CHAPTER 2

FUNDAMENTALS OF IMMUNITY

Abstract

There are three tiers of host defences against invading organisms – local defence mechanisms, acquired immunity (active and passive), and innate (natural) immunity. Systemic defence mechanisms are activated when organisms breach the local host defences. Specific immune mechanisms enable the body to recognise, destroy, and eliminate antigens that are recognised as "non-self". Thymus-derived lymphocytes (or "T-cells") and Bursa- or bone marrow-derived lymphocytes (or "B-cells") are primarily responsible for active immunity. Natural killer (NK) cells and killer T-cells destroy virus-infected cells or tumour cells by cytotoxic action. Memory cells developed during the primary immune response accelerate and enhance the secondary immune response, even if the second exposure occurs many years after the primary exposure. The *cluster of differentiation* (CD) system classifies antigens that are present on the surface of human white blood cells. Each CD is a separate molecule with a distinct molecular composition, specificity, and cellular distribution within the cells of the immune system. T4 cells (T-helper cells) "help" the action of other lymphocytes and are required for antibody production by B-cells and cytotoxic action of T8 cells (T-suppressor cells), which suppress immunoglobulin synthesis and act as a brake on immune response.

Key Words

Active immunity, Allergy, Antibody, Antibody titre, Antigen, B-lymphocytes, CD system, Cell-mediated immunity, Complement system, Helper cells, Herd immunity, Herd structure, Humoral Immunity, Hypersensitivity, Immunodeficiency, Immunoglobulin, Innate immunity, Natural immunity, Natural killer cells, Null cells, Suppressor cells, T-lymphocytes.

2.1 – INTRODUCTION

Millions of microorganisms are present in the environment. They also live on the surface of the skin and inside the body. There is a system of overlapping host defences, which provide resistance to infection by various microorganisms (Fudenberg *et al.*, 1976). An invading infectious organism stimulates multiple host defence mechanisms such as local and systemic immunity, non-specific and specific immunity, and cellular and humoral immunity. Immunity is that resistance associated with the presence of antibodies or cells that have a direct action on a pathogen or its toxin (Benenson, 1990). It includes all the physiological

mechanisms that endow the host with the capacity to neutralise, eliminate, or metabolise those substances (that are recognised as "foreign" or "non-self"), with or without injury to the host's tissues. When the immune response is beneficial, it is called "immunity" and when harmful, it is termed "allergy" or "hypersensitivity".

The presence of immunity (Latin: *immunitas* = freedom from) against a pathogen confers *freedom from infection* by that pathogen (Roitt, 1997). A person is said to be immune when he or she possesses specific protective antibodies or cellular immunity as a result of previous infection or immunisation. The immune system of a person may be conditioned by previous sensitisation to respond adequately to prevent clinical or subclinical infection (Benenson, 1990). An *antigen* is a substance (usually protein, polysaccharide, or glycolipid) that is capable of eliciting a specific immune response. Antigens may be introduced in the host's body by infection or immunisation (Last, 1983). *Antibodies* are protein molecules that are produced by the host's body in response to an extraneous or "foreign" substance such as an invading microorganism. Chemicals like benzene sulphonate may induce formation of antibodies since antibody formation is specific for a particular electron cloud structure. Antibodies have the capacity to bind specifically to a foreign substance (called "antigen") that has stimulated its production. The concentration of antibodies in the serum (called "titre") can be measured in individuals (Last, 1983). The WHO (1993) recommends that the word "gamma globulin" should not be used as a synonym for "immunoglobulin". All antibodies are immunoglobulin (Ig) molecules, but not vice versa (Fudenberg *et al.*, 1976). Some Ig molecules are abnormal proteins found in some diseases like myeloma.

2.2 – HOST DEFENCE MECHANISMS

There is a stratified system of host defence against invading microorganisms – *local defence mechanisms, natural* or *innate immunity*, and *acquired immunity*. Systemic defence mechanisms are activated when the invading microorganisms breach the local defences. Specific immune mechanisms enable the body to recognise, destroy, and eliminate antigens that are recognised as "non-self".

