IMMUNOLOGY :

- Immunology (Lt: *Immunis* — exempt; *ology* - study) is the branch of biology that is concerned with *immunity* or the study of immune systems.
- The term 'immunity' refers to the resistance exhibited by the host towards the injury caused by microorganisms and their products. It is a function of the immune systems in the body.
- The basic requirement of immune system is to recognize and distinguish between *self* (of host body) and *nonself* (foreign) and to eliminate the nonself invaders or altered self-cells or tissues. **Louis Pasteur** is the father of immunology.

Types of Immunity :

Immunity is classified basing on the nature and type of response.

- **1. Innate and acquired immunity :** Immunity is of two types: **Innate** and **acquired.**

I. Innate immunity :

- All the living organisms possess an inborn resistance to disease, which is referred to as **innate immunity** or **native immunity** or **natural immunity'.**
- It **is a nonspecific** immunity and does not depend on prior contact with the microorganisms.
- It includes the physical and chemical barriers provided by skin and mucous membranes. Also include some defences provided by antimicrobial proteins, natural killer cells, phagocytes, inflammation (increased permeability of blood capillaries), pain and fever.

II. Adaptive immunity:

- The resistance that an individual acquires during the lifetime is known as **adaptive immunity.**
- This type of immunity is more **specific.** It varies in individuals of a species. It also provides immunological memory. The basic requirement of immune system is to recognize and distinguish between self (of host body) and nonself (foreign) and to eliminate the nonself invaders or altered self-cells. It is mediated by lymphocytes. It requires the interaction between lymphocytes and antigen presenting cells or altered self cells. Adaptive immunity is either **active** or **passive**.

A. Active immunity :

- It is the resistance developed by an individual as result of antigenic stimulus. It is again of two types: **natural** or **artificial**.
- **a) Natural active immunity:** The immunity developed by the host in response to natural infection (antigen) from which a person recovers, e.g. lifetime immunity obtained by an individual after passing through infections such as small pox.
- **b) Artificial active immunity:** The immunity acquired by the host in response to the artificial inoculation of antigen e.g. Vaccination.

Passive immunity :

It is the resistance developed by the organism as results of transfer of antibodies which arc developed in an other organism.

- **a) Natural passive immunity:** The immunity transferred from mother to child by transfer of preformed antibodies.
- E.g. Antibodies transferred to child from mother through colostrum (colostrum is the first milk produced by mother after child birth, containing antibodies).
- **b) Artificial passive immunity:** The transfer of antibodies from an immunized donor (man or suitable animal) to non-immunized individual e.g.
- Injection of ATS, Anti Tetanus Serum (Anti Tetanus Serum: Serum containing antibodies for tetanus prepared from serum of horse) to man.

II. Humoral immunity and cell mediated immunity:

- The immune responses are classified into humoral and cell mediated responses.
- Based on the types of responses evoked, immunity is classified as humoral immunity and is mediated by antibodies released into the humors of the body like plasma, lymph etc.
- The humoral immunity is due to the interaction of B-cells with antigens.
- The immune response produced by the effector T-cells is known as **cell mediated immunity**.
- Activated T_H cells and cytotoxic T-cells are involved in this type of community.

III. Three lines of defence in the body : In the higher animals, the defence system works on three lines.

- **I) The first line of defence:** It is provided by barrier organs like skin, mucous membranes and the secretions like lysozyme of tears, lactoferretin of milk etc.
- **II) The second line of defence:** It is due to phagocytosis by the phagocytes, infected cell lysis by Natural killer cells, antimicrobial proteins, inflammation and fever.
- **III) The third line of defence.** It is through lymphocytes and antibodies.

