Diseases of the Immune System

Immunity: It is protection against infections.

The immune system is the collection of cells and molecules that are responsible for :-

1- Defending the body against the countless pathogenic microbes in the environment

2- Prevent the proliferation of cancer cells.

3- Mediate the healing of damaged tissue.

Defense against pathogens consists of two types of reactions:-

1-Innate immunity (also called natural, or native immunity) is mediated by **cells** and **proteins** that are always present (for this reason it termed innate) and poised to fight against infectious pathogens. and are called into action immediately in response to infection.

The major components of innate immunity are:-

A- Epithelial barriers of the skin, gastrointestinal tract, and respiratory tract, which prevent microbe entry.

B- Phagocytic leukocytes (neutrophils and macrophages).

C- A specialized cell type called dendritic cells (DCs), and the natural killer (NK) cell .

D- Several circulating plasma proteins, the most important of which are the proteins of the complement system .

Many pathogens have evolved to resist innate immunity, and protection against these infections requires the more specialized and powerful mechanisms called ***adaptive immunity*** .

2- Adaptive immunity (also called acquired or specific immunity):- It is normally silent and responds (or "adapts") to the presence of an infectious microbes by generating potent mechanisms for neutralizing and eliminating the pathogens.

The components of the adaptive immunity are **lymphocytes and their products , including antibodies.**

By convention , the terms "immune system" and "immune response" refer to adaptive immunity.

Diseases of the Immune System

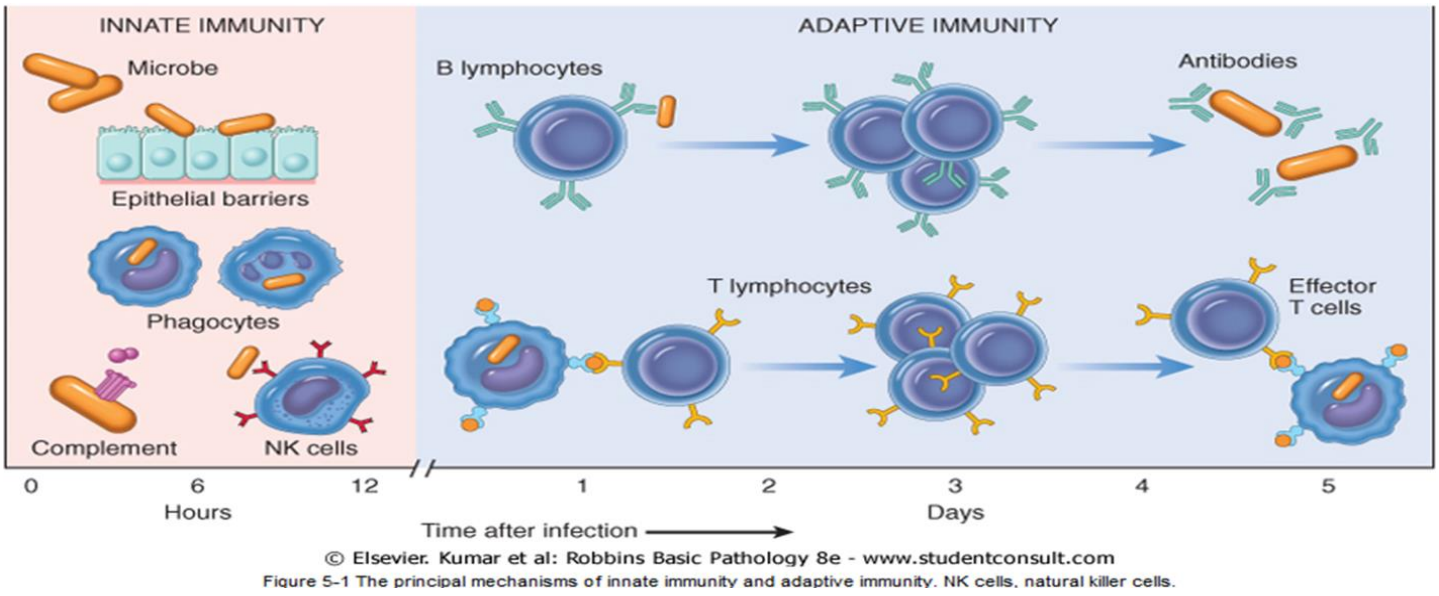

Figure 5-1 The principal mechanisms of innate immunity and adaptive immunity. NK cells, natural killer cells.

