**Basics of medical immunology**

**Overview of the Immune System**

The immune system is composed of two major subdivisions:

* + 1. The innate or non-specific immune system.
		2. The adaptive (acquired) or specific immune system.

Each of the subdivisions of the immune system **has both cellular and humoral** components by which they carry out protective function.

**Innate immunity**:

1. The first line of defense ,it is present since birth ,its onset is immediate
2. It is **not** antigen specific , **it is not efficient** in eliminating pathogens.
3. This type of immunity does not increase with repeated exposure to antigens and does not demonstrate immunological memory.

**It comprises:**Anatomic barriers to infections e.g. skin and mucous membranes, humoral barriers to infections e.g. lysozyme and complement and cellular barriers to infections as phagocytic cells e.g. monocytes, macrophages and neutrophils (Table 1).

**Adaptive or acquired immunity**: acts as a second line of defense and give protection against re-exposure to the same pathogen. It requires **some time** to react to an invading organism. It is characterized by being:

1. Inducible by a foreign antigen.
2. Antigen specific
3. Demonstrate immunological memory as it reacts **more rapidly** on subsequent exposure to the same organism.
4. Non-responsiveness to self. (Table 1)

**It comprises:** Lymphocytes; T and B cells.

Both innate and adaptive immune system**s interact** and **augment** each other through soluble substances as antibodies, complement and cytokines:

* 1. Phagocytic cells **present antigen** on their surface to stimulate specific T lymphocytes. Macrophages secrete **cytokines** that initiate specific immune response.
	2. T lymphocytes produce cytokines which **enhance** activities of **phagocytes.**
	3. Antibodies bind to pathogens and activate the complement system to destroy it or bind to pathogens and assist phagocytosis **(opsonization).**

**Table 1-Comparison of Innate and adaptive immunity**

|  |  |  |
| --- | --- | --- |
| **Feature**  |  **Innate** |  **Acquired**  |
| **Appearance**  |  **Since birth** |  **After exposure** |
| **Specificity** |  **Not-specific** |  **Specific** |
| **Onset**  |  **Immediate** |  **Delayed**  |
| **Memory**  |  **Not present** |  **Present**  |
| **Efficiency** |  **Less** |  **High,increase with repeated exposure**  |
| **Components** |  |  |
| **Anatomic and chemical barriers** | **Skin, mucosa,chemicals****(Lysozyme, intereferon γ and β), temperature,pH**  | **Lymph nodes, spleen, mucosal -associated lymphoid tissue** |
| **Blood proteins** | **Complement** | **Antibodies** |
| **Cells**  | **Phagocytes,NK**  | **T and B lymphocytes** |

**The immune system' cells include**:

1. **Myeloid cells** as neutrophils, basophils, eosinophils, macrophages and dendritic cells are formed by the myeloid progenitor (stem) cell.
2. **Lymphoid cells a**s B lymphocyte, T lymphocyte and Natural Killer cells are formed by lymphoid progenitor (stem) cell. (Fig 1).

The origin of system' cells is the bone marrow

**A- T-lymphocytes:** form **75%** of peripheral bloodlymphocytes.

**T cell development:** Precursor of T cells must migrate to the **t**hymus where they undergo differentiation into two distinct types of T cells, the CD4+ T helper cell and the CD8+ **pre**-cytotoxic T cell. The letter "T" is given for Thymus.

 The ratio of **T helper: T cytotoxic is 2:1.** (*N.B.:****CD*** *means clusters of differentiation***)**

**B- B-lymphocytes:** form **10%** of peripheral blood lymphocytes. They are produced and mature in **b**one marrow. Active B cells are called **plasma cells** which produce antibodies or immunoglobulins (Ig).

**C- Natural killer (NK)** **and lymphokine activated killer (LAK) cells**. They constitute 5 %-10%peripheral blood lymphocytes. They are large cells.

**There are two types of lymphoid organs in the body:** These are organized tissue where lymphocytes produced, mature, and interact with other non-lymphoid cells.

1. **Primary (central) lymphoid organs:** These are the bone marrow and thymus .
2. **Secondary lymphoid organs:** These are the sites where antigens meet lymphocytes and activate them. They include the lymph nodes, spleen and mucosal associated lymphoid tissue:

**Recirculation and turnover:** Mature lymphocytes circulate from blood to lymphatics to blood. Antigens are drained from site of infection by afferent lymphatics to lymphoid organs where they are recognized specifically for the

first time by naïve B or T lymphocytes which become activated, proliferate, differentiate and change to effector cells. Activated lymphocytes return to

blood via thoracic duct then to the site of infection in peripheral tissue to eliminate specific antigens.

**Memory cells:** These are lymphocytes which remain after elimination of infection to ensure rapid and potent response on repeated exposure.

**Clonal selection theory:** Lymphocytes express a receptor for antigen on their surface, and interaction of this receptor with the antigen is necessary for

activation of the cell. At any time, a given cell expresses **only one specific type of receptor**. Thus, each clone of lymphocytes is **mono-specific**.

**Innate Immunity**

**I-Anatomic barriers to infections:** it includes:

1. **Mechanical factors:** Skin, trapping effect of mucus, movement of cilia and peristalsis of intestine, flushing action of tears and saliva, sneezing and coughing.
2. **Chemical factors:**
	* + 1. [Lysozyme](http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=Lysozyme) and [phospholipase](http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=phospholipase) found in tears and saliva.
			2. The **low pH of sweat and gastric** secretions.
			3. [Defensins](http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=Defensins) (peptides) found in the lung and gastrointestinal tract.
3. **Biological factors**: The normal **flora o**f the skin and in the gastrointestinal tract prevent colonization of pathogenic bacteria

**II-Humoral barriers to infection**: Play an important role in inducing inflammation, which is characterized by [**edema**](http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=edema)and the **attraction** of

[phagocytic cells](http://cancerweb.ncl.ac.uk/cgi-bin/omd?phagocytes). These humoral factors are found in serum or they are formed at the site of infection, the most important is complement system.

**Complement System:** is the major humoral non-specific defense mechanism. They are group of plasma proteins**.** They are produced by liver cells, macrophages and gut epithelial cells.

**Components***:* The basic proteins are termed C1 to C9, in addition to factor B,D, properdin and other proteins.

It can be activated either spontaneously as part of innate immunity or by antigen-antibody reaction as part of adaptive (acquired) immunity aid clearance of immune complexes. **Activation** of components occur in cascade

manner, one step after the other. This is called **complement activation cascade.** Each activated component act as an enzyme to the next component.

**Pathways of complement activation:** There are three pathways:

* 1. The classical pathway.
	2. The lectin pathway.
	3. The alternative pathway.

**The alternative and lectin** are initiated by **the microbe** in absence of the antibody and are considered to be mechanisms of **innate** immunity.

**The classical pathway** is initiated by **antigen -antibody** complex and so it is part of **adaptive** immune response

**Classical pathway: C1 component** is activated by antigen- antibody reaction and act as an enzyme that cleaves C4 then C2 into two fragments a and b for each one. The C4b C2a complex form C3 convertase, which cleaves C3 into C3a and C3b.  C3b binds to the membrane of organism in association with C4b and C2a form **C4bC2aC3b** or C5 convertase that break down C5 and initiate the last step of complement activation.

**The lectin pathway:** It is very similar to the classical pathway. It is initiated by the binding of **plasma** mannose-binding **lectin** (MBL) to bacterial surfaces. MBL is structurally similar to the component C1 of the classical pathway and serve to activate C4.The subsequent steps are essentially the same as classical pathway.

**3-The alternative pathway:** C3 undergo **spontaneous** cleavage to C3b.The alternative pathway is induced when fragment C3b forms a **stable** bonds with surface microbial components like **endotoxins**.The microbe-bound C3b complex becomes a substrate for the binding of another protein called **Factor B** which is broken to **Bb** fragment. **C3bBbC3b** complex functions **as a** **C5 convertase**, to break down C5 and initiate the last step of complement activation.

**The last step** of complement activation **in all pathways** are initiated by splitting of C5 by C5 convertase **into C5a and C5b.** C5b binds to the remaining complement components, C6, C7, C8 and C9 sequentially to form complex called **"Membrane attack complex"** or MAC. This complex form **a pore** in the cell membrane of the microbe through which water and ions can enter, causing death of the cell by osmotic lysis.