Organs of the immune system :

- Immune system of an organism consists of several organs known as lymphoid organs.
- Based on function they are classified into two types. **Primary lymphoid organs and Secondary lymphoid organs.**
- **I) Primary lymphoid organs:** These are the major sites of **lymphopoiesis.** The lymphoid stem cells mature into immuno-competent cells. Bone marrow and thymus are the primary lymphoid organs. Bursa of Fabricius is also the primary lymphoid organ in birds.
- **II) Secondary lymphoid organs:** Immuno-competent cells transform into functional cells in the secondary lymphoid organs. **Spleen** and **lymph nodes** are the secondary lymphoid organ, where as **mucosa associated lymphoid tissue (MALT)** of gut, respiratory and urinogenital tracts is the secondary lymphoid tissue. These organs or tissues trap antigens and make them available for immunocompetent cells.

CELLS OF THE IMMUNE SYSTEM :

- Cells taking part in the immune responses and present in immune system are **lymphocytes, phagocytes and auxiliary cells.**

I. Lymphocytes : A type of WBC that has a large nuclens and little cytoplasm.

- Thy are the chief cells of the immune system. They occur as **B cells, T cells and large granular lymphocytes.**

i. B cells :

- Population of lymphocytes that produce circulatory antibodies are known as B-cells. These are formed from bone marrow in mammals and Bursa of Fabricius in birds.
- Mature B-cells synthesise and display the antibodies attached to their membranes. These antibodies take antigens. So mature B-cells are called **immunocompetent cells**.
- They transform into functional cells in secondary lymphoid organs.
- Functional B-cells divide into **memory cells** and effector cells called **plama cells**.
- Plama cells synthesize and secrete antibodies in to the fluids (humors). Memory cells produce antibodies against the antigens faster than the mature B-cells.

ii. T – cells :

- Pre T-cells produced from the stem cells of bone marrow differentiate into T-cells in thymus. These cells are also the immunocompetent cells.
- They also form into functional cells in secondary lymphoid organs.
- T-cells cannot recognize the circulating free antigens. They have **antigen-specific receptors**, which can recognise the antigens that are bound to the **antigen presenting cells** or **altered self-cells**.
- T-cell are known as T_4 (with CD_4 marker) and T_8 (with CD_8 marker) cells depending on the cell surface molecules. Functionally T-cell are two types T-helper cells and T-cytotoxic cells.

1. T-helper cells or T_H-cells :

- These cells are T_4 cells that help the B cells to produce antibodies. They help mononuclear phagoctes (MNP) in phagocytosis.
- Thus, these cells involve in humoral immunity. They also activate cytotoxic T-lymphocytes.
- Thus, they also involve in cell mediated immunity. Some of these cells, called T_{DH} cells, cause delayed hypersensitivity reactions.

2. T_C-cells :

- These cells are T_8-cells that differentiate into **effector cells** and **cytotoxic T lymphocytes (CTL)**, which are responsible for the cytolysis of infected host cells. Thus, these cells involve in cell mediated immunity.

iii. Large granular lymphocytes (LGL) :

- These cells damage the tumour cells and virus infected cells.
- They are seen in circulating fluids and tissues.
- They are of two types. **Natural killer cells (NK cells)** and **Killer cells (K cells)**.
- The Natural Killer cells destroy the infected cells in an antibody independent manner.
- The killer cells destroy the infected cells in an antibody dependent manner.

II. Phagocytes :

- They are specialised eating cells (L.phago = eat) for the engulfment of cellular and particulate matter. They are of two main types.

1. Mononuclear phagocytes (MNP) :

- These are long-lived phagocytic cells.
- These cells enter the blood as monocytes. These monocytes migrate to the connective tissues and transform into wandering macrophages called **histiocytes**.
- They also migrate to the different organs and transform into stationary cell like **kupffer** cells of liver, **synovial** cells of synovial cavity, and **microglial** cells of brain etc.

2. Polymorphonuclear neutrophils (PMN) :

- They are the short-lived phagocytic cells, which are polymorphonuclear leucocytes like neutrophils and eosinophils of blood.

III. Auxillary cells :

- Auxillary cells help lymphocytes in immune responses. These cells include **mast cells, basophils, antigen presenting cells (APC)** and **platelets.**
- Mast cells and basophils secrete inflammatory mediators, which cause inflammation in the surrounding tissues.
- Platelets also release inflammatory mediatory when activated during thrombogenesis.
- Antigen presenting cells (APCs) like **dendritic cells** present the antigens to T_H-cells. Macrophages and B-cells also act as APCs.

