Immunity

Chapter 17

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DEFINITION AND TYPES OF IMMUNITY

Immunity is defined as the capacity of the body to resist pathogenic agents. It is the ability of body to resist the entry of different types of foreign bodies like bacteria, virus, toxic substances, etc.

Immunity is of two types:

I. Innate immunity.
II. Acquired immunity.

INNATE IMMUNITY OR NON-SPECIFIC IMMUNITY

Innate immunity is the inborn capacity of the body to resist pathogens. By chance, if the organisms enter the body, innate immunity eliminates them before the development of any disease. It is otherwise called the natural or non-specific immunity.

This type of immunity represents the first line of defense against any type of pathogens. Therefore, it is also called non-specific immunity.

Mechanisms of Innate Immunity

Various mechanisms of innate immunity are given in Table 17.1.

ACQUIRED IMMUNITY OR SPECIFIC IMMUNITY

Acquired immunity is the resistance developed in the body against any specific foreign body like bacteria, viruses, toxins, vaccines or transplanted tissues. So, this type of immunity is also known as specific immunity.

It is the most powerful immune mechanism that protects the body from the invading organisms or toxic substances. Lymphocytes are responsible for acquired immunity (Fig. 17.1).

Types of Acquired Immunity

Two types of acquired immunity develop in the body:

1. Cellular immunity
2. Humoral immunity.

Lymphocytes are responsible for the development of these two types of immunity.

DEVELOPMENT AND PROCESSING OF LYMPHOCYTES

In fetus, lymphocytes develop from the bone marrow (Chapter 10). All lymphocytes are released in the circulation and are differentiated into two categories.

TABLE 17.1: Mechanisms of innate immunity

Structures and Mediators	Mechanism
Gastrointestinal tract	Enzymes in digestive juices and the acid in stomach destroy the toxic substances or organisms entering digestive tract through food Lysozyme present in saliva destroys bacteria
Respiratory system	Defensins and cathelicidins in epithelial cells of air passage are antimicrobial peptides Neutrophils, lymphocytes, macrophages and natural killer cells present in lungs act against bacteria and virus
Urinogenital system	Acidity in urine and vaginal fluid destroy the bacteria
Skin	The keratinized stratum corneum of epidermis protects the skin against toxic chemicals The β-defensins in skin are antimicrobial peptides Lysozyme secreted in skin destroys bacteria
Phagocytic cells	Neutrophils, monocytes and macrophages ingest and destroy the microorganisms and foreign bodies by phagocytosis
Interferons	Inhibit multiplication of viruses, parasites and cancer cells
Complement proteins	Accelerate the destruction of microorganisms

The two categories are:

1. T lymphocytes or T cells, which are responsible for the development of cellular immunity
2. B lymphocytes or B cells, which are responsible for humoral immunity.

■ T LYMPHOCYTES

T lymphocytes are processed in thymus. The processing occurs mostly during the period between just before birth and few months after birth.

Thymus secretes a hormone called thymosin, which plays an important role in immunity. It accelerates the proliferation and activation of lymphocytes in thymus. It also increases the activity of lymphocytes in lymphoid tissues.

Types of T Lymphocytes

During the processing, T lymphocytes are transformed into four types:

1. Helper T cells or inducer T cells. These cells are also called **CD4 cells** because of the presence of molecules called CD4 on their surface.
2. Cytotoxic T cells or killer T cells. These cells are also called **CD8 cells** because of the presence of molecules called CD8 on their surface.
3. Suppressor T cells.
4. Memory T cells.

Storage of T Lymphocytes

After the transformation, all the types of T lymphocytes leave the thymus and are stored in lymphoid tissues of lymph nodes, spleen, bone marrow and GI tract.

■ B LYMPHOCYTES

B lymphocytes were first discovered in the bursa of Fabricius in birds, hence the name B lymphocytes. **Bursa of Fabricius** is a lymphoid organ situated near the cloaca of birds. Bursa is absent in mammals and the processing of B lymphocytes takes place in liver (during fetal life) and bone marrow (after birth).

Types of B Lymphocytes

After processing, the B lymphocytes are transformed into two types:

1. Plasma cells.
2. Memory cells.

Storage of B Lymphocytes

After transformation, the B lymphocytes are stored in the lymphoid tissues of lymph nodes, spleen, bone marrow and the GI tract.

■ ANTIGENS

■ DEFINITION AND TYPES

Antigens are the substances which induce specific immune reactions in the body.

Antigens are of two types:

1. Autoantigens or self antigens present on the body's own cells such as 'A' antigen and 'B' antigen in RBCs.
2. Foreign antigen s or non-self antigens that enter the body from outside.

