The immune system

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Functions of the Lymphatic System

- Lymphatic capillaries reabsorb excessive tissue fluid and transport the fluid through the lymphatic pathway, and ultimately dispose it into the blood.

- Lymphatic capillaries called lacteals absorb certain fatty acids in the small intestine.

- Lymphatic system consists of tissues and organs that produce, mature, and store lymphocytes and macrophages, for body defense purposes.

- Lymph flows from lymphatic vessels into lymphatic trunks, and finally into collecting ducts where the lymph is disposed into the subclavian veins.
Anatomy of the immune system

(a) Tonsil is diffuse lymphoid tissue.

(b) Afferent lymph vessels

Thymus produces T lymphocytes.

Lymph nodes

Encapsulated lymphoid tissues

Gut-associated lymphoid tissue (GALT) is a diffuse lymphoid tissue.

Spleen

Lymph vessels

Bone marrow produces most blood cells.

Lymph node artery and vein

Clusters of immune cells intercept pathogens that invade interstitial fluid.
Lymphatic Vessels

- Structurally identical to the veins – vessel wall are composed of 3 thin layers of tissues, and contain valves to prevent backflow.

- Form specialized lymphatic organs called **lymph nodes** which store macrophages and lymphocytes to eliminate foreign substances in the lymph.

- **Collecting ducts**: formed by the convergence of larger lymphatic vessels called lymphatic trunks. Two collecting ducts drain all lymph fluid back to the blood – **thoracic duct** returns lymph form the body to the **left subclavian vein**, and **right lymphatic duct** returns lymph from the upper body to the **right subclavian vein**.

- **C. Lymph**: a clear fluid composed mainly of water, electrolytes, and some small plasma proteins.
Lymph nodes

- Specialized lymphatic organs attached to lymphatic vessels, to produce and store large numbers of lymphocytes and macrophages for body defense, so that lymph is almost free of foreign substances before it is returned to the blood.

- Found mainly in the neck, armpits, and abdominal cavity (attached to the mesentery membrane of the intestines).

- Absent in the central nervous system; may be because the CNS is already well protected by the méninges and the "blood – brain barrier" (a complex network of capillaries that is impermeable to almost all foreign substances).

- Inside each lymph node, connective tissue masses called nodules produce and stores large numbers of lymphocytes and macrophages, while spaces called sinuses allow lymph to pass.
Thymus gland

- Thymus gland: a bilobed endocrine gland located at the aortic arch.

- slowly degenerates and shrinks after puberty; in elderly persons, thymus is mostly composed of adipose tissue.

- stores a large number of inactive lymphocytes called Thymocytes which are activated by a thymus hormone called Thymyosin in a maturing process to become T-lymphocytes (or T-cells).

- T-lymphocytes are involved in cell-mediated immunity to directly attack antigens.
Spleen

- The largest lymphatic organ located on the left side of abdominal cavity.
- Structurally identical to lymph nodes, where nodules (containing macrophages and lymphocytes) and sinuses occur.
- Filters blood, not lymph, by allowing the entrance of blood through the spleen artery, and after filtering blood is transported to the liver via the hepatic portal vein, for further detoxification.
- About 5% of total blood volume enters the spleen, allowing it to be a blood reservoir.
Nonspecific resistance

- **Infections** are multiplication and colonization of microorganisms (bacteria, viruses, fungi, parasites, or worms) in body tissues.

- **Resistance** is the ability of the body to ward off infections using body defense mechanisms. (when a person lacks resistance, it is called **susceptibility**).

- **Nonspecific resistance** is a general defense mechanism against any foreign substances where it is quickly activated upon an invasion of antigen, but it is short-term and cannot recognize or remember the antigens.

- Includes autonomic responses such as coughing, sneezing, fever, and species resistance (where each species of living organism is only susceptible to its own set of infections due to body temperature and PH settings).
First line of body defense

- Consists of the **skin** and **mucous membrane**.
- includes mechanical and chemical factors, such as the **keratin protein** and **stratified squamous epithelium** in the epidermis of skin (mechanical factors) and sebum and sweat (chemical factors).
Second line of body defense

- Consists of a class of chemical substances called **Antimicrobial substances** where they degenerate or break up antigens.