SOLUBLE MEDIATORS OF IMMUNITY :

- There are three types of soluble mediator, **complement proteins, antibodies** and **cytokines**

1. Complement proteins :

- These proteins form a group of complex enzymatic proteins that mediates phagocytosis. These proteins activate inflammation**, opsonisation** (making bacterium more susceptible to phagocytosis) and cytolysis.

2. Cytokines :

- These are small soluble molecules secreted by immune cells or infected cells. They stimulate phagocytosis and cytolysis of the infected cell. The cytokines include **iterleukins** and **interferons.**
- **1) Interleukins (ILs)** are produced by leucocytes. They are primarily involved in differentiation of cell of immune system.
- **2) Interferons (IFNs)** are the antiviral proteins produced by virus-infected cells. These are involved in the protection of the neighbouring cells from the viruses of infected cells.
- Virus infected host cells produce **alpha and Beta interferons**
- T-lyphocytes produce **gamma interferons**
- Cytokines that induce neighbouring cells to synthesise antiviral proteins are **alpha and Beta interferons**

3. Antibodies :

- Antibodies are immunoglobulins (glycoproteins) that bind to **antigens**. They are highly specific.
- In humans, there are five classes of antibodies called **IgG, IgM, IgA, IgE** and **IgD.**
- **Rodney Porter** proposed the basic structure of an antibody. The basic structure includes four polypeptide chains, two light (L) chains and two heavy chains(H).
- One end of the antiobody molecule (F_{ab} end) binds to antigen and the other end of antibody (F_e end) interacts with phagocytes or one of the complement molecules.
- Antibodies recognize specific pathogens. Antibodies in the body fluids are **circulating antibodies. Surface antibodies** are present on the surface of the B-cells.

ANTIGENS :

- Antigens are the substances that can induce a detectable immune response. These molecules can be recognized by B-cells, T-cells or both.
- Antigen recognition is the foundation of all adaptive immune responses.
- **Free antigens** circulate in the body fluids.
- **Intracellular antigens** reside in the infected cells.
- Proteins, polysaccharides, lipoproteins, nucleo-proteins and nucleic acids act as complete antigens. Some heavy metals and others act as **hapten.**
- Hapten is a chemical that combines with an antibody but cannot initiate any immune response unless it is bound to a carrier before it is introduced into the host.
- The antigenic polypeptides are presented on the surface of the cell by specialised group of molecules called **major histocompatibility complex (MHC) molecules**.
- MHC molecules are of two types- class I and class II
- Class I molecules surface on all nucleated cells.
- These cells with the processed antigenic polypeptide on the MHC are called **altered self cells**.
- They present the antigens to T_8 cells for cell mediated immunity.
- Class II molecules surface on APCs. They present the antigens to T_4 cells for cell mediated or humoral immunity.
- Antigen-specific receptors present on the T-cells recognize the antigenic peptide, bound to the MHC molecules.

MECHANISM OF HUMORAL AND CELL MEDIATED IMMUNITIES :

i. Humoral immunity (HI) :

- These immune responses are due to the recognition of antigen by antibodies and subsequent changes in the B-cells.
- The free antigens bind to the F_{ab} end of the surface antibody on the immunocompetent B-cells in the secondary lymphoid organs.
- They transform into plasma cells and memory cells in these organs.
- Plasma cells release the circulating antibodies. These antibodies are useful in:

1) **Neutralising** the antigen by blocking the antigens. They prevent the attachment of viruses.
2) Antibodies attach to flagella of bacteria ad prevent their spreading in the host by **immobolising** the bacteria.
3) They cause the cross-linking of antigens leading to **agglutination** of insoluble antigens and **precipitation** of soluble antigens. These agglutinated and precipitated antigens are easily phagocytosed by the macrophages.
4) Antibodies **activate the complement** system.
5) Activate the **phagocytes**.
6) They **opsonise** the bacteria.

