Ministry of higher education and scientific research
University of Baghdad

College of Science
Department of Biotechnology

THEORETICAL IMMUNOLOGY LECTURES

Professor Dr. Mouruj A. Alaubydi **Assistance prof. Dr. Jenan MJ. Alsaffar**

Assistance prof. Wisal Salman **Lecturer Dr. Wassen W. Al Bassam**

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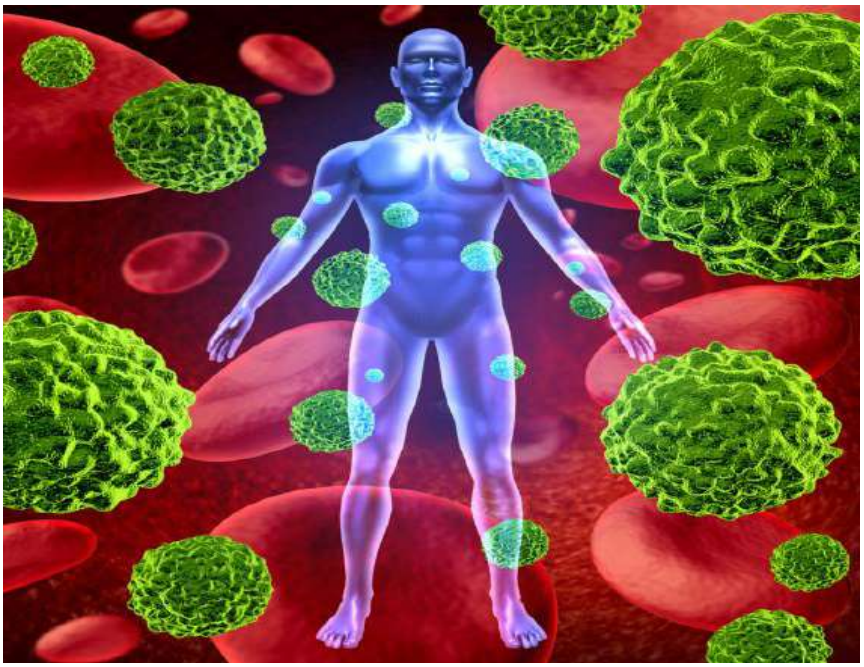


Immunology ***Lecture 1***

Dr. Mouruj Alaubydi **and** ***Dr. Jenan Alsaffar***

Immunology : The science that deal with studying the body's defenses. The immune system is typically associated with defending against foreign intruders, called pathogens, but it can fight against cancer as well.

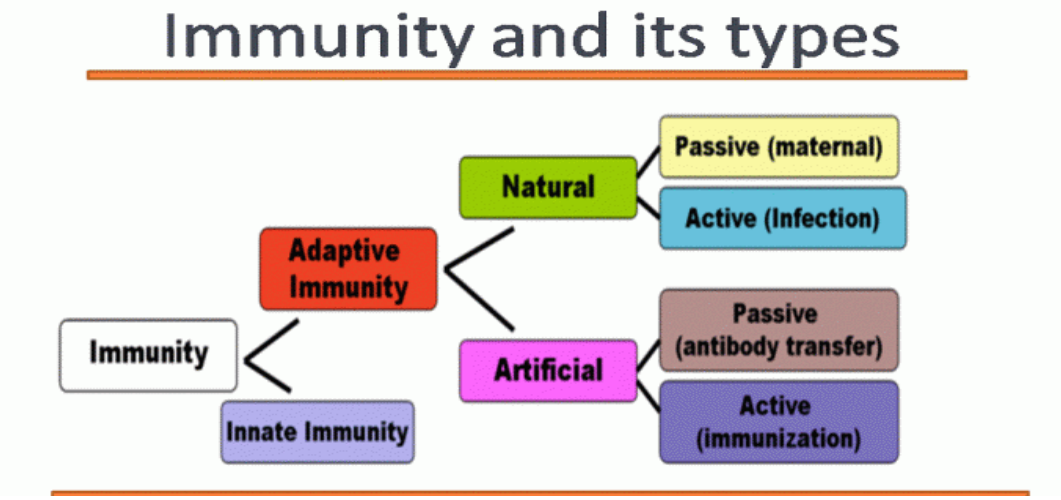
Basic immunology is a branch of immunology that looks at what generally happens in the immune system. For example, what functions do different types of immune cells and chemicals have? How do they react to different function?

Some basic immunologists focus their on the **innate immune system**, which protects against all possible intruders. **Innate immune system cells are neutrophils, Monocytes, Macrophages, Dendritic cells, Natural killer cells, Basophiles, Eosinophil's and others.**

Another basic immunologists focus is **the adaptive immune system**, targets **specific** pathogens. Scientists can study how a type of cell learns to recognize a specific pathogen, and what functions that cell has. Adaptive immune system cells are **B lymphocyte** which is responsible for **antibodies production(humoral immunity),** and **T lymphocytes** which is responsible for **cellular immunity**.

Immunity and its types: Innate and Acquired (adaptive) immunity

- **Immunity** is derived from Latin word *"immunis"* which means free from burden. In this case burden refers to disease caused by microorganisms or their toxic products.
- Therefore **Immunity** is defined as the state of resistance or in susceptibility to disease caused by particular microorganisms or their toxic products



Innate or Natural immunity:

- Immunity with which an individual is born is called innate or natural immunity. Innate immunity **acts as first line of defense** to particular microorganisms.

Component of the natural immunity :

1- Cellular / Mast cells, Neutrophils, Macrophages

2- Humoral/ Complement, Lysozyme, Interferon

Mechanism of innate immunity:

1- **Anatomical barrier**: **Skin and mucus membrane** are the examples of anatomical barriers that provides immunity.

*Skin consists of two distinct layer; a thin outer layer called epidermis and thick inner layer called dermis.

*Epidermis consists of mostly dead cell filled with keratin. Dermis is composed of connective tissue, hair follicle, sebaceous gland and sweat gland .They have mechanism to kill the pathogen before entry to body. Throughout lysozyme, acidic pH, sebum(oil), high salt concentration in sweat are antimicrobial agents found in skin and mucus membrane.

*Skin provides first line of defense by preventing entry of microorganisms. However skin may be penetrated by injury or insects.

*Below skin, the mucus membrane prevents the entry of microorganism to the body. And also it is secrets mucus surrounds the body tracts that entrap microorganisms.

2. Physicochemical barrier: includes physiological barrier and chemical barrier.

- **Physiological** conditions of body such as normal body temperature, normal body pH etc provides immunity.
- Some species are resistant to certain disease simply because of their higher body temperature. For example, mammals are susceptible to anthrax but birds are resistant to anthrax. It is because *Bacillus anthracis* are killed by higher body temperature of birds (39°C).
- Similarly, body pH also provides immunity. For example acidity of stomach kills most of the ingested bacteria and provides immunity. In infants stomach is less acidic. This is the reason why infants suffer more from gastrointestinal disturbance than adults.

- **Chemical barriers** include various antimicrobial chemicals found in body fluids. For examples, Lysozyme found in tear and mucus kills many Gram +ve bacteria.

- **Interferon** found in blood and lymph kills viruses. Other antimicrobial chemicals found in body fluids include complement proteins, collectins, etc.

3. Phagocytic barrier or Phagocytosis

Phagocytosis is an important defense mechanism of host to provide immunity. Most of the bacteria that enter into host are killed by phagocytic cells such as Neutrophils, monocytes and macrophages.

4. **Complement:** Subset of proteins consider as the main component in natural immunity.

5. **Inflammatory barrier** or **Inflammation**

- **Inflammation** is an important defense mechanism of host to prevent infection. It is induced in response to tissue damage caused by microorganism, toxins or by mechanical means.
- The inflammation may be acute; for e.g. in response to tissue damage or chromic; for e.g. Arthritis, cancer etc.
- **Main aim of inflammation is to prevent spread of injected microorganism or toxin from site of injection and kill them on spot by phagocytosis**.
- Acute phase proteins are sensitive indicators of the presence of the inflammatory disease and are especially useful in monitoring such disease.
- The innate immune cells (Mast cells, Neutrophils, Macrophages..etc) in response to inflammation are stimulated to eradicate intruders.

Types of innate immunity:

1. Species immunity:

- If one species is resistant to certain infection and the other species is susceptible to the same infection then it is called as species immunity.

- Physiological and metabolic differences between species determine species immunity. For example, Birds are resistant to anthrax but Human is susceptible. It is simply because higher body temperature of birds kills *Bacillus anthracis*.

2. Racial immunity:

- If one race is susceptible while other race is resistant to same infection, then it is called racial immunity.

- For examples; certain African race are more resistant to malaria and yellow fever where are Asian or Americans are susceptible to same infection. Similarly Orientals (East Asia) are relatively resistant to syphilis.

- Racial immunity is determined by difference in Socio-economic status, habitat, culture feeding habits, environments, genetic, etc.

3. Individual immunity:

- If one individual of certain race or cast is resistant while other individuals of same race or cast are susceptible to certain infection, then it is called as individual immunity
- Individual immunity is determined by various factors such as health status, nutritional status, previous illness, personal hygiene, genetic differences etc.
- For examples; Individual with genetic deficiency of glucose-6 phosphate dehydrogenase are resistant to Malaria.

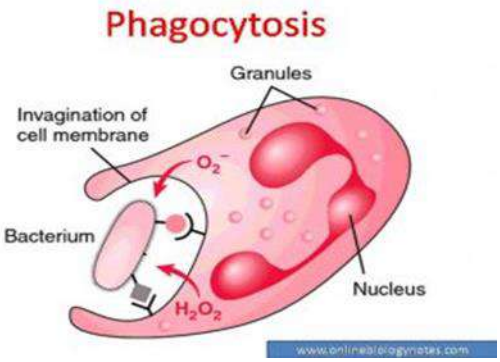
Dr. Mouruj Alaubydi **and** ***Dr. Jenan Alsaffar***

Cells of the Innate Immune System

There are many types of white blood cells or *leukocytes* that work to defend and protect the human body. In order to patrol the entire body, leukocytes travel by way of the circulatory system.

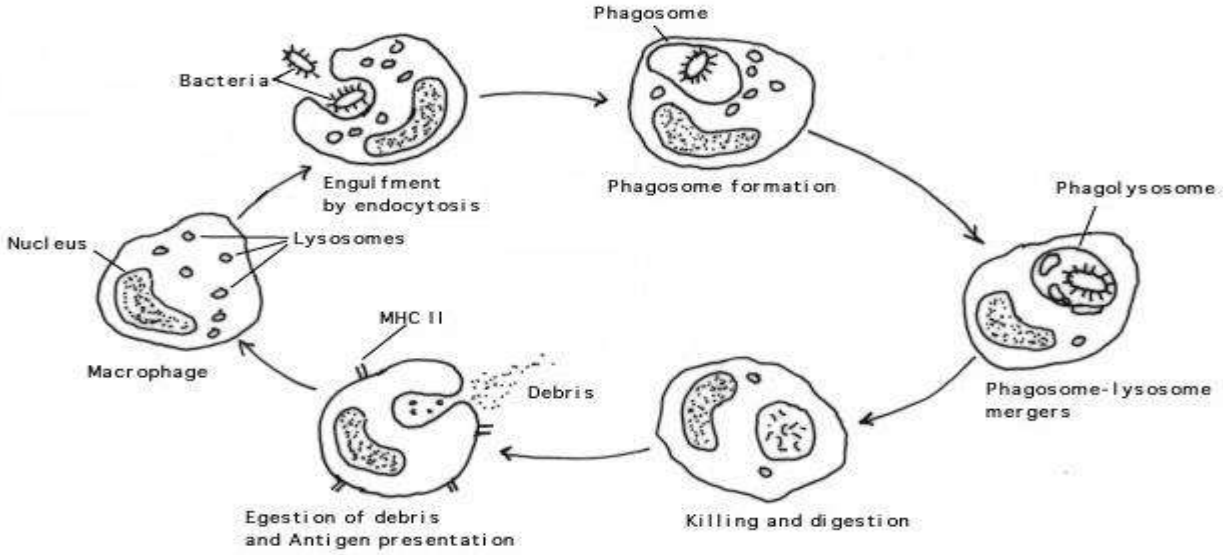
The following cells are leukocytes of the innate immune system:

- *Phagocytes*, or *Phagocytic cells*: Phagocyte means "eating cell", which describes what role phagocytes play in the immune response. Phagocytes circulate throughout the body, looking for potential threats, like bacteria and viruses, to engulf and destroy.



Phagocytosis diagram

Steps in phagocytosis:



1. At first phagocyte approaches to the site of infection
2. Adherance or attachment of antigen on the surface of phagocyte
3. Phagocyte extends pseudopodia around bacterial cell.
4. Pseudopodia gradually increase in size and finally fused so that bacteria is engulfed in the form of phagosome or food vacuole.
5. The phagosome and lysosome come nearer to each other and fuse to form phago-lysosome.
6. Inside phago-lysosome ingested bacteria is killed by hydrolytic and digestive enzyme of lysosome.
7. Required materials released from digested bacteria are absorbed into surrounding cytoplasm and undigested residues are excreted out by exocytosis.

Killing Mechanism of phagocytosis:

Killing of ingested bacteria during phagocytosis occur by two different mechanism

1. Oxygen dependent mechanism

This process is also known as respiratory burst. It is the major mechanism of killing of ingested bacteria during phagocytosis.

2. Oxygen independent mechanism:

- In this mechanism, ingested bacteria are killed by hydrolytic and digestive enzymes of lysozyme.

- ***Macrophages*:** Macrophages, are efficient phagocytic cells that can leave the circulatory system by moving across the walls of capillary vessels. The ability to roam outside of the circulatory system is important, because it allows macrophages to hunt pathogens with less limits. Macrophages can also release cytokines in order to signal and recruit other cells to an area with pathogens.
- ***Mast cells*:** Mast cells are found in mucous membranes and connective tissues, and are important for wound healing and defense against pathogens via the inflammatory response. When mast cells are activated, they release cytokines and granules that contain chemical molecules to create an *inflammatory cascade*. Mediators, such as histamine, cause blood vessels to dilate, increasing blood flow and cell trafficking to the area of infection. The cytokines released during this process act as a messenger service, alerting other immune cells, like neutrophils and macrophages, to make their way to the area of infection, or to be on alert for circulating threats.