- **interferon's** are protein substances secreted by fibroblast, certain leukocytes, and T-lymphocyte when tissue cells are invaded by viruses; these substances tend to allow neighboring, uninfected cells to be immune to other viral infections.

- **Lysozymes** found in the lysosomes of body cells help destroy antigens invaded into tissues.

- **Complement proteins** are produced by the liver to enhance other immune response (some of them directly attack the antigens).
Complement Activation

Classical pathway
antigen-antibody complex
+ C1 C4 C2 Complex

Alternative pathway
Microorganisms' cell wall polysaccharides
+ Factor B, Factor D, and Factor P (properdin)

Opsonization:
coats bacterial surfaces, which enhances phagocytosis

Causes inflammation:
stimulates histamine release, increased blood vessel permeability, chemotactic attraction of phagocytes, etc.

Insertion of MAC and cell lysis
(holes in target cell's membrane)

Pore
Complement proteins (C5b–C9)
Membrane of target cell
Third line of body defense

- Consists of **inflammation** and **phagocytosis**.

- **inflammation** is an autonomic response by body tissues when they are attacked by an antigen. It produces 4 major symptoms:
  - **Redness** (due to vasodilatation which causes hyperemia).
  - **Swelling** (due to increased capillary permeability which causes edema).
  - **Heat** (hyperemia brings more body heat to the inflamed tissue).
  - **Pain** (swelling stimulates pain receptors in inflamed tissue).

- Inflammation also involves fibrinogens which coagulate tissue fluid and stop the spreading of antigen.
Major actions during inflammation response

- 2. Capillary and venule permeability increase.
- 3. Tissue becomes red, swollen, warm, and painful.
- 4. White blood cells invade the region.
- 5. Pus may form as white blood cells, bacterial cells & cellular debris accumulate.
- 6. Body fluids seep into the area.
- 7. A clot containing threads of fibrin may form.
Inflammation response - continued

- 9. A connective tissue sac may form around the injured tissues.
- 10. Phagocytes are active.
- 11. Bacteria, dead cells, and other debris are removed.
- 12. Cells reproduce.
Phagocytosis

- phagocytosis involves leukocytes called **phagocytes** which have the ability to engulf the antigen.

- phagocytes include **eosinophil** (which only phagocytize antigens in the blood), **neutrophil** (which can phagocytize small antigens in connective tissues, out of the blood), and **monocyte** which develops into **macrophage** (which can phagocytize larger antigens in connective tissues).

- During phagocytosis, phagocytes in capillaries first adhere to the inner walls of capillary (a process called **Margination**), then they squeeze themselves across the pores in the capillary walls (a process called **diapedesis** which only neutrophil and monocyte can perform).
**Phagocytosis**

1. Microbe adheres to phagocyte.

2. Phagocyte forms pseudopods that eventually engulf the particle.

3. Phagocytic vesicle is fused with a lysosome.

4. Microbe in fused vesicle is killed and digested by lysosomal enzymes within the phagolysosome, leaving a residual body.

5. Indigestible and residual material is removed by exocytosis.

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Once macrophage is developed in connective tissue, it will be attracted by the histamine in the inflamed tissue, and will "crawl" in the connective tissue using "amoeboid motion" toward the injured tissue. This attraction is known as **positive chemotaxis**.

When macrophage arrive at the inflamed tissue –

- **Adhesion** (macrophage binds with antigen).
- **Ingestion** (macrophage engulfs antigen using end acidosis).
- **Digestion** (Lysol cymes in macrophage release Lysol cymes and break down antigen).
- **Excretion** (macrophage discard degenerated antigen using exocytose).
Phagocytosis

1. Lysosome
2. Antigen
3. Nucleus
4. Membrane proteins
5. Macrophage

Macrophage digests antigen in lysosome.

Antigen-presenting macrophage displays antigen fragments on surface receptors.
Specific resistance (or immunity)

- 1. highly specific body defense mechanisms that can recognize, destroy and remember the antigen. It is long-lasting (its memory cells retain antigen receptors for several decades), but takes longer time to fully develop (sometimes certain lymphocytes and antibodies take several weeks to months to be fully activated).