ii. Cell mediated immunity (CMI):

- APCs present antigen to the T_H-cells. These T_H-cells involve in humoral and cell mediated immunities. They activate B-cells to produce antibodies (humoral immunity).
- They also activate T_C cells to become cytotoxic T lymphocytes, which involve in killing the various infected cells and tumour cells (cell mediated immunity).
- These cytotoxic T lymphocytes produce proteins like **perforins** that form holes in the target cells so that fluids enter the cells and burst.
- They also produce cytokines. These cytokines activate the enzymes that fragment the host cell DNA.

IMMUNOLOGICAL DISORDERS :

- Any situation that results in the impairment of immune system is referred to as **Immunological disorder.**
- These disorders may result **from** primary or secondary immunodeficiencies. The deficiency caused by defective genes is called **primary immunodeficiency,** *e.g.* Stem ceil deficiency, B cell deficiency, T cell deficiency, phagocyte deficiency.
- **Secondary immuno deficiency is caused** by factors other than genetic factors. *eg.* infections, drugs, malnutrition, ageing etc.

I. Acquired immuno deficiency syndrome (AIDS):

- Acquired Immune Deficiency Syndrome is a transmissible, lethal, sexually transmitted disease caused by a virus that affects the immune system in the humanbeings. This was first studied in 1981 by **Center for Disease Control , USA. Luc Montagnier,** 1983 isolated the causative virus **of the** AIDS. **Robert Gallo** 1984 isolated the retrovirus from AIDS patient and called it **as HTLV** 3, which is later named as HIV

i. Causative agents :

- AIDS is mainly caused by two strains of retrovirus named as **Human Immune deficiencv Virus.**
- HIV_1 and HIV_2. HIV contains ssRNA (single strand RNA) as genetic material. It is surrounded by an outer lipid layer that contains number of viral proteins (glycoproteins).
- These proteins bind to host **cell surface receptors** during infection. The central protein core of the viral cell contains **ssRNA** as the genome and a few molecules of reverse transcriptase enzyme.
- Single stranded viral RNA is converted to double stranded DNA by **reverse transcriptase** in the host cell. The **DNA** thus formed integrates in the host cell DNA and becomes permanent part of the host cell genome. This integrated viral DNA is called provirus.

ii. Target cells of HIV and symptoms :

- HIV infects the cells that have CD_4 markers on the surface. The first target cells are T_H **lymphocytes** through macrophages. Loss of these cells leads to immune deficiency.
- The other target cells are **macrophages** and **dendritic cells.** They carry HIV to the central nervous system.
- The disease has five stages. The symptoms during the **first stage** are prolonged fever, weight loss of more than 10% of body weight, chronic diarrhoea, and headache, rash on the body and general malaise.
- **Second stage** is in between infection and the onset of clinical symptoms. It may last from few weeks to 13 years.
- **Third stage** is persistent generalised **lymhadenopathy** characterised by enlarged lymph glands. The fourth stage is the AIDS-related complexes characterised by secondary infections.
- The **fifth stage** is the development of secondary cancers along with other infections.
- Leucopenia and thrombocytopenia are common. 'Kaposis sarcoma', a type of cancer can also be caused.

iii. Transmission of HIV :

- HIV is transmitted through sexual contact, (both by hetero and homosexual methods), blood transfusions, tissue and organ transplantation, sharing the syringes by drug abusers and congenitally from mother to foetus through placenta.
- Normal social or domestic contact does not transmit the disease.

iv. Diagnosis :

- Diagnosis of HIV depends on the detection of anti-HIV antibodies in the serum of a suspected person. These antibodies can be detected within 2 weeks to 4 months of exposure to virus.
- HIV is diagnosed by ELISA (Enzyme Linked Immunosorbent Assay) technique. In this technique the blood of the suspected individual is added to HIV proteins, which can be recognised by change in color.