- ***Neutrophils*:** Neutrophils are phagocytic cells that are also classified as *granulocytes* because they contain granules in their cytoplasm. These granules are very toxic to bacteria and fungi, and cause them to stop proliferating or die on contact.

The bone marrow of an average healthy adult makes approximately 100 billion new neutrophils per day. **Neutrophils are typically the first cells to arrive at the site of an infection because there are so many of them in circulation at any given time.**

- ***Eosinophils*:** Eosinophils are granulocytes target multicellular parasites. Eosinophils secrete a range of highly toxic proteins and free radicals that kill bacteria and parasites. The use of toxic proteins and free radicals also causes tissue damage during allergic reactions, so activation and toxin release by eosinophils is highly regulated to prevent any unnecessary tissue damage.

While eosinophils only make up 1-6% of the white blood cells, they are found in many locations, including the thymus, lower gastrointestinal tract, ovaries, uterus, spleen, and lymph nodes.

- ***Basophils*:** Basophils are also granulocytes that attack multicellular parasites. Basophils release histamine, much like mast cells. The use of histamine makes basophils and mast cells key players in mounting an allergic response.

- ***Natural Killer cells*:** Natural Killer cells (NK cells), do not attack pathogens directly. Instead, natural killer cells destroy infected host cells in order to stop the spread of an infection. Infected or compromised host cells can signal natural kill cells for destruction through the expression of specific receptors and antigen presentation.

- ***Dendritic cells*:** Dendritic cells are antigen-presenting cells that are located in tissues, and can contact external environments through the skin, the inner mucosal lining of the nose, lungs, stomach, and intestines. Since dendritic cells are located in tissues that are common points for initial infection, they can identify threats and act as messengers for the rest of the immune system by antigen presentation. Dendritic cells also act as bridge between the innate immune system and the adaptive immune system.

Lecture -3

Dr. Jinan alsaffar &Dr. Mouruj Alaubydi

The internal defense system

The second part of natural immunity is **the internal defense system**, in which both **cells and soluble factors play essential parts**. **The internal defense system** is designed **to recognize molecules** that are unique to infectious organisms. This typically involves recognizing a **carbohydrate such as mannose that is found in microorganisms** and is not evident on **human cells**. White blood cells **seek out and destroy foreign cells by participating in phagocytosis**, which is **the engulfment of cells or particulate matter by leukocytes, macrophages, and other cells. This process destroys most of the foreign invaders that enter the body,** and it is the most important function of the internal defense system. **Phagocytosis is enhanced by soluble factors called acute phase reactants.**

Acute-Phase Reactants

Acute-phase reactants are normal serum constituents that increase rapidly by at least 25 percent due to infection, injury, or trauma to the tissues. Some of **the most important ones are C-reactive protein, serum amyloid A, complement components, mannose-binding protein, alpha1-antitrypsin, haptoglobin, fibrinogen, and ceruloplasmin.** They are produced primarily by hepatocytes (liver parenchymal cells) within 12 to 24 hours in response to an increase in certain intercellular signaling polypeptides called cytokines.

C - reactive protein

C-reactive protein is a homogeneous molecule with a molecular weight of 118,000 Dalton's and a structure that consists of five identical subunits held together by noncovalent bonds. **CRP** can be thought of as a primitive, **nonspecific form of antibody molecule that is able to act as a defense against microorganisms** or **foreign cells until specific antibodies can be produced**. CRP acts somewhat like an antibody**, as it is capable of opsonization (the coating of foreign particles), agglutination, precipitation, and activation of complement by the classical pathway**.

The Lymphoid System

The key cell involved in the immune response is the lymphocyte. Lymphocytes represent between 20 and 40 percent of the circulating white blood cells. The typical small lymphocyte is between 7 and 10 μm in diameter and has a large rounded nucleus that may be somewhat indented. These cells are unique, because they arise from a hematopoietic stem cell and then are further differentiated in the **primary lymphoid organs**. They can be separated **into two main classes**, depending on where this differentiation takes place. **The primary lymphoid organs** in humans are **the bone marrow and the thymus**. Once lymphocytes mature in the primary organs, they are released and make their way to **secondary organs**, which include the **spleen, lymph nodes, appendix, tonsils, and other mucosal-associated lymphoid tissue.**

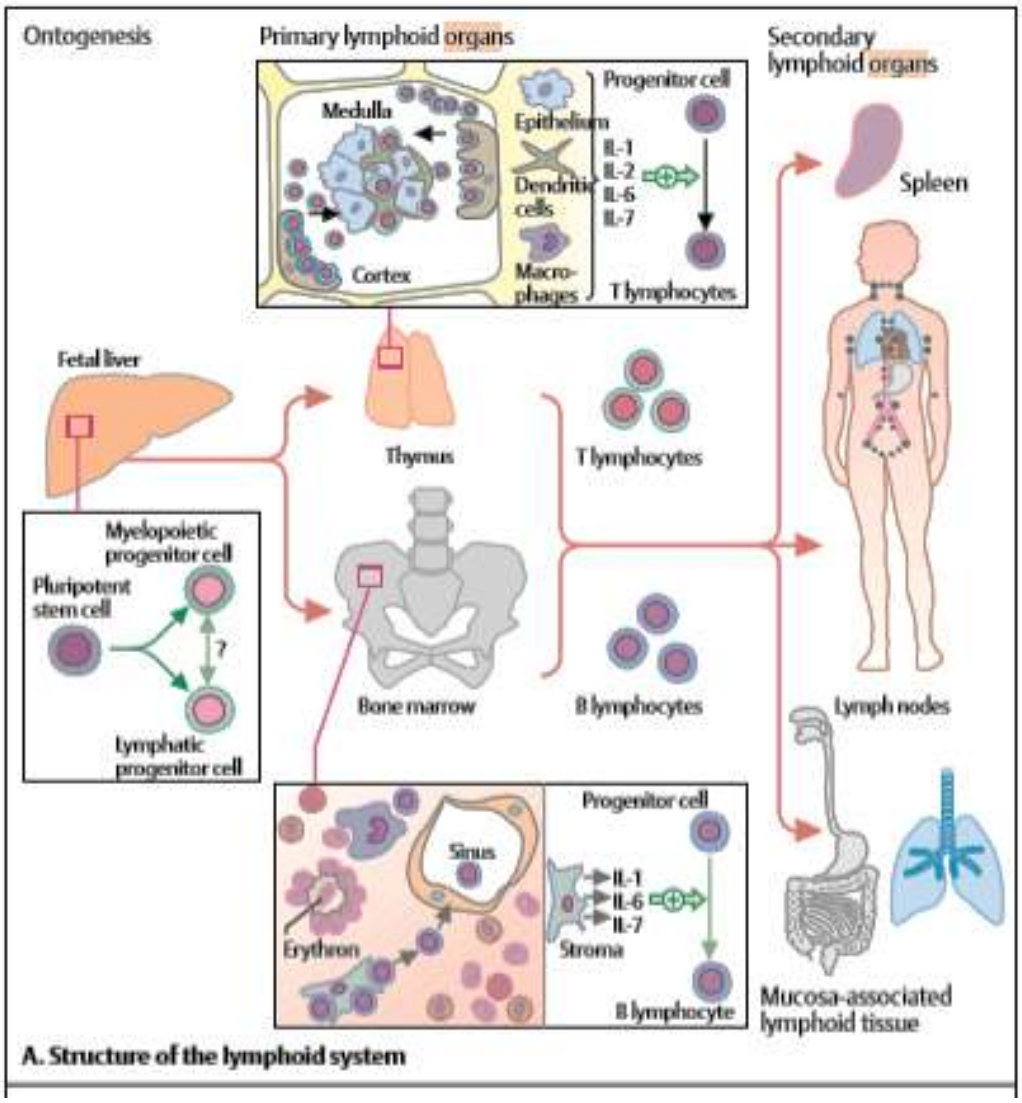
PRIMARY LYMPHOID ORGANS

Bone Marrow:

All lymphocytes arise from pluripotential hematopoietic stem cells that appear initially in the yolk sac of the developing embryo and are later found in the fetal liver. Bone marrow assumes this role when the infant is It can be considered the largest tissue of the body.

Bone marrow fills the core of all long bones and is **the main source** of **hematopoietic stem cells**, which develop into erythrocytes, granulocytes, monocytes, platelets, and lymphocytes.

Each of these lines has specific precursors that **originate** from the pluripotential **stem cells**. Most authorities agree that **T, B, and NK cells arise from a common precursor known as the common lymphoid precursor (CLP**)(see Fig. 1). Lymphocyte precursors are **further developed in the primary lymphoid organs**.



The bone marrow functions as the center for antigen independent lymphopoiesis. Lymphocyte stem cells **are released** from the marrow **and travel** to additional **primary lymphoid organs**. **One subset goes to the thymus** and develops into **T cells**. In humans**, B-cell maturation** takes place within the bone marrow itself. In peripheral blood, approximately 10 to 20 percent of **all lymphocytes are B cells**, 61 to 89 percent **are T cells**, and up to 22 percent **are NK cells**.

Thymus

T cells develop their identifying characteristics in the thymus, which is a small, flat, bilobed organ found in the thorax, or chest cavity, right below the thyroid gland and overlying the heart .In humans, it weighs an average of 30 g at birth, reaches about 35 g at puberty, and then gradually atrophies. The thymus diminishes in size, it is still capable of producing **T lymphocytes** until at least the fifth or sixth decade of life. Each lobe of the thymus is divided into lobules filled with epithelial cells that **play a**

central role in this differentiation process. Surface antigens are acquired as the lymphocytes travel from the cortex to the medulla over a period of 2 to 3 weeks. Mature T lymphocytes are then released from the medulla.

Progenitors of T cells appear in the fetus as early as 8 weeks in the gestational period. Thus, differentiation of lymphocytes appears to take place very early in fetal development and **is essential to acquisition of immunocompetence by the time the infant is born.**

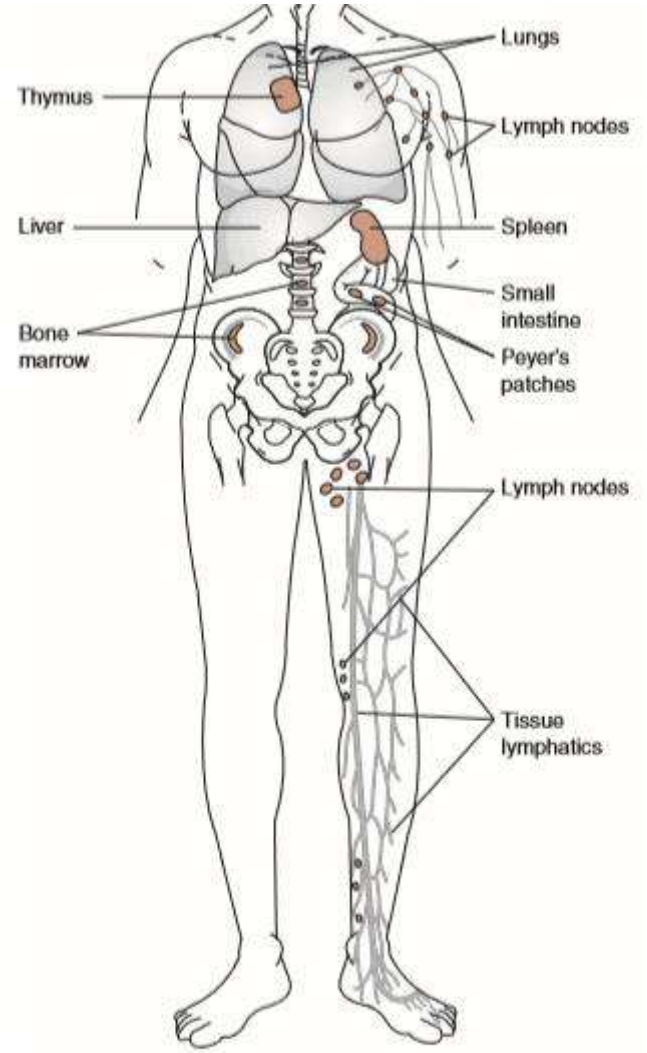


FIGURE 2–3. Sites of lymphoreticular tissue. Primary organs include the bone marrow and the thymus. Secondary organs are distributed throughout the body and include the spleen, lymph nodes, and mucosal-associated lymphoid tissue. The spleen filters antigens in the blood, while the lymphatic system filters fluid from the tissues. *(From Widmann, FK. An Introduction to Clinical Immunology. F. A. Davis, Philadelphia, 1989, with permission.)*

SECONDARY LYMPHOID ORGANS

Once differentiation occurs, mature T and B lymphocytes are released from the bone marrow and the thymus. They migrate to secondary lymphoid organs and become part of a recirculating pool. Each lymphocyte spends most of its life span in solid tissue, entering the circulation only periodically to go from one secondary organ to another. **The secondary lymphoid organs include the spleen, lymph nodes, tonsils, appendix, Peyer's patches in the intestines, and other mucosal-associated lymphoid tissue (MALT).**

Lymphocytes in these organs travel through the tissue and return to the bloodstream by way of the thoracic duct. A specific lymphocyte may make the journey from blood to secondary lymphoid organs and back one to two times per day. This continuous recirculation increases the likelihood of a lymphocyte coming into contact with its specific antigen**.**

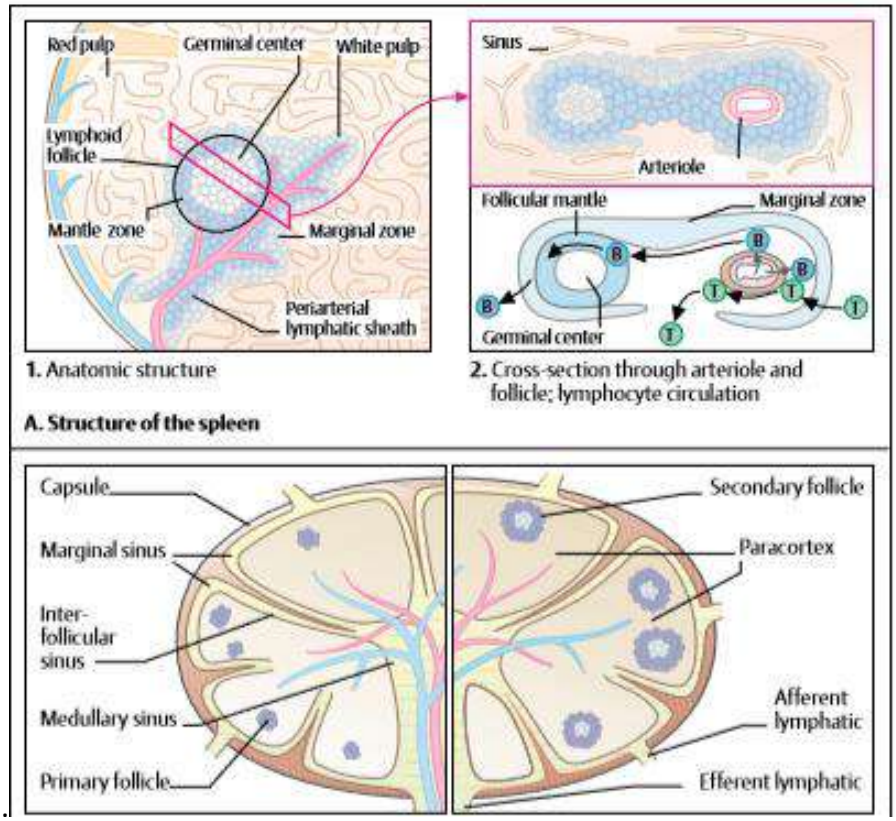
Spleen

The spleenis the largest secondary lymphoid organ, having a length of approximately 12 cm and weighing 150 g in the adult. It is located in the upper-left quadrant of the abdomen, just below the diaphragm and surrounded by a thin connective tissue capsule. The organ can be characterized as a large discriminating filter, as it removes old and damaged cells and foreign antigens from the blood.