Local Defence Mechanisms: The function of the bacterial flora is to suppress the growth of many pathogenic organisms. This suppression occurs by competition for essential nutrients or production of inhibitory substances such as colicins and acids. Other local defence mechanisms include the intact skin and mucosa; inhibition of microorganisms by the low pH generated by lactic acids, and fatty acids in sweat and sebaceous secretions; secretion of mucus, which traps microorganisms and particulate matter; ciliary movements, cough, and sneezing reflexes in the respiratory tract; washing action of tears, saliva, and urine; bactericidal components in body secretions (acid in gastric juice, spermine, and zinc in semen, lysozymes in tears, nasal secretions, and saliva); and immunoglobulin A (Roitt, 1997).

Natural or Innate Immunity: Natural (or innate) immunity is the species- or race-specific inherent resistance to a pathogen. An individual, by virtue of his or her constitutional and genetic make-up, possesses this type of immunity to infections. Prior contact with microorganisms or immunisation is not necessary for this type of immunity. For example, leprosy bacillus infects only humans and armadillo (an anteater) and not other animals. Humans are naturally immune to all plant pathogens and certain animal pathogens like canine distemper virus. Within a species, different races may show difference in susceptibility to infections. For example, some Africans are resistant to falciparum malaria due to presence of sickle cells, an abnormality of red blood cells. Non-specific responses include chemotaxis and release of mediators of inflammation.

Acquired Immunity: Acquired immunity is the resistance acquired by a host as a result of previous exposure to a pathogen, either by natural infection or by immunisation (Last, 1983). Basically, there are two types of acquired immunity – "passive" and "active". Active immunity includes "humoral" and "cellular" immunity.

2.3 – IMMUNOGLOBULINS

Ig molecules are glycoproteins containing two identical heavy polypeptide chains with molecular weight 50 kilo Daltons (kDa) and two light polypeptide chains with molecular weight 25 kDa. Each polypeptide chain contains an amino acid terminal (in variable or heterogeneous region) and a carboxy terminal (in constant region). Digestion of Ig molecule by proteolytic enzymes like papain produces two fragment antigen binding (Fab) and one fragment crystallizable (Fc) fragments. The Fc fragment lacks the ability to bind the antigen. All Ig molecules are measured in *Svedberg units* (also called "S value"). Higher the molecular weight, larger is the S value.

The normal immune system can generate an Ig for every possible antigen that the system may encounter during the life of an individual. This is done by constantly changing the amino acid sequences in the variable region of the Ig molecule. This avoids the production of millions of different Ig molecules. Ig molecules constitute 20–25 per cent of total serum proteins. Based on the structure of their *heavy* chain constant regions, Ig molecules are classified into five major classes – IgG, IgA, IgM, IgE, and IgD. Since these classes are all variants of the Ig molecule, they are termed as "isotypes". Constant regions of *light* chains also exist in isotypic forms, designated as kappa and lambda. Briefly speaking IgG protects the body fluids, IgA the body surfaces, IgM the blood stream, IgE mediates hypersensitivity, and the role of IgD is not known.

2.3.1 – Immunoglobulin G (IgG)

This class of antibodies comprises about 75 per cent of the total serum Ig. The normal serum concentration of IgG is 8–10 mg per mL. Exposure to an antigenic challenge (foreign antigen) for the first time leads to a rise in IgM titre for 2–3 days

(after a latent period). Later, the IgG antibodies appear if the antigenic stimulus is strong. The required dose of antigen for eliciting IgG type of response is about 50 times more than that required for eliciting IgM response. The IgG titre reaches a peak in 7–10 days and falls gradually over weeks or months. IgG is distributed almost equally between the intra- and extravascular fluid compartments. This can easily diffuse into the extra-vascular compartment since its molecular weight is only 150 kDa (7S). It is the only immunoglobulin, which is transported across placental barrier. It is also found in breast milk. Antibodies against Gram-positive bacteria, viruses, and toxins belong to this class of Ig. IgG facilitates binding of microorganisms to phagocytic cells (Roitt, 1997).

2.3.2 – Immunoglobulin A (IgA)

IgA is the second most abundant class of Ig and comprises about 15 per cent of total serum Ig. The normal serum level is 0.6 – 4.2 mg per mL. It provides local defence at the level of mucous membranes and has a half-life of about 6–8 days. It is a 7S molecule with a molecular weight of 160 kDa. IgA is secreted by mucosa associated lymphoid tissue (MALT). It is seen selectively in saliva, tears, and seromucous secretions of respiratory, genitourinary, and gastrointestinal tracts. Antibodies against a broad range of bacteria and viruses belong to this class of Ig (Gell *et al*., 1975). IgA does not cross placenta, but helps in protecting the newborn by its abundant presence in breast milk and colostrum. The role of IgA is to bind to the surface of bacteria or viruses and inhibit the attachment of such coated organisms to the surface of mucosal cells, thus preventing the entry of microorganisms into the tissues of the body.