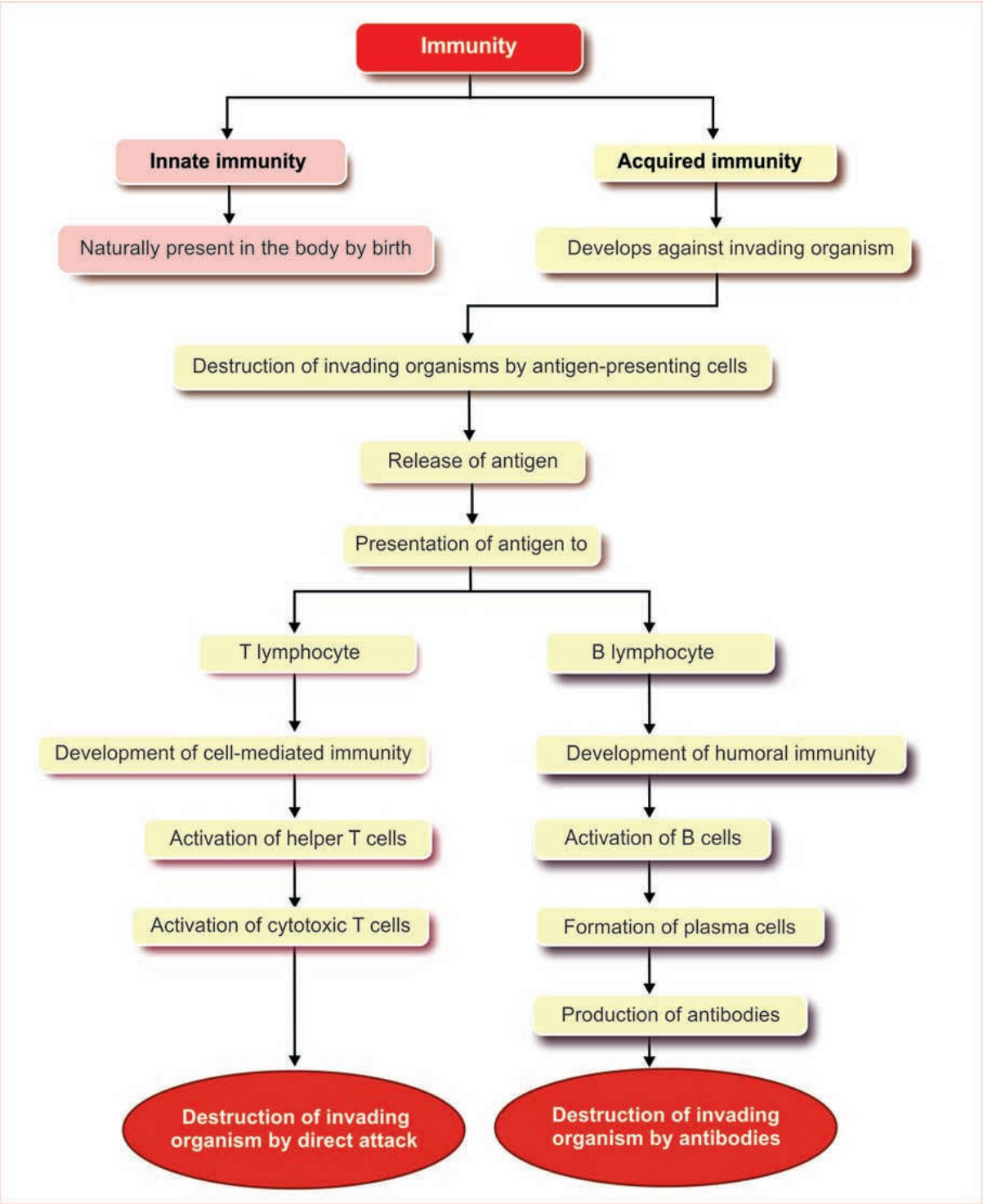

FIGURE 17.1: Schematic diagram showing development of immunity

■ NON-SELF ANTIGENS

Following are non-self antigens:

1. Receptors on the cell membrane of microbial organisms such as bacteria, viruses and fungi.
2. Toxins from microbial organisms.
3. Materials from transplanted organs or incompatible blood cells.
4. **Allergens** or allergic substances like pollen grains.

Types of Non-self Antigens

Non-self antigens are classified into two types, depending upon the response developed against them in the body:

1. Antigens, which induce the development of immunity or production of antibodies **(immunogenicity).**
2. Antigens, which react with specific antibodies and produce allergic reactions **(allergic reactivity).** (The allergic reaction is explained in the later part of this chapter).

CHEMICAL NATURE OF THE ANTIGENS

Antigens are mostly the conjugated proteins like lipoproteins, glycoproteins and nucleoproteins.

DEVELOPMENT OF CELL-MEDIATED IMMUNITY

INTRODUCTION

Cell-mediated immunity is defined as the immunity developed by cell-mediated response. It is also called cellular immunity or T cell immunity. It involves several types of cells such as T lymphocytes, macrophages and natural killer cells and hence the name cell mediated immunity. Cell-mediated immunity does not involve antibodies.

Cellular immunity is the major defense mechanism against infections by viruses, fungi and few bacteria like tubercle bacillus. It is also responsible for delayed allergic reactions and the rejection of transplanted tissues.

Cell-mediated immunity is offered by T lymphocytes and it starts developing when T cells come in contact with the antigens. Usually, the invading microbial or non-microbial organisms carry the antigenic materials. These antigenic materials are released from invading organisms and are presented to the helper T cells by antigen-presenting cells.

ANTIGEN-PRESENTING CELLS

Antigen-presenting cells are the special type of cells in the body, which induce the release of antigenic materials from invading organisms and later present these materials to the helper T cells.

Types of Antigen-Presenting Cells

Antigen-presenting cells are of three types:

1. Macrophages
2. Dendritic cells
3. B lymphocytes.

Among these cells, macrophages are the major antigen-presenting cells.

1. *Macrophages*

Macrophages are the large phagocytic cells, which digest the invading organisms to release the antigen. The macrophages are present along with lymphocytes in almost all the lymphoid tissues.

2. *Dendritic Cells*

Dendritic cells are nonphagocytic in nature. Based on the location, dendritic cells are classified into three categories:

i. Dendritic cells of spleen, which trap the antigen in blood.
ii. Follicular dendritic cells in lymph nodes, which trap the antigen in the lymph.
iii. Langerhans dendritic cells in skin, which trap the organisms coming in contact with body surface.

3. *B Lymphocytes*

Recently, it is found that B lymphocytes also act as antigen-presenting cells. Thus, the B cells function as both antigen-presenting cells and antigen receiving cells. However, B cells are the least efficient antigen-presenting cells and need to be activated by helper T cells.

Role of Antigen-presenting Cells

Invading foreign organisms are either engulfed by macrophages through phagocytosis or trapped by dendritic cells. Later, the antigen from these organisms is digested into small peptide products. These antigenic peptide products move towards the surface of the antigen-presenting cells and bind with human leukocyte antigen (HLA). HLA is a genetic matter present in the molecule of class II major histocompatiblility complex (MHC), which is situated on the surface of the antigen-presenting cells.

B-cells ingest the foreign bodies by means of pinocytosis. Role of B cells as antigen-presenting cells in the body is not fully understood.

MHC and HLA

Major histocompatibility complex (MHC) is a large molecule present in the short arm of chromosome 6. It is made up of a group of genes which are involved in immune system. It has more than 200 genes including HLA genes. HLA is made up of genes with small molecules. It encodes antigen-presenting proteins on the cell surface.

Though MHC molecules and HLA genes are distinct terms, both are used interchangeably. Particularly in human, the MHC molecules are often referred as HLA

molecules. MHC molecules in human beings are divided into two types:

1. Class I MHC molecule: It is found on every cell in human body. It is specifically responsible for presentation of endogenous antigens (antigens produced intracellularly such as viral proteins and tumor antigens) to cytotoxic T cells.
2. Class II MHC molecule: It is found on B cells, macrophages and other antigen-presenting cells. It is responsible for presenting the exogenous antigens (antigens of bacteria or viruses which are engulfed by antigen-presenting cells) to helper T cells.

Presentation of Antigen

Antigen-presenting cells present their class II MHC molecules together with antigen-bound HLA to the helper T cells. This activates the helper T cells through series of events (Fig. 17.2).

