaves into C3a and C3b.
- C3b initiates formation of a membrane attack complex (MAC).
- MAC causes cell lysis by interfering with a cell’s ability to eject Ca^{2+}.
- C3b also causes opsonization, and C3a causes inflammation.

Fever
- Abnormally high body temperature in response to invading microorganisms.
- The body’s thermostat is reset upwards in response to pyrogens, chemicals secreted by leukocytes and macrophages exposed to bacteria and other foreign substances.
- High fevers are dangerous because they can denature enzymes.
- Moderate fever can be beneficial, as it causes:
  - The liver and spleen to sequester iron and zinc (needed by microorganisms).
  - An increase in the metabolic rate, which speeds up tissue repair.

Adaptive (Specific) Defenses
- The adaptive immune system is a functional system that:
  - Recognizes specific foreign substances.
  - Acts to immobilize, neutralize, or destroy them.
  - Amplifies inflammatory response and activates complement.

Adaptive Immune Defenses
- The adaptive immune system is antigen-specific, systemic, and has memory.
- It has two separate but overlapping arms:
  - Humoral, or antibody-mediated immunity.
  - Cellular, or cell-mediated immunity.

Antigens (Ags)
- Substances that can mobilize the immune system and provoke an immune response.
- The ultimate targets of all immune responses are mostly large, complex molecules not normally found in the body (nons elf).
### Complete Antigens
- Important functional properties
  - Immunogenicity – the ability to stimulate proliferation of specific lymphocytes and antibody production
  - Reactivity – the ability to react with the products of the activated lymphocytes and the antibodies released in response to them
- Complete antigens include foreign protein, nucleic acid, some lipids, and large polysaccharides

### Haptens (Incomplete Antigens)
- Small molecules, such as peptides, nucleotides, and many hormones, that are not immunogenic but are reactive when attached to protein carriers
- If they link up with the body's proteins, the adaptive immune system may recognize them as foreign and mount a harmful attack (allergy)
- Haptens are found in poison ivy, dander, some detergents, and cosmetics

### Antigenic Determinants
- Only certain parts of an entire antigen are immunogenic
- Antibodies and activated lymphocytes bind to these antigenic determinants
- Most naturally occurring antigens have numerous antigenic determinants that:
  - Mobilize several different lymphocyte populations
  - Form different kinds of antibodies against it
- Large, chemically simple molecules (e.g., plastics) have little or no immunogenicity

### Self-Antigens: MHC Proteins
- Our cells are dotted with protein molecules (self-antigens) that are not antigenic to us but are strongly antigenic to others
- One type of these, MHC proteins, mark a cell as self
- The two classes of MHC proteins are:
  - Class I MHC proteins – found on virtually all body cells
  - Class II MHC proteins – found on certain immune response cells

### MHC Proteins
- Are coded for by genes of the major histocompatibility complex (MHC) and are unique to an individual
- Each MHC molecule has a deep groove that displays a peptide, which is a normal cellular product of protein recycling
- In infected cells, MHC proteins bind to fragments of foreign antigens, which play a crucial role in mobilizing the immune system
Cells of the Adaptive Immune System

- Two types of lymphocytes
  - B lymphocytes – oversee humoral immunity
  - T lymphocytes – non-antibody-producing cells that constitute the cell-mediated arm of immunity
- Antigen-presenting cells (APCs):
  - Do not respond to specific antigens
  - Play essential auxiliary roles in immunity

Lymphocytes

- Immature lymphocytes released from bone marrow are essentially identical
- Whether a lymphocyte matures into a B cell or a T cell depends on where in the body it becomes immunocompetent
  - B cells mature in the bone marrow
  - T cells mature in the thymus

Lymphocytes

- B cells and T cells
  - T cells mature in the thymus under negative and positive selection pressures
    - Negative selection – eliminates T cells that are strongly anti-self
    - Positive selection – selects T cells with a weak response to self-antigens, which thus become both immunocompetent and self-tolerant
  - B cells become immunocompetent and self-tolerant in bone marrow