- If there are anti-HIV antibodies already in the blood sample, they will bind to viral proteins. The person is said to be HIV positive.
- **ELISA** test is only a screening test. **Western blotting method** is used to confirm HIV in the patient.

v. Treatment of HIV infection and prophylaxis :

- Different remedial measures are based on different physiological processes, which are taking place in HIV, right from infection to the release of new virions.
- A modified form of thymine called Azidothymine (AZT) or **Zidovudine** is used to prevent reverse transcription.
- **Dideoxy-cytidine** (DDC) and **dideoxyinosine** (DD1) can also be used. The specific anti HIV agents are not potentially effective to cure the disease.
- Hence, it is advised to follow prophylactic methods to avoid AIDS. Safe sex, proper sterilization of hospital syringes and needles and screening the blood for HIV before blood transfusions are some of the important prophylactic methods.

II. Hepatitis :

- Hepatitis is a disease characterized by inflammation and damage to liver. It may be acute (sudden) or chronic (prolonged).
- Hepatitis is caused by specific viruses and rarely by bacteria *(Leptospira* sp.). It also occurs as an autoimmune disorder.
- The symptom of the disease includes malaise (state of inactivity), anorexia (loss of appetite), nausea, jaundice, liver failure, cirrhosis (fibrosis of liver), hepatic coma, atrophy of gonads etc.
- Only viral hepatitis is discussed here, since they are often related with immunodeficiency.

Viruses causing hepatitis :

- Five different types of viruses are known to cause hepatitis.
- They are : Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, Hepatitis D virus and Hepatitis E virus.

1. Hepatitis A (Infectious hepatitis or epidemic hepatitis) :

- It is a highly infectious disease caused by a typical **enterovirus** referred to as **hepatitis A virus** (HAV).
- Incubation period is 15 to 45 days. Infection mainly occurs due to contamination of water or food. The virus replicates in liver. It is referred to as short incubation hepatitis.
- **Treatment and prevention:** Active immunization with an inactivated viral vaccine proved to be effective.
- Infection can be controlled by improving the sanitary conditions, hygiene and by avoiding overcrowding.

2. Hepatitis B(serum hepatitis or serum jaundice):

- Serum hepatitis is the most common form of parenterally transmitted viral hepatitis. It is caused by **hepatitis B virus** (HBV), a **hepadna virus** present in the blood.
- Symptoms in acute condition are same as in other viral hepatitis. But frequently it passes of asymptomatically. Incubation period is 30 to 180 days. It is known as the long incubation hepatitis.
- It can spread in the intravenous drug abusers or male homosexuals, between mother and child (intrauterine pre and post natal infection) and also in association with tattooing, ear piercing and acupuncture. It causes cirrhosis and hepatocellular carcinoma.
- **Treatment and prevention:** It can be prevented by immunizing the individuals with Hepatitis B vaccine.
- Sterilisation of needles and testing the blood before it being used for transfusion are suggested as preventive methods.

3. Hepatitis C :

- Hepatitis C virus is Non A Non B hepatitis virus. Incubation period is 42 to 50 days. It is common in parenteral drug (other than oral) abusers.
- This virus also spreads through blood transfusion and blood products tranfusion.
- Other less common viruses that cause hepatitis are Hepatitis-D virus and Hepatitis – E virus.
- Hepatitis-D virus can not survive independently and requires Hepatitis – B for its multiplication.

III. Hypersensitivity :

- Hypersensitivity is defined as an exaggerated immune response. It manifests on the second exposure to the same antigen. These mani-festations include inflammation or tissue damage.

Types of hypersensitivity :

- Four types of hypersensitivity reactions are recognized based on the effector molecules formed during the reactions. Type I, II and III are immediate type of reactions and Type IV is the delayed type of reaction.

1. Type I hypersensitivity (IgE dependent hypersensitivity)

- It is also called **allergy or anaphylaxis.** The term anaphylaxis *(ana* = *without ; phylaxis* = protection) is coined by **Richet,** 1902. It is defined as an exaggerated secondary response of an organism for an antigen to which it is already sensitized by the release of IgE antibodies.
- Even though the term allergy is used for all hypersensitivity reactions now it is referred to only type-I hypersensitivity reactions.
- Antigens called **allergens** like drugs, faeces, house dust mite, animal danders, pollen grains, food allergens etc. are responsible for this type of hypersensitivity.