Splenic tissue can be divided into two main types: **red pulp and white pulp**. The red pulp makes up more than one half of the total volume, and its function is to **destroy old red blood cells**. Blood flows from the arterioles into the red pulp and then exits by way of the splenic vein. **The white pulp comprises** approximately 20 percent of the total weight of the spleen and contains the lymphoid tissue, which is arranged around arterioles in a periarteriolar lymphoid sheath (PALS).

This sheath contains **mainly T cells**. Attached to the sheath are primary follicles,which **contain B cells** that are not yet stimulated by antigen.Surrounding the PALS is a marginal zone containing **dendritic cells that trap antigen**. Lymphocytes enter and leave this area by means of the many capillary branches that connect to

the arterioles. Each day, an adult's blood volume passes through the spleen approximately four times, **where lymphocytes and macrophages can constantly survey for infectious agents or other foreign matter.**



Lymph Nodes

Lymph nodes are located along lymphatic ducts and serve as central collecting points for lymph fluid from adjacent tissues. Lymph fluid arises from passage of fluids and low molecular-weight solutes out of blood vessel walls and into the interstitial spaces between cells.

Lymph nodes are especially numerous **near joints** and where the **arms and legs join the body**. Nodes range in size from 1 mm to about 25 mm in diameter. **Filtration is a main function** of these organs. The lymph fluid flows slowly through spaces called sinuses, which are lined with **macrophages**, creating an ideal location for **phagocytosis t**o take place. The tissue is organized into an **outer cortex, a paracortex, and an inner medulla**.

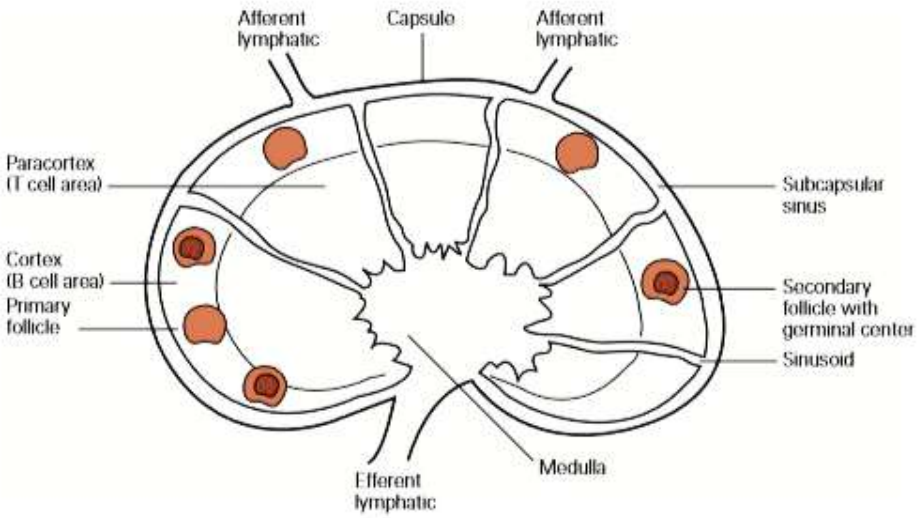


FIGURE 2–5. Structure of a lymph node. A lymph node is surrounded by a tough outer capsule. Right underneath is the subcapsular sinus, where lymph fluid drains from afferent lymphatic vessels. The outer cortex contains collections of B cells in primary follicles. When stimulated by antigen, secondary follicles are formed. T cells are found in the paracortical area. Fluid drains slowly through sinusoids to the medullary region and out the efferent lymphatic vessel to the thoracic duct.

Lymphocytes and any foreign antigens present enter nodes via afferent lymphatic vessels. Numerous lymphocytes also enter the nodes from the bloodstream by means of specialized venules called high endothelial venules, **located in Para cortical areas**. **The outermost layer, the cortex**, contains **macrophages** and **aggregations of B cells** in primary follicles similar to those found in the **spleen.** These are the mature, **resting B cells** that have not yet been exposed to antigen. **Specialized cells called follicular dendritic cells** are also located here. They are found only in lymphoid follicles.

Secondary follicles consist of antigen-stimulated proliferating B cells. **Plasma cells**, which actively secrete **antibody, and memory cells**, which are just a step away from forming plasma cells, are present. Generation of **B-cell memory is a primary function of lymph nodes**.

T lymphocytes are mainly localized in the paracortex, the region between the follicles and the medulla. **T lymphocytes** are in close proximity to antigen-presenting cells called interdigitating cells. **The medulla is less densely populated but contains some T cells (in addition to B cells), macrophages, and numerous plasma cells. Particulate antigens are removed as the fluid travels across the node from cortex to medulla.**

The transit time through.

<u>Other Secondary Organs</u>

Additional areas of lymphoid tissue include the MALT **tonsils**, **appendix**, and **cutaneous-associated lymphoid tissue**. MALT, the mucosal associated lymphoid

tissue, **is found in the gastrointestinal**, **respiratory**, and **urogenital tracts**. Here**, macrophages and lymphocytes** are localized at some of the main ports of entry for foreign organisms. **Peyer's patches** represent a specialized type of MALT and are located at the lower ileum of the intestinal tract.

The tonsils are another area of lymphoid tissue found in the mucous membrane lining of the oral and pharyngeal cavities. Their function is to respond to pathogens entering the respiratory and alimentary tracts. **An additional location of lymphoid tissue is the appendix**. All of these secondary organs function **as potential sites for contact with foreign antigen**, and they increase the probability of an immune response. The epidermis contains a number of intraepidermal lymphocytes. Most of these are **T cells, which are uniquely positioned to combat any antigens that enter through the skin.** This association of lymphocytes is known as the cutaneous-associated lymphoid tissue.

Within each of these secondary organs**, T and B cells are** segregated and perform specialized functions. B cells **differentiate into memory cells and plasma cells and are responsible for humoral immunity or antibody** formation. **T cells play a role in cell-mediated immunity**, and as such, **they produce sensitized lymphocytes** that **secrete cytokines**. **Cytokines** are small polypeptides that regulate the functions of lymphocytes and other cells involved in the immune response. The characteristics and markers for each type of lymphocyte are considered separately.

Third Line of Defense: Acquired or Developed or adaptive immunity:

- Immunity which is developed later in life after microbial infection in host is called as Acquired or developed immunity. Acquired immunity is provided by **Humoral** (Antibodies and cytokines) and certain **cellular** represented by B , T-lymphocytes and plasma cells.
- Components of acquired immunity such as Antibodies and cells are **specific** to particular microorganism. Therefore, acquired immunity is also known as **Specific immunity**.

Characteristics of Acquired immunity:

***Specificity *Self/non-self-recognition *Immunological memory *Diversity**

Types of acquired immunity:

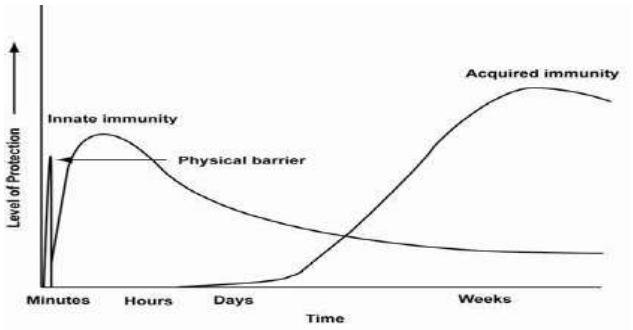
1. Active immunity 2. Passive immunity

1. Active immunity:

- If host itself produces antibodies, it is called active immunity.
- It is of two types; artificial active immunity and natural active immunity.
- **Artificial active immunity:** Immunity provided by vaccination.
- **Natural active immunity:** immunity provided by natural infection.

2. Passive immunity:

- If host does not produce antibodies itself but antibodies produced in other host provides immunity, then it is known as Passive immunity.
- It is of two types; natural passive immunity and Artificial passive immunity
- **Natural passive immunity:** IgG antibody produced in mother cross placenta and protects fetus up to 6-month old age.



- **Artificial passive immunity:** if preformed antibody are injected into host for immunity, e.g. Anti-venom, Rabies vaccine (* it is not a vaccine, it is preformed anti rabies antibody)

Diagram illustrate the interaction between innate and adaptive immunity

Table: Illustrate the differences between innate and adaptive immunity

S.N.	Characteristics	Innate Immunity	Adaptive immunity
1.	Presence	Innate immunity is something already present in the body. Generally inherited and Present at birth	Adaptive immunity is created in response to exposure to a foreign substance. Cannot be inherited and develops during a person's lifetime
2.	Specificity	Non-Specific	Specific and can distinguish between self and non-self
3.	Response	Fights any foreign invader and Rapid	Fight only specific infection Slow (1-2 weeks)
4.	Potency	Limited and Lower potency	High potency
5.	Memory	No memory	Long term memory
6.	Works Against	microbes	Microbes and non-microbial substances called antigens
7.	Diversity	Limited	High
8.	Complement system activation	Alternative and lectin pathways	Classical pathway
9.	Composition	The innate immune system is composed of physical and chemical barriers, phagocytic leukocytes, dendritic cells, natural killer cells, and plasma proteins.	Adaptive immune system is composed of B cells and T cells.

Adaptive immune cells:

Lymphocytes and plasma cells

The adaptive immune system is comprised of the **humoral and cellular systems.** Each of the two arms of the adaptive immune system has fundamental mechanisms allowing the body to attack an invading pathogen. The immunologically specific cellular component of the immune system is organized around two classes of specialized cells, **T** and **B lymphocytes.** Lymphocytes recognize foreign antigens, directly destroy some cells, or produce antibodies as **plasma cells.**

Virgin or naïve lymphocytes

Virgin or naïve lymphocytes are cells that have not encountered their specific antigen. These cells do express high molecular- weight variants of leukocyte common antigen.

Memory cells are populations of long-lived T or B cells that have been stimulated by antigen. They can make a quick response to a previously encountered antigen. **Memory B cells carry surface IgG as their antigen receptor; memory T cells express the CD45RO variant of the leukocyte common antigen** and **increased levels of cell-adhesion molecules , chemical mediators involved in inflammatory processes throughout the body**

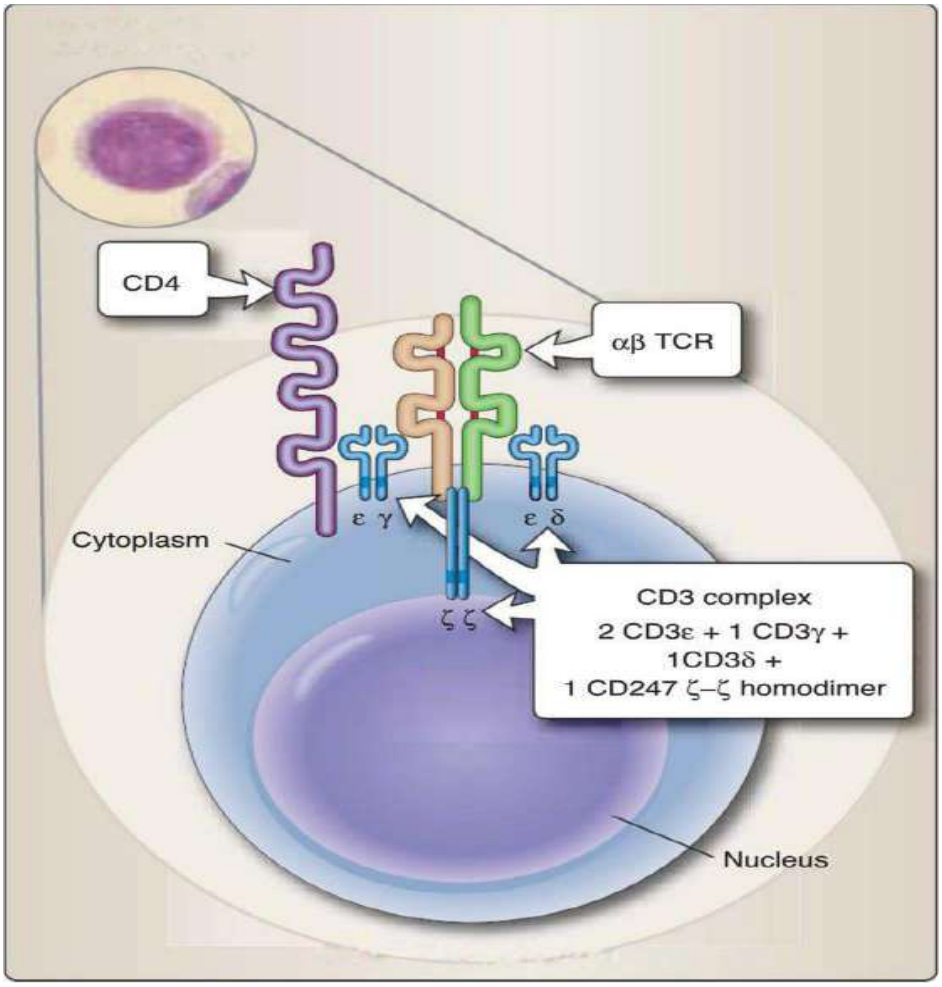
Development of T lymphocytes

Most lymphocytes found in the circulating blood are **T cells derived from bone marrow progenitor cells** that mature in the thymus gland . These cells are responsible for **cellular immune responses** and **are involved in the regulation of antibody reactions in conjunction with B lymphocytes**.