Types of adaptive immunity

1-Humoral immunity, mediated by soluble proteins called **antibodies** that are produced by **B lymphocytes** (also called B cells). Antibodies provide protection against **extracellular microbes** in the blood , mucosal secretions, and tissues.

2-Cell-mediated (or cellular) immunity:- mediated by T lymphocytes (also called T cells).

T lymphocytes are important in defense against **intracellular microbes**. They work by either directly killing infected cells (accomplished by **cytotoxic T lymphocytes**) or by activating phagocytes to kill ingested microbes, via the production of soluble protein mediators called **cytokines** (made by **helper T cells**) .

When the immune system is inappropriately triggered or not properly controlled, the same mechanisms that are involved in host defense will cause tissue injury and disease.

The reaction of the cells of innate and adaptive immunity may be manifested as **inflammation** which is a beneficial process, but it is also the basis of many human diseases.

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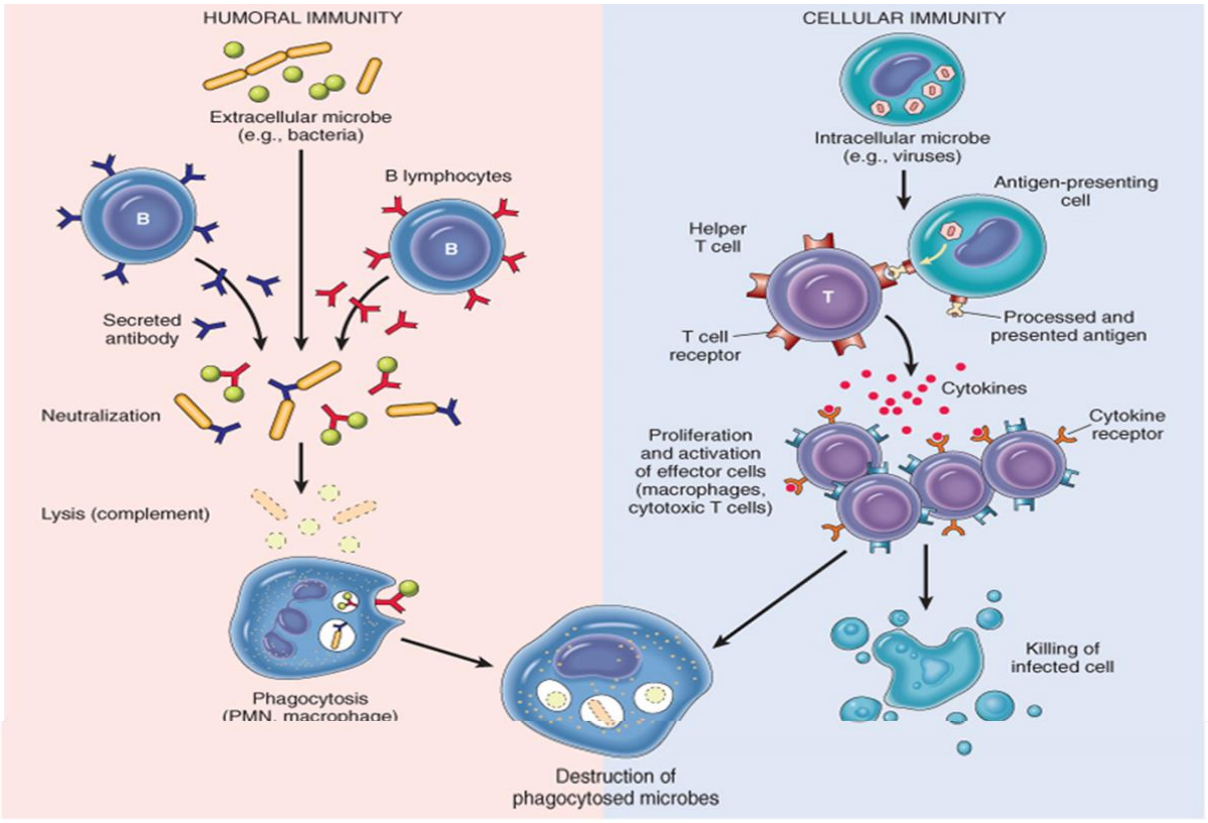

Figure 5-2 Humoral and cell-mediated immunity. In humoral immunity, B lymphocytes secrete antibodies that eliminate extracellular microbes. In cell-mediated immunity, T lymphocytes either activate macrophages to destroy phagocytosed microbes or kill infected cells. PMN, polymorphonuclear leukocyte.