Immunocompetent B or T cells

- Display a unique type of receptor that responds to a distinct antigen
- Become immunocompetent before they encounter antigens they may later attack
- Are exported to secondary lymphoid tissue where encounters with antigens occur
- Mature into fully functional antigen-activated cells upon binding with their recognized antigen
- It is genes, not antigen, that determine which foreign substance our immune system will recognize and resist

Immunocompetent B or T cells
Antigen-Presenting Cells (APCs)

- Major roles in immunity are:
  - To engulf foreign particles
  - To present fragment of antigens on their own surfaces, to be recognized by T cells
- Major APCs are dendritic cells (DCs), macrophages, and activated B cells
- The major initiators of adaptive immunity are DCs, which actively migrate to the lymph nodes and secondary lymphoid organs and present antigens to T and B cells

Macrophages and Dendritic Cells

- Secrete soluble proteins that activate T cells
- Activated T cells in turn release chemicals that:
  - Rev up the maturation and mobilization of DCs
  - Prod macrophages to become activated macrophages, which are insatiable phagocytes and release bactericidal chemicals

Adaptive Immunity: Summary

- Two-fisted defensive system that uses lymphocytes, APCs, and specific molecules to identify and destroy nonself particles
- Its response depends upon the ability of its cells to:
  - Recognize foreign substances (antigens) by binding to them
  - Communicate with one another so that the whole system mounts a response specific to those antigens

Humoral Immunity Response

- Antigen challenge – first encounter between and antigen and a naive immunocompetent cell
- Takes place in the spleen or other lymphoid organ
- If the lymphocyte is a B cell:
  - The challenging antigen provokes a humoral immune response
  - Antibodies are produced against the challenger

Clonal Selection

- Stimulated B cell growth forms clones bearing the same antigen-specific receptors
- A naive, immunocompetent B cell is activated when antigens bind to its surface receptors and cross-link adjacent receptors
- Antigen binding is followed by receptor-mediated endocytosis of the cross-linked antigen-receptor complexes
- These activating events, plus T cell interactions, trigger clonal selection
Clonal Selection

- Antibody production
  - Plasma cells
  - Memory cells

Fate of the Clones

- Most clone cells become antibody-secreting plasma cells
- Plasma cells secrete specific antibodies at the rate of 2000 molecules per second
- Secreted antibodies:
  - Bind to free antigens
  - Mark the antigens for destruction by specific or nonspecific mechanisms
- Clones that do not become plasma cells become memory cells that can mount an immediate response to subsequent exposures to an antigen

Immunological Memory

- Primary immune response – cellular differentiation and proliferation, which occurs on the first exposure to a specific antigen
  - Lag period: 3 to 6 days after antigen challenge
  - Peak levels of plasma antibody are achieved in 10 days
  - Antibody levels then decline

Immunological Memory

- Secondary immune response – re-exposure to the same antigen
  - Sensitized memory cells respond within hours
  - Antibody levels peak in 2 to 3 days at much higher levels than in the primary response
  - Antibodies bind with greater affinity, and their levels in the blood can remain high for weeks to months

Active Humoral Immunity

- B cells encounter antigens and produce antibodies against them
  - Naturally acquired – response to a bacterial or viral infection
  - Artificially acquired – response to a vaccine of dead or attenuated pathogens
- Vaccines – spare us the symptoms of disease, and their weakened antigens provide antigenic determinants that are immunogenic and reactive
Passive Humoral Immunity

- Differs from active immunity in the antibody source and the degree of protection
  - B cells are not challenged by antigen
  - Immunological memory does not occur
  - Protection ends when antigens naturally degrade in the body
- Naturally acquired – from the mother to her fetus via the placenta
- Artificially acquired – from the injection of serum, such as gamma globulin

Antibodies (Ab)

- Also called immunoglobulins (Igs)
  - Constitute the gamma globulin portion of blood proteins
  - Are soluble proteins secreted by activated B cells and plasma cells in response to an antigen
  - Are capable of binding specifically with that antigen
- There are five classes of antibodies: IgD, IgM, IgG, IgA, and IgE