Approximate Percentage of Lymphocytes in Lymphoid Organs		
Lymphoid Organ	**T Lymphocytes (%)**	**B Lymphocytes (%)**
Thymus	100	0
Blood	80	20
Lymph nodes	60	40
Spleen	45	55
Bone marrow	10	90

Early Cellular Differentiation and Development

A.Thymus-derived cells: T cells are the key players in most adaptive immune responses. They participate directly in immune responses as well as orchestrating and regulating the activities of other cells.


CD4
αβ TCR
ε γ
ε δ
Cytoplasm
ζ ζ
CD3 complex
2 CD3ε + 1 CD3γ +
1CD3δ +
1 CD247 ζ–ζ homodimer
Nucleus

* Types of T cells:

1. CD4 + T cells: These cells account for approximately two-thirds of mature CD3+ T cells. CD4 molecules displayed on the surfaces of these T cells recognize a non-peptide-binding portion of MHC class II molecules (Fig. above) . As a result, CD4 + T cells, also known as **helper T (Th)** cells, are "restricted" to the recognition of pMHC class I I complexes and **some act as Regulatory T cells**. **Regulatory T cells may also maintain tolerance**. Characteristically, **they inhibit the activity of auto-reactive lymphocytes**. Treg cells express both CD4 and CD25 molecules and are thought to be important inhibitors of immune- mediated inflammatory diseases such as inflammatory bowel disease.

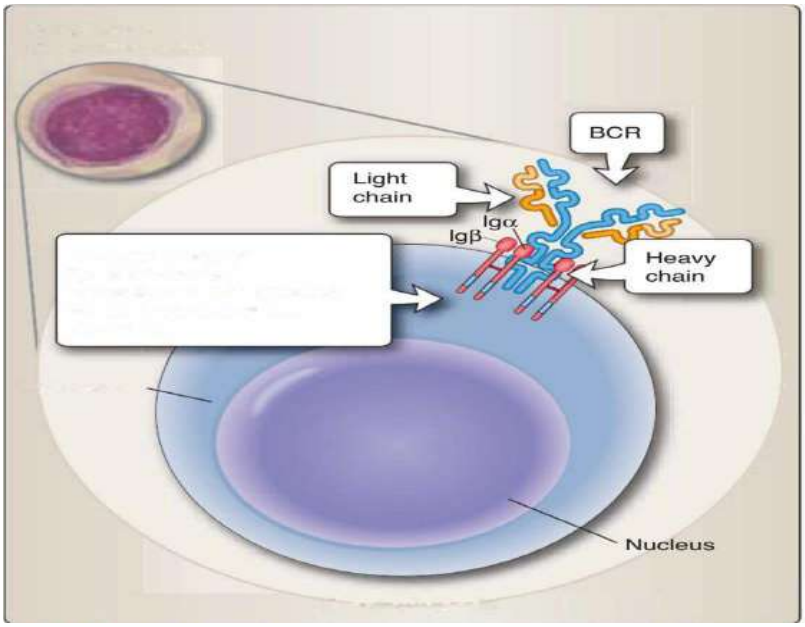
2.CD8 +T cells: account for approximately one-third of all mature CD3+ T cells. CD8 molecules displayed on the surfaces of these T cells recognize the non-peptide-binding portion of MHC class I molecules. As a result, CD8 T cells are "restricted" to the recognition of pMHC I complexes . Functionally, CD8+ T cells are also known as **cytotoxic T (Tc)** and **some act as suppressor T (Ts)** cells. Tc cells identify body cells that are infected with intracellular organisms, such as viruses and intracellular bacteria, and eliminate the cells harboring these organisms. Ts cells function to down-regulate and thus control adaptive immune responses.

B . Bone marrow-derived cells

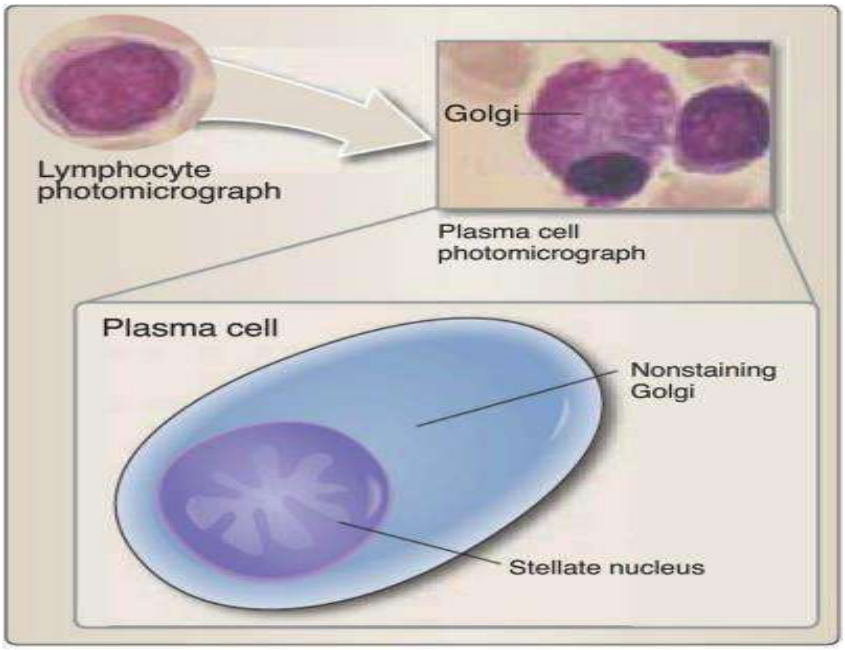
Not all lymphocytes of bone marrow origin are destined for thymus education. Certain cells of lymphoid lineage **remain and develop within the bone marrow** and are the precursors of immunoglobulin-producing lymphocytes. These bone marrow-derived lymphocytes, also known as **B lymphocytes or B cells**, **synthesize immunoglobulin and display it on their surfaces**, **where it functions as their BCR**. **Plasma cells are derived from differentiated , mature B cells and both synthesize and secrete immunoglobulin**.

1 . B cells arise from pluripotent hematopoietic stem cells in the bone marrow. They do not migrate to the thymus but develop within the bone marrow. B cell is specific, that is, it produces immunoglobulin of only one antibody specificity that recognizes only one epitope. It is the extreme diversity among B cells, each producing a single form of immunoglobulin , that generates the overall diversity of the immunoglobulin (or antibody) response

2. Plasma cells derive from **terminally differentiated B cells and are immunoglobulin producing and immunoglobulin-secreting cells.**



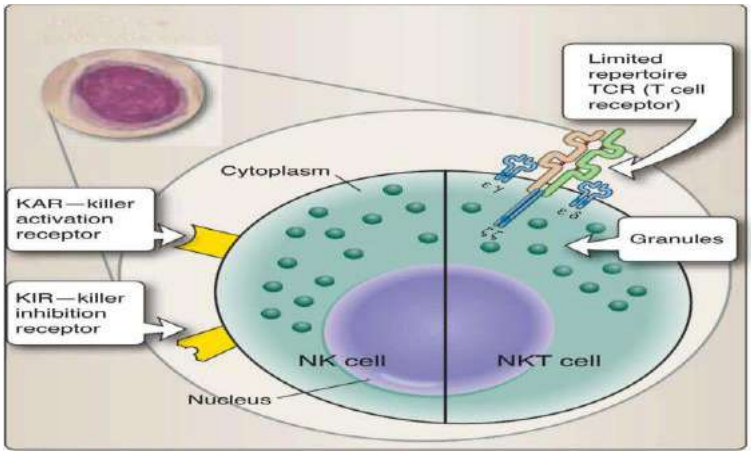
They cease to use immunoglobulin as a membrane receptor and instead secrete it into the fluids around the cells. **Plasma cells, with increased size and metabolic activity, are factories that produce large quantities of immunoglobulin during their short life span of less than 30 days.** They are characterized by basophilic cytoplasm, a nucleus that has a stellate (star like) pattern with in it, and non-staining Golgi (Fig. down).



C. Natural killer cells:

Approximately 5% to 10% of peripheral blood lymphocytes **lack both T-cell (CD3) and B-cell (surface immunoglobulin) markers**. These cells are known as **natural killer (NK) cells** to reflect **their ability to kill certain virally infected cells and tumor cells without prior sensitization** . Their **granular appearance** is caused by the presence of **cytoplasmic granules** containing **perforin and granzyme** that can be

released to **damage the membranes of the cells they attack.** NK cells **develop within the bone marrow and lack TCR produced by rearrangement of TCR genes**. However, they do bear another set of receptors called **killer activation receptors (KARs) and killer inhibition receptors (KIRs)** that allow them to recognize host cells that might need to be destroyed. In addition, a unique subset of T cells, designated **NKT because they share some functional characteristics with NK cells, develop within the thymus and express a rearranged TCR of extremely limited repertoire** (Fig. below). Unlike conventional T cells, **NKT cells respond to lipids, glycolipids, or hydrophobic peptides presented by a specialized, non-classical MHC class I molecule**, and secrete large amounts of cytokines.



IMMUNOGENS AND ANTIGENS

Immune responses arise as a result of exposure to foreign stimuli. The compound that evokes the response is referred to either as **antigen** or as **immunogen. An antigen is any agent capable of binding specifically to components of the immune system, such as the B cell** receptor (**BCR)** on **B lymphocytes** and **soluble antibodies**. By contrast, **an immunogen is any agent capable of inducing an immune response and is therefore immunogenic.**

The distinction between the terms is **necessary** because there are many compounds that are **incapable** of **inducing an immune response**, yet they are capable of **binding with components** of the **immune system** that have been induced specifically against them. Thus **all immunogens** are **antigens**, but not all **antigens are immunogens**. This **difference** becomes obvious in the case of **low molecular weight compounds**, a group of substances that includes many **antibiotics and drugs**. By themselves, these compounds are **incapable of inducing** an immune response but when they are coupled with much larger entities, such as **proteins**, the **resultant conjugate** induces an immune response that is directed against various parts of the conjugate, including the **low molecular weight** compound.

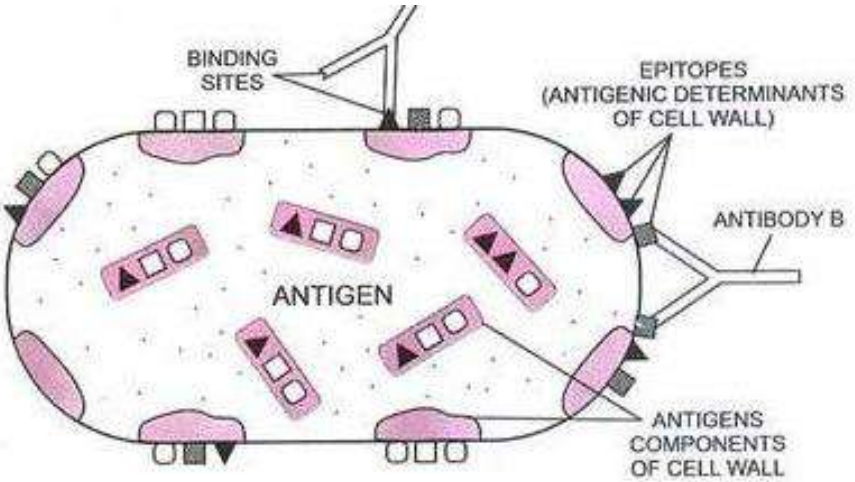


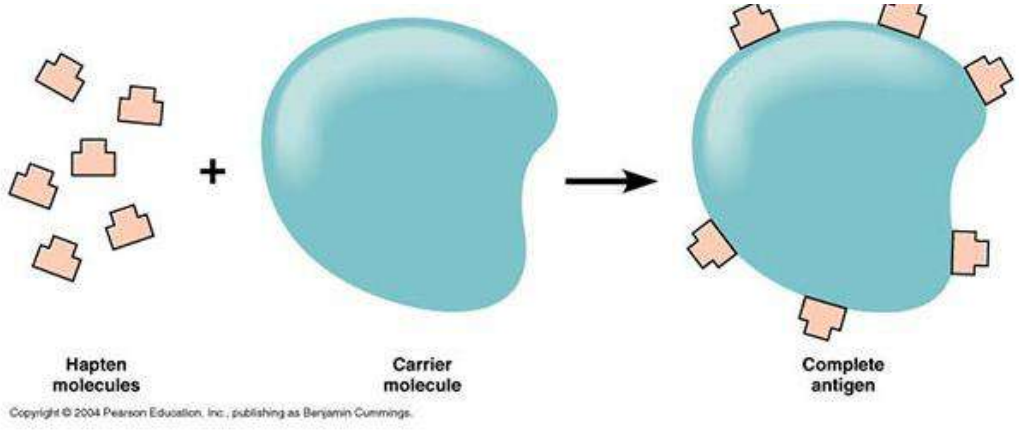
Diagram showing an antigen with epitopes (antigenic determinants). Two attached antibodies are also shown.\

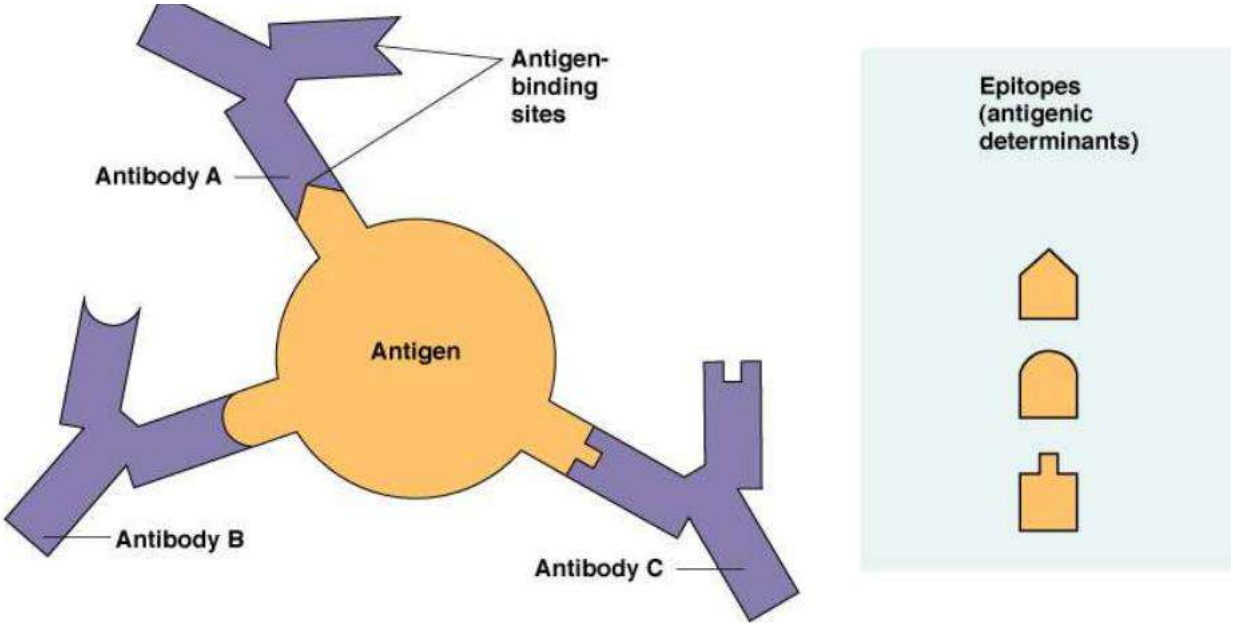
Antigenicity: refers to **the ability of a compound to bind with antibodies or with cells of the immune system. This binding is highly specific**; the immune components are capable of recognizing various physicochemical aspects of the compound. The binding between antigen and immune components **involves several weak forces** operating over short distances (**van der Waals forces, electrostatic interactions, hydrophobic interactions, and hydrogen bonds); it does not involve covalent bonds**.