Cells and tissues of the immune system

1- Lymphocytes, which have specific receptors for antigens and mediate adaptive immune responses .

2- Specialized antigen-presenting cells (APCs), which capture and display microbial and other antigens to the lymphocytes .

3- Various effector cells, which eliminate microbes and other antigens .

1- Lymphocytes

Lymphocytes are present in the circulation and in various lymphoid organs. Lymphocytes develop from precursors in the generative lymphoid organs as two types :-

T lymphocytes are so called because they mature in the thymus,

B lymphocytes mature in the bone marrow.

Diseases of the Immune System

Each **T or B lymphocyte** expresses receptors for a single antigen , and the total population of lymphocytes (numbering about 10^{12} in humans) is capable of recognizing tens or hundreds of millions of antigens .

T Lymphocytes

Thymus-derived lymphocytes (T lymphocytes) develop into the effector cells of cellular immunity and "help" B cells to produce antibodies against the antigens .

T cells constitute 60% to 70% of the lymphocytes in peripheral blood and are the major lymphocyte population in splenic periarteriolar sheaths and lymph node interfollicular zones .

T cells cannot recognize free or circulating antigens; instead, the vast majority (>95%) of T cells sense only peptide fragments of proteins displayed by molecules of the major histocompatibility complex (MHC) or Human Leukocyte Antigen [HLA] complex).The MHC was discovered on the basis of studies of graft rejection or acceptance (tissue, or "histo," compatibility) .

The normal function of MHC molecules is to display peptides for recognition by T lymphocytes. thus perform their function of killing infected cells or activating phagocytes that have ingested protein antigens or B lymphocytes to produce antibodies.

B Lymphocytes

Bone marrow-derived lymphocytes (B, lymphocytes) are the effector cells of humoral immunity. the cells that produce antibodies, the mediators of humoral immunity .

B cells make up 10% to 20% of the circulating peripheral lymphocyte population . They are also present in bone marrow and in the follicles of peripheral (secondary) lymphoid organs (lymph nodes, spleen, tonsils, and other mucosal tissues).

After stimulation, B cells differentiate into ***plasma cells***, which secrete large amounts of antibodies There are five classes of immunoglobulins : IgG, IgM, IgA, IgE ,and IgD .

Natural Killer Cells

Natural killer (NK) cells are lymphocytes that arise from the common lymphoid progenitor that gives rise to T and B lymphocytes. NK cells are cells of innate immunity and have limited set of receptors. Therefore, . they do not have specificities as diverse as do T cells or B cells.

NK cells have two types of receptors—inhibitory and activating.

-The inhibitory receptors recognize self class I MHC molecules, which are expressed on all healthy cells .

-The activating receptors recognize molecules that are expressed on stressed or infected cells or cells with DNA damage .

Normally, the effects of the inhibitory receptors dominate over those of the activating receptors, thereby preventing activation of the NK cells. Infections (especially viral infections) releasing the NK cells from inhibition. The net result is that the NK cells are activated and kill and eliminate the infected or stressed cells .

2-Antigen-Presenting Cells (APCs)

These cells are specialized to capture microbial antigens and display them to lymphocytes. these cells are **Dendritic cells (DCs)** and **macrophages**.

1-Dendritic Cells

These cells have numerous fine cytoplasmic processes that resemble dendrites, from which they derive their name.

A- Interdigitating DCs, are non phagocytic cells that function to capture and present antigens to T cells .

These cells are located under epithelia, the common site of entry of microbes and foreign antigens and in the interstitia of all tissues, where antigens may be produced. DCs within the epidermis are **called Langerhans cells**.

DCs are present in the T-cell zones of lymphoid tissues, where they present antigens to T cells . DCs are also present in non lymphoid organs, such as the heart and lungs, where they are capture the microbes that have invaded the tissues .

B- follicular dendritic cells (FDCs). They are present in lymphoid follicles in the spleen and lymph nodes. These cells display antigens to activated B lymphocytes in lymphoid follicles and promote antibody responses .

2-Macrophages ingest microbes and other particulate antigens and display them for recognition by T lymphocytes. These T cells in turn activate the macrophages to kill the microbes, the central reaction of cell-mediated immunity.