**Functions of complement:**

1. **Elimination** of microbes by lysis.
2. **Opsonization**: enhance phagocytosis as phagocytic cells recognize C3b coating the microbe through their C3b receptors.
3. **Clearance** **of immune complexes** asRBC's have C3 receptors, so they recognize C3b bound to antigen-antibody complex and carry them to spleen and liver.
4. **Contributes to inflammation** and tissue damage: **C3a and C5a** produced during complement activation are known as **anaphylotoxins** which release mediators of inflammation as histamine and others and attract and **activate polymorphonuclear cells (PMNs)** ( chemotaxis ) and macrophages so enhance killing of ingested microbes**.**

**Table 2 -Criteria of the three complement pathways**

|  |  |  |  |
| --- | --- | --- | --- |
| **Feature** | **Classical** | **Lectin** | **Alternative** |
| Immunity | Adaptive | **Innate** | **Innate** |
| Activation | **Ag-Ab complex** | Lectin bound to surface of microbe | Microbial components e.g. endotoxins |
| Role of antibody  | important | No role | No role |
| Role of factor B | No role | No role | important |
| Role of mannose-binding lectin  | No role | important | No role |
| Complement components involved | **C1,**4,2,3,5,6,7,8,9 | **C4**,2,3,5,6,7,8,9 | **C3**,5,6,7,8,9 |

**III-Cellular barriers to infection**: Part of the inflammatory response is the attraction of polymorphonuclear, [eosinophils](http://cancerweb.ncl.ac.uk/cgi-bin/omd?eosinophil) and macrophages and natural killer cells to sites of infection. These cells are the main line of defense in innate immune system.

 **Types of phagocyte**s : Dendritic cells are present in those tissues that are in contact with the external environment, such as the [skin](https://en.wikipedia.org/wiki/Skin) ([Langerhans cell](https://en.wikipedia.org/wiki/Langerhans_cell)s) and mucous membrane ,monocytes in the blood and differentiate into macrophages in tissue, PMNs which are **short-lived** and eosinophils that contribute to host defense against parasites.

 **Phagocytic cells** **have a variety of receptors** on their cell membranes it include :

1. **Pattern recognition receptors** (PRRs) that bind to pathogen -associated molecular patterns (PAMPs) present on the surface of infectious agents .Example :
2. **Toll-like receptors** which recognize **broad molecules** on infectious agents.
3. **Scavenger receptors**: bind of polyanions on bacterial surfaces.
4. **Fc receptors** : bind to Fc region of antibody coating pathogens.
5. **Complement receptors**:for the third component of complement, C3b coating pathogens. When antibody and complement help phagocytosis the process is called **opsonization**.

**Both** antibody and complement are called **opsonin**.

**Functions of phagocyte**s:

**A-Internalization of microorganisms :**Internalized microorganisms are contained in **phagolysosomes**. Some organisms **are resistant to phagocytosis** due to factors such as a polysaccharide **capsule or waxy wall .**

**B-Cytokine production*:*** to activateinnate and adaptive immune responses, and so increases phagocyte killing ofmicroorganisms and regulates the immune response e.g **Interleukins-1(IL-1) and 6 (IL-6) are pro-inflammatory cytokines.**

**C-Killing of microorganisms:** Microorganisms are killed intracellularly and extracellularly. **Killing process is either:**

1. **Oxygen-dependent intracellular killing**: a number of oxygen-containing compounds are produced which kill the bacteria being phagocytosed e.g. Hydrogen peroxide (H2O2).
2. **Oxygen independent intracellular killing:** Bacteria can be killed by pre-formed substances released from granules **or lysosomes** when they fuse with the phagosome e.g. lysozyme, elastase, hydrolase ….

**D-Antigen presentation:**Macrophages also function as antigen-presenting cells (APCs).

**Natural killer cells:** one of the innate lymphoid cells **(ILCs)**, it represent **5-10%** of peripheral lymphocytes. Do not contain T-cell receptors (TCR) and do not require prior stimulationor antigen presentation. They **non**-specifically kill **virus infected and tumor** cells. Upon exposure to cytokines such **as IL-2 and IFN-gamma**, NK cells become **lymphokine-activated killer (LAK) cells,** which are capable of killing malignant cells. LAK cell therapy is used for the treatment of cancer .

**IV**- **Inflammation:** is initiated by chemical mediators (cytokines) released at site of infection. This result in vasodilatation and migration of leucocytes to the site of infection**.**

**Antigens**

**Definitions**

**Immunogen:** A substance that **induces** a specific immune response.

**Antigen (Ag):** An antigen is a specific compound binding specific antibody or T cell receptor (TCR).

**Hapten:** They are molecules of low molecular weight so can never induce an immune response when administered by themselves but can do this when coupled to a **larger protein**,"**carrier" molecule**.

**Epitope or antigenic determinant:** A portion of the antigen binds to an unique antigen binding site on antibody or T cell receptor( TCR). This portion is made of amino acids. Antigenis made of different epitopes**.** Antigens having similar epitopes are **cross-reactive antigens**

**Antibody (Ab):** A specific protein which is produced in response to an immunogen and which reacts with an antigen.

**Factors influencing immunogenicity:**

1. **Factors related to the immunogen**
2. **Factors related to biological system**
3. **Methods of administration**

**A-Factors related to the immunogen:**

1. **Foreignness**
2. **Size:** The larger the molecule the more immunogenic. **Exceptions:** insulin has a low molecular weight (MW) and is immunogenic while carbon has high MW is not immunogenic.
3. **Chemical Composition:** In general, the more complex the substance the more immunogenic it will be:
* Peptides are strongly immunogenic.
* Carbohydrates are immunogenic
* Lipids are only immunogenic when combined with a lipid carrier**,** they act as haptens.
1. **Physical form:** Particulate antigens are more immunogenic than soluble ones and denatured antigens are more immunogenic than the native form.
2. **Degradability:** Antigens that are easily phagocytosed are generally more immunogenic. They usually **are T-dependent antigens**.

**B- Factors related to biological system:**

* 1. **Genetic Factors:** Some substances are immunogenic in one individual but not in others (i.e. responders and non-responders).
	2. **Age:** The very young and very old ages have a diminished ability to mount an immune response due to immaturity or aging of immune system.

**C-Methods of administration:**

* 1. **Dose:** There is a dose of immunogen above or below which the immune response will not be optimal i.e. **tolerance.**
	2. **Route:** Subcutaneous(SC) and intramuscular (IM) are better than the intravenous or intragastric routes.The antigen is slowly absorbed and there is prolong exposure to the immune system.
	3. **Adjuvants**: These are substances can enhance the immune response as they delay the absorption of antigen and prolong the period of their exposure to the immune system e.g. Aluminium hydroxide in diphtheria-tetanus (DT) vaccine..

**Types of antigens:**

1. **T-independent Antigens:** They are antigens which can directly stimulate the B cells to produce antibody without the requirement for T cell help. The type of immunoglobulin secreted is **Ig M** and there are **no memory cells formed. Polysaccharides** are T-independent antigens. They are resistant to degradation and thus persist for longer periods of time and continue to stimulate the immune system.
2. **T-dependent Antigens:** Antigens that must be phagocytosed, processed and presented to helper T cells by an antigen presenting cell **(APC)** to induce an immune response. The type of immunoglobulins secreted are Ig M which switch to either Ig G, Ig A, Ig E. There **are memory cells formed. Proteins are T-dependent antigens.** Most antigens are T-dependent antigens.
3. **Superantigens:** These are antigens which **non-specifically** activate a large fraction of the T cells through **beta** segments of TCR. Activation of T cells also requires that the superantigen bind to ***beta*** chain of **class II** MHC molecules on the surface of antigen presenting cells (APC); however **they are not processed** and **not presented by APC**. The release of huge amount of biologically active cytokines by activated T cells is called **“ cytokine storm”** which cause a lot of pathology . e.g  **include:** Staphylococcal toxic shock toxin (toxic shock syndrome).

|  |  |  |
| --- | --- | --- |
| **Feature** | **Ordinary antigen** | **Superantigens** |
| **Processing inside APCs** | **Yes** | **No** |
| **Presentation in complex with MHC** | **Yes** | **No** |
| **Specificity to TCR** | **High** | **No** |
| **Binding site of TCR** | **Variable region of α and β chains** | **Variable region of β chains** |
| **Memory cells** | **Yes** | **No** |
| **Adaptive immune response** | **Stimulated** | **Suppressed** |

**Table 3**

**Difference between ordinary and super antigens**

**Major Histocompatibility Complex (MHC)**

**MHC gene complex:** is a collection of genes located on chromosome 6 control **MHC antigens**. These antigens, and their genes, can be divided into three major classes: **class I**, **class II** and **class III**.