Immunogenicity: is the ability of a particular substance, such as an antigen or epitope, to provoke an immune response in the body of a human and other animal. In other words, immunogenicity is the ability to induce a **humoral** and/or **cell-mediated immune responses.**

Epitope : is immunologically **active regions of an immunogen** (or antigen) that binds to **antigen-specific membrane receptors** on lymphocytes or to secreted antibodies. It is also called **antigenic determinants**.

Hapten: **Small foreign molecule that is not antigenic**. It's a type of antigen that elicits production of antibodies only when combined with another antigenic molecule, then antibodies are formed when they will recognize hapten.





Chemical Nature of Antigens (Immunogens)

A. **Proteins:** The vast majority of immunogens are **proteins**. These may be pure proteins or they may be glycoproteins or lipoproteins. In general, **proteins are usually very good immunogens**
B. **Polysaccharides:** Pure polysaccharides and lipopolysaccharides are good immunogens.
C. **Nucleic Acids:** Nucleic acids are usually **poorly** immunogenic. However, they may become immunogenic when single stranded or when **complexed with proteins**.
D. **Lipids:** In general lipids are **non-immunogenic**, although they may be **haptens.**

Types of antigen on the basis of their class (Origin)

E. **1. Exogenous antigens**

*These antigens enter the body or system and start circulating in the body fluids and trapped by the **APCs** (**A**ntigen **p**resenting **c**ells such as macrophages, dendritic cells, etc.).

*The uptakes of these exogenous antigens by APCs are mainly **mediated by the phagocytosis**. Examples: bacteria, viruses, fungi …etc.

*Some antigens start out as exogenous antigens, and later become endogenous (for example, intracellular viruses).

2. Endogenous antigens

*These are body's own cells or sub fragments or compounds or the antigenic products that are produced.

*The endogenous antigens **are processed by the macrophages** which are later accepted by the **cytotoxic T – cells.**

REQUIREMENTS FOR IMMUNOGENICITY

A substance must possess the following characteristics to be immunogenic: (1) foreignness; (2) high molecular weight; (3) chemical complexity (4) degradability and interaction with host major histocompatibility complex (MHC) molecules.

Foreignness

Animals normally do not respond immunologically to self. Thus, for example, if a rabbit is injected with its own serum albumin, **it will not mount an immune response**; it recognizes the albumin as self. By contrast, if rabbit serum albumin is injected into a guinea pig, the guinea pig **recognizes** the rabbit serum albumin **as foreign** and **mounts an immune response** against it. To prove that the rabbit, which did not respond to its own albumin, is immunologically competent, it can be injected with guinea pig albumin. The competent rabbit will mount an immune response to guinea pig serum albumin **because it recognizes** the substance as foreign. Thus, the first requirement for a compound to be **immunogenic** is **foreignness**. **In general**, compounds that are **part of self** are **not immunogenic** to that individual. However , there are **exceptional cases** in which an individual mounts an immune response against his or her own tissues. This condition is termed **autoimmunity.**

High Molecular Weight

The second feature that determines whether a compound is immunogenic is its molecular weight. In general, small compounds that have a molecular weight of less than 10KDa (e.g., penicillin, progesterone, aspirin) are not immunogenic; those of molecular weights between 1,000 and 6,000Da (e.g., insulin, adrenocorticotropic hormone [ACTH]) may or may not be immunogenic; and those of **molecular weights equal or greater** than 10KDa (e.g., albumin, tetanus toxin) are **generally immunogenic**. In short, relatively small substances have **decreased immunogenicity.**

Chemical Complexity

The third characteristic is **Chemical Structure**. Proteins and polysaccharides are among the **most potent immunogens**, although relatively **small polypeptide chains**, **nucleic acids**, and even **lipids** can, given the appropriate circumstances, be immunogenic. **Proteins**: **Large heterologous proteins express a wide diversity of antigenic determinants and are potent immunogens**. It must be noted that the immunogenicity of a protein is **strongly i**nfluenced by its chemical composition. **In general, the more complex substance is chemically the more immunogenic it will be**. It is presumed that presence of an **aromatic radical** is essential for rigidity and antigenicity of a substance.

Degradability: Antigens that are easily phagocytosed are generally more immunogenic.

This is because for most antigens (T-dependent antigens) the development of an immune response requires that the antigen be phagocytosed, processed and presented to helper T cells by an antigen presenting cell (APC).

Other factors: Such as

1. **Age:** Age can also influence immunogenicity. Usually the very young and the very old have a diminished ability to elicit and immune response in response to an immunogen.
2. **Genetic Factors:** Some substances are immunogenic in one species but not in another .Similarly, some substances are immunogenic in one individual but not in others (i.e. responders and non-responders). The species or individuals may lack or have altered genes that code for the receptors for antigen on B cells and T cells. They may not have the appropriate genes needed for the APC to present antigen to the helper T cells.

ADJUVANTS

To enhance the immune response to a given immunogen, various additives or vehicles are often used. An adjuvant (from the Latin, adjuvare, "to help") **is a substance that, when mixed with an immunogen, enhances the immune response against the immunogen.** It is important to distinguish between a carrier for a **hapten and an adjuvant**. A hapten will become

immunogenic when **conjugated covalently to a carrier**; it will not become immunogenic if mixed with an adjuvant. Thus an adjuvant enhances the immune response to immunogens but does not confer immunogenicity on haptens. The identification of adjuvants for use with vaccines is growing because many new vaccine candidates lack sufficient immunogenicity.

Adjuvant mechanisms include (1) increasing the biological or immunological half-life of vaccine antigens. (2) Increasing the production of local inflammatory cytokines; and (3) improving antigen delivery and antigen processing and presentation by APCs, especially the dendritic cells.

PRIMARY AND SECONDARY RESPONSES

The **first exposure** of an individual to an immunogen is referred to as the **primary immunization**, which generates a **primary response**. Many events take place during this primary immunization:

1/cells process antigen,

2/triggering antigen-specific lymphocytes to proliferate and differentiate;

3/T-lymphocyte subsets interact with other subsets and induce the latter to differentiate into T lymphocytes with specialized function;

4/T lymphocytes also interact with B lymphocytes, inducing them to synthesize and secrete antibodies.

A second exposure to the same immunogen results in a **secondary response**. This may occur after the response to the first immune event has leveled off or has totally subsided (within weeks or even years). The secondary response differs from the primary response in many respects. Most notably and biologically relevant is the

1/**much quicker onset**

2/the much higher magnitude of the response.

In a sense, this secondary (and subsequent) exposure behaves as if the body **remembered** that it had been previously **exposed** to that same immunogen. In fact, secondary and subsequent responses exploit the expanded number of antigen-specific lymphocytes generated in response to the primary immune. The secondary response is also **called the memory or anamnestic response**. The B and T lymphocytes that participate in the memory response are termed **memory cells**.

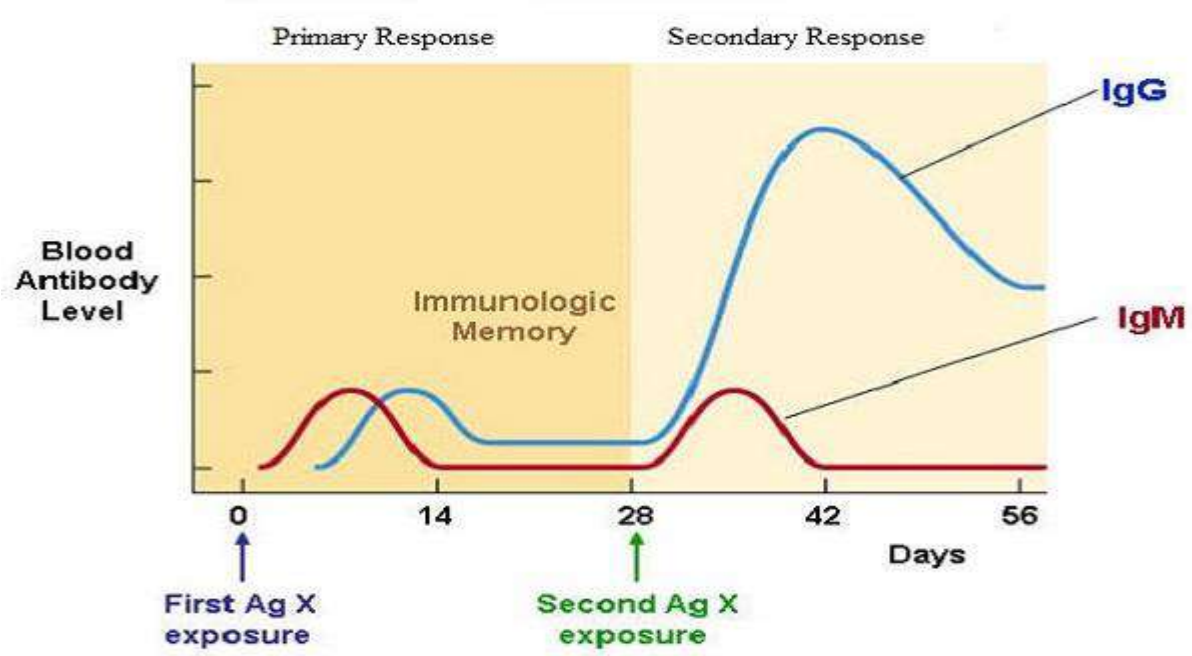


Fig. Immune Response and Secretion of antibodies

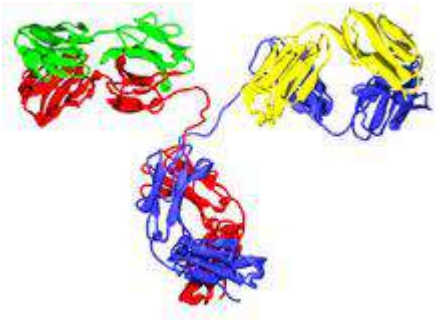
Antibody

An **antibody** (AB), also known as an **immunoglobulin** (Ig), is a large Y-shape produced **by plasma cells** that is used by the immune system to **identify and neutralize foreign objects** such as bacteria and viruses. The antibody recognizes **a unique part** of the foreign antigen, called an **epitope**. Each tip of the "Y" of an antibody contains a **paratope** (a structure analogous to a lock) that is **specific** for **one particular epitope** (similarly analogous to a key) on an antigen, allowing these two structures to bind together with precision. The production of antibodies is the main function of the humoral immune system.

Antibodies can occur in **two physical forms**, a **soluble form** that is secreted from the cell, and **a membrane-bound form that is attached to the surface of a B cell** and is referred to as the **B cell receptor (BCR).** The BCR is found only on the surface of B cells and **facilitates the activation of these cells and their subsequent differentiation into either antibody factories called plasma cells** or **memory B cells** (that will survive in the body and remember that same antigen) .Thus the **B cells can respond faster upon future exposure**. In most cases, interaction of the B cell with a T helper cell is necessary to produce full activation of the B cell and, therefore, **antibody generation following antigen binding**. **Soluble antibodies are released into the blood and tissue fluids**, as well as many **secretions** to continue to survey for invading microorganisms.

Structure

Antibodies are heavy (~150 kDa) globular plasma proteins. They have sugar chains **added to some of their amino acid residues**. In other words, antibodies are ***glycoproteins*.** The basic functional unit of each antibody is an immunoglobulin (Ig) monomer (containing only one Ig unit); secreted antibodies can also be **dimeric** with two Ig units as **with IgA**, or **pentameric** with five Ig units, like mammalian **IgM**.