Diseases of the Immune System

3-Effector Cells

Many different types of leukocytes perform the ultimate task of the adaptive immune response, which is to eliminate infections. These include :-

1- NK cells are front- line effector cells because of their ability to rapidly react against "stressed" cells .

2- Antibody-secreting plasma cells are effector cells of humoral immunity.

3-T lymphocytes, both CD4+ helper T cells and CD8+ CTLs cytotoxic T cells, are effector cells of cell-mediated immunity. These lymphocytes secrete **cytokines** that recruit and activate other leukocytes, such as neutrophils and eosinophils, which will function in defense against various pathogens.

4- Macrophages, bind microbes that are coated with antibodies or complement, and phagocytose and destroy these microbes , thus serving as effector cells of **humeral immunity**. Macrophages also respond to signals from helper T cells and improve their ability to destroy phagocytosed microbes , thus serving as effector cells of **cellular immunity.**

Lymphoid Tissues

The lymphoid tissues of the body are divided into:-

1- Generative (primary) organs, where lymphocytes express antigen receptors and mature . these include thymus and bone marrow .

2- Peripheral (secondary) lymphoid organs, where adaptive immune responses develop. the peripheral organs are the lymph nodes, spleen, and mucosal and cutaneous lymphoid tissues .

HYPERSENSITIVITY DISEASES

Under normal conditions , the immune response prevents disease , but occasionally ,the inapproperiate activation of the immune system can lead to debilitating or life-threatening illness like :-

1- Allergic or hypersensitivity reactions.

2- Transplantation immunopathology.

3-Autoimmune disorders .

4- Immunodeficiency disorders .

Causes of Hypersensitivity Diseases

1-*Autoimmunity.* Normally, the immune system does not react against an individual's own antigens. This phenomenon is called ***self-tolerance***. Sometimes, self-tolerance fails, resulting in reactions against one's own cells and tissues that are called ***autoimmunity***. The diseases caused by autoimmunity are referred to as ***autoimmune diseases***.

2- *Reactions against microbes.* If the reactions against microbial antigens is sever or the microbial antigen is persistent. The excessive antibodies bind to the microbial antigens and produce immune complexes, which deposit in tissues and trigger inflammation; as in *poststreptococcal glomerulonephritis* .T-cell responses against persistent microbes may give rise to severe inflammation, as in tuberculosis and other infections . In *viral hepatitis,* the virus that infects liver cells is not cytopathic but it is recognized as foreign by the immune system. Cytotoxic T cells eliminate the infected cells, and this normal immune response damages liver cells .

3- Reactions against environmental antigens. Most healthy individuals do not react against common environmental substances (e.g., pollens, animal danders , or dust mites), but almost 20% of the population is "allergic" to these substances.

1- Allergic or hypersensitivity reactions

Hypersensitivity it is define as an exaggerated immune response to a foreign antigen resulting in injury to the host . its caused by **exogenous environmental antigens** called **allergens** such as dust , pollen , drug , foods , microbes ,and chemicals or **endogenous self-antigens also called autoimmune disease**.

Allergens Any foreign substances capable of inducing an immune response . many different chemicals of natural and synthetic origin are known as allergens. exposure to allergen can be through inhalation , ingestion ,injection ,or skin contact .

Hypersensitivity reactions are four types :-

1-Immediate (type I) hypersensitivity.

2-Antibody-mediated disorders (type II hypersensitivity).

3-Immune complex–mediated disorders (type III hypersensitivity)

4-T cell–mediated disorders (type IV hypersensitivity) .

1- immediate (Type I) Hypersensitivity (often called allergy)

Immediate hypersensitivity is a tissue reaction that occurs rapidly (typically within minutes) after the interaction of antigen with **IgE** antibody that is bound to the surface of mast cells in a sensitized host .

The reaction is initiated by entry of an antigen, which is called an allergen because it triggers allergy. Many allergens are environmental substances that are harmless for most persons on exposure. Some people apparently inherit genes that make them susceptible to allergies .

Immediate hypersensitivity may occur as a local reaction that is merely annoying (e.g., seasonal rhinitis, or hay fever), severely debilitating (asthma), or even fatal (anaphylaxis).

Diseases of the Immune System

- **Activation of TH2 cells and production of IgE antibody**

Allergens may be introduced by inhalation, ingestion, or injection.