Sequence of Events during Activation of Helper T cells

1. Helper T cell recognizes the antigen displayed on the surface of the antigen-presenting cell with the help of its own surface receptor protein called T cell receptor.
2. Recognition of the antigen by the helper T cell initiates a complex interaction between the helper T cell receptor and the antigen. This reaction activates helper T cells.
3. At the same time, macrophages (the antigen-presenting cells) release interleukin-1, which facilitates the activation and proliferation of helper T cells.
4. Activated helper T cells proliferate and the proliferated cells enter the circulation for further actions.

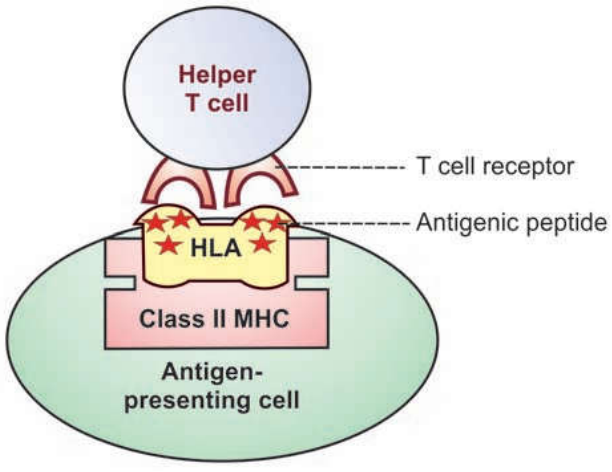

FIGURE 17.2: Antigen presentation. The antigen-presenting cells present their class II MHC molecules together with antigen-bound HLA to the helper T cells. MHC = Major histocompatiblility complex. HLA = Human leukocyte antigen.

5. Simultaneously, the antigen which is bound to class II MHC molecules activates the B cells also, resulting in the development of humoral immunity (see below).

■ ROLE OF HELPER T CELLS

Helper T cells (CD4 cells) which enter the circulation activate all the other T cells and B cells. Normal, CD4 count in healthy adults varies between 500 and 1500 per cubic millimeter of blood.

Helper T cells are of two types:

1. Helper-1 (TH1) cells
2. Helper-2 (TH2) cells.

Role of TH1 Cells

TH1 cells are concerned with cellular immunity and secrete two substances:

i. Interleukin-2, which activates the other T cells.
ii. Gamma interferon, which stimulates the phagocytic activity of cytotoxic cells, macrophages and natural killer (NK) cells.

Role of TH2 Cells

TH2 cells are concerned with humoral immunity and secrete interleukin-4 and interleukin-5, which are concerned with:

i. Activation of B cells.
ii. Proliferation of plasma cells.
iii. Production of antibodies by plasma cell.

■ ROLE OF CYTOTOXIC T CELLS

Cytotoxic T cells that are activated by helper T cells, circulate through blood, lymph and lymphatic tissues and destroy the invading organisms by attacking them directly.

Mechanism of Action of Cytotoxic T Cells

1. Receptors situated on the outer membrane of cytotoxic T cells bind the antigens or organisms tightly with cytotoxic T cells.
2. Then, the cytotoxic T cells enlarge and release cytotoxic substances like the lysosomal enzymes.
3. These substances destroy the invading organisms.
4. Like this, each cytotoxic T cell can destroy a large number of microorganisms one after another.

Other Actions of Cytotoxic T Cells

1. Cytotoxic T cells also destroy cancer cells, transplanted cells, such as those of transplanted heart or kidney or any other cells, which are foreign bodies.

2. Cytotoxic T cells destroy even body's own tissues which are affected by the foreign bodies, particularly the viruses. Many viruses are entrapped in the membrane of affected cells. The antigen of the viruses attracts the T cells. And the cytotoxic T cells kill the affected cells also along with viruses. Because of this, the cytotoxic T cell is called killer cell.

ROLE OF SUPPRESSOR T CELLS

Suppressor T cells are also called regulatory T cells. These T cells suppress the activities of the killer T cells. Thus, the suppressor T cells play an important role in preventing the killer T cells from destroying the body's own tissues along with invaded organisms. Suppressor cells suppress the activities of helper T cells also.

ROLE OF MEMORY T CELLS

Some of the T cells activated by an antigen do not enter the circulation but remain in lymphoid tissue. These T cells are called memory T cells.

In later periods, the memory cells migrate to various lymphoid tissues throughout the body. When the body is exposed to the same organism for the second time, the memory cells identify the organism and immediately activate the other T cells. So, the invading organism is destroyed very quickly. The response of the T cells is also more powerful this time.

SPECIFICITY OF T CELLS

Each T cell is designed to be activated only by one type of antigen. It is capable of developing immunity against that antigen only. This property is called the specificity of T cells.

DEVELOPMENT OF HUMORAL IMMUNITY

INTRODUCTION

Humoral immunity is defined as the immunity mediated by antibodies, which are secreted by B lymphocytes. B lymphocytes secrete the antibodies into the blood and lymph. The blood and lymph are the body fluids (**humours** or **humors** in Latin). Since the B lymphocytes provide immunity through humors, this type of immunity is called humoral immunity or B cell immunity.

Antibodies are the gamma globulins produced by B lymphocytes. These antibodies fight against the invading organisms. The humoral immunity is the major defense mechanism against the bacterial infection.

As in the case of cell-mediated immunity, the macrophages and other antigen-presenting cells play an important role in the development of humoral immunity also.

ROLE OF ANTIGEN-PRESENTING CELLS

The ingestion of foreign organisms and digestion of their antigen by the antigen-presenting cells are already explained.

Presentation of Antigen

Antigen-presenting cells present the antigenic products bound with HLA (which is present in class II MHC molecule) to B cells. This activates the B cells through series of events.

Sequence of Events during Activation of B Cells

1. B cell recognizes the antigen displayed on the surface of the antigen-presenting cell, with the help of its own surface receptor protein called B cell receptor.
2. Recognition of the antigen by the B cell initiates a complex interaction between the B cell receptor and the antigen. This reaction activates B cells.
3. At the same time, macrophages (the antigen-presenting cells) release interleukin-1, which facilitates the activation and proliferation of B cells.
4. Activated B cells proliferate and the proliferated cells carry out the further actions.
5. Simultaneously, the antigen bound to class II MHC molecules activates the helper T cells, also resulting in development of cell-mediated immunity (already explained).

Transformation B Cells

Proliferated B cells are transformed into two types of cells:

1. Plasma cells
2. Memory cells.

ROLE OF PLASMA CELLS

Plasma cells destroy the foreign organisms by producing the antibodies. Antibodies are globulin in nature. The rate of the antibody production is very high, i.e. each plasma cell produces about 2000 molecules of antibodies per second. The antibodies are also called immunoglobulins.