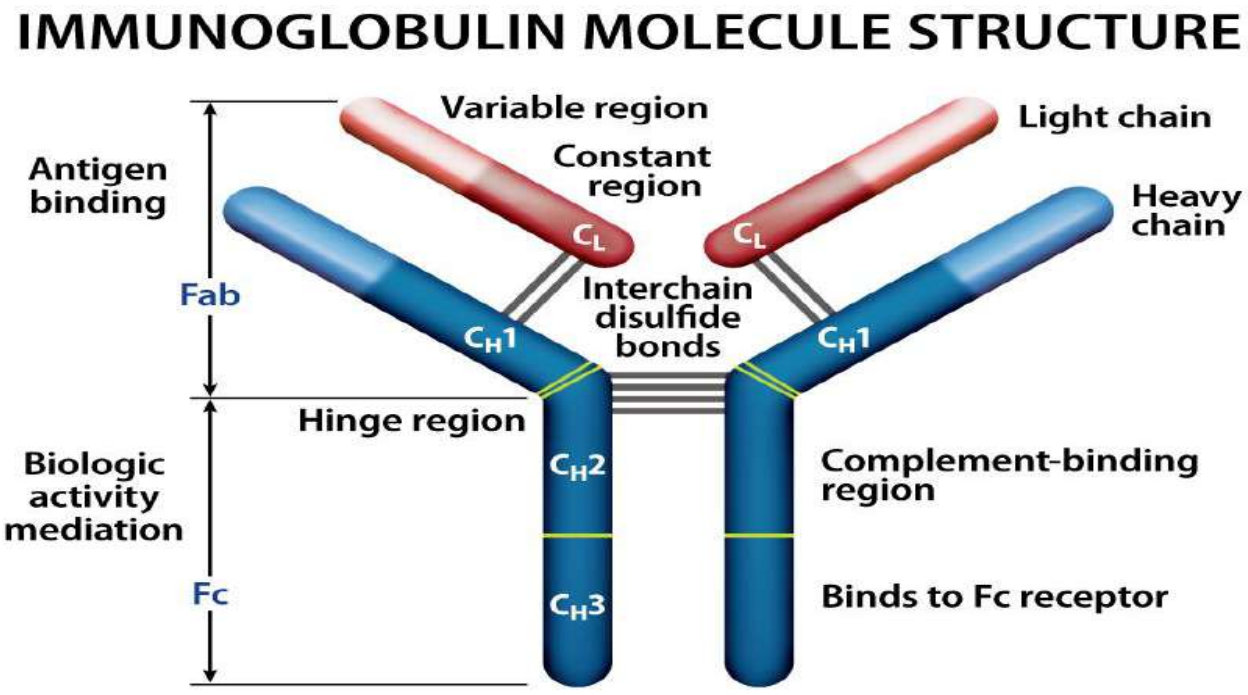


Immunoglobulin domains.

The Ig monomer is a "Y"-shaped molecule that consists of four polypeptide chains; two identical *heavy chains* and two identical *light chains* connected by disulfide bonds. Each chain is composed of structural domains called immunoglobulin domains. These domains contain about 70–110 amino acids and are classified into different categories (for example, **variable and constant**) **according to their size and function**.

Heavy chain

There are **five types** of mammalian Ig heavy chain denoted by the Greek letters: α, δ, ε, γ, and μ. The type of heavy chain present defines the *class* of antibody; these chains are found in IgA, IgD, IgE, IgG, and IgM antibodies, respectively. **Distinct heavy chains differ in size and composition.**



Each heavy chain has two regions, **the *constant region* and the *variable region***. The constant region is identical in all antibodies of the same isotype, but differs in antibodies of different isotypes. The variable region of each heavy chain is approximately 110 amino acids long and is composed of a single Ig domain.

Light chain

In mammals there are **two types of immunoglobulin light chain**, which are called **lambda (λ) and kappa (κ)**. A light chain has two successive domains: one constant domain and one variable domain.

CDRs, Fab and Fc Regions

Some parts of an antibody have the same functions. The arms of the Y, for example, contain the sites that can bind to antigens (in general, identical) and, therefore, **recognize specific foreign objects**. This region of the antibody is called the ***Fab (fragment, antigen-binding) region***. It is composed of one constant and one variable domain from each heavy and light chain of the antibody. The paratope is shaped at the **amino terminal end** of the antibody monomer by the variable domains from the heavy and light chains. the **complementarity determining regions** (CDRs), are also called idiotypes(The variable part of an **antibody** including the unique antigen binding site). the adaptive immune system is regulated by interactions between idiotypes.

The base of the Y plays a role in modulating immune cell activity. This region is called the ***Fc (Fragment, crystallizable) region,*** and is composed of two heavy chains that contribute two or three constant domains depending on the class of the antibody. Thus, the Fc region ensures that each antibody generates an appropriate immune response for a given antigen, by binding to a specific class of Fc receptors, and other immune molecules, such as complement proteins. By doing this, it mediates **different physiological effects** including **recognition of opsonized particles, lysis of cells, and degranulation of mast cells, basophils, and eosinophils.**

In summary, whilst the Fab region of the antibody determines its antigen specificity, the Fc region of the antibody determines the antibody's class effect. Since possible classes of heavy chains in

antibodies include alpha, gamma, delta, epsilon, and mu, and they define the antibody's isotypes IgA, G, D, E, and M, respectively. **It also implies that Fab-mediated effects are directed at microbes or toxins, while Fc mediated effects are directed at effector cells or effector molecules (though this class effect may be mediated by the Fab region rather than the Fc region).**

Function:

Activated B cells **differentiate** into either **antibody-producing cells called plasma cells** that secrete soluble antibody or **memory cells** that survive in the body for years afterward in order to allow the immune system to remember an antigen and respond faster upon future exposures. **Possible class effects of antibodies include: Opsonisation, agglutination, hemolysis, complement activation, mast cell degranulation, and neutralization .**

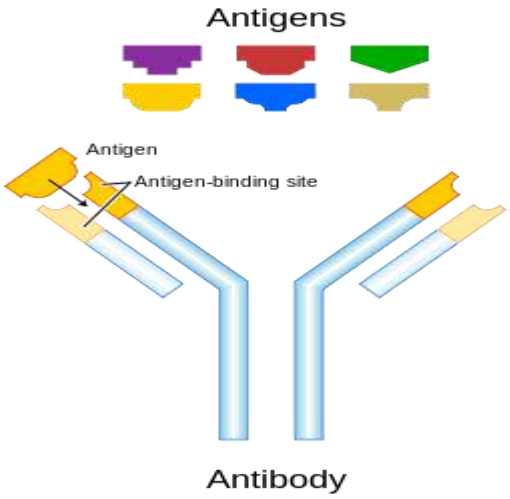
At the prenatal and neonatal stages of life, the presence of antibodies is provided by passive immunization from the mother. Early endogenous antibody productions vary for different kinds of antibodies, and usually appear within the first years of life. Since antibodies exist freely in the bloodstream, they are said to be part of the **humoral immune system.** Circulating antibodies are produced by clonal B cells that **specifically respond to only one antigen** (an example is a virus capsid protein fragment).

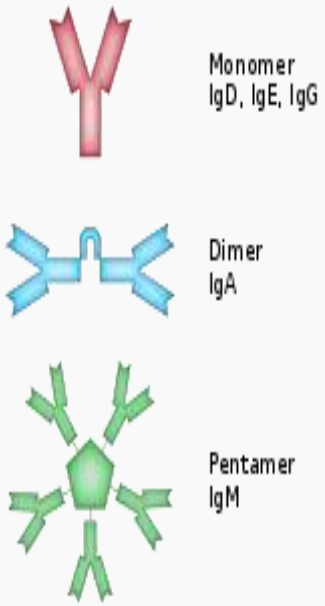
Though **the general structure of all antibodies** is very similar, **a small region at the tip of the protein is extremely variable, allowing millions of antibodies with slightly different tip structures, or antigen-binding sites, to exist. This region is known as the *hyper variable region*.** This enormous diversity of antibodies allows the immune system to recognize an equally wide variety of antigens. The large and diverse population of antibodies is generated by

1- Random combinations of a set of gene segments that encode different antigen-binding sites (or *paratopes*), followed by
2- Random mutations in this area of the antibody gene, which create further diversity.

Antibody genes also re-organize in a process called class switching that changes the base of the heavy chain to another, creating

a different isotype of the antibody that retains the antigen-specific variable region. This allows a single antibody to be used by several different parts of the immune system.



Name	Types	Description	Antibody Complexes
IgA	2	Found in mucosal areas, such as the gut, respiratory tract and urogenital tract, and prevents colonization by pathogens. Also found in saliva, tears, and breast milk as dimer, while in blood as monomer.	
IgD	1	Functions mainly as an antigen receptor on B cells that have not been exposed to antigens. It has been shown to activate basophils and mast cells to produce antimicrobial factors.	
IgE	1	Binds to allergens and triggers histamine release from mast cells and basophils, and is involved in allergy. Also protects against parasitic worms.	
IgG	4	In its four forms (IgG1, IgG2, IgG3, IgG4), provides the majority of antibody-based immunity against invading pathogens. **The only antibody capable of crossing the placenta to give passive immunity to the fetus.**	
IgM	1	Expressed on the surface of B cells (monomer) and in a secreted form (pentamer) with very **high avidity**. Eliminates pathogens in the early stages of B cell-mediated (humoral) immunity before there is sufficient IgG.	

Isotypes

Antibodies can come in different varieties known **as isotypes or classes**. In placental mammals there are five antibody isotypes known as IgA, IgD, IgE,

IgG, and IgM. They are each named with an "Ig" prefix that stands for immunoglobulin, another name for antibody, and differ in their biological properties, functional locations and ability to deal with different antigens, as depicted in the table. **The different suffixes of the antibody isotypes denote the different types of heavy chains the antibody contains, with each heavy chain class named alphabetically: α, γ, δ, ε, and μ. This gives rise to IgA, IgG, IgD, IgE, and IgM, respectively.**

The antibody isotype of a B cell changes during cell development and activation. Immature B cells, which have never been exposed to an antigen, express only the IgM+ isotype in a cell surface bound form. The B lymphocyte, in its mature ready-to-respond form, is known as "**naive B lymphocyte**." The naive B lymphocyte express both surface IgM+ and IgD+. The co-expression of both these immunoglobulin isotypes renders the B cell 'mature' and ready to respond to antigen. B cell activation follows engagement of the cell-bound antibody molecule with an antigen, causing the cell to divide and differentiate into an antibody-producing cell called a plasma cell. In this activated form, the B cell starts to produce antibody in a secreted form rather than a membrane-bound form. Some daughter cells of the activated B cells undergo isotype switching, a mechanism that causes the production of antibodies to change from IgM or IgD to the other antibody isotypes, IgE, IgA, or IgG, that have defined roles in the immune system.

Antibodies contribute to immunity by :

1-They prevent pathogens or its toxins from entering or damaging cells by binding to them.

2-they stimulate removal of pathogens **by macrophages** and other cells by coating the pathogen; and they trigger destruction of pathogens by stimulating other **immune responses such as the complement pathway**.

Natural antibodies

Humans and higher primates also produce "natural antibodies" that are present in serum before viral infection. **Natural antibodies have been defined as antibodies that are produced without any previous infection, vaccination, other foreign antigen exposure or passive immunization**. These antibodies can activate the classical complement pathway leading to lysis of enveloped virus particles long before the adaptive immune response is activated.

Classes of Immunoglobulins

There are five classes of immunoglobulins in human serum. They are named based on the nature of heavy chains they have. They are IgG immunoglobulin G Gamma(¥), IgA immunoglobulin A(α), IgM immunoglobulin M(μ), IgD immunoglobulin D(§), IgE immunoglobulin E(£). Immunoglobulin IgG has four sub types. There are IgG1,IgG2.IgG3,IgG4. Similarly IgA has two sub types IgA1, IgA2.
Properties of immunoglobulins

Immunoglobulins have the following general properties

1- Immunoglobulins are glycoproteins, they have a shape of y or T, The molecular weight ranges from 150000 to 950000.
2- Typically an Ig molecule is made up of four poly peptide chains of which 2 are light chains and the remaining2 are heavy chains.
3- The half-life varies from 2 to 25 days.
4- They contain disulfide bonds, they agglutinate antigens.
5- They form precipitate with antigens.
6- They cross placenta (IgG).
7- They have allergic activity (IgE).
8- They are involved in complement fixation (IgG, IgM).

Functions of immunoglobulins

The main function of the immunoglobulins is protection of body against the invading microorganisms. The protective role is carried out in the following ways:

1. Agglutination antigens, 2. Precipitation antigens,3. Neutralization antigens,4. Lysis of antigens,5. Opsonisation,6. Aid in phagocytosis,7.Chemotaxis,8.Activation of mast cells and basophils.

Immunoglobulin G (IgG)

1. IgG is Immunoglobulin G. It is antibody, it is glycoprotien.it is Y shaped it is relatively stable.
2. This is the predominant class of immunoglobulin and accounts for approximaztely70% of total immunoglobulin in human serum.
3. IgG produced particularly during secondary immune response
4. IgG has half -life of 25 days.
5. There are 4 antigenically distinct subclasses of IgG namely IgG1,IGg2, IgG3, IGg4. IgG1 The major one forming 67% of the total IgG followed by IgG2-22%, IgG3 7% ,IgG4 – 4%.
6. The striking difference between the subclasses is the **position and number of interchain disulfide bridges.**
7. The **large number of disulfide bound in IgG3 is associated with a long hinge region** consisting of 62 amino acids **and this results in the higher molecular weight of IgG3**.

Biological properties of IgG.

1. IgG is the only immunoglobulin that crosses the ***human placenta*** and thus offers a passive ***protection*** to the newborn for about 6-9 months.
2. IgG **activates the classical pathway of complement during antigen antibody reactions**
3. IgG **Neutralizes toxins** and **viruses**.
4. By binding to bacteria IgG **Opsonises** them, thereby enhance their **phagocytosis** and **elimination**. This process is known as **opsonisation.**

Immunoglobulin A(IgA)

IgA is the second abundance among the immunoglobulins (about 10-15%) next to IgG. **Two** subclasses of IgA exist namely **IgA1, IgA2**.
IgA namely **secretory IgA is seen in the external seromucous secretions of respiratory, gastro intestinal and urinogenital tracts.**

Biological properties of IgA

1. IgA inhibit the adherence of microbes to the mucosa of the respiratory, gastro intestinal and urinogenital tracts thereby prevent them from colonizing and invading the different organs of these tracts.
2. IgA does not fix complement but is found to activate the alternate complement pathway thereby **neutralizes** local toxins, **promote phagocytosis** and activate **bacteriolytic** activity. But this occurs only in the presence of lysozyme.
3. IgA present in the **colostrum** protects the baby from intestinal pathogens. So, breast feeding reduces gastrointestinal infections in infants by reducing the entry of pathogens of the environment**.**

Immunoglobulin M (IgM)

1.**IgM** is an antibody. It is the **largest of the immunoglobulins**. It is often referred as the **macroglobulin because of its high molecular weight 950000**.The polymers of **usually 5 molecules pentamers**.