2.3.3 – Immunoglobulin M (IgM)

IgM constitutes about 10 per cent of the total serum Ig, with a normal serum level of 0.5–2 mg per mL. IgM has a half-life of about 10 days. Its molecular weight is 900,000–1,000,000 Da (19S) and hence it is called the *millionaire molecule*. Because of their size, IgM antibodies are confined to the blood stream and do not cross the placenta. Hence, the presence of IgM in blood of fetus or newborn indicates intrauterine infection. It is the earliest immunoglobulin to be synthesised by the fetus, beginning at about 20 weeks of gestation. IgM forms the first line of defence against bacteraemia. The size and valency of the IgM makes it a very effective agglutinating and cytolytic agent (Roitt, 1997). On exposure to an antigenic challenge for the first time, IgM antibodies are formed after a latent period of 3–10 days. The IgM titre rises for 2–3 days and declines quickly. Since the IgM response is short-lived, its presence usually indicates acute or recent infection.

2.3.4 – Immunoglobulin E (IgE)

IgE, an 8S molecule with a molecular weight of 190 kDa, is normally present in very low concentrations in the serum. Produced mainly in the submucosa of respiratory and intestinal tracts, it has a half-life of 2–3 days. IgE has an affinity

for the surface of mast cells and binds to Fc receptors on the membranes of blood basophils and tissue mast cells. Linkage of allergens with Fc receptor-bound IgE molecules results in degranulation of basophils and mast cells, leading to allergic manifestations. IgE levels are elevated in allergic conditions such as asthma, hay fever, and eczema; and when intestinal parasites are present. It does not cross the placental barrier. IgE is responsible for defence against parasitic infestations, symptoms of atopic allergy, and immediate anaphylactic reactions (Roitt, 1997).

2.3.5 – Immunoglobulin D (IgD)

IgD is mostly intravascular and has a serum concentration of 3 mg per mL. Its molecular weight is 180 kDa. It has a half-life of 2–8 days and its main role is not yet known. Since IgD is found abundantly on the surface of B-lymphocytes along with IgM, it may have a role in regulating lymphocyte activation and suppression.

2.4 – PASSIVE IMMUNITY

When antibodies produced in one host (human or animal) are administered to another host for the purpose of protection against disease, it is called "passive immunity". The body of the host does not produce its own antibodies but depends on readymade antibodies. Passive immunity may be induced *naturally* by transplacental transfer of maternal antibodies, and by transfer of maternal antibodies via breast milk and colostrum. It can also be induced *artificially* by the administration of a preparation containing protective antibodies (immunoglobulin, antitoxin, or antisera) from sensitised humans or animals (Benenson, 1990). A "biological shield" comprising maternal antibodies that are transferred across the placenta or through breast milk and colostrum protects babies born of immune mothers for duration of up to 3 months or longer. After birth, these maternal antibodies are gradually lost over a period of 6 months.

The recipient's immune system does not play any role and hence secondary response does not occur. There is no antigenic stimulus since pre-formed antibodies are transferred or administered. Its main advantage is that the protection is conferred immediately and there is no latent period. Passive immunisation is indicated for protection of a non-immune host who is faced with threat of an infection and when there is insufficient time for active immunisation to take effect. The immunity is of a short duration (few days to few months) and lasts till the passively transferred antibodies are metabolised and eliminated.

2.5 – ACTIVE IMMUNITY

Active immunity is the resistance developed in response to a stimulus by an antigen (Last, 1983). This usually lasts for months or years, and can be induced *naturally* by clinical or sub-clinical infection, or *artificially* by administering

antigen (attenuated or killed) or toxin (Benenson, 1990). The duration of naturally induced active immunity varies with the type of pathogen and is usually lifelong after diseases such as measles. Thymus-derived lymphocytes (or "T-cells") and Bursa or bone marrow derived lymphocytes (or "B-cells") are primarily responsible for active immunity. T-cells promote differentiation of non-lymphoid cells, regulate production of antibodies by B-cells, and are also responsible for delayed-type hypersensitivity (DTH) and cytotoxic ("cell-killing") action. *Null cells* are non-T non-B leukocytes that do not possess the antigen-binding receptors that distinguish T- and B-cell lineages. They lack immunological memory and specificity.

