IMMUNOLOGY (AN INTRODUCTION)

The main function of the immune system is to prevent or limit infections by microorganisms such as bacteria, viruses, fungi, and parasites. Protection is provided primarily by the cell-mediated and antibody-mediated (humoral) arms of the immune system. Two other major components of the immune system are complement and phagocytes.

The cell-mediated arm consists primarily of **T lymphocytes** (e.g., helper T cells and cytotoxic T cells) whereas the **antibody-mediated arm** consists of **B lymphocytes** (and plasma cells).

The main functions of antibodies are :

(1) to neutralize toxins and viruses and

(2) to opsonize bacteria, making them easier to phagocytize.

Cell-mediated immunity, on the other hand, inhibits organisms such as fungi, parasites, and certain intracellular bacteria; it also kills virus-infected cells and tumor cells.

Both the cell-mediated and antibody-mediated responses are characterized by three important features:

(1) they exhibit remarkable **diversity** (i.e., they can respond to millions of different antigens);

(2) they have a **long memory** (i.e., they can respond many years after the initial exposure because memory T cells and memory B cells are produced);

(3) they exhibit exquisite **specificity** (i.e., their actions are specifically directed against the antigen that initiated the response).

The combined effects of certain cells (e.g., T cells, B cells, macrophages, and neutrophils) and certain proteins (e.g., antibodies and complement) produce an inflammatory response, one of the body's main defense mechanisms.

12.1 SPECIFICITY OF THE IMMUNE RESPONSE

Cell-mediated immunity and antibody are both highly specific for the invading organism. How do these specific protective mechanisms originate? The process by which these host defenses originate can be summarized by **three actions**:

1. the recognition of the foreign organism by specific immune cells,
2. the activation of these immune cells to produce a specific response (e.g., antibodies), and
3. the response that specifically targets the organism for destruction.

12.1.1 Cell-mediated Immunity

In the following example, a bacterium, e.g., *Mycobacterium tuberculosis*, enters the body and is ingested by a macrophage. The bacterium is broken down, and fragments of it called antigens or epitopes appear on the surface of the macrophage in association with class II major histocompatibility complex (MHC) proteins.

The antigen-class II MHC protein complex interacts with an antigen-specific receptor on the surface of a helper T lymphocyte. Activation and clonal proliferation of this antigen-specific helper T cell occur as a result of the production of interleukins, the most important of which are interleukin-1 (produced by macrophages) and interleukin-2 (produced by lymphocytes). These activated helper T cells, aided by activated macrophages, mediate one important component of cellular immunity, i.e., a **delayed hypersensitivity reaction specifically against *M. tuberculosis*.**

Cytotoxic T lymphocytes are also specific effectors of the cellular immune response, particularly against virus-infected cells.

12.1.2. Antibody-mediated Immunity

Antibody synthesis typically involves the **cooperation of three cells: macrophages, helper T cells, and B cells.** After processing by a macrophage, fragments of antigen appear on the surface of the macrophage in association with class II MHC proteins.

The antigen-class II MHC protein complex binds to specific receptors on the surface of a helper T cell, which then produces interleukins such as interleukin-2 (T cell growth factor), interleukin-4 (B cell growth factor), and interleukin-5 (B celldifferentiation factor). These factors **activate the B cell**

capable of producing antibodies specific for that antigen. (the interleukins are nonspecific; the specificity lies in the T cells and B cells and is mediated by the antigen receptors on the surface of these cells.)

The activated B cell proliferates and differentiates to form many plasma cells that secrete large amounts of immunoglobulins (antibodies).

Although antibody formation usually involves helper T cells, **certain antigens, e.g., bacterial polysaccharides, can activate B cells directly,** without the help of T cells, and are called T cell-independent antigens.

The specificity of the response is provided by the antigen receptor (T cell receptor [TCR]) on the surface of both the CD4-positive T cell and the CD8-positive T cell and by the antigen receptor (IgM) on the surface of the B cell. The interleukins, on the other hand, are not specific.

12.2 NATURAL & ACQUIRED IMMUNITY

Immunity may be **natural (innate) or acquired (adaptive).**

(1) Natural immunity is resistance not acquired through contact with an antigen. It is nonspecific and includes host defenses such as barriers to infectious agents (e.g., skin and mucous membranes), certain cells (e.g., natural killer cells), certain proteins (e.g., the complement cascade and interferons), and other processes such as phagocytosis and inflammation. Natural immunity does not improve after exposure to the organism, in contrast to acquired immunity, which does. In addition, natural immune processes have no memory, whereas acquired immunity is characterized by long-term memory. The acute-phase response, which consists of an increase in the levels of various plasma proteins, e.g., C-reactive protein and mannose-binding protein, is also part of natural immunity. These proteins are synthesized by the liver and are nonspecific responses to microorganisms and other forms of tissue injury. The liver synthesizes these proteins in response to certain cytokines, namely, interleukin-1, interleukin-6, and tumor necrosis factor, produced by the macrophage after exposure to microorganisms. Some acute-phase proteins bind to the surface of bacteria and activate complement which can kill the bacteria.