Classes of Antibodies

- IgD – monomer attached to the surface of B cells, important in B cell activation
- IgM – pentamer released by plasma cells during the primary immune response
- IgG – monomer that is the most abundant and diverse antibody in primary and secondary response; crosses the placenta and confers passive immunity
- IgA – dimer that helps prevent attachment of pathogens to epithelial cell surfaces
- IgE – monomer that binds to mast cells and basophils, causing histamine release when

Basic Antibody Structure

- Consist of four looping polypeptide chains linked together with disulfide bonds
  - Two identical heavy (H) chains and two identical light (L) chains
- The four chains bound together form an antibody monomer
- Each chain has a variable (V) region at one end and a constant (C) region at the other
- Variable regions of the heavy and light chains combine to form the antigen-binding site
Antibody Structure
- Antibodies responding to different antigens have different V regions but the C region is the same for all antibodies in a given class.
- C regions form the stem of the Y-shaped antibody and:
  - Determine the class of the antibody
  - Serve common functions in all antibodies
  - Dictate the cells and chemicals that the antibody can bind to
  - Determine how the antibody class will function in elimination of antigens

Mechanisms of Antibody Diversity
- Plasma cells make over a billion different types of antibodies
- Each cell, however, only contains 100,000 genes that code for these polypeptides
- To code for this many antibodies, somatic recombination takes place
  - Gene segments are shuffled and combined in different ways by each B cell as it becomes immunocompetent
  - Information of the newly assembled genes is expressed as B cell receptors and as antibodies

Antibody Diversity
- Random mixing of gene segments makes unique antibody genes that:
  - Code for H and L chains
  - Account for part of the variability in antibodies
  - V gene segments, called hypervariable regions, mutate and increase antibody variation
  - Plasma cells can switch H chains, making two or more classes with the same V region

Antibody Targets
- Antibodies themselves do not destroy antigen; they inactivate and tag it for destruction
- All antibodies form an antigen-antibody (immune) complex
- Defensive mechanisms used by antibodies are neutralization, agglutination, precipitation, and complement fixation

Complement Fixation and Activation
- Complement fixation is the main mechanism used against cellular antigens
- Antibodies bound to cells change shape and expose complement binding sites
- This triggers complement fixation and cell lysis
- Complement activation:
  - Enhances the inflammatory response
  - Uses a positive feedback cycle to promote phagocytosis
  - Enlists more and more defensive elements

Other Mechanisms of Antibody Action
- Neutralization – antibodies bind to and block specific sites on viruses or exotoxins, thus preventing these antigens from binding to receptors on tissue cells
- Agglutination – antibodies bind the same determinant on more than one antigen
  - Makes antigen-antibody complexes that are cross-linked into large lattices
  - Cell-bound antigens are cross-linked, causing clumping (agglutination)
- Precipitation – soluble molecules are cross-linked into large insoluble complexes
**Mechanisms of Antibody Action**

- Neutralization: neutralizes bacterial toxins
- Agglutination: causes bacterial clumping
- Complement activation: leads to lysis

**Monoclonal Antibodies**

- Commercially prepared antibodies are used:
  - To provide passive immunity
  - In research, clinical testing, and treatment of certain cancers
- Monoclonal antibodies are pure antibody preparations
  - Specific for a single antigenic determinant
  - Produced from descendents of a single cell

**Monoclonal Antibodies**

- Hybridomas – cell hybrids made from a fusion of a tumor cell and a B cell
  - Have desirable properties of both parent cells – indefinite proliferation as well as the ability to produce a single type of antibody

**Cell-Mediated Immune Response**

- Since antibodies are useless against intracellular antigens, cell-mediated immunity is needed
- Two major populations of T cells mediate cellular immunity
  - CD4 cells (T4 cells) are primarily helper T cells (T<sub>H</sub>)
  - CD8 cells (T8 cells) are cytotoxic T cells (T<sub>C</sub>) that destroy cells harboring foreign antigens

**Cell-Mediated Immune Response**

- Other types of T cells are:
  - Delayed hypersensitivity T cells (T<sub>DH</sub>)
  - Suppressor T cells (T<sub>S</sub>)
  - Memory T cells