- 2. Lymphocytes (B & T) are able to differentiate foreign substances as antigens because before birth, these cells recognize all cells in the body as "self" and after birth, when foreign substances invade into tissues, lymphocytes would recognize them as "nonself" which activates immune responses.
Lymphocytes

- 3. Antigens are usually proteins or polysaccharides on the outer walls of microorganisms, which when recognized by lymphocytes as "nonself" stimulate immune responses.
Antibody- Mediated immunity (AMI)

1. After **B-cells** are matured in the liver and blood, they will become "activated B-cells" whenever an antigen is detected.

2. Activated B-cells will look for the antigen and bind to it using their receptors which are developed specifically for that antigen.

3. Once activated B-cell binds with antigen, it differentiates into **plasma cells** (which release **antibodies** to destroy the antigen, in a process called **primary immune response**) and **memory B-cells** (which retain those antigen receptors for future recognition of that antigen, a process called **secondary immune response**).
B- Lymphocytes

- Antibody Structure

An antibody molecule is composed of two identical light chains and two identical heavy chains, linked by disulfide bonds.
Steps in Antibody Production – B cell activity

1. **Antigen** – bearing agents enter tissues.

2. **B cell** becomes activated when it encounters an antigen that fits its antigen receptors, either alone or more of ten in conjunction with helper T cells.

3. Activated B cells proliferates, enlarging its clone. B cells clone differentiate further into plasma cells, which secrete **antibodies**.

4. Some of the newly formed B cells differentiate further to become **plasma cells**.

5. Antibodies combine with antigen – bearing agents, helping to destroy them.

6. Plasma cells synthesize and secrete Antibodies whose molecular structure is similar to activated B cell’s antigen receptors.
Function of Antibodies

1. Activates B lymphocytes
2. Acts as opsonins
3. Causes antigen clumping and inactivation of bacterial toxins
4. Activates antibody-dependent cellular activity
5. Triggers mast cell degranulation
6. Activates complement

Antigen binds to antibody
Antigen binding site

Memory cells → Plasma cells → Secrete antibodies

Enhanced phagocytosis

NK cell or eosinophil

Bacterial toxins
Antibodies released by plasma cells belong to a class of globular protein called **immunoglobulin (Ig)**.

- **IgG** - found in tissue fluid and plasma (80% of all Ig’s) – defends against bacterial cells, viruses, and toxins; activates complement (set of enzymes that attack the antigens).

- **IgA** – found in Exocrine gland secretions – Defends against bacterial cells and viruses.

- **IgM** – found in plasma- reacts with antigens occurring naturally on some red blood cell’s membrane following certain blood transfusions; activates complement.

- **IgD** – found in surface of most B lymphocytes - causes B cell activation.

- **IgE** - found in exocrine gland secretions – promotes allergic reactions.
**Action of antibodies**

**TABLE 21.3 Immunoglobulin Classes (continued)**

IgG is the most abundant and diverse antibody in plasma, accounting for 75–85% of circulating antibodies. It protects against bacteria, viruses, and toxins circulating in blood and lymph, readily fixes complement, and is the main antibody of both secondary and late primary responses. It crosses the placenta and confers passive immunity from the mother to the fetus.

IgA monomer exists in limited amounts in plasma. The dimer (illustrated), referred to as secretory IgA, is found in body secretions such as saliva, sweat, intestinal juice, and milk, and helps prevent attachment of pathogens to epithelial cell surfaces (including mucous membranes and the epidermis).

IgE is slightly larger than the IgG antibody. It is secreted by plasma cells in skin, mucosae of the gastrointestinal and respiratory tracts, and tonsils. Its stem region becomes bound to mast cells and basophils, and when its receptor ends are triggered by an antigen, it causes the cells to release histamine and other chemicals that mediate inflammation and an allergic reaction. Typically only traces of IgE are found in plasma, but levels rise during severe allergic attacks or chronic parasitic infections of the gastrointestinal tract.
Actions of Antibodies

- **Direct Attack:**
  - **Agglutination** – Antigens clump.
  - **Precipitation** – Antigens become insoluble.
  - **Neutralization** – Antigens lose toxic properties.