T helper 2 (TH2) cells are recruited to the site of allergic reactions in response to chemokines that are produced locally called **eotaxin** , which also recruits eosinophils to the same site.

The TH2 cells are secrete several cytokines, including IL-4, IL-5, and IL-13, which are responsible for all the reactions of immediate hypersensitivity . IL-4 stimulates B cells to produce IgE . IL-5 activates eosinophils that are recruited to the reaction, and IL-13 acts on epithelial cells and stimulates mucus secretion.

- **Sensitization of mast cell by IgE antibody** Mast cell are derived from blood precursor cells in the bone marrow . mast cells are distributed throughout connective tissue , near surfaces that exposed to environmental antigens especially in areas beneath the skin and mucous membranes of respiratory , gastrointestinal , and genetourinary tracts ,and adjacent to blood and lymph vessels .

Mast cells express a high-affinity receptor for the Fc portion of the of IgE, called FcεRI.

- **Activation of mast cells** Mast cells have granules that contain potent mediator of allergic reactions . during the sensitization , the allergen specific IgE antibodies attach to receptors on these mast cells triggers a series of events that lead to **degranulation** of the sensitized mast cells , causing release of their allergy producing mediators which include :-

1- Histamine a potent vasodilator that increase the permeability of capillaries and venules , smooth muscle contraction, and increased secretion of mucous .

2- Adenosine (which causes bronchoconstriction and Inhibits platelet aggregation) and chemotactic factors for neutrophils and eosinophils .

3- Proteases which may damage tissues , cleave complement components to produce additional chemotactic and inflammatory mediator .

4- Acetylcholine produce bronchial smooth muscle contraction and dilation of small blood vessels .

5-Prostaglandin and leukotrienes is the most abundant mediator generated by mast cells. It produce responses similar to histamine and acetylcholine .

6- Cytokines. These include TNF and chemokines, which recruit and activate leukocytes .

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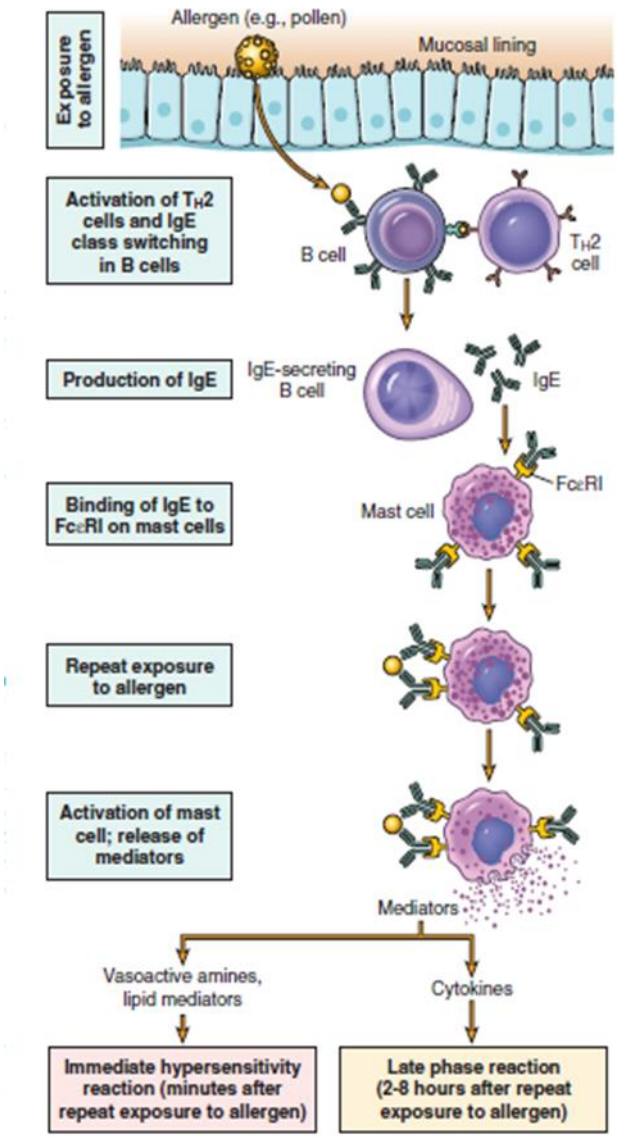

Sequence of events in immediate (type I) hypersensitivity. Immediate hypersensitivity reactions are initiated by the introduction of an allergen, which stimulates TH2 responses and IgE production. IgE bindsto Fc receptors (FcεRI) on mast cells, and subsequent exposure to the allergen activates the mast cells to secrete the mediators .