* **Class I MHC:** Class I MHC molecules are found on the surface **of all nucleated cells**. They contain two separate polypeptide chains:
	+ MHC -encoded ***alpha*** chain.
	+ **Non-MHC**-encoded ***beta2*** microglobulinor beta-chain encoded by **a gene outside the MHC complex**
* **Class II MHC** molecules are found **on the surface of professional antigen presenting cells (APCs)** (B lymphocytes, macrophages and monocytes, dendritic cells and skin associated (Langerhans) cells. They contain **two separate** polypeptide chains: one ***alpha-*** and one ***beta***- polypeptide chain which are **encoded by MHC II-genes**

**Two important regions** are present in class I and II MHC:

1. Peptide-binding region: is a groove that interacts with amino acids in the peptide fragment.
2. Immunoglobulin-like region: T cells that recognize MHC molecules, binds to this region.

**Inheritance:** MHC genes are inherited as a group (**haplotype:** a group of genes on a single chromosome), one from each parent.

**MHC antigen expression on cells:** MHC antigens are expressed on the cell surface in a **co-dominant** manner: products of both parental genes are found on the same cells.

**MHC association with diseases:** A number of diseases have been found to occur at a higher frequency in individuals with certain MHC haplotypes e.g celiac disease (DR3). No definite reason is known for this association.

**There is variety of shapes** of **MHC I and MHC II**. T cell recognize a certain peptide only when it bound to a MHC of certain shape and will not recognize this peptide if it is bound to another MHC with another shape.

**Important aspects of MHC**

* 1. Mature T cells respond to foreign antigens, but not self protein (tolerance).
	2. Only a single binding site exists on a class I or class II MHC molecule; all peptides must bind to the same site.
	3. Cytokines, especially interferon gamma (IFN-gamma), increase the level of expression of class I and class II MHC molecules.

**Antigen Presenting Cells (APCs)**

The fragmentation of proteins of the pathogen and association of the resulting peptides with each of the two classes of MHC molecules are called antigen processing and presentation. This is carried out by macrophages, dendritic cells (DCs) and B cells. They are concentrated in the **peripheral lymphoid tissue** such as lymph nodes, where the antigen is trapped, digested and presented to the recirculating T cells. They are the only cells capable of activating naive T cells.

**Proteins of pathogens** that are fragmented in **the cytoplasm of APCs** are transported to the cell surface in the form of a stable complex with **MHC class I.** This complex is **only** presented to cytotoxic T cells **(CD8)**. The antigens fragmented in cytoplasm are called **endogenous** antigens. e.g Viruses replicate within nucleated cells in the cytoplasm and produce endogenous antigens that can associate with **class I MHC**. By killing infected cells, cytotoxic T cells **(CD8)** control the spread of the virus.

**Proteins of pathogens taken in by endocytosis** are fragmented in intracellular vesicles **like phagosomes**, lysosomes of the APCs and the resulting peptide fragments are transported to the cell surface and are associated with the **class II** **MHC** molecules. This complex is **only** presented to helper T cells **(CD4), which is activated and give rise to** Th2 cells which secrete cytokines that assist B cells to make antibody against bacteria, which limits the growth of these organisms.

The antigens fragmented in intracellular vesicles are called **exogenous antigens**. e.g Bacteria mainly reside and replicate extracellularly.

For some bacteria that grow intracellularly inside the vesicles of cells like macrophages e.g. *Mycobacteria tuberculosis* , **Th1** produced and secrete cytokines that activate macrophages to kill the intracellular bacteria.

**T-Cell Mediated Immunity**

Cell-mediated responses are effective against **intracellular** pathogens. This type of immunity is mediated by T cells. Also T cells play a central role in humoral immune (antibody) responses.

**Origin and maturation of T-cells:** Lymphoid progenitor (stem) cells give rise to T precursors which must migrate to the thymus where they undergo differentiation. **T-cells at this stage are CD4+/CD8+ (dual positive).**

* **Central tolerance** **(negative selection)**: occurs during the early differentiation of T cells in the thymus which undergo apoptotic death when bind to self antigens. After negative selection, T-cells down regulate to either CD4 or CD8. Mature T-cells traffic to regional lymphoid organs or peripheral tissues
* **Peripheral tolerance**: Some autoreactive T-cells escape from the thymus to the periphery but undergo apoptotic death .
* T-cells that have not previously encountered antigen are termed **naive** and migrate to regional lymphoid tissue, while **activated or memory T-cells** selectively migrate to **peripheral tissue.**

**Two distinct types of T cells, helper T cell and pre-cytotoxic T cell.**

1. **T helper cells (Th)**: Express **CD4** molecules on their surface. Their main function is to help other cells of the immune system by secretion of cytokines. Two types of T helper cells are produced in the thymus: T helper 1 (Th1) cells and T helper 2 (Th2) cells.
2. **T helper 1 cells** whichhelp CD8+ pre-cytotoxic cells to differentiate into cytotoxic T cells, and activate macrophages to eliminate intracellular bacteria. e.g *Mycobacterium* *tuberculosis*.
3. **T helper 2 cells**: They help B cells to differentiate into plasma cells and produce antibodies.
4. **T helper 17** :Secrete **cytokines 17** ,**attract phagocytes** and induce secretion of **anti-microbials** by endothelial cells.
5. **T-cytotoxic (Tc) lymphocytes:** Express **CD8** molecules antigen and kill specifically host cells that have pathogens in their cytoplasm. Antigens of **tumor cells and viral antigens** are presented on the cell surface in association with **MHC class I** where they are recognized and killed directly by cytotoxic T cells.
6. **Regulatory T cells (Formerly called suppressor cells):** specifically suppress immune responses of both B and T cells, either directly or by production of cytokines e.g **IL-10 and transforming growth factor** .

**The specificity of cell mediated immune responses** resides in the T cell receptor **(TCR)** which recognizes peptide (antigen) bound to major histocompatibility **complex** (MHC) molecules expressed on the surface of nucleated cells. Every TCR on an individual T cell has **one** specificity.

**T cell surface molecules:**

**1-T cell receptor (TCR):** recognize one **specific MHC-antigen complexes**.

**2-****CD3 complex**: transmit signals to the interior of the T cell when the associated TCR binds antigen-MHC complex.It is found close to the TCR.

**3-Accessory molecules and co-stimulatory molecules:**

**a-Accessory molecules**: increase strength of adhesion between a T cell and an antigen presenting cell or target cell examples: CD4 on helper T cells and CD8 on cytotoxic T cells.

**b-Costimulatory molecules** : deliver a **second signal** required for the T cell to become activated Example**: CD 28 molecule** present on all T cells for antigen recognition it should bind **to B7 present on antigen presenting cells**

**4-Other surface molecules**: **CD 40 ligand** (CD40L) is involved in the activation of B cells by T cells. It binds to a molecule on B cells called CD40.

**Activation and generation of T cell immunologic memory**

**Primary response**: Clones of T cells with the TCRs specific for the peptide- MHC complex is activated through two signals: **The first signal** is the binding to specific peptide-MHC complex presented by APCs.**The second signal** by binding to **CD 28** on the T cell to **B7 on the APC** as co-stimulator molecule. Without this signal the T cell becomes non-responsive, a condition called **anergy.**

**Activated T cell becomes a lymphoblast** which proliferate (clonal expansion) and differentiate to become effector cells. The **cytokine IL-2** secreted by The T cell itself help in its proliferation and differentiation.

**Secondary response**: Not all of the activated Tduring primary challenge with antigen die. Some of them are long lived cells and constitute **memory cells.** Upon secondary challenge with antigen not only naive T cells are activated in addition to memory cells thus there is **a shorter lag time** in the secondary response.

**Memory T-cells** **may not require** co-stimulation by CD28

**A-Central role of subpopulations of helper T cells:** When a naive CD4+ T cell (Th cell) responds to antigen in secondary lymphoid tissues, it is capable of differentiating into effector Th1 cell or a helper Th2 cell, which release **distinctive** patterns of cytokines. Functionally these subpopulations, when activated, affect different cells.

1. **T helper 1: Th1** cells produce cytokines(**IL-2,** **IFN-gamma**, TNF-B). Th1 responses are induced by bacterial and viral antigens and activate CD8 T cells, NK cells, and macrophages to kill cells with intra-cellular microorganisms.
2. **T helper 2 cells** produce **IL-4 and IL-5 I,L-10** and IL-13 that increase production of eosinophils and mast cells and enhance production of antibody by B cells, especially IgE.