**Importance of Humoral and Cellular Responses**

- Humoral response
  - Soluble antibodies
    - The simplest ammunition of the immune response
    - Interact in extracellular environments such as body secretions, tissue fluid, blood, and lymph
Importance of Humoral and Cellular Responses

- Cellular response
  - T cells recognize and respond only to processed fragments of antigen displayed on the surface of body cells
  - T cells are best suited for cell-to-cell interactions, and target:
    - Cells infected with viruses, bacteria, or intracellular parasites
    - Abnormal or cancerous cells
    - Cells of infused or transplanted foreign tissue

Antigen Recognition and MHC Restriction

- Immunocompetent T cells are activated when the V regions of their surface receptors bind to a recognized antigen
- T cells must simultaneously recognize:
  - Nonself (the antigen)
  - Self (a MHC protein of a body cell)

Chapter 20

The Immune System: Innate and Adaptive Body Defenses

Part C

MHC Proteins

- Both types of MHC proteins are important to T cell activation
- Class I MHC proteins
  - Always recognized by CD8 T cells
  - Display peptides from endogenous antigens

Class I MHC Proteins

- Endogenous antigens are:
  - Degraded by proteases and enter the endoplasmic reticulum
  - Transported via TAP (transporter associated with antigen processing)
  - Loaded onto class I MHC molecules
  - Displayed on the cell surface in association with a class I MHC molecule

Class I MHC Proteins

- Processed endogenous antigens bind to the groove of class I MHC molecules
- Free peptides bind to the groove of class I MHC molecules
- Loaded MHC protein is transported to the plasma membrane, where it displays the antigenic peptide
- T helper (Th) cells recognize the MHC complex and interact with the cell
- Activated T cells secrete cytokines and activate other immune cells
- Endogenous antigens are degraded by proteases
Class II MHC Proteins

- Class II MHC proteins are found only on mature B cells, some T cells, and antigen-presenting cells
- A phagosome containing pathogens (with exogenous antigens) merges with a lysosome
- Invariant protein prevents class II MHC proteins from binding to peptides in the endoplasmic reticulum

Class II MHC Proteins

- Class II MHC proteins migrate into the phagosomes where the antigen is degraded and the invariant chain is removed for peptide loading
- Loaded Class II MHC molecules then migrate to the cell membrane and display antigenic peptides for recognition by CD4 cells

Antigen Recognition

- Provides the key for the immune system to recognize the presence of intracellular microorganisms
- MHC proteins are ignored by T cells if they are complexed with self protein fragments

If MHC proteins are complexed with endogenous or exogenous antigenic peptides, they:
- Indicate the presence of intracellular infectious microorganisms
- Act as antigen holders
- Form the self part of the self-antiself complexes recognized by T cells

T Cell Activation: Step One – Antigen Binding

- T cell antigen receptors (TCRs):
  - Bind to an antigen–MHC protein complex
  - Have variable and constant regions consisting of two chains (alpha and beta)
- MHC restriction – T\textsubscript{H} and T\textsubscript{C} bind to different classes of MHC proteins
- T\textsubscript{H} cells bind to antigens linked to class II MHC proteins
- Mobile APCs (Langerhans’ cells) quickly alert the body to the presence of antigen by migrating to the lymph nodes and presenting antigen
**T Cell Activation: Step One — Antigen Binding**

- $T_C$ cells are activated by antigen fragments complexed with class I MHC proteins
- APCs produce costimulatory molecules that are required for $T_C$ activation
- TCR that acts to recognize the self-antiself complex is linked to multiple intracellular signaling pathways
- Other T cell surface proteins are involved in antigen binding (e.g., CD4 and CD8 help maintain coupling during antigen recognition)

**T Cell Activation: Step Two — Costimulation**

- Before a T cell can undergo clonal expansion, it must recognize one or more costimulatory signals
- This recognition may require binding to other surface receptors on an APC
  - Macrophages produce surface B7 proteins when nonspecific defenses are mobilized
  - B7 binding with the CD28 receptor on the surface of T cells is a crucial costimulatory signal
- Other costimulatory signals include cytokines and interleukin 1 and 2