(2) Acquired immunity occurs after exposure to an agent, improves upon repeated exposure, and is specific. It is mediated by antibody and by T lymphocytes, namely, helper T cells and cytotoxic T cells. The cells responsible for acquired immunity have long-term memory for a specific antigen. Acquired immunity can be active or passive.

12.3 ACTIVE & PASSIVE IMMUNITY

Active immunity is resistance induced after contact with foreign antigens, e.g., microorganisms. This contact may consist of clinical or subclinical infection, immunization with live or killed infectious agents or their antigens, or exposure to microbial products (e.g., toxins and toxoids). In all these instances, the host actively produces an immune response consisting of antibodies and activated helper and cytotoxic T lymphocytes.

The main advantage of active immunity is that **resistance is long-term**. Its major **disadvantage is its slow onset**, especially the primary response.

Passive immunity is **resistance based on antibodies preformed in another host**. Administration of antibody against diphtheria, tetanus, botulism, etc. makes large amounts of antitoxin immediately available to neutralize the toxins. Likewise, preformed antibodies to certain viruses (e.g., rabies and hepatitis A and B viruses) can be injected during the incubation period to limit viral multiplication. Other forms of passive immunity are IgG passed from mother to fetus during pregnancy and IgA passed from mother to newborn during breast-feeding.

The main advantage of passive immunization is the prompt availability of large amounts of antibody; **disadvantages are the short life-span of these antibodies** and possible hypersensitivity reactions if globulins from another species are used.

Passive-active immunity involves giving both preformed antibodies (immune globulins) to provide immediate protection and a vaccine to provide long-term protection. These preparations should be given at different sites in the body to prevent the antibodies from neutralizing the immunogens in the vaccine. This approach is used in the prevention of tetanus, rabies and hepatitis B.

12.4 HUMORAL IMMUNITY

Humoral (antibody-mediated) immunity is directed primarily against

(1) toxin-induced diseases,

(2) infections in which virulence is related to polysaccharide capsules (e.g., pneumococci, meningococci, *Haemophilus influenzae*), and

(3) certain viral infections.

In this chapter the kinetics of antibody synthesis, i.e., the primary and secondary responses, are described.

12.4.1 The primary response

When **an antigen is first encountered**, antibodies are detectable in the serum after a longer **lag period** than occurs in the secondary response. The lag period is typically 7-10 days but can be longer depending on the nature and dose of the antigen and the route of administration (e.g., parenteral or oral). A small clone of B cells and plasma cells specific for the antigen is formed. The serum antibody concentration continues to **rise for several weeks**, then **declines** and may drop to very low levels. The **first antibodies to appear are IgM followed by IgG or IgA**. IgM levels decline earlier than IgG levels.

12.4.2 The secondary response

When there is a **second encounter with the same antigen or a closely related** (or cross-reacting) one, months or years after the primary response, there is a **rapid antibody response** (the lag period is typically only 3-5 days) to **higher levels than the primary response.** This is attributed to the persistence of antigen-specific "memory cells" after the first contact. These memory cells proliferate to form a large clone of specific B cells and plasma cells, which mediate the secondary antibody response.

During the secondary response, **the amount of IgM produced is similar to that after the first contact with antigen. However, a much larger amount of IgG antibody is produced** and the levels **tend to persist much longer than in the primary response**.

With each succeeding exposure to the antigen, the antibodies tend to bind antigen more firmly. Antibody binding improves because mutations occur in the DNA that encodes the antigen-binding site.

12.4.4 Functions of antibodies

The primary function of antibodies is **to protect against infectious agents** or their products. Antibodies provide resistance because they can

(1) neutralize toxins and viruses and

(2) opsonize microorganisms.

Opsonization is the process by which antibodies make microorganisms more easily ingested by phagocytic cells. This occurs by either of two reactions:

(1) The Fc portion of IgG interacts with its receptors on the phagocyte surface to facilitate ingestion; or

(2) IgG or IgM activates complement to yield C3b, which interacts with its receptors on the surface of the phagocyte.