**B- Effector cytotoxic T cells (CD8):** The main function of Tc cells is to destroy abnormal cells such as **viral infected cells and tumor cells.** Cytotoxic T lymphocytes are **not fully mature when they exit the thymus**. They are called pre-cytotoxic cells. They must first differentiate, this occur in response to two signals:

* + - * 1. **Specific antigen** associated with **class I** MHC.
				2. **Cytokines** such as IL-2, and IFN-gamma secreted by Th1.

**Features of cytotoxic-mediated lysis ,they are** antigen-specific **and** are **not** injured when they lyse target cells.

**Mechanism of Killing by Tc cells:**

1. **Release of granules:** Activated cytotoxic T cell secrete **perforin** which form a pore in the target membrane. Another enzyme is secreted called **granzymes** pass through the pore and **induce apoptosis** or death of the target cell.
2. **Fas-ligand** a surface molecule of cytotoxic T cell binds to a death-inducing receptor on target cells called Fas-receptor thus **induces cell apoptosis** or cell death

**Immunoglobulins**

**Definition:**Immunoglobulins are glycoprotein molecules that are produced by plasma cells in response to an immunogen. They are involved in destruction of **extracellular** pathogens and prevent their spread from cell to cell. They are **specific** to the antigen.

**Origin and differentiation of B cell:** They are produced and mature in **b**one marrow. Active B cells are called **plasma cells** which produce antibodies

* **Central tolerance**: occurs during the early differentiation of B cells in the bone marrow it undergo apoptotic death when they encounter cell-associated or soluble self antigen (negative selection).
* **Peripheral tolerance**: occurs in secondary lymphoid organs after the exit of autoreactive B from the bone marrow

**Stages of immunoglobulin production** :B-lymphocyte is the cell responsible for immunoglobulin production. Naïve B-lymphocyte i.e cell not exposed to any foreign antigen have surface receptors:

* 1. **B-cell receptor (BcR):** They are of identical specificity and they are specific to one specific antigen. **They are monomer of**  Ig M and Ig D
	2. **CD40 receptors** for CD40 ligand on the surface of T cell .
	3. Major histocompatibility antigen type II (MHC-II): These molecules are essential for antigen presentation to T helper cells.

**B-cell effector populations and functions**

* Plasma cells are differentiated B-cells; it secrete high levels of antibody. They lack cell surface immunoglobulin **so cannot** present antigen.
* B-cell antigen presentation: as it express MHC class II and possess co-stimulatory molecules such as B7 and CD40 to allow antigen presentation to CD4 T-cells.
* Memory B-cells. Long-lived non-proliferating B-cells available for

antigen re-challenge. **They lack** monomer Ig M and Ig D.

**Activation of B cells:** The maturenaïve B cell circulate in the blood and enters secondary lymphoid organs e.g. the lymph node, if the antigen is presented to T helper cells, the B cells is trapped in the T cell zone and B cell activation occursto become lymphoblast which proliferate and form a **clonal expansion**, differentiate to become plasma cells and secrete antibody specific for the antigen. B cell can switch to produce IgG, A, E antibodies **with the same specificity.** Some B cells do not differentiate and instead become **memory cells.** This type of activation is **called T-cell dependent activation.** Activated naïve B cells must receive two signals:

* + 1. The first signal comes **from antigen** **cross linking** the B cell receptor (BCR).
		2. The second signal (co-stimulatory signal) comes from [co-stimulation](http://en.wikipedia.org/wiki/Co-stimulation) provided by activated [**T helper 2** cell](http://en.wikipedia.org/wiki/T_cell).

The B cell engulfs the bound antigen, degrades it into peptides and presents them on the cell surface in association with MHC class II molecules. Primed **T helper 2** cell recognized this complex and secrete cytokines mainly:

1. CD 40 Ligand (CD40L) which bind to its receptor on B cell surface.
2. IL 4 and IL 5 which stimulate B cells. (Fig 18 ).

B cells could be activated directly without the help of T cells, called **T-cell independent activation**.This type of activation provide an early and specific antibody response**. Only Ig M** is produced and the B cell cannot switch to other isotypes. **Memory cells** are **not** produced.

**Immunoglobulins:** There are 5 classes or isotype of immunoglobulins: Ig **G,** Ig **A**, Ig **M,** Ig **E,** Ig **D**.

**The basic structure of the immunoglobulins**: All immunoglobulins have a four chains structure as their basic unit; two identical light (L) chains and two identical heavy (H) chains assembled to form a Y-shaped molecule. Each light chain is attached to one heavy chain.

**The light chain**: either **one** of two types: kappa (κ) **or** lambda (λ), that **differ**s in the **constant** regions but **don’t differ in function**.

**The heavy chain:** There are **five types** of heavy chains, called gamma (γ), alpha (α), mu (µ), delta (δ) and epsilon (ε) that **differ** in the **constant** regions.

**Domains :** The light and heavy chains are subdivided into regions or domains. These regions are:

1. **Variable** regions (domains) show a wide variation in amino acid composition.
2. **Constant** regions (domains) show a constant amino acid composition.
* **The Light Chain** consists of **one** variable region VL and **one** constant region CL.
* **The Heavy Chain** consists of **one** variable region VH and **3-4 constant** regions CH1 - CH3 (or CH4)
* **The amino-terminal** portion of immunoglobulin is formed of the variable domains of **both** **light** chains and **heavy** chains and they contain **the antigen binding sites** of the antibody **(Fab).**
* **The carboxy terminals** portion is formed of the constant regions **of both heavy chains**. It forms the **Fc fragment** which **has the biological activities** of the immunoglobulin. (Fig 20)
* **Hypervariable regions**: Each variable region of the heavy chain or the light chain **contains 3 hypervariable regions or** Complementarity-determining regions  **CDRs,** which is located at **the junction of the V and C regions. CDR i**s the portion of the Ig molecule that contributes most to **antigen binding** it is called **paratope** and it is complementary to the epitope of the antigen.

* **All chains are held together by disulfide bonds**
* **Hinge Region** : This is the region at which the arms of the antibody molecule forms a Y, it gives **flexibility** at this point.

**Biological Functions of immunoglobulins**: Each immuno-globulin binds to a specific antigenic determinant. The valency of antibody refers to the number of antigenic determinants that an individual antibody molecule can bind. The valency of all antibodies **is at least two**, as each Ig molecule has two Fab fragments. The immunoglobulins mediate a variety of biological activities it includes:

1. **Agglutination:** Antibodies can bind to and cross-linkcells **or particles**, causing an aggregate formation. Agglutination entrap microbes and inhibit their motility, making them more susceptible to destruction e.g. by phagocytes.
2. **Neutralization:** It is the binding of antibodies to **soluble** molecules (e.g. toxin) so inhibits it to bind to host cell surfaces.
3. **Opsonization:** Antibody coat microbes and **promote ingestion** by phagocytes. Macrophages, monocytes, PMN's and some lymphocytes **have Fc receptors** for the Fc region of immunoglobulin (Ig). A consequence of binding to the Fc receptors is that the cell can now internalize the antigen better. The term **opsonin** is used to describe substances that **enhance phagocytosis.**
4. **Fixation of complement:** Interaction of antibody with antigen initiates complement activation leading to release biologically active molecules that cause either **direct lysis** of the pathogen or bind to **complement receptors** on phagocytes, facilitate engulfment of pathogen or opsonization.
5. **Antibody-dependent cell mediated cytotoxicity (ADCC):** When antibody **coat large microbes** as bacteria, protozoa, it can attract NK cell which bind to the Fc portion of the antibody through their Fc receptors present on their surface. This process facilitate adhesion of NK cells and stimulate its cytotoxic activity.**(Fig 16)**
6. **Some immunoglobulins bind to receptors on the placenta,** which results in transfer of the immunoglobulin across the placenta. As a result, the transferred maternal antibodies provide immunity to the fetus and newborn.