- **Activation of complement:**
  - **Opsonization** - Alters cell membranes so cells are more susceptible to phagocytosis.
  - **Chemotaxis** - Attracts macrophages and neutrophils into region.
  - **Inflammation** – Promotes local tissue changes that help prevent spread of antigens.
  - **Lysis** – Cell membranes rupture.
Mechanism of antibody action

Adaptive defenses → Humoral immunity

Antigen → Antigen-antibody complex → Antibody

Inactivates by

Neutralization (masks dangerous parts of bacterial exotoxins; viruses)

Agglutination (cell-bound antigens)

Precipitation (soluble antigens)

Complement

Fixes and activates

Enhances

Phagocytosis

Inflammation

Nucleus
Chemotaxis
Histamine release

Enhances

Leads to

Cell lysis

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Cell- Mediated immunity (CMI)

1. After T-cells are matured in the thymus gland, they will be released into the blood and become "activated T-cells" whenever an antigen is detected.

2. A specialized macrophage called antigen–presenting cell (APC) finds the antigen and brings it to the activated T-cells.
CMI - continued

- 3. Activated T-cells bind to the antigen using their specific receptors.

- 4. Once active T-cell binds with antigen, it differentiates into:
  - **killer T-cells** (which directly attack the antigen).
  - **helper T-cells** (which release **lymphokines** to facilitate plasma cells in AMI, and release **cytokines** to enhance killer T-cells).
  - **memory T-cells** (which retain specific antigen receptors for future attach of the same antigen).
  - **suppressor T-cells** (which inhibit plasma cells, killer T-cells, and helper T-cells when the antigen is destroyed).
Major types of T cells

Adaptive defenses → Cellular immunity

Lymphocyte
Red bone marrow

Maturation

Class II MHC protein
CD4
Thymus

Activation

APC (dendritic cell)

Class I MHC protein
CD8

Activation

APC (dendritic cell)

Lymphoid tissues and organs

Blood plasma

Regulatory T cell
Helper T cells

Cytotoxic T cells
T cell activity

1. **Antigen – bearing agents** enter tissues.

2. Accessory cells, such as **macrophages**, phagocytize antigen bearing agent, and the macrophage’s lysosomes digest the agent.

3. Antigens from the digested **antigen – bearing agents** are displayed on the surface of the membrane of the accessory cell.

4. **Helper T cell** becomes activated when it encounters a displayed antigen that fits its antigen receptors.

5. Activated helper T cells releases **cytokines** when it encounters a B cell that has previously combined with an identical antigen-bearing agent.

6. Cytokines stimulate the B cells to proliferate.
7. some of the newly formed B cells differentiate into antibody–secreting plasma cells.

8. Antibodies combine with antigen–bearing agents, helping to destroy them.
T cells attack infected cells
Immune response to viruses
Cytokines

- Cytokines: T-cells synthesize and secrete polypeptides called cytokines (or lymphokines) that enhance certain cellular responses to antigens.

- Types of cytokines:
  1. colony – stimulating factors: stimulate bone marrow to produce lymphocytes.
  2. Interferons: Block viral replication, stimulate macrophages to engulf viruses, stimulate B cells to produce antibodies, attack cancer cells.
3. **Interleukins**: control lymphocyte differentiation and growth.
   - Interleukin I-helps activate T-cells.
   - Interleukin II- stimulates synthesis of cytokines and causes T-cells to proliferate and activate cytotoxic T-cells.

4. **Tumor necrosis factor**: stops tumor growth, releases growth factors, causes fever that accompanies bacterial infection, stimulates lymphocyte differentiation.
Types of Acquired Immunity

- **Naturally acquired**
  - **Active**
    - Infection; contact with pathogen
  - **Passive**
    - Antibodies pass from mother to fetus via placenta; or to infant in her milk

- **Artificially acquired**
  - **Active**
    - Vaccine; dead or attenuated pathogens
  - **Passive**
    - Injection of immune serum (gamma globulin)
Types of Immunity

- I. Naturally acquired active immunity:
  - person is exposed to a living antigen.
  - immune system develops lymphocytes and antibodies, providing extremely long-term resistance (possibly for the rest of the person's life).
  - Example – a person has been invaded by the influenza virus, resulting in the production of T-cells, B-cells, and antibodies to fight against the flu.
II. Artificially acquired active immunity:

- person is injected with a vaccine composed of weakened or dead antigen.
- immune system develops lymphocytes and antibodies, providing relatively long-term resistance (possibly for decades).
- stimulation of an immune response without the severe symptoms of a disease.
- Example – a person is vaccinated with the Salk polio vaccine which is made from the polio virus, resulting in the production of T-cells, B-cells, and antibodies for the virus.
III. **Artificially acquired passive immunity:**

- person is injected with a vaccine composed of antibodies (Igs) for a particular antigen.
- immune system is not activated (no lymphocytes or antibodies are produced), providing only short-term resistance (about 2-3 months).
- Immunity for a short time without stimulating an immune response.
- Example – a person is vaccinated with the "flu shot" which contains only antibodies developed for a particular type of influenza virus.
IV. Naturally acquired passive immunity:

- person receives antibodies from another person (e.g. mother to fetus, or person to person during blood transfusion).