2. The Serum level of IgM is very low , about 2-5mg/ml. This low serum level due to its short half -life(5days)

3. No subclasses **for IgM**.

4. **It is the earliest immunoglobulin to be synthesized by fetus , starting about 5th month of the fetal life.**

Biological properties

1. It is first antibody to appear in the ***primary of immune response*** but it does not persist for long because of short life, It is therefore an useful indicator of recent infection.
2. Maternal IgM does not cross the placenta but the human fetus can synthesis IgM, if its B cells are antigenically stimulated as in ***congenital infections***.
3. By having multiple antigen binding sites (5-10)IgM has a high functional affinity for ***multivalent antigens***. By multivalence it can also inhibit the mobility of pathogens and enhance ***their phagocytosis.***
4. It is also show properties such as ***opsonisation, complement fixation, agglutination, cytolysis, ect.***
5. Because of its macromolecular size it is primarily localized in blood and thus protects against the ***blood serum infections.***

ImmunoglobulinIgD (IgD)

1. IgD is slightly larger than IgG, having a molecular weight of 180000.The large size of IgD may be associated with an extended hinge region.
2. IgD is limited to blood serum. The average **serum level is 0.03mg/dl**.
3. The half -life of IgD is 2-3 days.
4. Two subclasses of IgD namely IgD1andIgD2 have been found.
5. It is found associated with the surface of B lymphocytes.

Biological properties

1. IgD has not been **shown to have antibody activity and does not mediate any of the effector functions** attributed to immunoglobulins.
2. IgD which is found associated with the surface of B lymphocytes along with IgM is found to act as antigen receptor.

Immunoglobulin E(IgE)

1. Immunoglobulin E is a monomer having a typical immunoglobulin structure.
2. It has molecular weight of 190000 which is slightly higher than that of IgG.
3. It is heat labile immunoglobulin whereas IgG, IgA, IgM, IgD are heat stable.
4. It is found only in traces in the serum and the average serum level is 0.0004mg/dl.
5. The very low level of IgE is only because it is synthesized by very ***few plasma cells*** in the body. But in the persons with ***allergic*** conditions its level may be 50 to 100 times higher than that of the normal persons.
6. High levels of IgE is also encountered in ***intestinal helminthic infections***.
7. IgE has half -life 2-3 days
8. It has special ***attraction to mast cells and basophils*** which bear receptors for the ***Fc region of IgE*** on their plasma membrane.
9. IgE is usually known as ***skin sensitizing antibody***, originally named as **regain.**

Biological properties

1. High level of IgE in children with worm infestation seems to have a ***protective role***. This protective function is either by IgE acting directly on the parasites or by producing ***vasoactive amines***.(histamin).
2. The IgE –***antigen interaction on mast cells results*** in **degranulatio**n of mast cells with the release of the vasoactive amines.
3. IgE mediates ***reaginic*** (allergic) hypersensitivity type 1

Complement System

Complement is a **collective term for a system of enzymes and proteins that function in both the innate and adaptive branches of the immune system as soluble means of protection against pathogens that evade cellular contact.** A series of circulating and self-cell-surface regulatory proteins keep the complement system in check. In the innate immune system, complement can be activated in two ways: via the alternative pathway, in which antigen is recognized by particular characteristics of its surface, or via the mannan-binding lectin (MBL) pathway. Complement can also be activated in the adaptive immune system via the classical pathway that begins with antigen-antibody complexes.

Regardless of the pathway type of activation.

functions of complement include

1- Lysis of bacteria, cells, and viruses;

2-Promotion of phagocytosis (opsonization);

3-Triggering of inflammation and secretion of immune-regulatory molecules

4- Clearance of immune complexes from circulation.

Complement receptors: The complement system is a complex set of **soluble molecules** that generate various reactions that **attract immune cells to the site of infection** and **lead to destruction of microbes**. Some of these activities are accomplished by the binding of certain complement components or their fragments to microbial surfaces and **"tagging"** that microbe for destruction by other elements of the immune system. Cell-surface bound complement receptors on **phagocytic cells and B cells** recognize these bound complement fragments and facilitate the binding, ingestion, and internal degradation of the tagged microbes.

Complement pathways

There are three main pathways for complement

1. **Classical pathway:** Interaction of antibody with antigen initiates the classical pathway of complement activation. This biochemical cascade of enzymes and protein fragments facilitates destruction of microbes by the **membrane attack complex (MAC),** by **increased opsonization through C3b binding of microbial surfaces** and **by the production of anaphylotoxins C3a, C5a, and C4a.**

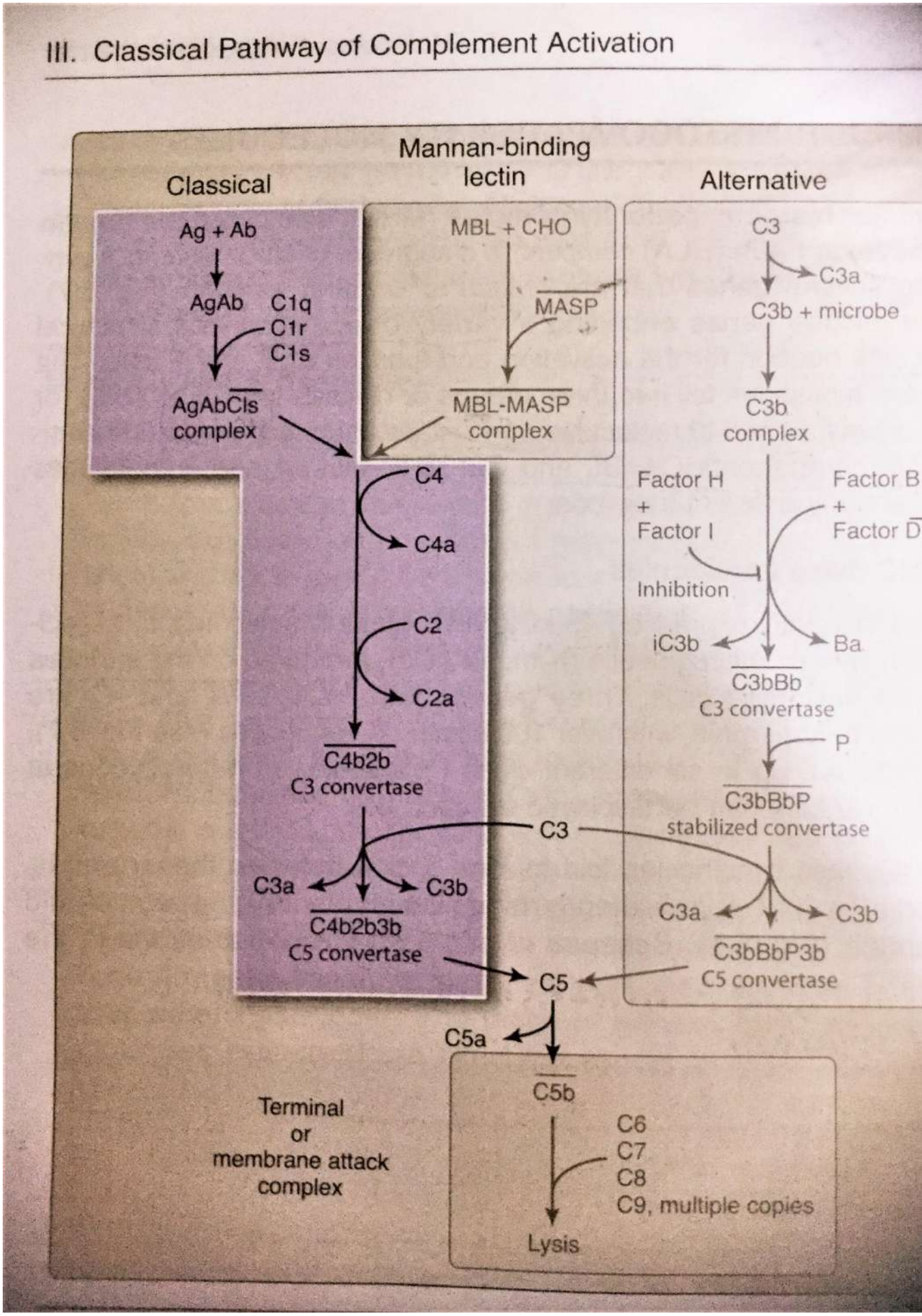
2. **Mannan-binding lectin pathway: Lectins are proteins that bind to specific carbohydrates.** This pathway is activated by binding of mannan-binding lectin (MBL) to mannose-containing residues of glycoproteins on certain microbes (e.g., Listeria spp., Salmonela spp., Candida albicans). **MBL is an acute phase protein**, one of a series of serum proteins whose levels can rise rapidly in response to infection, inflammation, or other forms of stress.

3. **The alternative pathway** is **initiated by cell-surface constituents** that are recognized as foreign to the host, such as **LPS . Various enzymes (e.g., kallikrein, plasmin, elastase**) cleave C3, the most abundant (≈1300 mg/ml) serum complement component, into several smaller fragments. One of these, **the continuously present, short-lived, and unstable C3b fragment, is the major opsonin of the complement system and readily attaches to receptors on cell surfaces.**

4- Recently the scientists are added the fourth one which is the "**Lytic form**". **The terminal or lytic pathway can be entered from the alternative, mannan-binding lectin, or classical pathway of complement activation.** Attachment of **C5b** to the bacterial membranes initiates formation of the membrane attack complex (MAC) and lysis of the cell .

Anaphylotoxins: The small fragments (C3a, C4a, C5a) generated by the cleavage of C3 and C5 in the alternative pathway and of C3, C4, and C5 in the MBL pathway act as anaphylotoxins. **Anaphylotoxins attract and activate different types of leukocytes** . They draw additional cells to the site of infection to help eliminate the microbes. **C5a has the most potent effect, followed by C3a and C4a.**

III. Classical Pathway of Complement Activation



Lecture 11 **Dr. Mouruj Alaubydi and Dr. Jenan Alsaffar**

Hypersensitivity

Can be **defined as a normal but exaggerated or uncontrolled immune response to an antigen that can produce inflammation, cell destruction, or tissue injury. The term immunization, or sensitization, describes an immunologic reaction dependent on the host's response to a subsequent exposure of antigen**. Small quantities of the antigen may favor sensitization by restricting the quantity of antibody formed. An unusual reaction, such as an allergic or hypersensitive **reaction that follows a second exposure to the antigen**, reveals the existence of the sensitization.

TYPES OF ANTIGENS AND REACTIONS

Antigens that trigger allergic reactions are called **allergens. These low-molecular-weight substances can enter the body by being inhaled, eaten, or administered as drugs.** Hypersensitivity reactions can occur in response to different types of antigen, including **environmental substances**, **infectious agents**, **food, and self-antigens**.

1- **Environmental Substances**: Environmental substances in the form of small molecules can trigger several types of hypersensitivity reactions. Dust can enter the respiratory tract, mimicking parasites, and stimulate an antibody response.

2- Infectious Agents

Not all infectious agents are capable of causing hypersensitivity reactions. The influenza virus can cause hypersensitivity that results in damage to epithelial cells in the respiratory tract.

3- **Self Antigens**

Very small immune responses to self-antigens is normal and occur in most people.

4- **Food Allergies:** According to the National Institute of Allergy and Infectious Diseases (NIAID), food allergy (FA) is an important public health problem that affects adults and children and may be increasing in prevalence.

TYPES OF HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions

Type	Name	Mechanism	Antigen	Onset
I	Generalized Anaphylactic Localized – Hay fever, Asthma	IgE-Ag triggers, Mast cell editors	Allergen	Minutes
II	Cytotoxic (Ag + Ab)	IgG or IgM binds to cell surface or complement	Cell surface molecule	Few Hours
III	Immune complex	Immune complexes, Inflammation, with or without complement	Soluble or particulate	Few Hours
IV	Cell Mediated	Cytokines (T cells, Macrophages , CTL)	Chemicals, intracellular	1-3 Days

Type I Reactions

Type I hypersensitivity reactions can range from **life-threatening anaphylactic reactions** to **milder manifestations** associated with food allergies. **Is the basis of acute allergic reactions caused by molecules released by mast cells when an allergen interacts with membrane-bound IgE**. Several groups of agents cause anaphylactic reactions. **The two most common agents are drugs** (e.g., systemic penicillin) and **insect stings**. Insects of the order Hymenoptera (e.g., common hornet, yellow jacket, yellow hornet, paper wasp) are examples of insects causing the most serious reactions. Immune-mediated IgE adverse food reactions can be fatal. **The mediators of anaphylaxis are (Histamine, Leukotrienes, Basophil kallikrein, Serotonin, Platelet-activating factor, Eosinophil chemotactic factor of anaphylaxis, Prostaglandins)**