Antibodies are released into lymph and then transported into the circulation. The antibodies are produced until the end of lifespan of each plasma cell, which may be from several days to several weeks.

■ ROLE OF MEMORY B CELLS

Memory B cells occupy the lymphoid tissues throughout the body. The memory cells are in inactive condition until the body is exposed to the same organism for the second time.

During the second exposure, the memory cells are stimulated by the antigen and produce more quantity of antibodies at a faster rate, than in the first exposure. The antibodies produced during the second exposure to the foreign antigen are also more potent than those produced during first exposure. This phenomenon forms the basic principle of vaccination against the infections.

■ ROLE OF HELPER T CELLS

Helper T cells are simultaneously activated by antigen. Activated helper T cells secrete two substances called interleukin-2 and B cell growth factor, which promote:

1. Activation of more number of B lymphocytes.
2. Proliferation of plasma cells.
3. Production of antibodies.

■ ANTIBODIES OR IMMUNOGLOBULINS

An antibody is defined as a protein that is produced by B lymphocytes in response to the presence of an antigen. Antibody is gamma globulin in nature and it is also called immunoglobulin (Ig). Immunoglobulins form 20% of the total plasma proteins. Antibodies enter almost all the tissues of the body.

Types of Antibodies

Five types of antibodies are identified:

1. IgA (Ig alpha)
2. IgD (Ig delta)
3. IgE (Ig epsilon)
4. IgG (Ig gamma)
5. IgM (Ig mu).

Among these antibodies, IgG forms 75% of the antibodies in the body.

Structure of Antibodies

Antibodies are gamma globulins with a molecular weight of 1,50,000 to 9,00,000. The antibodies are formed by two pairs of chains, namely one pair of heavy or long chains and one pair of light or short chains. Each heavy chain consists of about 400 amino acids and each light chain consists of about 200 amino acids.

Actually, each antibody has two halves, which are identical. The two halves are held together by disulfide bonds (S–S). Each half of the antibody consists of one heavy chain (H) and one light chain (L). The two chains in each half are also joined by disulfide bonds (S – S). The disulfide bonds allow the movement of amino acid chains. In each antibody, the light chain is parallel to one end of the heavy chain. The light chain and the part of heavy chain parallel to it form one arm. The remaining part of the heavy chain forms another arm. A hinge joins both the arms (Fig. 17.3).

Each chain of the antibody includes two regions:

1. Constant region
2. Variable region.

1. *Constant Region*

Amino acids present in this region are similar in number and placement (sequence) in all the antibodies of each type. So, this region is called constant region or **Fc** (Fragment crystallizable) region. Thus, the identification and the functions of different types of immunoglobulins depend upon the constant region. This region binds to the antibody receptor situated on the surface of the cell membrane. It also causes complement fixation. So, this region is also called the complement binding region.

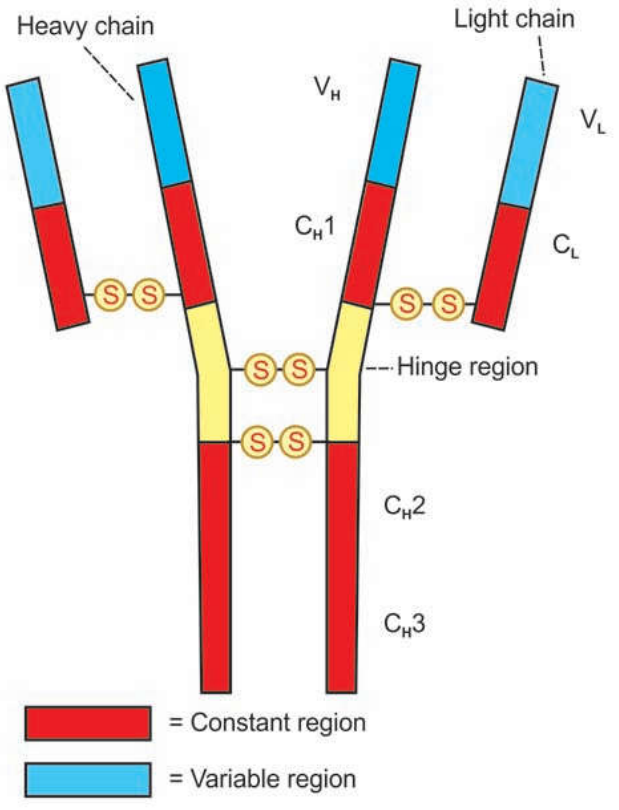

FIGURE 17.3: Structure of antibody (IgG) molecule. V_L = Variable region of light chain, V_H = Variable region of heavy chain, C_L = Constant region of light chain, C_H1, C_H2 and C_H3 = Constant regions of heavy chains.

2. *Variable Region*

Variable region is smaller compared to constant region. Amino acids occupying this region are different in number and placement (sequence) in each antibody. So, it is called the variable region. This region enables the antibody to recognize the specific antigen and to bind itself with the antigen. So, this region of the chain is called antigen-binding region or **Fab** (Fragment antigen binding) region.

Functions of Different Antibodies

1. IgA plays a role in localized defense mechanism in external secretions like tear
2. IgD is involved in recognition of the antigen by B lymphocytes
3. IgE is involved in allergic reactions
4. IgG is responsible for complement fixation
5. IgM is also responsible for complement fixation.

Mechanism of Actions of Antibodies

Antibodies protect the body from invading organisms in two ways (Fig. 17.4):

1. By direct actions
2. Through complement system.

1. *Direct Actions of Antibodies*

Antibodies directly inactivate the invading organism by any one of the following methods:

i. Agglutination: In this, the foreign bodies like RBCs or bacteria with antigens on their surfaces are held together in a clump by the antibodies.
ii. Precipitation: In this, the soluble antigens like tetanus toxin are converted into insoluble forms and then precipitated.
iii. Neutralization: During this, the antibodies cover the toxic sites of antigenic products.
iv. Lysis: It is done by the most potent antibodies. These antibodies rupture the cell membrane of the organisms and then destroy them.

2. *Actions of Antibodies through Complement System*

The indirect actions of antibodies are stronger than the direct actions and play more important role in defense mechanism of the body than the direct actions.