Natural killer (NK) cells that belong to this group of null cells constitute 5–10 per cent of the peripheral blood lymphocytes. They are large granular lymphocytes, which bear CD16 and CD56 co-receptors. They non-specifically destroy virus-infected cells or tumour cells by cytotoxic action. Their granules contain "tumour necrosis factor-*beta*" and various "granzymes". Granzyme B functions as cytotoxin of the NK cells (Roitt, 1997).

2.6 – HUMORAL IMMUNITY

Humoral immunity is directed primarily against extracellular organisms. The humoral defences include lysozymes, complement system, acute phase proteins (C-reactive protein and mannose binding proteins), interferons (that block the replication of viruses), and antibodies. Microorganisms that penetrate the skin or mucosa are destroyed by lysozymes and by phagocytosis with intracellular digestion. The main phagocytic cells are polymorphonuclear leukocytes (neutrophils) and macrophages. In response to a stimulus by a foreign antigen, *B-cells* are activated to form plasma cells. These plasma cells produce antibodies, which act specifically against the antigens present on the surface of the microorganisms. The clonal progeny of the plasma cells produce antibody molecules with the same antigen binding specificity. Humoral immunity can be determined *in vitro* quantitatively by measuring antibody titres and qualitatively by enzyme-linked immunosorbent assay (ELISA) and fluorescent antibody absorption test.

The Complement System

The complement system is a supporting system for humoral immune response. It is a multi-enzyme cascade, which attracts the phagocytic cells to the invading microorganisms. The complement system comprises 11 proteins (10 per cent of serum globulins). Most of the proteins are heat labile. They are usually present in inactive form and need to be activated. The complement system has four subsections:

- Classical pathway, which is always activated by antigen-antibody complex.
- Properdin system (Latin: *pro* = for; *perdere* = destruction). Also called the "alternative pathway". Antibodies may activate this system.
- Amplification system for augmenting the above mentioned pathways.
- Common effector pathway.

Effects of Complement Reaction

- Amplification of humoral immune response by promoting immune adherence and cytolysis.
- Beneficial cytolysis – Holes are produced on the cell membrane. The diameter of each hole is about 100 Angstrom units (A°). 1 A° = 10^{-8} cm. This results in loss of osmotic integrity of the cell, causing cytolysis. Many Gram-negative bacteria and parasites are killed extracellularly by complement-bound eosinophils (Roitt, 1997).
- Harmful cytolysis – e.g. immunological membrane damage.
- Type II hypersensitivity reactions – e.g. acute glomerulonephritis and rheumatic fever due to streptococcal antigens, drug-induced haemolytic anaemia.
- Type III hypersensitivity reactions – e.g. Arthus reaction, erythema nodosum leprosum, and serum sickness.
- Neutralization of viruses.
- Role in blood coagulation and fibrinolysis.

2.6.1 – Primary Immune Response

When an animal or human is exposed to a foreign antigen for the first time, IgM antibodies are formed after a *latent period* (or lag phase). The latent period is of variable duration, depending on the type of antigen. For example, latent period is 2–3 weeks for diphtheria toxoid and only a few hours for pneumococcal polysaccharide vaccine. During this latent period, the antigen is recognised as "foreign". The IgM titre rises for 2–3 days, till it reaches a peak. This is followed by a steady phase when the rate of IgM synthesis equals the rate of its catabolism. Later, IgM titre declines quickly, reaching pre-exposure levels. If the antigenic stimulus is strong, IgG antibodies appear. The IgG titre reaches a peak in 7–10 days and falls gradually over weeks or months. For eliciting IgG type of response, the required dose of antigen is about 50 times more than that required for eliciting an IgM response.

During the later part of the primary immune response, antigen-containing immune complexes localise in lymphoid follicles (follicular dendritic cells) and initiate the development of germinal centres, where the memory-B cells develop. The *memory cells* (or "primed cells") educate the reticuloendothelial system and are responsible for "immunological memory". T-independent antigens cannot elicit immunological memory or a secondary response. The primary immune response is influenced by type and dose of antigen, route of administration of the antigen, presence of adjuvants, and nutritional status of the host.