**T Cell Activation: Step Two — Costimulation**

- Primary T cell response peaks within a week after signal exposure
- T cells then undergo apoptosis between days 7 and 30
- Effector activity wanes as the amount of antigen declines
- The disposal of activated effector cells is a protective mechanism for the body
- Memory T cells remain and mediate secondary responses to the same antigen
Cytokines

- Mediators involved in cellular immunity, including hormonelike glycoproteins released by activated T cells and macrophages
- Some are costimulators of T cells and T cell proliferation
- Interleukin 1 (IL-1) released by macrophages costimulates bound T cells to:
  - Release interleukin 2 (IL-2)
  - Synthesize more IL-2 receptors

Helper T Cells (T\textsubscript{H})

- Regulatory cells that play a central role in the immune response
- Once primed by APC presentation of antigen, they:
  - Chemically or directly stimulate proliferation of other T cells
  - Stimulate B cells that have already become bound to antigen
- Without T\textsubscript{H}, there is no immune response

Cytokines

- IL-2 is a key growth factor, which sets up a positive feedback cycle that encourages activated T cells to divide
- It is used therapeutically to enhance the body’s defenses against cancer
- Other cytokines amplify and regulate immune and nonspecific responses
- Examples include:
  - Perforin and lymphotoxin — cell toxins
  - Gamma interferon — enhances the killing power of macrophages
  - Inflammatory factors

Helper T Cells (T\textsubscript{H})
**Cytotoxic T Cells (T_C)**
- T_C cells, or killer T cells, are the only T cells that can directly attack and kill other cells.
- They circulate throughout the body in search of body cells that display the antigen to which they have been sensitized.
- Their targets include:
  - Virus-infected cells
  - Cells with intracellular bacteria or parasites
  - Cancer cells
  - Foreign cells from blood transfusions or transplants

**Mechanisms of T_C Action**
- In some cases, T_C cells:
  - Bind to the target cell and release perforin into its membrane
  - Perforin causes cell lysis by creating transmembrane pores

**Other T Cells**
- Suppressor T cells (T_S) – regulatory cells that release cytokines, which suppress the activity of both T cells and B cells
- Delayed-type hypersensitivity cells (T_DH) – cells instrumental in promoting allergic reactions called delayed hypersensitivity reactions
- Gamma delta T cells – 10% of all T cells found in the intestines that are triggered by binding to MICA receptors

**Summary of the Primary Immune Response**
- Other T_C cells induce cell death by:
  - Secreting lymphotixin, which fragments the target cell’s DNA
  - Releasing tumor necrosis factor (TNF), which triggers apoptosis
  - Secreting gamma interferon, which stimulates phagocytosis by macrophages
**Immunodeficiencies**
- Congenital and acquired conditions in which the function or production of immune cells, phagocytes, or complement is abnormal
  - SCID – severe combined immunodeficiency (SCID) syndrome; genetic defects that produce:
    - A marked deficit in B and T cells
    - Abnormalities in interleukin receptors
    - Defective adenosine deaminase (ADA) enzymes
  - SCID is fatal if untreated; treatment is with bone marrow transplants

**Acquired Immunodeficiencies**
- Hodgkin’s disease – cancer of the lymph nodes leads to immunodeficiency by depressing lymph node cells
- Acquired immune deficiency syndrome (AIDS) – cripples the immune system by interfering with the activity of helper T (CD4) cells
  - Characterized by severe weight loss, night sweats, and swollen lymph nodes
  - Opportunistic infections occur, including pneumocystis pneumonia and Kaposi’s sarcoma

**AIDS**
- Caused by human immunodeficiency virus (HIV) transmitted via body fluids – blood, semen, and vaginal secretions
- HIV enters the body via:
  - Blood transfusions
  - Contaminated needles
  - Intimate sexual contact, including oral sex
- HIV:
  - Destroys T4 cells
  - Depresses cell-mediated immunity