Complement system is the one that enhances or accelerates various activities during the fight against the invading organisms. It is a system of plasma enzymes, which are identified by numbers from C_1 to C_9. Including the three subunits of C_1 (C_{1q} C_{1r} C_{1s}), there are 11 enzymes in total. Normally, these enzymes are in inactive form and are activated in three ways:

a. Classical pathway
b. Lectin pathway
c. Alternate pathway.

a. *Classical pathway*

In this the C_1 binds with the antibodies and triggers a series of events in which other enzymes are activated in sequence. These enzymes or the byproducts formed during these events produce the following activities:

i. *Opsonization:* Activation of neutrophils and macrophages to engulf the bacteria, which are bound with a protein in the plasma called opsonin.
ii. *Lysis:* Destruction of bacteria by rupturing the cell membrane.
iii. *Chemotaxis*: Attraction of leukocytes to the site of antigen-antibody reaction.
iv. *Agglutination:* Clumping of foreign bodies like RBCs or bacteria.
v. *Neutralization:* Covering the toxic sites of antigenic products.
vi. *Activation of mast cells and basophils, which liberate histamine:* Histamine dilates the blood vessels and increases capillary permeability. So, plasma proteins from blood enter the tissues and inactivate the antigenic products.

b. *Lectin pathway*

Lectin pathway occurs when mannose-binding lectin (MBL), which is a serum protein binds with mannose or fructose group on wall of bacteria, fungi or virus.

c. *Alternate pathway*

Complementary system is also activated by another way, which is called alternate pathway. It is due to a protein in circulation called factor I. It binds with polysaccharides present in the cell membrane of the invading organisms. This binding activates C_3 and C_5, which ultimately attack the antigenic products of invading organism.

Specificity of B Lymphocytes

Each B lymphocyte is designed to be activated only by one type of antigen. It is also capable of producing antibodies against that antigen only. This property of B lymphocyte is called specificity. In lymphoid tissues, the lymphocytes, which produce a specific antibody, are together called the clone of lymphocytes.

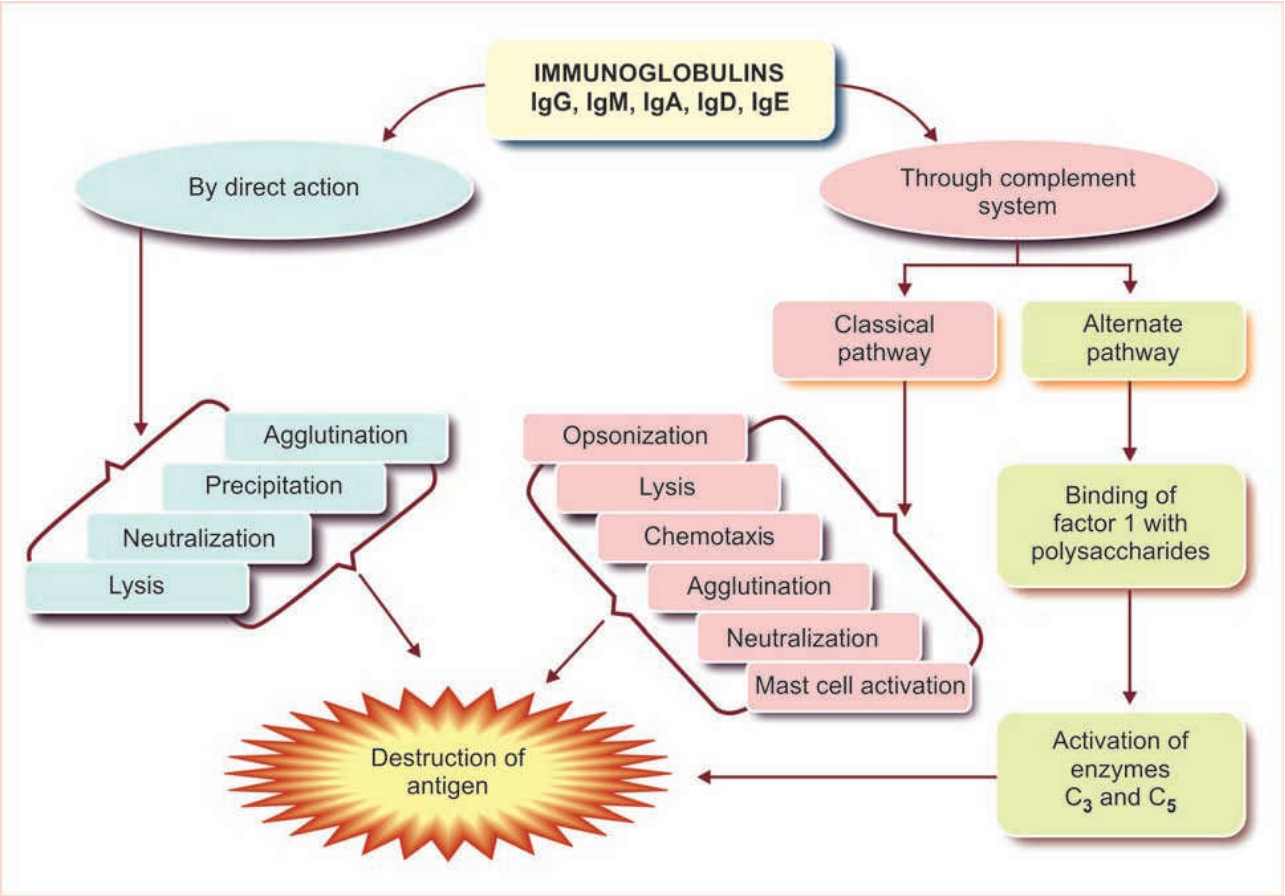

FIGURE 17.4: Mechanism of action of immunoglobulins

NATURAL KILLER CELL

Natural killer (NK) cell is a large granular cell that plays an important role in defense mechanism of the body. It has an indented nucleus. Considered as the third type of lymphocyte, it is often called the non-T, non-B cell. It is derived from bone marrow. NK cell is said to be the first line of defense in specific immunity, particularly against viruses.

NK cell kills the invading organisms or the cells of the body without prior sensitization. It is not a phagocytic cell but its granules contain hydrolytic enzymes such as perforins and granzymes. These hydrolytic enzymes play an important role in the lysis of cells of invading organisms.

Functions of Natural Killer (NK) Cell

Natural killer cell:

1. Destroys the viruses
2. Destroys the viral infected or damaged cells, which might form tumors
3. Destroys the malignant cells and prevents development of cancerous tumors
4. Secretes cytokines such as interleukin-2, interferons, colony stimulating factor (GM-CSF) and tumor necrosis factor-α. Cytokines are explained later in this chapter.

CYTOKINES

Cytokines are the hormone-like small proteins acting as intercellular messengers (cell signaling molecules) by binding to specific receptors of target cells. These non-antibody proteins are secreted by WBCs and some other types of cells. Their major function is the activation and regulation of general immune system of the body.