2.6.2 – Secondary Immune Response

Following exposure to an antigen in a previously primed individual, B- and T-lymphocytes collaborate to initiate a *secondary response* (also called "booster" or "anamnestic" response). Due to immunological memory, there is an accelerated

and enhanced response, even if the second exposure occurs many years after the primary exposure. After a brief period of production of IgM antibodies, there is a larger and more prolonged output of IgG antibodies. Protein antigens are eliminated within days or weeks. Polysaccharide antigens may persist for years. As compared to the primary immune response, the secondary response exhibits a shorter lag phase, an accelerated response due to rapid production of antibodies from already primed B-cells in the memory pool, an enhanced response due to recall of precommitted memory cells, longer duration of response, higher affinity of antibodies for antigens, and collaboration between B-cells and T-cells. A few days after the secondary response, B-memory cells migrate from mucosa-associated lymphoid tissue (MALT) to bone marrow and mature to form *plasma cells*.

2.7 – CELL-MEDIATED IMMUNITY

Cellular immunity is mediated by T-lymphocytes, which do not secrete antibodies but are responsible for recognition of "self" and "non-self". Cell-mediated immunity (CMI) is responsible for foreign body reaction, rejection of "foreign" tissue grafts (or allografts), chemically induced hypersensitivity such as contact dermatitis, immunity against some tumours, and immunity against intracellular organisms (e.g. viruses, *Mycobacteria*, *Salmonella*, *Brucella*, and fungi). CMI can be determined in vivo by skin tests such as Mantoux and Mitsuda tests, or in vitro by lymphocyte transformation test (LTT).

2.7.1 – Major Histocompatibility Complex

Each vertebrate has a major histocompatibility complex (MHC), which is responsible for rejection of transplants. Class I MHC molecules are present on virtually all the cells of the body and they signal cytotoxic T-cells. Class II MHC molecules are associated with B-cells and macrophages. They signal T-helper cells (Roitt, 1997). Macrophages, activated B-lymphocytes and dendritic cells are among the cells that have *antigen-presenting* function. They process the antigen and present it to helper T-cells and cytotoxic T-cells. The T-cell receptor can only recognise antigens being presented by a cell membrane bound protein molecule of the MHC. In a special type of immunisation, immunologically competent lymphocytes are injected. This confers *adoptive immunity*.

2.7.2 – The CD System

CD is an acronym for *cluster of differentiation*. The CD system is a system of classification of antigens that are present on the surface of human white blood cells (leukocytes). The International Leukocyte Antigen Workshops have identified 130 antigens, and have given them CD designations. Each CD is a separate molecule with a distinct molecular composition, specificity, and cellular distribution

within the cells of the immune system. CD4 is a co-receptor, which is used by MHC Class II-restricted T-cells in recognising foreign antigens. In humans, the CD4 co-receptor is borne on about two-thirds of the peripheral blood T-lymphocytes, monocytes, macrophages, and most thymocytes. The normal CD4 cell count is between 950 and 1,700 cells per micro litre of blood.

The CD8 co-receptor is used by MHC Class I-restricted T-cells and is borne on most thymocytes, NK cells and about one-third of the peripheral blood T-lymphocytes. *Helper cells* (also called "T4" or "CD4 T-lymphocytes") comprise about two-thirds of the T-lymphocytes in the peripheral blood. They bear CD4 receptors on their surfaces. They are capable of recognising foreign antigens in association with MHC Class II. On activation by foreign antigens, they secrete chemicals called "cytokines". There are about 40 different types of cytokines, which have overlapping effects. Interleukin-2 (IL-2) is a cytokine, which is responsible for proliferation of T-cells. IL-4, also a cytokine, increases production of antibodies by B-cells. T4 (or CD4) cells are required for optimal production of antibodies by B-cells and for cytotoxic action of T8 cells. Thus, T4 cells "help" the action of other lymphocytes.

Suppressor cells (also called "T8", or "CD8 T-lymphocytes") comprise 20–30 per cent of the T-lymphocytes in the peripheral blood. They bear CD8 receptors on their surfaces. These cells suppress immunoglobulin synthesis and act as a brake on immune response. On activation by foreign antigens, they differentiate and proliferate with the help of IL-2, which is secreted by T4 cells. T8 cells also produce an antiviral cytokine, called CD8 cell-produced antiviral factor (CAF), which directly inhibits the replication of HIV in T4 cells, without causing their lysis.