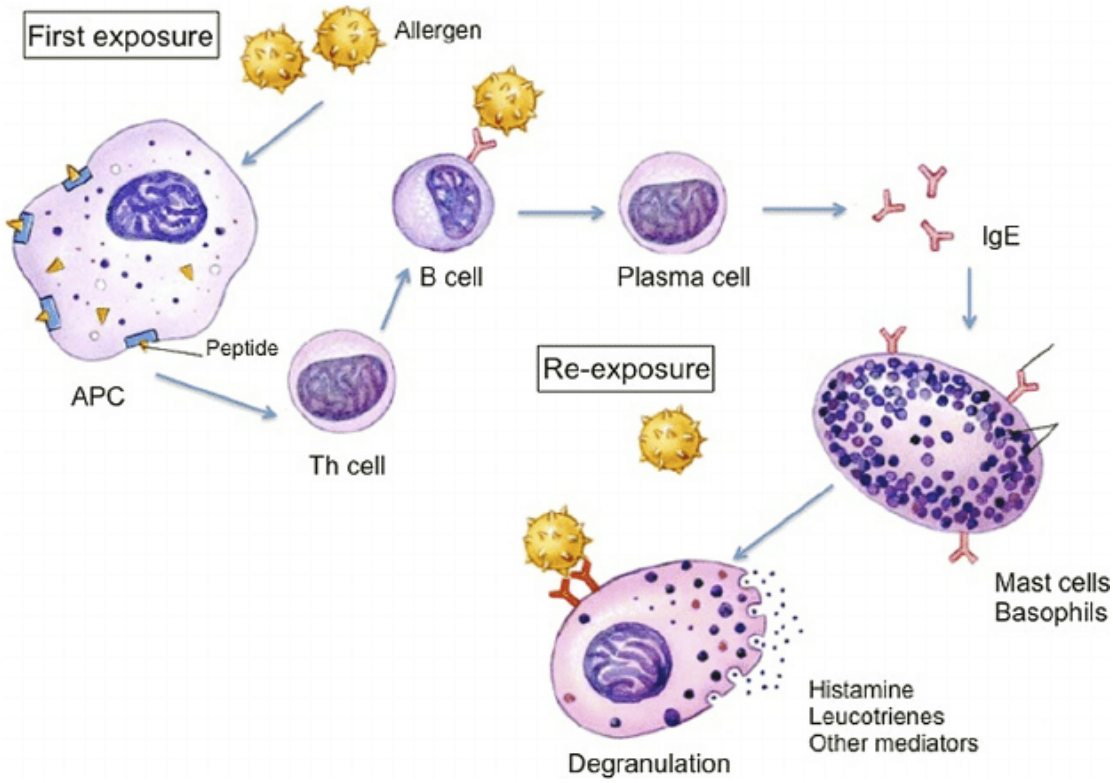


Figure: Type 1 hypersensitivity reaction

Type II Reactions

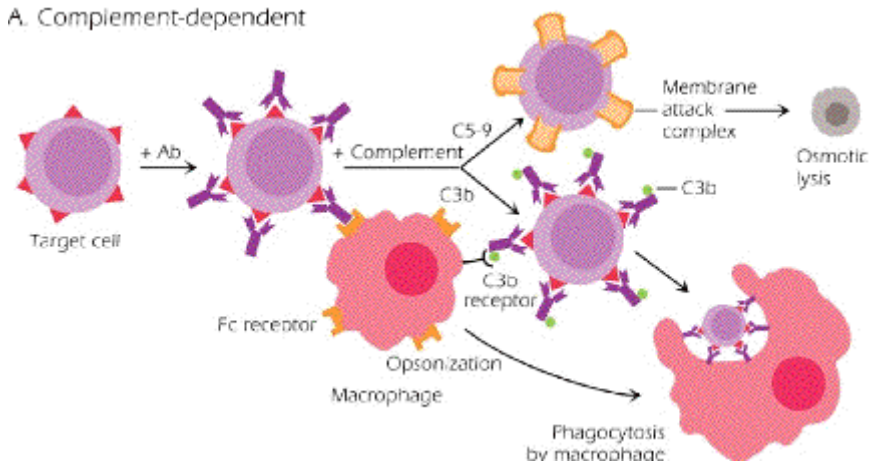
Type II hypersensitivity reactions are a consequence of **IgG or IgM binding to the surface of cells**. **Three different mechanisms** of antibody-mediated injury exist in type II hypersensitivity, as follows:

1. **Antibody-dependent, complement-mediated cytotoxic reactions**. These are characterized by the **interaction of IgG or IgM antibody with cell-bound antigen.** This binding of an antigen and antibody can result in the **activation of complement and destruction of the cell (cytolysis)** to which the antigen is bound. Such as

Transfusion Reactions. Transfusion reactions are examples of antibody-dependent, complement-mediated cytotoxic reactions. The term ***transfusion reaction*** **generally refers to the adverse consequences of incompatibility between patient and donor erythrocytes**. Transfusion reactions can include **hemolytic (red blood cell [RBC]–lysing) reactions occurring during or shortly after a transfusion**, shortened post transfusion survival of RBCs, an allergic response, or disease transmission (**Hemolytic reactions**).

Hemolytic Disease of the Fetus and Newborn.

Hemolytic disease of the fetus and newborn (HDFN) results from excessive destruction of fetal RBCs by maternal antibodies. HDFN in the fetus or neonate is clinically characterized by anemia and jaundice. If the hemoglobin breakdown product that visibly produces jaundice (bilirubin) reaches excessive levels in the newborn's circulation, it will accumulate in lipid-rich nervous system tissue and can result in mental retardation or death.



2. Antibody-dependent, cell-mediated cytotoxicity. This depends on the initial binding of specific antibodies to target cell surface antigens. The antibody-coated cells are lysed by effector cells, such as natural killer (NK) cells and macrophages, expressing Fc receptors.

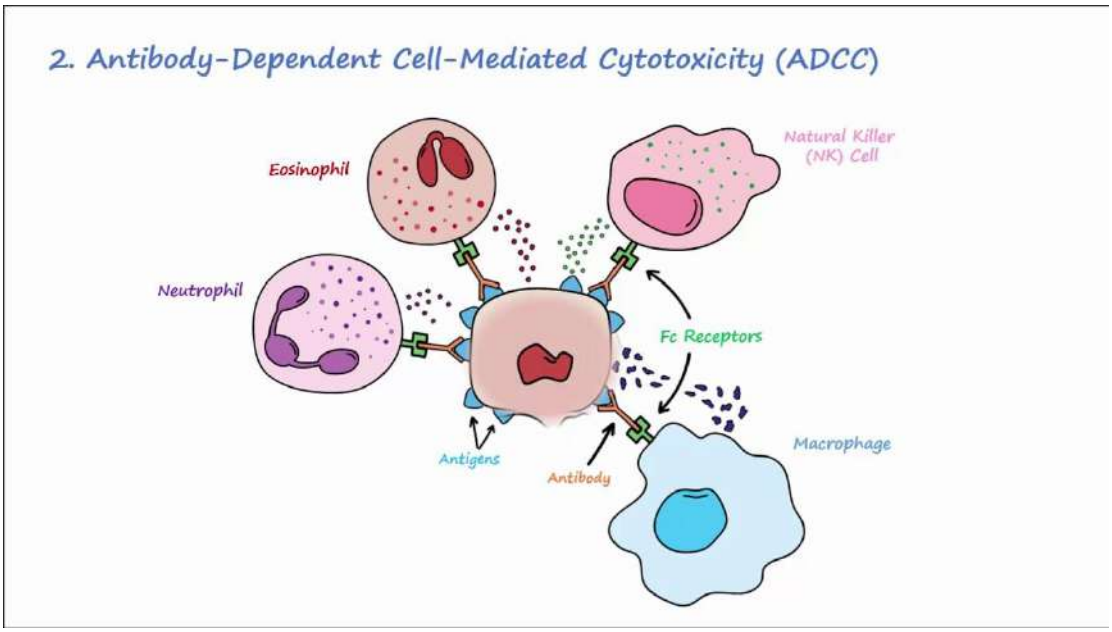
Autoantibodies can also attack and damage components of solid tissues, as in Good pasture's syndrome. In this disorder, IgG autoantibodies bind a glycoprotein in the basement membrane of the kidney's glomeruli and the lungs. Anti–basement membrane antibody activates complement that can trigger an inflammatory response. This group of diseases can be detected by demonstrating the presence of autoantibodies.

Type II Hypersensitivity and Antibodies

That Affect Cell Function

In another type II hypersensitivity reaction, antibodies bind to cells and affect their function. These antibodies simply stimulate the target organ function

without causing organ damage. In some cases, such as wegener's granulomatosis, stimulation of cells by autoantibody leads to tissue damage.



3. Antireceptor antibodies. These disturb the normal function of receptors. Less often, antibodies may modify the function of cells by binding to receptors for hormones (autoimmune hypersensitivity against solid tissue), such as autoimmune thyroid disease. Such as autoantibodies can also attack and damage components of solid tissues. These antibodies can **simply stimulate the target organ function without causing much target organ damage**, as in Graves' disease.

Type III (Immune Complex) Reactions

Type III hypersensitivity reactions are **caused by the deposition of immune complexes in blood vessel walls and tissues**. Repeated antigen exposure leads to sensitization with the production of **an insoluble antigen-antibody complex**. **As these complexes are deposited in tissues, the complement system is activated, macrophages and leukocytes are attracted, and immune-mediated damage occurs.**

The formation of immune complexes under normal conditions protects the host because they facilitate the clearance of various antigens and invading microorganisms by the mononuclear phagocyte system. In immune complex reactions (disease), antigen-antibody complexes form in the soluble or fluid

phase of tissues or in the blood and assume unique biological functions, such as interaction with complement and with cellular receptors.

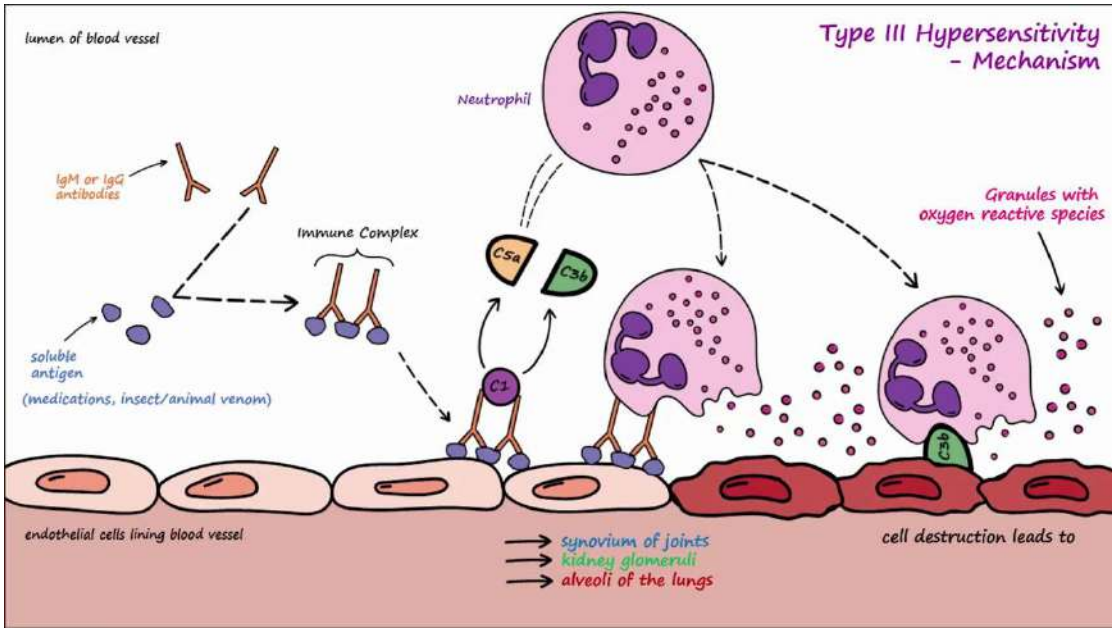
Other type III (immune complex) reactions include serum sickness and certain aspects of autoimmune diseases. **Circulating soluble immune complexes are responsible for or associated with various human diseases in which exogenous and endogenous antigens can trigger a pathogenic immune response and result in immune complex disease.** Examples(Rheumatoid arthritis, systemic lupus erythematosus, mixed connective tissue disease, systemic sclerosis, glomerulonephritis)

Mechanism of Tissue Injury

1. Antibody can react **with soluble antigens in the circulation** and form immune complexes that may disseminate and lodge in any tissue with a large filtration area and cause lesions of immune complex disease.

2. Antibody can react **with antigen secreted or injected locally into the interstitial fluid**. The classic example is the experimental Arthus reaction, the basic model of local immune complex disease .

3. Antibody can also react **with structural antigens that form part of the cell surface membranes or with fixed intercellular structures** such as the basement membranes. Systemic immune complex disease serum sickness is an example of soluble and tissue-fixed antigen involvement.



Type IV Cell-Mediated Reactions

Type IV **cell-mediated immunity** consists of immune activities that **differ from antibody-mediated immunity.** Cell-mediated immunity is moderated by the link between T lymphocytes and phagocytic cells (i.e., monocyte-macrophages). Lymphocytes (T cells) do not recognize the antigens of microorganisms or other living cells but are immunologically active through various types of direct cell to cell contact and by the production of soluble factors.

Characteristics

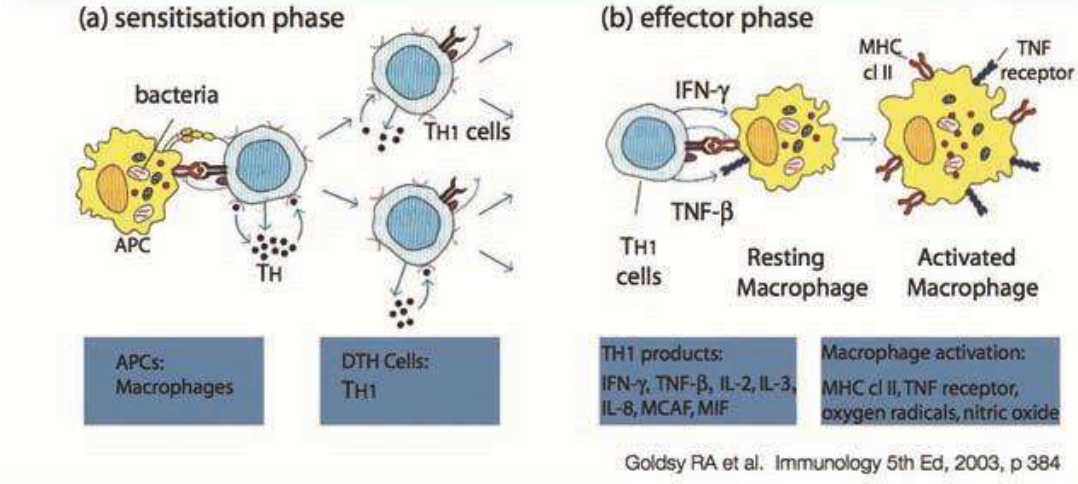
• **Type IV delayed-type hypersensitivity (DTH)** involves antigen-sensitized T cells or particles that remain phagocytized in a macrophage and are encountered by previously activated T cells for a second or subsequent time. T cells respond directly, or by the release of lymphokines, to exhibit contact dermatitis and allergies of infection. **One of the mechanisms of cell-mediated immunity is delayed hypersensitivity. Delayed hypersensitivity is a major mechanism of defense against various intracellular pathogens, including mycobacteria, fungi, and certain parasites.** Such as

• Rejection of foreign tissue grafts, elimination of tumor cells bearing neoantigens

• Formation of chronic granulomas

type IV hypersensitivity is allergic contact dermatitis caused by metals (e.g., nickel, mercury, copper), sunscreen agents, disinfectants, perfumes and fragrances, and pesticides. Pulmonary hypersensitivity can be caused by inorganic dust particles.

Type IV (Cell Mediated) Hypersensitivity



APCs: Macrophages

DTH Cells: TH1

TH1 products: IFN-γ, TNF-β, IL-2, IL-3, IL-8, MCAF, MIF

Macrophage activation: MHC cl II, TNF receptor, oxygen radicals, nitric oxide

Goldsy RA et al. Immunology 5th Ed, 2003, p 384