Antibodies can be induced actively in the host or acquired passively and are thus immediately available for defense. In medicine, passive immunity is used in the neutralization of the toxins of diphtheria, tetanus, and botulism by antitoxins and in the inhibition of such viruses as rabies and hepatitis A and B viruses early in the incubation period.

12.5 CELL-MEDIATED IMMUNITY

Although humoral (antibody-mediated immunity) is an important host defense against many bacterial and viral diseases, in many other bacterial infections (especially intracellular infections such as tuberculosis) and viral infections, it is primarily the cell-mediated arm that imparts resistance and aids in recovery. Furthermore, cell-mediated immunity is important in **defense against fungi, parasites, and tumors and in the rejection of organ transplants.** The strongest evidence for the importance of cell-mediated immunity comes from clinical situations in which its suppression (by immunosuppressive drugs or disease, e.g., AIDS) results in overwhelming infections or tumors.

The constituents of the cell-mediated immune system include several cell types:

1. **macrophages,** which present the antigen to T cells;
2. **helper T cells**, which participate in antigen recognition and in regulation (helper and suppressor) functions;
3. **natural killer (NK) cells**, which can inactivate pathogens;
4. **cytotoxic T cells**, which can kill virus-infected cells with or without antibody.

Macrophages and helper T cells produce cytokines that activate helper and cytotoxic T cells, leading to the killing of the pathogen or tumor cell.

13. HYPERSENSITIVITY (ALLERGY)

When an immune response results in **exaggerated or inappropriate reactions harmful to the host**, the term hypersensitivity or allergy is used. The clinical manifestations of these reactions are typical in a given individual and occur on contact with the specific antigen to which the individual is hypersensitive.

The first contact of the individual with the antigen sensitizes, i.e., induces the antibody, and then the subsequent contacts elicit the allergic response.

Hypersensitivity reactions can be subdivided into four main types. Types I, II, and III are antibody-mediated, whereas type IV is cell-mediated. Type I reactions are mediated by IgE, whereas types II and III are mediated by IgG.

Table 1

Mediator	Type	Reaction
Antibody (IgE)	I (immediate, anaphylactic)	IgE antibody is induced by allergen and binds to mast cells and basophils. When exposed to the allergen again, the allergen cross-links the bound IgE, which induces degranulation and release of mediators, e.g., histamine.
Antibody (IgG)	II (cytotoxic)	Antigens on a cell surface combine with antibody; this leads to complement-mediated lysis, e.g., transfusion or Rh reactions, or autoimmune hemolytic anemia.
Antibody (IgG)	III (immune complex)	Antigen-antibody immune complexes are deposited in tissues, complement is activated, and polymorphonuclear cells are attracted to the site. They release lysosomal enzymes, causing tissue damage.
Cell	IV (delayed)	Helper T lymphocytes sensitized by an antigen release lymphokines upon second contact with the same antigen. The lymphokines induce inflammation and activate macrophages, which, in turn, release various mediators.

13.1 TYPE I: IMMEDIATE (ANAPHYLACTIC) HYPERSENSITIVITY

An immediate hypersensitivity reaction occurs when **antigen binds to IgE on the surface of mast cells** with the consequent **release of several mediators**. The process begins when an antigen induces the formation of IgE antibody, which binds firmly by its Fc portion to basophils and mast cells.

Reexposure to the same antigen results in cross-linking of the cell-bound IgE and release of pharmacologically active mediators within minutes ("immediate reaction").

Cyclic nucleotides and calcium play essential roles in release of the mediators. An increase in cyclic GMP within these cells increases mediator release, whereas an increase in cyclic AMP decreases the release. Therefore, drugs that increase intracellular cyclic AMP, such as epinephrine, are used to treat type I reactions. Epinephrine also has sympathomimetic activity, which is useful in treating type I reactions.

The clinical manifestations of type I hypersensitivity can appear in various forms, e.g., urticaria (also known as hives), eczema, rhinitis and conjunctivitis (also known as hay fever), and asthma. The most severe form is systemic anaphylaxis, in which severe bronchoconstriction and hypotension (shock) can be life-threatening. No single mediator accounts for all the manifestations of type I hypersensitivity reactions. Some **important mediators** and their effects are as follows:

Atopy: Atopic disorders are immediate-hypersensitivity reactions that exhibit a strong familial predisposition and are associated with elevated IgE levels. Several processes seem likely to play a role in atopy, for example, failure of regulation at the T cell level (e.g., increased production of interleukin-4 leads to increased IgE synthesis), enhanced uptake and presentation of environmental antigens, and hyperreactivity of target tissues.