Cytokines are distinct from the other cell-signaling molecules such as growth factors (Chapter 1) and hormones (Chapter 65).

TYPES OF CYTOKINES

Depending upon the source of secretion and effects, cytokines are classified into several types:

1. Interleukins
2. Interferons
3. Tumor necrosis factors

4. Chemokines
5. Defensins
6. Cathelicidins
7. Platelet-activating factor.

Source of secretion and actions of these cytokines are given in Table 17.2.

1. *Interleukins*

Interleukins (IL) are the polypeptide cytokines which are produced mainly by the leukocytes and act on other leukocytes.

Types of interleukins

So far, about 16 types of interleukins are identified. IL-1, IL-2, IL-3, IL-4, IL-5, IL-6 and IL-8 play important role in the process of immunity. Recently IL-12 (otherwise called natural killer cell stimulatory factor) and IL-11 are also considered as important cytokines.

2. *Interferons*

Interferons (IFN) are the glycoprotein molecules. These cytokines are considered as antiviral agents.

Types of interferons

Interferons are of three types namely, INF-α, INF-β and INF-γ.

3. *Tumor Necrosis Factors*

Tumor necrosis factors (TNF) are of three types, TNF-α (cachectin), TNF-β (lymphotoxin) and TNF-γ.

4. *Chemokines*

Cytokines having chemoattractant action are called chemokines.

5. *Defensins*

Defensins are the antimicrobial peptides.

Types of defensins

Two types of defensins are identified in human:

i. α-defensins, secreted by neutrophils, macrophages and paneth cells in small intestine.
ii. β-defensins, secreted by airway epithelial cells (respiratory tract), salivary glands and cutaneous cells.

6. *Cathelicidins*

Cathelicidins are also the antimicrobial peptides which play an important role in a wide range of antimicrobial activity in air passage and lungs.

7. *Platelet-activating Factor*

Platelet-activating factor (PAF) accelerates agglutination and aggregation of platelets.

IMMUNIZATION

Immunization is defined as the procedure by which the body is prepared to fight against a specific disease. It is used to induce the immune resistance of the body to a specific disease. Immunization is of two types:

1. Passive immunization
2. Active immunization.

PASSIVE IMMUNIZATION

Passive immunization or immunity is produced without challenging the immune system of the body. It is done by administration of serum or gamma globulins from a person who is already immunized (affected by the disease) to a non-immune person.

Passive immunization is acquired either naturally or artificially.

Passive Natural Immunization

Passive natural immunization is acquired from the mother before and after birth. Before birth, immunity is transferred from mother to the fetus in the form of maternal antibodies (mainly IgG) through placenta. After birth, the antibodies (IgA) are transferred through breast milk.

Lymphocytes of the child are not activated. In addition, the antibodies received from the mother are metabolized soon. Therefore, the passive immunity is short lived. The significance of passive immunity that is obtained before birth is the prevention of Rh incompatibility in pregnancy.

Passive Artificial Immunization

Passive artificial immunization is developed by injecting previously prepared antibodies using serum from humans or animals. Antibodies are obtained from the persons affected by the disease or from animals, particularly horses which have been immunized artificially. The serum containing the antibody (antiserum) is administered to people who have developed the disease (therapeutic). It is also used as a prophylactic measure. Prophylaxis refers to medical or public health procedures to prevent a disease in people who may be exposed to the disease in a later period.

This type of immunity is useful for providing immediate protection against acute infections like tetanus, measles, diphtheria, etc. and for poisoning by insects, snakes and venom from other animals. It is also used as a prophylactic measure. However, this may result

TABLE 17.2: Cytokines

Cytokine	Source of secretion	Action
Interleukins	1. T cells 2. B cells 3. Eosinophils 4. Basophils 5. Monocytes 6. Mast cells 7. Macrophages 8. NK cells	1. Activation of T cells, macrophages and natural killer (NK) cells 2. Promotion of growth of hemopoietic cells and B cells 3. Acceleration of inflammatory response by activating eosinophils 4. Chemotaxis of neutrophils, eosinophils, basophils and T cells 5. Destruction of invading organisms
Interferons	1. WBCs 2. NK cells 3. Fibroblasts	1. Fighting against viral infection by suppressing virus multiplication in target cells 2. Inhibition of multiplication of parasites and cancer cells 3. Promotion of phagocytosis by monocytes and macrophages 4. Activation of NK cells
Tumor necrosis factors	1. T cells 2. B cells 3. Mast cells 4. Macrophages 5. NK cells 6. Platelets	1. Causing necrosis of tumor 2. Activation of general immune system 3. Production of vascular effects 4. Promotion of inflammation
Chemokines	1. T cells 2. B cells 3. Monocytes 4. Macrophages	Attraction of WBCs by chemotaxis
Defensins	1. Neutrophils 2. Macrophages 3. Paneth cells in small intestine 4. Airway epithelial cells 5. Salivary glands 6. Cutaneous cells	1. Role in innate immunity in airway surface and lungs 2. Killing the phagocytozed bacteria 3. Antiinflammatory actions 4. Promotion of wound healing 5. Attraction of monocytes and T cells by chemotaxis
Cathelicidins	1. Neutrophils 2. Macrophages 3. Airway epithelial cells 4. Macrophages	Antimicrobial activity in air passage and lungs
Platelet-activating factor	1. Neutrophils 2. Monocytes	Acceleration of agglutination and aggregation of platelets

in complications and anaphylaxis. There is a risk of transmitting HIV and hepatitis.

■ ACTIVE IMMUNIZATION

Active immunization or immunity is acquired by activating immune system of the body. Body develops resistance against disease by producing antibodies following the exposure to antigens. Active immunity is acquired either naturally or artificially.

Active Natural Immunization

Naturally acquired active immunity involves activation of immune system in the body to produce antibodies. It is achieved in both clinical and subclinical infections.

Clinical infection

Clinical infection is defined as the invasion of the body tissues by pathogenic microorganisms which reproduce, multiply and cause disease by injuring the cells, secreting a toxin or antigen-antibody reaction. During infection, the plasma cells produce immunoglobulins to destroy the invading antigens. Later, due to the activity of memory cells, body retains the ability to produce the antibodies against the specific antigens invaded previously.

Subclinical infection

Subclinical infection is defined as an infection in which symptoms are very mild and do not alert the affected subject. The disease thus produced may not be severe

to develop any manifestations. However, it causes the activation of B lymphocytes, resulting in production of antibodies.