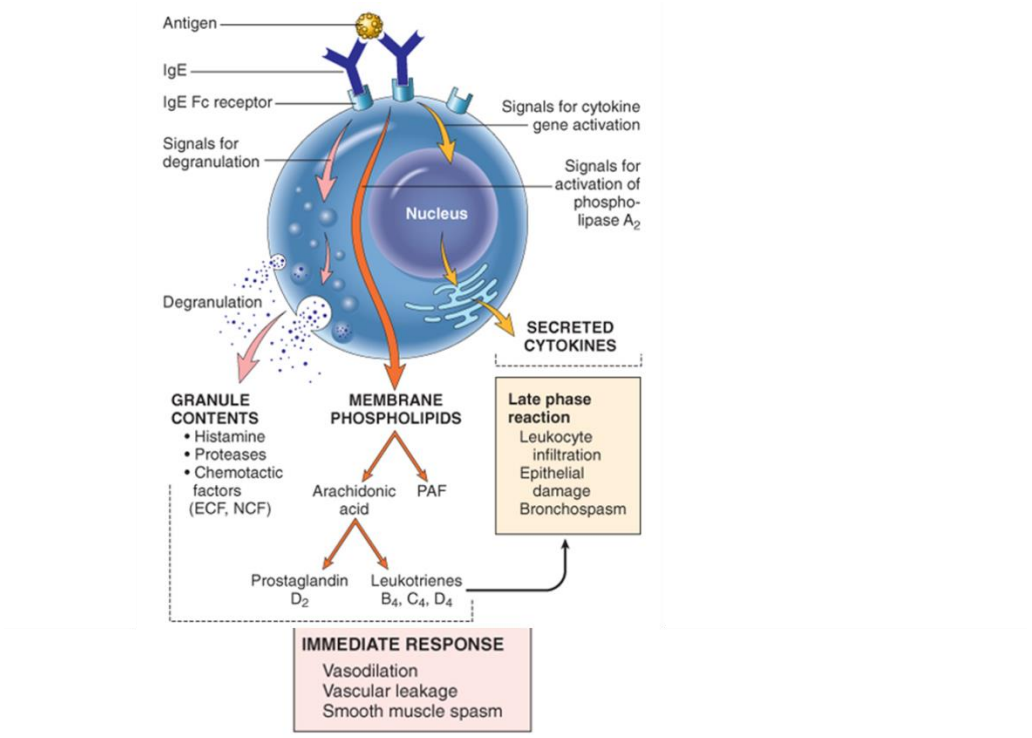

Figure 5-9 Mast cell mediators. Upon activation, mast cells release various classes of mediators that are responsible for the immediate and late-phase reactions. ECF, eosinophil chemotactic factor; NCF, neutrophil chemotactic factor (neither of these has been biochemically defined); PAF, platelet-activating factor.

Clinical and Pathologic Manifestations

Type I hypersensitivity reactions may present as a systemic reaction (anaphylaxis) or localized reaction (atopy) .

- Systemic anaphylactic reactions

Result from parenteral administration (injection) of protein antigens as bee venom or drugs (e.g., penicillin)

May also result from ingested allergens (seafood , nuts , and legumes).

Signs and symptoms

anaphylaxis has rapid onset (within minutes), there will be :-

1- itching

2-urticaria .

3- skin erythema appear

4- respiratory difficulty caused by pulmonary bronchoconstriction and hypersecretion of mucus.

5- Laryngeal edema may causing upper airway obstruction.

6- Vomiting, abdominal cramps, and diarrhea .

7- , there may be systemic vasodilation with fall in blood pressure *(anaphylactic shock),* and death within minutes.

-***Local reactions (atopic)***

occur when the antigen is confined to a particular site, usually related to the route of exposure such as skin (contact, causing urticaria), gastrointestinal tract (ingestion, causing diarrhea), or lung (inhalation, causing bronchoconstriction). The common forms of atopic reaction are food allergies, hay fever, and certain forms of asthma .

The term ***atopy*** is used to imply familial predisposition to such localized reactions.

Type I hypersensitivity reactions plays an important protective role in parasitic infections. IgE antibodies are produced in response to many helminthic infections, and their physiologic function is to target helminths for destruction by eosinophils and mast cells.