Killer T-cells are cytotoxic cells that bear CD8 co-receptors. They can recognise foreign antigens in association with MHC Class I. These cells proliferate and differentiate in response to IL-2 secreted by T-helper cells. Killer T-cells do not require complement. Killer T-cells are responsible for antibody-dependent cell-mediated cytotoxicity (ADCC), destruction of virus-infected cells or tumour cells by forming pores on their membranes with the help of a cytolysing chemical called "perforin", and destruction of contents of target cells by releasing enzyme-filled vesicles.

All T-cells bear CD3 surface antigens and can be counted using anti-CD3 markers. Since all B-cells bear surface IgM, they can be counted using fluorescent anti-IgM markers. *Null cells* cannot be counted using either anti-CD3 or anti-IgM markers.

2.8 – MUCOSAL IMMUNE SYSTEM

Lymphoid tissue present in the gut may be *encapsulated* (e.g. liver and spleen) or *non-encapsulated* (organized or diffused lymphoid tissue).

Encapsulated Lymphoid Tissue: The inner cortical area of the *lymph node* contains B-cells, while the paracortical area contains T-cells. Lymphoid tissue in *spleen* is present in the white pulp and along the cords of Billroth in the red pulp.

Non-Encapsulated Lymphoid Tissue: Diffuse lymphoid tissue in lamina propria of gastrointestinal and respiratory tracts constitutes MALT. Organised lymphoid tissue is present in tonsils (lingual, pharyngeal, palatine), appendix, and Peyer's patches in the intestine. The Peyer's patches in the gut generate most of the mucosal activated T- and B-lymphocytes, which subsequently migrate to other mucosal sites in the gut and genital mucosa. This intermucosal movement of activated lymphocytes constitutes the "common mucosal immune system".

2.9 – VACCINATION

In vaccination, a relatively harmless antigen is used as a primary stimulus in order to impart immunological memory so that, any subsequent contact with a virulent antigen will lead to a rapid and enhanced immune response. Booster doses are given after specific time intervals to elicit a rapid and increased response on the basis of previously developed immunological memory. Humoral immunity can protect against only one type of antigen, while cellular immunity can protect against multiple antigens of the same microorganism. Hence, for generating humoral immunity against multiple serotypes of the same organism, polyvalent vaccines would be required.

2.10 – HERD IMMUNITY

It is the level of resistance of a group of individuals to an invasion and subsequent spread by an infectious agent, based on the resistance to infection, of a high proportion of individual members of the group (Last, 1983). The *Illustrated Stedman's Medical Dictionary* defines "herd immunity" as protection of a group or community, beyond that afforded by immunisation of individuals. Herd immunity is influenced by *resistance* of a large proportion of individuals in a group or community, which may be due to prevailing clinical or subclinical infection in the host species or the level of immunisation of the herd, and *herd structure*, which includes: (a) host population belonging to the herd species, (b) presence and distribution of animal hosts and insect vectors, and (c) environmental and social factors that favour or inhibit the transmission of infection from host to host. The herd structure varies constantly because of population migration, births, and deaths.

Public Health Aspects

Herd immunity may be determined by serological surveys. If the herd immunity is maintained at high levels by an immunisation programme, the number of vulnerable individuals is reduced to a small proportion of the total population (Last, 1983; Benenson, 1990). It is not necessary to achieve 100 per cent herd immunity in a population for containing an epidemic or to control a disease. However, there being no herd immunity against tetanus, 100 per cent immunisation coverage is essential for its control (Last, 1983; Benenson, 1990). In diseases such as

poliomyelitis and diphtheria, high levels of herd immunity may lead to elimination of the diseases, in course of time. The eradication of smallpox was not due to high levels of herd immunity (achieved by immunisation programme) but due to elimination of the source of infection (by surveillance and containment measures).

2.11 – HYPERSENSITIVITY

Hypersensitivity leads to immuno-inflammation or immunologically mediated tissue damage. Coombs and Gell (1963) described the types of hypersensitivity reactions.

Type I (Immediate Hypersensitivity): In allergic individuals, IgE is produced in response to antigens like pollen, food, clothing, dust, and drugs. Sensitised mast cells and basophils release vasoactive amines. *Systemic anaphylaxis* occurs when a majority of the body's mast cells are sensitised. Localised immuno-inflammation can occur in the skin (urticaria), nasal mucous membrane (allergic rhinitis), or bronchial mucous membrane (extrinsic asthma).