Active Artificial Immunization

Active artificial immunization is a type of immunization is achieved by the administration of vaccines or toxoids.

Vaccines

Vaccine is a substance that is introduced into the body to prevent the disease produced by certain pathogens. Vaccine consists of dead pathogens or live but attenuated (artificially weakened) organisms. The vaccine induces immunity against the pathogen, either by production of antibodies or by activation of T lymphocytes.

Edward Jenner produced first live vaccine. He produced the vaccine for **smallpox** from **cowpox virus.** Nowadays, vaccines are used to prevent many diseases like measles, mumps, poliomyelitis, tuberculosis, smallpox, rubella, yellow fever, rabies, typhoid, influenza, hepatitis B, etc.

Toxoids

Toxoid is a substance which is normally toxic and has been processed to destroy its toxicity but retains its capacity to induce antibody production by immune system. Toxoid consists of weakened components or toxins secreted by the pathogens. Toxoids are used to develop immunity against diseases like diphtheria, tetanus, cholera, etc.

The active artificial immunity may be effective life-long or for short period. It is effective lifelong against the diseases such as mumps, measles, smallpox, tuberculosis and yellow fever. It is effective only for short period against some diseases like cholera (about 6 months) and tetanus (about 1 year).

■ IMMUNE DEFICIENCY DISEASES

Immune deficiency diseases are a group of diseases in which some components of immune system is missing or defective. Normally, the defense mechanism protects the body from invading pathogenic organism. When the defense mechanism fails or becomes faulty (defective), the organisms of even low virulence produce severe disease. The organisms, which take advantage of defective defense mechanism, are called opportunists.

Immune deficiency diseases caused by such opportunists are of two types:

1. Congenital immune deficiency diseases
2. Acquired immune deficiency diseases.

■ CONGENITAL IMMUNE DEFICIENCY DISEASES

Congenital diseases are inherited and occur due to the defects in B cell or T cell or both. The common examples are **DiGeorge syndrome** (due to absence of thymus) and severe combined immune deficiency (due to lymphopenia or the absence of lymphoid tissue).

■ ACQUIRED IMMUNE DEFICIENCY DISEASES

Acquired immune deficiency diseases occur due to infection by some organisms. The most common disease of this type is acquired immune deficiency syndrome (AIDS).

Acquired Immune Deficiency Syndrome (AIDS)

AIDS is an infectious disease caused by immune deficiency virus (HIV). A person is diagnosed with AIDS when the CD4 count is below 200 cells per cubic millimeter of blood.

AIDS is the most common problem throughout the world because of rapid increase in the number of victims. Infection occurs when a glycoprotein from HIV binds to surface receptors of T lymphocytes, monocytes, macrophages and dendritic cells leading to the destruction of these cells. It causes slow progressive decrease in immune function, resulting in opportunistic infections of various types. The common opportunistic infections, which kill the AIDS patient are **pneumonia (Pneumocystis carinii)** and malignant skin cancer **(Kaposi sarcoma).** These diseases are also called AIDS-related diseases.

After entering the body of the host, the HIV activates the enzyme called **reverse transcriptase.** HIV utilizes this enzyme and converts its own viral RNA into viral DNA with the help of host cell DNA itself. Now, the viral DNA gets incorporated into the host cell DNA and prevents the normal activities of the host cell DNA. At the same time, the HIV increases in number inside the host's body. The infected host cell ruptures and releases more number of HIV into the bloodstream. After exposure to HIV, no symptoms develop for several weeks. This is the incubation period. The patient develops symptoms only when sufficient number of infected cells is ruptured. The common symptoms are fatigue, loss of weight, chronic diarrhea, low-grade fever, night sweats, oral ulcers, vaginal ulcers, etc. This phase prolongs for about three years before the disease is diagnosed.

Mode of transmission

The HIV infection spreads when secretions from the body of infected individual come in contact with blood of the recipient through the damaged skin or mucous membrane. The most common ways of infection are

contaminated blood transfusion, contaminated needles or other invasive instruments, transmission from mother to fetus during pregnancy, transmission from mother to child during delivery or breastfeeding and vaginal sexual intercourse.

Prevention

Prevention of AIDS is essential because the authentic treatment for this disease has not been established so far. Progress in the development of effective treatment is very slow. Moreover, the maximum duration of survival after initial infection is only about 10 to 15 years. So, it is necessary to prevent this disease.

Following safety measures should be followed to prevent AIDS:

1. Public must be educated about the seriousness and prevention of the disease.
2. HIV infected persons should be educated to avoid spreading the disease to others.
3. Blood should be screened for HIV before transfusion.
4. Intravenous drug users should not share the needles.
5. Pregnant women should get the blood tested for HIV. If the mother is infected, the treatment with zidovudine may reduce incidence of infection in infants. The baby must be given zidovudine for 6 weeks after birth.
6. Young adults and teenagers must be informed about the safer sex techniques and use of condoms. The need for limitation of sexual partners must be emphasized.

AUTOIMMUNE DISEASES

Autoimmune disease is defined as a condition in which the immune system mistakenly attacks body's own cells and tissues. Normally, an antigen induces the immune response in the body. The condition in which the immune system fails to give response to an antigen is called tolerance. This is true with respect to body's own antigens that are called self antigens or autoantigens. Normally, body has the **tolerance** against self antigen. However, in some occasions, the tolerance fails or becomes incomplete against self antigen. This state is called autoimmunity and it leads to the activation of T lymphocytes or production of autoantibodies from B lymphocytes. The T lymphocytes (cytotoxic T cells) or autoantibodies attack the body's normal cells whose surface contains the self antigen or autoantigen.

Thus, the autoimmune disease is produced when body's normal tolerance decreases and the immune system fails to recognize the body's own tissues as 'self'.

Autoimmune diseases are of two types:

1. Organ specific diseases which affect only one organ
2. Organ nonspecific or multisystemic diseases, which affect many organs or systems.

HUMAN LEUKOCYTE ANTIGEN SYSTEM AND AUTOIMMUNE DISEASES

Human leukocyte antigen (HLA) is a group of genes on human chromosome 6. These genes encode the proteins which function in the cells to transport the antigens from within the cell towards the cell surface. HLA is the product of major histocompatilility complex.

HLA system monitors the immune system in the body (see above). The HLA molecules are recognized by the T and B lymphocytes and hence the name called antigens. HLA is distributed in almost all the tissues of the body. Antibodies are directed against the tissues possessing the HLA, leading to autoimmune diseases. Most of the autoimmune diseases are HLA linked.