The predisposition to atopy is genetic, and symptoms are induced by exposure to the specific allergens. These antigens are typically found in the environment (e.g., pollens and house dust) or in foods (e.g., shellfish and nuts). Exposure of nonatopic individuals to these substances does not elicit an allergic reaction. Common clinical manifestations include hay fever, asthma, eczema, and urticaria.

Many sufferers give immediate-type reactions to skin tests (injection, patch, or scratch) containing the offending antigen.

The cause of atopy is uncertain. Reduced numbers of suppressor T cells and a predisposition to an abnormally high IgE response have been proposed.

Drug Hypersensitivity Drugs, particularly antimicrobial agents such as penicillin, are now among the most common causes of hypersensitivity reactions. Usually it is not the intact drug that induces antibody formation. Rather, a metabolic product of the drug, which acts as a hapten and binds to a body protein, does so. The resulting antibody can react with the hapten or the intact drug to give rise to type I hypersensitivity. When reexposed to the drug, the person may exhibit **rashes, fevers, or local or systemic anaphylaxis of variable severity**. Reactions to very small amounts of the drug can occur, e.g., in a skin test with the hapten. A clinically useful example is the skin test using penicilloyl-polylysine to reveal an allergy to penicillin.

Desensitization Major manifestations of anaphylaxis occur when large amounts of mediators are suddenly released as a result of a massive dose of antigen abruptly combining with IgE on many mast cells. This is systemic anaphylaxis, which is potentially fatal. Desensitization can prevent systemic anaphylaxis.

Acute desensitization involves the administration of very small amounts of antigen at 15-minute intervals. Antigen-IgE complexes form on a small scale, and not enough mediator is released to produce a major reaction. This permits the administration of a drug or foreign protein to a hypersensitive person, but hypersensitivity is restored days or weeks later.

Chronic desensitization involves the long-term administration at weekly intervals of the antigen to which the person is hypersensitive. This stimulates the production of IgG-blocking antibodies in the serum, which can prevent subsequent antigen from reaching IgE on mast cells, thus preventing a reaction.

Treatment & Prevention of Anaphylactic Reactions Treatment includes drugs to counteract the action of mediators, maintenance of an airway, and support of respiratory and cardiac function. **Epinephrine, antihistamines, corticosteroids, or cromolyn sodium,** either singly or in combination, should be given. Cromolyn sodium prevents release of mediators, e.g., histamine, from mast cell granules. Prevention relies on identification of the allergen by a skin test and avoidance of that allergen.

13.2 TYPE II: CYTOTOXIC HYPERSENSITIVITY

Cytotoxic hypersensitivity occurs when **antibody directed at antigens of the cell membrane activates complement.** This generates a **membrane attack complex, which damages the cell membrane.** The antibody **(IgG or IgM)** attaches to the antigen via the Fab region and acts as a bridge to complement via the Fc region. As a result, there is **complement-mediated lysis as in hemolytic anemias, ABO transfusion reactions, or Rh hemolytic disease**. In addition to causing lysis, complement activation attracts phagocytes to the site, with consequent release of enzymes that damage cell membranes.

Drugs (e.g., penicillins, phenacetin, quinidine) can attach to surface proteins on red blood cells and initiate antibody formation. Such autoimmune antibodies (IgG) then interact with the cell surface and result in **hemolysis.** The direct antiglobulin (Coombs) test is typically positive. Other drugs (e.g., quinine) can attach to platelets and induce autoantibodies that lyse them to produce thrombocytopenia with bleeding tendency. Others (e.g., hydralazine) may modify host tissue and favor the production of autoantibodies directed at cell DNA, with results resembling those of systemic lupus erythematosus.

Certain infections, e.g., Mycoplasma *pneumoniae* infection, can induce antibodies that cross-react with red cell antigens, resulting in hemolytic anemia. **In rheumatic fever**, antibodies against the group A streptococci cross-react with cardiac tissue.

13.3 TYPE III: IMMUNE-COMPLEX HYPERSENSITIVITY

Immune-complex hypersensitivity occurs when **antigen-antibody complexes induce an inflammatory response in tissues.** Normally, immune complexes are promptly removed by the reticuloendothelial system, but **occasionally they persist and are deposited in tissues**, resulting in

several disorders. In persistent microbial or viral infections, immune complexes may be deposited in organs, e.g., the kidneys, resulting in damage. In autoimmune disorders, "self" antigens may elicit antibodies that bind to organ antigens or deposit in organs as complexes, especially in joints (arthritis), kidneys , (nephritis), or blood vessels (vasculitis).