- Immune system is not activated, providing only short-term resistance (up to about 6 months).

- Short – Term immunity for infant, without stimulating an immune response.

- Example – fetus before birth usually receives sufficient antibodies from the mother that it will have resistance for up almost a year after birth.
Autoimmune Diseases

- Diseases caused by the failure of lymphocytes and macrophages to recognize "self" body cells, resulting in the activation of immune response against one's own tissues. In most cases, no effective treatments are available.

- **Myasthenia gravis**
  - Immunity against the neuromuscular junctions.
  - Patients become weak and they lose voluntary control of their skeletal muscles.

- **Multiple sclerosis**
  - Immunity against the myelin sheaths of axons.
  - Patients slowly lose proper nervous control of their muscles and other body activities.
- **Rheumatoid arthritis**
  - Immunity against tissues at skeletal joints (especially synovial joints).
  - Patients have painful joints and lose control of body movement, body posture, and strength.

- **Scarlet fever**
  - Initiated by streptococcus bacteria which cause the "strep throat".
  - Immunity against the heart muscle because the surface of the bacteria has certain proteins being similar to those on the cardiac muscle cells.
  - If not treated with antibiotic drugs, may lead to rheumatic fever where immunity is developed against the heart muscle and will degenerate heart actions.
Acquired Immunodeficiency Syndrome (AIDS)

- Caused by the **Human immunodeficiency Virus (HIV)** which infects lymphocytes and suppresses immunity.

- First discovered in homosexual male patients in Los Angeles and New York, who developed rare disorders like *pneumocystis pneumonia* and Kaposi's sarcoma.

- HIV infects **lymphocytes** (particularly **helper T-cell**) and some epithelial cells. The exact mechanism of pathogenesis is still unknown, but the most popular hypothesis is that HIV directly destroys T-cells, resulting in a strong suppression of the immune system.

- HIV can also infect **macrophages** or "hide" inside macrophages and monocytes for a long time – this may explain why some HIV + victims can remain asymptomatic for years, and why HIV can cross the "**blood – brain barrier**" and attack the nervous system.
In U.S., AIDS cases are distributed in 5 main groups: homosexual or bisexual men (70% of all cases), intravenous drug users (19%), heterosexual men or women with multiple sex partners (4%), blood transfusion patients (2%), and mother to fetus transmission (1%).

HIV is usually spread by blood, sexual contact, drug needle, or through pregnancy; and not by food, water, coughing, sneezing, kissing, hugging, utensils, shaking hands, or toilet seats.

4 phases of symptoms:

1. Fever, headache, rash, weight loss, swollen lymph nodes, anti-HIV antibodies in blood (these initial symptoms are known as "AIDS-related complex" or ARC).

2. After years of ARC, T-cells and helper T-cells decline in number, now patients are susceptible to opportunistic infections.
3. HIV–infected macrophages cross the "blood–brain" and attack the brain, causing severe headache, abnormal reflexes, or brain tumor.

4. Patients develop cancer, usually Kaposi's sarcoma, carcinomas of mouth and rectum, or B-cell lymphoma [note: ADIS victims are not killed directly by HIV, but diseases developed during the second, third, or forth phase].

5. Experimental drugs include AZT (which has been discontinued), peptide T, Retrovirus, DDS, DDI, and the latest are the protease inhibitors. [most of these drugs tries to inhibit the synthesis or action of reverse transcriptase].
Transplant types

- **Isograft**: Donor - Identical Twin
  
  Example - Bone marrow transplant from healthy twin to twin who has leukemia.

- **Autograft**: Donor – self
  
  Example – skin graft from one part of body to replace burned skin.

- **Allograft**: Donor – same species
  
  Example – kidney transplant from relative or closely matched donor.

- **Xenograft**: Donor – different species
  
  Example – Heart valve from a pig.