**Table 4-Comparison between properties of immunoglobulin subclasses**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Property**  | **Ig G** | **Ig M**  | **Ig A** | **Ig E** | **Ig D** |
| **Structure** | Monomer | Pentamer | Monomer-dimer in secretion | Monomer | Monomer |
| **% of serum immunoglobulin**  | **75%** | 8-10% | **15-20%** | least | **1%** |
| **Distribution**  | **Extra** and **intra-**vascular  | **Only in blood** –and as monomer on B lymphocytes  | **Surface** mucosa- secretions - tears, saliva, colostrum | Mast cells  | On B-lymphocytes  |
| **Immune response**  | Secondary | **Primary**-indicate **recent infection**  |  |  |  |
| **Placental transfer** | **+** | - |  | - | - |
| **Other important role**  | Anti-Rh | First immunoglobulin **in fetus**  cold agglutinins  | **Local mucosal immunity** respiratory mucus and GIT | In **allergy** and **parasitic** infection  |  |

***Other important properties***

**Immunoglobulin M (IgM):**

* 1. It is the first Immunoglobulin made by the fetus. Its presence in the fetus indicates **intrauterine infection.**
	2. Being a pentameric structure IgM is:
		+ Good complement fixing Ig, efficient in lysis of organisms
		+ Very good in agglutination
		+ It is mainly confined to blood
		+ **Incapable to bind to Fc receptors and cannot mediate antibody- dependent cell mediated cytotoxicity (ADCC) as the 5 Fc fragments are**  **held together** by disulphide bonds or J chain
	3. Surface IgM exists as a **monomer on B cell** and acts as a receptor **(BcR)** for thymus dependent antigen.

**Immunoglobulin A (IgA):**

1. Serum IgA is a **monomer**
2. Secretory IgA, found in secretion, is a dimer, possess a **J chain** and another protein called the **secretory piece** or **T piece is made in epithelial cells** and added to the IgA as it passes into the secretions(Fig 24). **The secretory piece helps IgA to b**e transported across mucosa and protect the Ig A molecules from proteolytic digestion and degradation in the secretions.

**Immunoglobulin E (IgE):**

1. Exists as a monomer
2. It is the **least common serum** Immunoglobulin since it binds very tightly to Fc receptors on **basophils** and **mast cells** even before interacting with antigen.
3. It is involved in **allergic reactions** as a consequence of its binding to basophils on mast cells it leads to **type I hypersensitivity reaction.**
4. Play a role in **parasitic** helminth diseases as eosinophils have Fc receptors for IgE.Binding of eosinophils to IgE-coated helminths results in their killing.

 **Immunoglobulin class switching (or isotype switching)**: It is a biological mechanism that changes an [antibody](http://en.wikipedia.org/wiki/Antibody) from one class to another. During this process, the **constant region of the** [**heavy chain**](http://en.wikipedia.org/wiki/Heavy_chain) **is changed**. There is **no** change in variable region of the heavy chain or both regions of light chain. Cytokines secreted by T helper play a role in the **immunoglobulins class switching process:**

1. **IL-4** differentiate B cell clone (plasma cells) to **Ig E** secreting cells.
2. **IL-5** stimulates plasma cells to be **Ig A** producer.
3. **IL-4, IL-5 and IL-6**, stimulate secretion of **IgG** by plasma cell.
4. **Transforming growth factor-beta(TGF-):** Encourage B cell clone (plasma cells) to switch Ig to **IgA**

**Primary and Secondary immune response**

**Primary immune response:** When an antigen isfirst encountered, antibodies are detectable in the serum after **a lag period** between **7-10 days**. A small clone of B cells and plasma cells specific for the antigen is formed. The serum antibody concentration continue to rise for several weeks **then declines rapidly**

The first antibodies to appear are **Ig M, followed by IgG** or IgA. IgM level declines earlier than IgG.

**Secondary immune response:** When there is second exposure with the same antigen, months or years several differences are noted:**First**,the **lag period is shorter** is only **3-5 days**. **Second,** the activity rises at a **more rapid** rate and reaches **higher** levels, about 10 times greater than in the primary response. This is attributed to the persistence of antigen-specific **memory cells** after the first contact. These memory cells can proliferate to form large clone of specific B cells and plasma cells **The main type of antibody produced is IgG.**

**Table 5-Primary and secondary immune response**

|  |  |  |
| --- | --- | --- |
| **Character** | **Primary**  | **secondary** |
| **Lag period** | **Long** | **short** |
| **Antibody level** | **Low** | **Ten times higher** |
| **Duration** | **Short** | **long** |
| **Decline rate** | **Rapid** | **Slow** |
| **Ig class**  | **Mainly Ig M** | **Mainly Ig G** |
| **Memory cells** | **Absent** | **present** |

A much larger amount **of Ig G** is produced and the antibody level is **maintained at high levels**, falling slowly over a long period of time. With each succeeding exposure to the antigen, the antibody response can be stimulated to a higher level. **For this reason vaccines** are given in several **booster dose.**

**Heterophile antibodies**: These are antibodies induced by antigens that cross react with another one. This is due to similarity in antigenic determinants. For example antibodies against Group A Streptococcus cell walls can also react with human heart tissue as in rheumatic fever.

**Monoclonal antibodies:** These **are specific** antibodies produced to a single epitope (of an antigen) by a single clone of B cells. This could be achieved by fusing a myeloma cell with an antibody-producing B cell. Such hybridoma produce unlimited quantities of **antibody of one specificity** called monoclonal antibodies that are useful in diagnostic tests and in a variety of clinical situation.

A-**Diagnostic applications:** example Detection of HLA antigens ,detection and typing of virus .

**B-Therapeutic applications:**

1. Prevention of Rh incompatibility using monoclonal anti-Rh D**.**
2. Treatment of cancer: **Magic bullet therapy** using tumor specific antibody linked to cytotoxic drugs.
3. Immunotherapy to virus diseases.

**Cytokines:**are a different group of proteins released by different types of cells involved in both natural and specific immunity and act as intercellular mediators in immune processes.

**Properties:**

1. Not specific to antigens
2. Its secretion is brief and limited.
3. Not stored as pre-formed molecules.
4. Highly potent as they act at a low concentration.
5. Bind to receptors on target cells with high affinity.
6. Pleotropic i.e the same cytokine may have multiple effects.
7. Many cytokines have similar actions (they are **redundant**).
8. Influence the synthesis of other cytokines.
9. Influence the action of other cytokines, their effects can be **antagonistic, additive or synergistic** i.e greater than additive.

**Cytokines can be grouped according to function:**

1- **Mediators and regulators of** **natural immunity**:Tumor Necrosis Factor-alpha (TNF-α),Interleukins-1,6,10,12,Interferon: IFN-α and IFN- and Chemokines.

**2-Mediators and regulators of specific immunity**:Interleukins-2,4,5,10 ,interferon-gamma (IFN-gamma),transforming growth factor- (TGF-) and tumour necrosis factor.

1. **Stimulators of hematopoeisis**:Interleukins-3 and Colony-Stimulating Factors (CSFs).

**Functions of some cytokines:**

**I-Mediators and regulators of natural immunity:** they are produced by **activated macrophages.**

1. **Tumor Necrosis Factor** (TNF-α)**, IL-1, IL-6** and chemokines are called proinflammatory cytokines.

**Actions:** It attract polymorphonuclear leukocytes (PMNs) to the site of infection by **gram negative bacteria** . It acts on the hypothalamus to produce fever.

1. **Interferon type I: These are IFN-α and IFN**-β**:** Their secretion is induced mainly by viral infected cells and protect nearby cells**.**

**Actions**:

1. Inhibition of viral replication: Interfere the translation of viral mRNA.
2. Inhibit cell proliferation e.g as for tumor cells.
3. Increase the expression of MHC I so viral peptide-MHC complex is better recognized by cytotoxic T cells (CD8).
4. Activation of NK cells.

**II- Mediators and regulators of specific Immunity:** These cytokines some are secreted by **T h 1 cells a**nd some by Th2 and some by both.

**Interleukin-2:** Is produced mainly by **T h1** cells (CD4+).

**Actions:** promote T and B cell proliferation and activates NK cell .

**Interleukin-4:** It is produced mainly **by Th2** (CD4+) required for antibody production **by B cells.**It stimulates development of Th2 cells from

 naïve T helper cells ( CD4+) and promotes their growth .It stimulates immunoglobulin class switching to the **IgE isotype.**

3- **Interleukin-5**: It is produced mainly by the **Th2.** It promotes growth and differentiation of eosinophils and activates mature **eosinophils.**

**IL-4 and IL-5 function together:** IL4 class switch Ig to IgE which opsonizes helminthes, then bind to **eosinophils** which upon activation by IL-5 kill the helminths.