- They enter the body through mouth or nose and stimulate humoral immune response resulting in the production of IgE antibodies.
- IgE antibodies produced in this reaction, called **reagins,** are bound to basophils and mast cells by the F_C end and sensitize these cells. The dose of antigen required for sensitizing the mast cell is known as the **priming dose** and the responses are the primary responses.
- On sensitisation, mast cells and basophils produce granulesin their cytoplasm i.e. **granulation of the cytoplasm.**
- These granules contain the inflammatory mediators. If the second dose of the same antigen combines with the F_{ab} end of the antibody fixed on them as t-cell, the mediators are released **i.e. degranulation.**
- The dose required for degranulation of mediators is shocking dose.
- Degranulated mediators cause inflammatory reactions. These inflammatory reactions include prevention of blood clotting by heparin, vasodilation in the peripheral blood vessels by **histamines**, attraction of **histiocytes** to the site of injury by histamines, vasoconstriction of the deeper blood vessels by serotonins, increased vascular permeability by **bradykinins**, **prostaglandins** and **platelet activating factor** (PAF) etc.
- Hypersensitivity I can cause both local and systemic reactions. Dust-mite allergy is also a localized reaction. Erythema, asphyxia, urticaria, rhinitis, eczema, asthma etc. are the common manifestations of the localized anaphylactic reactions. Penicillin sensitivity causing tetany is a systemic reaction.
- Genetic or in born predisposition to develop allergiesis called atopy.

2. Type II hypersensitivity: Antibody mediated cytotoxicity

- This is mediated by IgG or IgM antibodies that bind to the cell surface or tissues. These antibodies react with cell surface antigens or extracellular matrix antigens.
- These antibodies bind either to self antigens (autoimmune reactions) or foreign antigens (isoimmune reactions, if react with the antigens of the other individual of the same species and alloimmune reactions, if react with the antigens of the individual of the another species).
- F_C end of the antibody is attached to the killer cells or complement. This leads to the lysis of the cell or tissue. Hence these reactions are called antibody mediated cytotoxic hypersensitivity reactions. e.g: Blood transfusion reactions and haemolytic disorder of the new born. In these reactions the antigen of one blood group and the antibodies of a different group react resulting in lysis of the cells.

3. Type III hypersensitivity or immune complex mediated hypersensitivity

- Immune complexes are formed due to antigen antibody reactions. Antibodies involved are IgM and IgG.
- These antibodies react with the soluble antigens in the serum leading to the fonnation of circulating antigen antibody complexes.
- These complexes are removed effectively by the eosinophils and monocytes.
- Occasionally these complexes persist and deposit in various tissues and organs.
- The F_C ends of these antibodies attach to phagocytes or complement, leading to cell damage.
- These reactions may be localized or systemic. Antigens may be exogenous or endogenous. e.g. Serum sickness (caused due to intravenous administration of antigens) is a systemic exogenous reaction. Farmer's lung is a localized exogenous reactions.
- Rheumatoid arthritis (chronic Inflammation of the synovial membrane) is theendogenousreaction.

4. Type IV hypersensitivity or delayed hyper-sensitivity (Cell mediated hypersensitivity)

- Type IV hypersensitivity results from cell mediated immune reactions caused by T_{DH} cells. It occurs with in 24 hrs, after coming in contact with antigen.
- The fist phase is the sensitising phase. In the sensitising phase APCs present allergens to receptors of T_{DH} cells. Contact between antigen and T_{DH} cells activates T_{DH} cells to proliferate and release cytokines.
- The second phase is the effector phase. In the effector phase these cytokines attract and activate lymphocytes, macrophages and basophils. So that extensive tissue damage results due to interaction among all these cells. *e.g.* Test for tuberculin infection and contact dermatitis.