COMMON AUTOIMMUNE DISEASES

Common autoimmune diseases are:

1. Insulin-dependent diabetes mellitus
2. Myasthenia gravis
3. Hashimoto thyroiditis
4. Graves disease
5. Rheumatoid arthritis.

1. *Insulin-dependent Diabetes Mellitus*

Insulin-dependent diabetes mellitus (IDDM) is very common in childhood and it is due to HLA-linked autoimmunity.

Common causes for IDDM

i. Development of islet cell autoantibody against β-cells in the islets of Langerhans in pancreas.
ii. Development of antibody against insulin and glutamic acid decarboxylase.
iii. Activation of T cells against islets.

Other details of IDDM are given in Chapter 69.

2. *Myasthenia Gravis*

This neuromuscular disease occurs due to the development of autoantibodies against the receptors acetylcholine in neuromuscular junction. Details of myasthenia gravis are given in Chapter 34.

3. *Hashimoto Thyroiditis*

Hashimoto thyroiditis is common in the late middle-aged women. The autoantibodies impair the activity of thyroid

follicles leading to hypothyroidism. Hypothyroidism is explained in detail in Chapter 67.

4. Graves Disease

In some cases, the autoantibodies activate thyroid-stimulating hormone (TSH) receptors leading to hyperthyroidism. The details of this disease are given in Chapter 67.

5. Rheumatoid Arthritis

Rheumatiod arthritis is the disease due to chronic inflammation of synovial lining of joints (synovitis). The synovium becomes thick, leading to the development of swelling around joint and tendons. The characteristic symptoms are pain and stiffness of joints. The chronic inflammation occurs due to the continuous production of autoantibodies called rheumatoid arthritis factors (RA factors).

ALLERGY AND IMMUNOLOGICAL HYPERSENSITIVITY REACTIONS

The term allergy means hypersensitivity. It is defined as abnormal immune response to a chemical or physical agent **(allergen).** During the first exposure to an allergen, the immune response does not normally produce any reaction in the body. Sensitization or an initial exposure to the allergen is required for the reaction. So, the subsequent exposure to the allergen causes variety of inflammatory responses. These responses are called allergic reactions or immunological hypersensitivity reactions.

Immunological hypersensitivity reactions may be innate or acquired. These reactions are mediated mostly by antibodies. In some conditions, T cells are involved. Common symptoms include sneezing, itching and skin rashes. However, in some persons the symptoms may be severe.

Common allergic conditions are:

1. Food allergy
2. Allergic rhinitis
3. Bronchial asthma
4. Urticaria.

ALLERGENS

Any substance that produces the manifestations of allergy is called an allergen. It may be an antigen or a protein or any other type of substance. Even physical agents can develop allergy.

Allergens are introduced by:

1. Contact (e.g.: chemical substance)
2. Inhalation (e.g.: pollen)
3. Ingestion (e.g.: food)
4. Injection (e.g.: drug).

Common Allergens

1. *Food substances:* Wheat, egg, milk and chocolate.
2. *Inhalants:* Pollen grains, fungi, dust, smoke, perfumes and disagreeable odor.
3. *Contactants:* Chemical substances, metals, animals and plants.
4. *Infectious agents:* Parasites, bacteria, viruses and fungi.
5. *Drugs:* Aspirin and antibiotics.
6. *Physical agents:* Cold, heat, light, pressure and radiation.

IMMUNOLOGICAL HYPERSENSITIVE REACTIONS

Immunological hypersensitive reactions to an agent give rise to several allergic conditions and autoimmune diseases.

Hypersensitive reactions are classified into five types:

Type I or anaphylactic reactions.
Type II or cytotoxic reactions.
Type III or antibody-mediated reactions.
Type IV or cell-mediated reactions.
Type V or stimulatory/blocking reactions.

Type I or Anaphylactic Reactions

Anaphylaxis means exaggerated reactions of the body to an antigen or other agents to which the body is sensitized already. It is also called immediate hypersensitive reaction because it develops within few minutes of exposure to an allergen. Anaphylactic reactions are mediated by IgE and other factors involved in inflammation (inflammation means the protective response of the tissues to the damage or destruction of cells).

When the body is exposed to an allergen, the IgE immunoglobulins are produced. Also called reagins or sensitizing antibodies, these immunoglobulins bind with the surface receptors of mast cells and circulating basophils. Mast cells are the granulated wandering cells found in connective tissue and beneath the mucous membrane in the throat, lungs and eyes.

During subsequent exposure of the body to the same allergen, the allergen IgE antibody reaction takes place. This leads to degranulation of mast cells and basophils, with the release of some chemical mediators such histamine. The chemical mediators produce the hypersensitivity reactions. Most serious reactions are fall in blood pressure (due to vasodilatation),obstruction of air passage and difficulty in breathing (due to bronchoconstriction) and shock (Chapter 116).

Type II or Cytotoxic Reactions

Cytotoxic reactions involve mainly the IgG antibodies, which bind with antigens on the surface of the cells, particularly the blood cells. The affected cells are destroyed. Sometimes, IgM and IgA antibodies are also involved. The diseases developed due to cytotoxic reactions are hemolytic diseases of newborn in case of Rh incompatibility and **autoimmune hemolytic anemia.**

Type III or Antibody-mediated Reactions

Excess amounts of antibodies like IgG or IgM are produced in this type. The antigen-antibody complexes are precipitated and deposited in localized areas like joints causing **arthritis,** heart causing **myocarditis** and glomeruli of kidney producing **glomerulonephritis.**

Type IV or Cell-mediated Reactions

This type of hypersensitivity is also called delayed or slow type of hypersensitivity. It is found in allergic reactions due to the bacteria, viruses and fungi. It is also seen in contact dermatitis caused by chemical allergens and during rejection of transplanted tissues. An example of type IV reaction is the delayed reaction after intradermal injection of tuberculin in persons who are previously affected by tuberculosis (tuberculosis skin test or **Mantoux test**). The important feature of delayed type of hypersensitivity is the involvement of T lymphocytes rather than the antibodies.

Type V or Stimulatory/Blocking Reactions

It is seen in autoimmune diseases like Graves' disease (stimulatory reactions) and myasthenia gravis (blocking reactions).

Graves' disease: Normally, TSH combines with surface receptors of thyroid cells and causes synthesis and secretion of thyroid hormones. The secretion of thyroid hormones can be increased by thyroid-stimulating antibodies (TSAB) produced by plasma cells (B lymphocytes). The excess secretion of thyroid hormone leads to Graves' disease.

Myasthenia gravis: It is due to the development of IgG autoantibodies (see above).