1. **Interferon type II**-**IFN-gamma**: This protein is produced by **the Th1,** cytotoxic T cells **(CD8+),** and **NK cells**. IFN-gamma play a role in both natural and specific immunity:
2. **Innate immunity:** It enhances the microbicidal function of macrophages
3. **Adaptive Immunity:**
* Stimulates the expression of class I and class II MHC molecules and co-stimulatory molecules on antigen presenting cells.
* Promotes the differentiation of naïve helper T cells into Th1 cells.
* Activates polymorphonuclear leukocytes (PMN) and cytotoxic T cells and increases the cytotoxicity of NK cells.
1. **Transforming growth Factor** (TGF-beta): It is an **inhibitory cytokine** produced by T cells, macrophages, and many other cell types.

**Actions:**

1. **Inhibits /blocks** **T cells, macrophages and** the effects of pro-inflammatory cytokines.
2. **Acts as a growth factor** that promotes **wound healing**.

**III- Stimulators of Hematopoiesis: Colony-Stimulating Factors (CSFs):** It is produced by T cells, macrophages, endothelial cells, fibroblasts promotes growth and differentiation of monocytes,macrophages and granulocyte.

**Cytokine therapy:**

* + - 1. Both Type I and Type II interferons are used in treating patients with viral infections such as *Hepatitis B and C* viruses*.*
			2. Treatment of cancer by IFN- gamma and alpha and IL-2 .
			3. Colony-Stimulating Factors are used to treat leucopenia and bone marrow depression.

**Immunization**

Immunization is the means of providing specific protection against most common pathogens.

**Specific immunity** can be acquired either by passive or by active immunization and both modes of immunization can occur by natural or artificial means.

**A- Passive Immunity**: is the transfer of gamma-globulins, immune cells from an immune donor to a non-immune individual. Immunity acquired is immediate, temporary and of short duration till antigen elimination.

**Passive immunity** may be acquired naturally or artificially.

* 1. **Naturally acquired**: from mother to fetus through placental transfer of IgG or [colostral](http://cancerweb.ncl.ac.uk/cgi-bin/omd?colostrum) transfer of IgA.
	2. **Artificially acquired by injection with gamma-globulins** obtained from immune individuals or animal. This is used in treatment of serious infections e.g. in diphtheria, tetanus, measles, rabies, etc. and as a prophylactic measure in cases of **hypo-gammaglobulinemia**.

Gamma-globulins of **human** origin are preferable and are used in some cases such as diphtheria, tetanus, gas gangrene, botulism.

**Disadvantage of passive acquired immunity:**

* + - Effective for only a short duration.
		- Result in complications such as **serum sickness** and [anaphylaxis](http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=anaphylaxis&action=Search+OMD).
		- Carry the risk of transmitting hepatitis and HIV.
1. **Passive transfer of cell-mediated immunity** can be used in certain diseases as cancer, immunodeficiency but carry the risk of graft versus host disease.

**B- Active Immunity**: This refers to immunity produced by the body following exposure to antigens resulting in specific stimulation of B and or T cells. The immunity is acquired after a period of time and it is not immediate. It lasts after antigen elimination due to the development of memory cells.

* + 1. **Naturally acquired**: Exposure to different pathogens leads to sub-clinical or clinical infections which result in a protective immune response against these pathogens.
		2. **Artificially acquired**: Immunization may be achieved by giving live or dead pathogens or their components. Vaccines used for active immunization consist of live attenuated organisms

,killed whole organisms ,microbial components or secreted toxins, which have been detoxified

1. **Live vaccines*:*** are used against a number of **viral** infections e.g. polio (Sabin), measles, mumps, rubella, chicken pox, yellow fever, *etc*.
	* The only example of live bacterial vaccine is the one against tuberculosis (*Mycobacterium bovis*: BCG).
	* They carry a serious risk of causing overt disease in immuno-compromised individuals.
2. **Killed vaccines***:* Prepared by killingbacteria with heat, chemical or UV irradiation.
	* Most **bacterial** vaccines **are kille**d organisms e.g. typhoid, cholera, plague, pertussis, *etc*.
	* Viral vaccines include those for polio (Salk), influenza, rabies, influenza.
3. **Microbial components** *or secreted toxins*:
	* Cell wall components e.g. **capsule** in cases of pneumococcus, etc.
	* Antigenic proteins: e.g HBsAg for hepatitis-B virus .
	* A modified form of the toxin (toxoid) is used as a vaccine *e.g.* diphtheria, tetanus.

The protective immunity may be:

* + Life long as in measles, mumps, rubella, small pox, tuberculosis,
	+ Short for six months e.g cholera
	+ In general, immunity following vaccination weakened by time and revaccination (a booster) may be required after a set period of time.

**Table 6 -Difference between active and passive immunity**

|  |  |  |
| --- | --- | --- |
| **Feature** | **Active** | **Passive** |
| Immune system | Important,active B and/or T cells  | Play no role |
| **Onset** | Delay  | Immediate |
| **Duration of immunity** | **Long** | **Short** |
| **Memory cells**  | **Present**  | **Absent** |
| **Examples** | **Natural:**clinical-subclinical infections**Artificial:**vaccines | **Natural:** Transplacental transfer of Igs**Artificial:**Injection of gamma -globulins |

* + Active immunization may cause fever, malaise and discomfort,arthritis (rubella), convulsions, sometimes fatal (pertussis), or neurological disorders (influenza).
	+ **Schedule of immunization used in Egypt At the age of**
1. First month BCG and hepatitis B vaccine
2. 2-4-6 months :(diphtheria, pertussis, tetanus, polio, hepatitis B)
3. 9th month: measles vaccine
4. 13 or 15 months (mumps, measles, rubella MMR).

rejection

**Immune response and therapy**

The immune response to infections can be enhanced or suppressed e.g during transplantation/ autoimmune disease

**Therapeutic interventions include:**

1. Active immunization. Used for selected microorganisms and in cancer
2. Passive immunization : Transfer of specific immunoglobulin
3. Adoptive transfer. Cells can be transfused into individuals. Examples

bone marrow transplantation

1. Cytokines. Specific cytokines (**IL-2**, interferon-alpha or TNF alpha) are used to enhance immune responses .Colony-stimulating factors such as GM-CSF or G-CSF may be used in neutropenic hosts
2. Steroids are used to suppress inflammation and lymphocyte activation and prevent autoimmune diseases or transplant

rejection

1. Cytotoxic drugs are cytotoxic used in immunosuppression of T- and B-cells

**Hypersensitivity Reactions**

**Hypersensitivity** refers to undesirable reactions produced by the normal immune system. These reactions vary from local tissue damage to systemic fatal reactions.

**Hypersensitivity reactions** can be divided into **four types** based **on the mechanisms** involved and **time taken** for the reaction.**:**

* + - 1. Immediate type, hypersensitivity type I .
			2. Antibody-mediated, hypersensitivity type II.
			3. Immune complexes-mediated, hypersensitivity type III.
			4. T-cell-mediated, or **delayed hypersensitivity type IV.**

**Type I Hypersensitivity:** Also known as **immediate** or [**anaphylactic**](http://cancerweb.ncl.ac.uk/cgi-bin/omd?anaphylaxis) hypersensitivity. The reaction may be minor or fatal. The reaction takes 15 - 30 minutes from the time of exposure to the antigen. The reaction is mediated by **IgE**. Some patients have **genetic pre-disposition** to form high level of Ig E to environmental antigens or allergens.

**Mechanism of Type I Hypersensitivity:**

* 1. **Sensitization:** Involves the production of Ig E in response to **allergens** under control of Th2. First exposure to allergens stimulate the secretion of IL-4 by Th2 inducing class switching from Ig M to Ig E. Ig E has very high affinity for its Fc receptor on mast cells and basophils.
	2. **Degranulation of mast cells:** A subsequent exposure to the same allergen, it cross links the cell-bound IgE and triggers the release of various pharmacologically active substances. **Cross-linking** of IgE Fc-receptor is important in mast cell triggering.

**The most important active substances released are:**

* 1. **Mediators of early-phase reaction mainly:** Histamine, platelet activation factor (PAF) all are preformed in mast cells and are responsible for the early symptoms after 15-30 minutes. There is increase in vascular permeability and smooth muscle contraction resulting in different symptoms.
	2. **Mediators of late-phase reaction:** They include prostaglandins and leukotrienes. They are not preformed and

are synthesized upon exposure to allergens and for this reason the reaction is delayed and occurs after 5-6 hours. Other cytokines are released from degranulated mast cells e.g. eosinophil and neutrophil chemotactic factors .