Type II (Cytotoxicity): Types of type II hypersensitivity reactions are: (a) complement-mediated hypersensitivity, e.g. drug-induced haemolytic anaemia, immune-mediated thrombocytopenic purpura, acute glomerulonephritis, rheumatic heart disease, and Goodpasteur syndrome; (b) stimulatory hypersensitivity (or Type-V hypersensitivity) in which, the antibody binds to receptors on the cell membrane causing stimulation (*not* destruction). Hyperthyroidism due to antithyroid antibodies is an example; (c) ADCC, also called Type-VI hypersensitivity, which involves killer T-cell mediated cell damage. Hashimoto's disease is an example.

Type III (Immune Complex Diseases): Normally, macrophages or monocytes remove antigen–antibody complexes. In type III hypersensitivity, antigen–antibody complexes are slowly cleared from circulation or tissues. Immuno-inflammation is initiated in joints, kidney, lung, and choroid plexus. Examples of immune complex diseases are Arthus reaction, erythema nodosum leprosum, and serum sickness.

Type IV (Delayed-Type Hypersensitivity or DTH): Immuno-inflammation is initiated by T-lymphocytes that secrete lymphokines. The types of DTH include *infection-type of DTH* (caseation in tuberculosis, nerve damage in tuberculoid leprosy, and granuloma formation in chronic diseases), and *chronic dermatitis-type DTH* (contact dermatitis).

2.12 – IMMUNE DEFICIENCY

A compromised host lies open, as a form of exposed, all-purpose culture plate. He not only admits many kinds of ambient organisms with ease, but usually does so in relative silence – Paul Russel (cited by Rubin & Young, 1994).

Congenital deficiency refers to deficiency in immunity, which is present since birth and may be inherited or due to developmental defects. Defects in B-cells result in hypogammaglobulinaemias characterised by low levels of gamma globulins (antibodies) in the blood. Congenital deficiency of CMI will result in death within the first 6 months of life. However, a baby born with deficient humoral immunity may even survive up to 6 years without replacement therapy (Gell *et al*., 1975). Individuals with T-cell defects tend to have more severe and persistent infections as compared to those with defective B-cell function. Thus, cellular immunity is more protective than humoral immunity. The complement system can also be affected by defects in function, leading to increased vulnerability to infection.

Extremes of age (infancy and old age) and pregnancy are physiological states in which the immunity is lowered. Pathological conditions causing deficiency of non-specific and specific immunity include: (a) infections such as measles, kala azar, diphtheria, and whooping cough; (b) abnormal mental states such as emotional shock and stress; (c) physical fatigue; (d) nutritional deficiencies; (e) changes in living environment; (f) malignancies; (g) metabolic disorders; and (h) corticosteroids and anti-cancer drugs (WHO, 1976). Renal disease (causing excessive protein loss) and protein-losing enteropathy can cause deficiency of Ig. Malnutrition, particularly iron deficiency, can reduce cell-mediated immune response. Recognition of opportunistic infection in an immune-deficient host requires awareness and keen observation by a clinician. A "syndrome" is a symptom complex, in which the symptoms and/or signs coexist more frequently than would be expected by chance (Last, 1983).

REFERENCES

Benenson A.S., 1990, Control of communicable diseases in man, 15th edn. Washington DC: American Public Health Association.

Fudenberg H.H., *et al*. 1976, Basic and clinical immunology. Los Altos, California: Lange Medical Publications.

Gell P.G.H., *et al*. (eds.), 1975, Clinical aspects of immunology, 3rd edn. Oxford: Blackwell Science.

Illustrat ed Stedman's Medical Dictionary, 1982, 24th edn. Baltimore: Williams & Wilkins.

Last J.M. (ed)., 1983, A dictionary of epidemiology. Oxford: Oxford University Press.

Roitt I.M., 1997, Roitt's essential immunology, 9th edn. Oxford: Blackwell Science.

Rubin R.H. and Young L.S., 1994, Clinical approach to infection in the compromised host, 3rd edn. London: Plenum Medical Book.

WHO, 1976, Public Health Papers. No. 72. Geneva: WHO.

WHO, 1993, Direction to Contributors to the Bulletin. Bull WHO 61 (1).