Wherever immune complexes are deposited, they **activate the complement system**. Polymorphonuclear cells are attracted to the site, and inflammation and tissue injury occur. Two typical type III hypersensitivity reactions are the Arthus reaction and serum sickness.

Arthus Reaction If animals are given an antigen repeatedly until they have high levels of IgG antibody and that antigen is then injected subcutaneously or intradermally, intense edema and hemorrhage develop, reaching a peak in 3-6 hours. Antigen, antibody, and complement are deposited in vessel walls; polymorphonuclear cell infiltration and intravascular clumping of platelets then occur. These reactions can lead to vascular occlusion and necrosis. A clinical manifestation of the Arthus reaction is **hypersensitivity pneumonitis (allergic alveolitis)** associated with the inhalation of thermophilic actinomycetes **("farmer's lung").**

Serum Sickness Following the injection of foreign serum (or, more commonly these days, certain drugs), the antigen is excreted slowly. During this time, antibody production starts. The simultaneous presence of antigen and antibody leads to the formation of immune complexes, which may circulate or be deposited at various sites. Typical serum sickness results in fever, urticaria, arthralgia, lymphadenopathy, splenomegaly, and eosinophilia a few days to 2 weeks after injection of the foreign serum or drug.

Immune-Complex Diseases Many clinical disorders associated with immune complexes have been described, although the antigen that initiates the disease is often in doubt. Several representative examples are described below.

A. Glomerulonephritis: Acute poststreptococcal glomerulonephritis is a well-accepted immune-complex disease. Its onset follows several weeks after a group A beta-hemolytic streptococcal infection, particularly of the skin, and often with nephritogenic serotypes of *Streptococcus pyogenes*. Typically, the complement level is low, suggesting an antigen-antibody reaction. Lumpy deposits of immunoglobulin and C3 are seen along glomerular basement membranes by immunofluorescence, suggesting the presence of antigen-antibody complexes. It is assumed that streptococcal antigen-antibody complexes, after being deposited on glomeruli, fix complement and attract neutrophils, which start the inflammatory process.

Similar lesions with "lumpy" deposits containing immunoglobulin and C3 occur in infective endocarditis, serum sickness, and certain **viral infections**, e.g., hepatitis B.

13.4 TYPE IV: DELAYED (CELL-MEDIATED) HYPERSENSITIVITY

Delayed hypersensitivity is a function of **helper (CD4) T lymphocytes**, not antibody. It can be transferred by immunologically committed (sensitized) T cells, not by serum. **The response is "delayed"; i.e., it starts hours (or days) after contact with the antigen** and often lasts for days. It consists mainly of mononuclear cell infiltration (macrophages and helper [CD4] T cells) and tissue induration, as typified by the tuberculin skin test.

Clinically Important Delayed Hypersensitivity Reactions

A. Contact Hypersensitivity: This manifestation of cell-mediated hypersensitivity occurs after sensitization with simple chemicals (e.g., nickel, formaldehyde), plant materials (e.g., poison ivy, poison oak), topically applied drugs (e.g., sulfonamides, neomycin), some cosmetics, soaps, and other substances. In all cases, the small molecules acting as haptens enter the skin, attach to body proteins, and become complete antigens. Cell-mediated hypersensitivity is induced, particularly in the skin. Upon a later skin contact with the offending agent, the sensitized person develops erythema, itching, vesicles, eczema, or necrosis of skin within 12-48 hours. Patch testing on a small area of skin can sometimes identify the offending antigen. Subsequent avoidance of the material will prevent recurrences.

B. Tuberculin-Type Hypersensitivity: Delayed hypersensitivity to antigens of microorganisms occurs in many infectious diseases and has been used as an aid in diagnosis. It is typified by the tuberculin reaction. When a patient previously exposed to *Mycobacterium* tuberculosis is injected with a small amount of tuberculin (PPD) intradermally, there is little reaction in the first few hours. Gradually, however, induration and redness develop and reach a peak in 48-72 hours. A positive skin test indicates that the person has been infected with the agent, but it does not confirm the presence of current disease.

A positive skin test response assists in diagnosis and provides support for chemoprophylaxis or chemotherapy. In systemic mycotic infections (e.g., coccidioido-mycosis and histoplasmosis), a positive skin test with the specific antigen indicates exposure to the organism. Cell-mediated hypersensitivity develops in many viral infections. In protozoan and helminthic infections, skin tests may be positive, but they are generally not as useful as specific serologic tests.