**Clinical syndromes:**

* + 1. **Localized reactions or atopy:** Reactions are restricted to one organ and may be induced by different allergens that could **be inhaled** e.g pollens, house dust ,**contact** as nylon, wool, animal fur, or by **ingestion.**

**2-Systemic reactions or anaphylaxis:** The most severe form of immediate hypersensitivity and involves broncho-constriction, hypotension that can be

life threatening. This reaction is caused by widespread mast cell degranulation in response to a **systemic antigen**.e.g.:After exposure to penicillin or after treatment with antitoxin serum in cases of diphtheria and tetanus.

**Diagnostic tests** include:

1. Intradermal tests: In which antigen extract is injected in skin, an immediate wheal and flare reaction is formed within 15-20 minutes develops at site of injection.
2. Measurement of total Ig E and specific IgE against the suspected allergens by ELISA.

**Treatment:**

* 1. **Hyposensitization** It is done by repeated administration of small doses of allergens. The production of IgG-blocking antibodies prevent allergen from reaching Ig E.
	2. Avoid exposure to allergen.
	3. Anaphylactic shock is treated by immediate administration of adrenaline, corticosteroids and inhalation of oxygen.
	4. Symptomatic treatment is done by using anti-histaminics.

**Type II hypersensitivity:** It is also **known as cytotoxic hypersensitivity** and may affect a variety of organs and tissues.

**Mechanism of type II Hypersensitivity:** Primarily mediated by antibodies of the IgM or IgG classes and complement. The antigens **are cell-bound or surface antigens.**

Surface antigens could be endogenous or exogenous chemicals ([haptens](http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=hapten)) attach to the cells. Phagocytes and NK cells may also play a role (ADCC). The reaction time is minutes to hours. The lesion produced is caused by:

* + 1. Lysis of the cells due to fixation of complement by antigen antibody complex.
		2. Lysis by NK or antibody-dependent-cytotoxic cells ( ADCC).
		3. Opsonization with or without complement fixation.

**Clinical syndromes: include** Rh incompatibility ,blood group incompatibility graft rejection and **autoimmune diseases**. Also drug-induced hemolytic anemia, [granulocytopenia](http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=granulocytopenia) and

[thrombocytopenia](http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=thrombocytopenia&action=Search+OMD) where antibodies react with drugs attached to the surface of cells lead to its destruction upon complement fixation. In addition to

**Diagnostic test :** Detection of circulating antibody against the tissues involved.

**Treatment involves** anti-inflammatory and immuno-suppressive agents.

**Type III Hypersensitivity**: Also known **as immune complex hypersensitivity which** may be **generalized** *e.g.* serum sickness or **localized**, involve individual organs like skin (*e.g.* Arthus reaction)

Joints (*e.g.*, rheumatoid arthritis) ,Kidneys (*e.g.*, lupus nephritis)

**Mechanism of Type III Hypersensitivity:** It is mediated by **soluble** immune complexes formed of:

1. Antibodies which are mostly of the IgG class, although IgM may also be involved.
2. Soluble antigen i.e. it is **not attached** to the organ involved.

Small soluble immune complexes may escape phagocytosis become deposited in basement membrane of blood vessels of joints, kidneys and fixation of complement and aggregation of platelet occur.

**Complement activation** result in formation of C3a and C5a known as anaphylatoxins which:

1. React with receptors on mast cells and release of histamines causing vasodilatation.
2. C5a is chemotactic **for neutrophils** to engulf immune-complex. Neutrophils release lysosomal enzymes and destroy basement membrane.

**Platelet aggregation** result in formation of microthrombi causing local ischemia and further tissue damage.

The reaction may take **3-10 hours** after exposure to the antigen, as in [Arthus reaction](http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=arthus).

**Clinical syndromes**:

* + 1. **Localized reaction example: Arthus reaction**: Inflammation caused by deposition of immune complexes at a localized site e.g. repeated subcutaneous injection **of low dose** of a foreign antigen at the same site as in case of insulin injection in treatment of diabetes and rabies vaccination.
		2. **Generalized reaction example Serum sickness:** After injection of a **large dose** of foreign antigen e.g. antitoxic serum as in passive immunization with horse serum for the diphtheria or tetanus is excreted slowly. During this time antibodies are produced. Soluble immune complexes are formed circulate or be deposited at various sites. Symptoms develop **few days to 2 weeks** after

injection of antigen in the form of fever, urtecaria, arthralgia, lymphadenopathy and splenomegaly.

**Diagnostic tests involve:**Presence of immune complexes in serum and **depletion in the level of complement.**

**Treatment:**Anti-inflammatory agents e.g. corticosteroids, anti-histaminics.

* **Type IV Hypersensitivity:** Also known as **cell mediated** or **delayed** type. The response is delayed, it starts hours **or days** after contact with the antigen.

**Mechanism of Type IV Hypersensitivity:** The **mechanism involve** tissue **d**amage by **sensitized T** lymphocytes which secrete a number of cytokines and attract ,activate monocytes and macrophages Neutrophils are not usually involved in this type of hypersensitivity reaction.

**Clinical syndromes:**

* 1. **Tuberculin (Mantoux)reaction** which peaks **48** hours after the intradermal injection of antigen (purified protein derivatives or **PPD**). The lesion is characterized by [induration](http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=induration) due to accumulation of sensitized lymphocytes, monocytes and macrophages.
	2. **Contact dermatitis:** Occurs after topical application of allergen e.g. cosmetics, drugs which **act as hapten** and bind to body protein.
	3. **Granuloma formation:** Intra-cellular bacteria resist cidal effects of activated macrophages and persist in the form of chronic infection.

There is continuous production of cytokines by Th1 resulting in accumulation of large number of activated macrophages and formation of central core of granuloma. Granuloma is formed in the body **to isolate** the organisms that resist intracellular destruction. Necrosis occur in the central core due to this isolation, dead tissue resemble cheese and the process is called **caseation necrosis.**

* 1. **Autoimmune diseases.**
	2. **Graft rejection.**

**Diagnostic tests include:In vivo** test include delayed cutaneous reaction (*e.g..* Montoux test) and **in vitro tests** include: IL-2 production.

**Treatment:** Corticosteroids and immunosuppressive agents.

**Table 7 -Comparison of types I-IV hypersensitivity reactions**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Characteristic**  | **Type I** | **Type II** | **Type III** | **Type IV** |
| **Time**  | **30 min**-6 hrs | 5-12 hrs | 3-10hrs | **48hrs-72hrs** |
| **Mediators**  | **Ig E** | Ig G-Ig M | Ig G-Ig M | T cells |
| **Response to intradermal injection of antigen**  | Wheal and flare | - | Erythema and edema | Induration and erythema |
| **Examples**  | Asthma, anaphylaxis | Transfusion reaction, drug -induced allergy | Arthus reaction -serum sickness | Tuberculin test ,graft rejection tumor immunity |

. **Tolerance and Autoimmunity**

**Tolerance** means **specific** immunological **non-reactivity to an antigen**. The most important form of tolerance is non-reactivity to self antigens. **Tolerance could be naturally induced central or peripheral as described before in T cell chapter . It could be artificially induced** to non-self (foreign) antigens. It involves T cells , B lymphocytes and natural killer cells.It is helpful in the treatment of allergy, autoimmune diseases and to facilitate organ transplantation.

**Mechanisms of tolerance induction:**

1. **Clonal deletion** by **negative selection as shown in chapter of T cells**
2. **Clonal anergy:** Auto-reactive T cells, when exposed to antigenic peptides on antigen presenting cells (APC) which do not possess co-stimulatory molecules (B7), become [anergic](http://cancerweb.ncl.ac.uk/cgi-bin/omd?action=Search&query=anergic) to the antigen.B cells when exposed to large amounts of soluble antigen down regulate their surface IgM and become anergic.
3. **Clonal ignorance:** T cells reactive to self antigen not represented in the thymus will mature and migrate to the periphery, but they may never encounter the appropriate antigen because it is sequestered in inaccessible tissues. **Such cells may die** out for lack of stimulus.

**Immunologic features of tolerance**

* 1. Specific, it can exist in T-cells, B cells or both.
	2. Tolerance may be present in neonatal period because of immaturity of the immune system.
	3. Tolerance can be broken naturally as in autoimmune disease

**AUTOIMMUNITY:** can be defined as **breakdown** of mechanisms responsible for **self tolerance** and induction of an immune response against components of the self which causes damage to the self. Both antibodies and effector T cells can be involved in the damage in autoimmune diseases.