**AIDS**
- HIV multiplies in lymph nodes throughout the asymptomatic period
- Symptoms appear in a few months to 10 years
  - Attachment
    - HIV’s coat protein (gp120) attaches to the CD4 receptor
    - A nearby protein (gp41) fuses the virus to the target cell
  - HIV enters the cell and uses reverse transcriptase to produce DNA from viral RNA
  - This DNA (provirus) directs the host cell to make viral RNA (and proteins), enabling the virus to reproduce and infect other cells

**Autoimmune Diseases**
- Loss of the immune system’s ability to distinguish self from nonself
- The body produces autoantibodies and sensitized Tc cells that destroy its own tissues
- Examples include multiple sclerosis, myasthenia gravis, Graves’ disease, Type 1 (juvenile) diabetes mellitus, systemic lupus erythematosus (SLE), glomerulonephritis, and rheumatoid arthritis
Mechanisms of Autoimmune Disease

- Ineffective lymphocyte programming — self-reactive T and B cells that should have been eliminated in the thymus and bone marrow escape into the circulation
- New self-antigens appear, generated by:
  - Gene mutations that cause new proteins to appear
  - Changes in self-antigens by hapten attachment or as a result of infectious damage
- Foreign antigens resemble self-antigens:
  - Antibodies made against foreign antigens cross-react with self-antigens

Hypersensitivity

- Immune responses that cause tissue damage
- Different types of hypersensitivity reactions are distinguished by:
  - Their time course
  - Whether antibodies or T cells are the principle immune elements involved
  - Antibody-mediated allergies are immediate and subacute hypersensitivities
  - The most important cell-mediated allergic condition is delayed hypersensitivity

Immediate Hypersensitivity

- Acute (type I) hypersensitivities begin in seconds after contact with allergen
- Anaphylaxis — initial allergen contact is asymptomatic but sensitizes the person
  - Subsequent exposures to allergen cause:
    - Release of histamine and inflammatory chemicals
    - Systemic or local responses
    - The mechanism involves IL-4 secreted by T cells
    - IL-4 stimulates B cells to produce IgE
    - IgE binds to mast cells and basophils causing them to degranulate, resulting in a flood of histamine release and inducing the inflammatory response

Local Type I Responses

- Reactions include runny nose, itching reddened skin, and watery eyes
- If allergen is inhaled, asthmatic symptoms appear — constriction of bronchioles and restricted airflow
- If allergen is ingested, cramping, vomiting, and diarrhea occur
- Antihistamines counteract these effects

Systemic Response: Anaphylactic Shock

- Response to allergen that directly enters the blood (e.g., insect bite, injection)
- Basophils and mast cells are enlisted throughout the body
- Systemic histamine releases may result in:
  - Constriction of bronchioles
  - Sudden vasodilation and fluid loss from the bloodstream
  - Hypotensive shock and death
- Treatment — epinephrine is the drug of choice

Subacute Hypersensitivities

- Caused by IgM and IgG, and transferred via blood plasma or serum
  - Onset is slow (1–3 hours) after antigen exposure
  - Duration is long lasting (10–15 hours)
- Cytotoxic (type II) reactions
  - Antibodies bind to antigens on specific body cells, stimulating phagocytosis and complement-mediated lysis of the cellular antigens
  - Example: mismatched blood transfusion reaction
Subacute Hypersensitivities

- Immune complex (type III) hypersensitivity
  - Antigens are widely distributed through the body or blood
  - Insoluble antigen-antibody complexes form
  - Complexes cannot be cleared from a particular area of the body
  - Intense inflammation, local cell lysis, and death may result
  - Example: systemic lupus erythematosus (SLE)

Delayed Hypersensitivities (Type IV)

- Onset is slow (1–3 days)
- Mediated by mechanisms involving delayed hypersensitivity T cells (T_{DH} cells) and cytotoxic T cells (T_{C} cells)
- Cytokines from activated T_{C} are the mediators of the inflammatory response

Delayed Hypersensitivities (Type IV)

- Antihistamines are ineffective and corticosteroid drugs are used to provide relief
- Example: allergic contact dermatitis (e.g., poison ivy)
- Involved in protective reactions against viruses, bacteria, fungi, protozoa, cancer, and rejection of foreign grafts or transplants