**General classification**: Autoimmune diseases are generally classified on the basis of the organ or tissue involved. These diseases may fall in:

* + - 1. **Organ-specific category** in which the immune response is directed against antigen(s) associated with the target organ being damaged. e. Grave's disease (thyroid gland).
			2. **Non-organ-specific category** in which the antibody is directed against an antigen not associated with the target organ e.g.Rheumatoid arthritis(anti-IgG ),systemic lupus erythematosus.

**Genetic predisposition for autoimmunity:** Association between certain HLA types and autoimmune diseases has been noted. e.g.rheumatoid arthritis is associated with DR4

**Etiology of autoimmunity disease : This could be due to :**

1. **Antigen**
* **Release of sequestered antigen:** example from organs as testis and brain as a result of accidental traumatic injury or surgery can result in the stimulation of an immune response and initiation of an autoimmune disease.
* **Alteration of self antigens** by chemical and viral infections
* **Cross reactive antigens:** Antigens on certain pathogens may have antigenic determinants **which cross react** with self antigens and immune response against these determinants may lead to effector cell or antibodies against tissue antigens, example rheumatic fever .
* **Escape of auto-reactive clones**: The negative selection in the thymus may not be fully functional to eliminate self reactive cells. Not all self antigens may be represented in the thymus .
1. **Breakdown in the immune system** due to either loss of regulatory T cells, polyclonal activation of lymphocytes by some viruses and bacteria

**Mechanisms of tissue damag**e:

1. Antigen-antibody reaction (Type II hypersensitivity): e.g autoimmune hemolytic anemia
2. Immune complex deposition: (type III) e.g. rheumatoid arthritis
3. Delayed type hypersensitivity (type IV): e.g. ulcerative colitis..
4. Organ-specific antibodies: e.g. Anti-thyroid antibodies increase the response of cell receptors to TSH in Grave's disease .This lead to thyrotoxicosis.

**Diagnosis**: Antibodies against **cell/tissue** associated antigens are detected by immunofluorescence e.g anti-thyroid antibodies, anti-smooth muscle..Antibodies against **soluble** antigens are detected by **latex** test.e.g. Rheumatoid factor ( this a Ig M produced against Ig G of the patient). There is elevation of total serum immunoglobulins and **decreased level of serum complement, due to uptake in immune complexes.**

**Tumor Immunology**

**Immunosurveillance:** lymphocytes recognize and eliminate continuously a rising transformed cells.

**Tumor associated antigens:** A number of alterations occur in the cell during transformation result in appearance of antigens .

**Examples of tumor antigens:**

1. **Onco-fetal antigens** (**TATA**)**:** **Alpha-fetoprotein** (**AFP) in liver cancer** and **carcino-embryonic antigen** (**CEA**) in cancer colon
2. **In case of viral tumors** the surface antigens **are shared** by all tumors induced by the same virus and are associated with **MHC.** Important oncogenic viruses hepatitis-B virus in hepatic carcinoma,

**3- In case of chemically-induced tumors:** Any two tumors induced by the same chemical,do not share common tumor specific antigens.

**Immune mechanisms of tumor rejection:** All components of the immune system non-specific and specific; humoral and cellular can affect the growth and progression of a tumor:

1. **Natural killer (NK), monocytes and macrophages**  have direct cytotoxicity effect by releasing TNF-αand by antibody dependent cytotoxicity of NK cells.
2. **T cells: by** cytotoxic T cells (Tc cells) ,the majority of tumor antigens are displayed as class I MHC-associated peptides.

**As for** helper T cells ,tumor antigen are presented by APCs in association of class II MHC .T helper cells secrete cytokines that activate **Tc cells**, macrophages, NK cells and B cells.

1. **B cells:**They are one of the antigen presenting cells (APCs) which present tumor antigen in association with class II MHC to Th cells and produce specific antibodies to tumor antigens:

**Escape from immuno-surveillance:**

1. Tumors may not express surface antigens that are immunogenic.
2. In early stage the amount of antigen may be too small to stimulate the immune system.
3. Some viruses block the expression of co-stimulatory molecules (e.g. B7)
4. Some tumors may shed their unique antigens which block antibodies and T cells from reacting with malignant cells.
5. Several human cancer cells expressed high levels of programmed death-ligand 1 (PD-L1) which bind to their receptor on T cells and delivers inhibitory signals to these cells.

**Immuno-diagnosis: by labeled** monoclonal antibodies

**Tumor markers:** are tumor antigens detected in early tumor formation present in patient serum. They are useful **in follow up** for tumor regression, they include CEA:Cancer colon. ,PSA:Cancer prostate.

**Immunotherapy:** Both active and passive means of stimulating the non-specific and specific immune systems have been employed.

**Active immunotherapy:**

* + 1. **Non-specific**: By injection of BCG
		2. **Specific**: Killed tumor cells or their extract are injected with BCG vaccine or other adjuvants.

**Passive immunotherapy:**

1. **Non-specific:** Natural killer cells and Lymphokine-activated killer cells (LAK) cells of the patients are stimulated in vitro using cytokines mainly IL2 and are then reinfused .
2. **Specific:** Antibodies alone or coupled to drugs e.g. cytototoxic drugs,toxins given to the patient.,this is called  **" magic bullet"** when reach the target site kill tumor cells .T cells infiltrating the tumor are extracted, stimulated in vitro by IL-2 and tumor antigen then reinfused.

**3- Combined therapy:** By administration of LAK cells and specific antibody.

**Immunodeficiency**

Diseases caused by defective immunity are called immunodeficiency diseases. Some result from genetic abnormalities in one or more components of the immune system, these are called **primary** immunodeficiencies. Other defects in the immune system may be acquired as result of nutritional abnormalities or infections and are called **secondary** immunodeficiencies**.**

**Secondary immunodeficiencies could be associated with :**

1. **Malnutrition:** This is commonest cause
2. **Infections:**The most common is acquired immunodeficiency syndrome **(AIDS).** There is a decrease in the number of helper-inducer (CD4) T cells.
3. **Aging:** These include a progressive decrease in the size of thymus, a decrease in CD4 cells functions.
4. **Malignancies**
5. **Chemotherapeutic agents**
6. **Other conditions** are sickle cell anemia, diabetes mellitus, burns, rheumatoid arthritis

**Primary immunodeficiencies**

**Specific immune system :**

1. Defects **in stem cells** differentiation , involve T-cells, B-cells example severe combined Immunodeficiency which is **x-linked**. Patients are susceptible to a variety of bacterial, viral, mycotic and protozoan infections. The patient **must not** **receive live vaccine**
2. **DiGeorge's syndrome:** aplasia or hypoplasia of the thymus.
3. **B cell immunodeficiency:** Complete absence of all classes to selective deficiency of a single class or subclass of antibody **example :** x-linked infantile hypo-gammaglobulinemia,transient hypogammaglobulinemia when IgG synthesis is delayed till 2-3 years old due to poor T cell help.
4. **IgA deficiency:** is the commonest of all immunodeficiencies ,the patients are very susceptible to superficial infections Anti-IgA antibodies (IgG) are detected in patients who **should not be treated** with gamma-globulins.
5. **Hyper-IgM immunodeficiency:** These patients cannot make a switch from IgM to other classes which is attributed to a defect in CD40L on their CD4 cells.

**II- Nonspecific immune systems:** Primary immuno-deficiencies of the non-specific immune system include defects in phagocytic and NK cells and the complement system.

1. Defects of the phagocytic system: Infection occur without pus formation.
2. Defects in classical and alternative complement pathways and C3 .Patients exhibit increased susceptibility to infection: to meningitis caused by capsulated organisms,e.g *S. pneumoniae, N. meningitidis,and H. influenzae.*
3. Deficiency of NK cells: The patient is susceptible to **viral and tumor** diseases.

**Signs that indicate the presence of immunodeficiency disorder**: Persistent, recurrent infections by opportunistic microorganisms, poor response to treatment, development of certain types of cancers.

**Diagnosis**:

1. General assessment: by physical examination and family history.
2. Special assessment for
3. Screening immunoglobulin levels,enumeration of B cells by using fluorescein labelled monoclonal antibodies
4. Screening T cells and natural killer cells by using fluorescein labelled monoclonal antibodies and doing cutaneous delayed hypersensitivity.
5. Tests for phagocytic cell functions and count
6. Tests complement function and levels of individual complement components