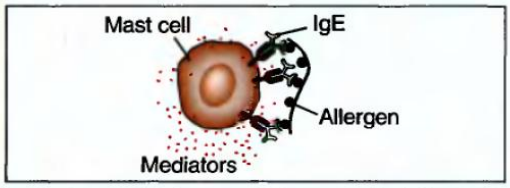
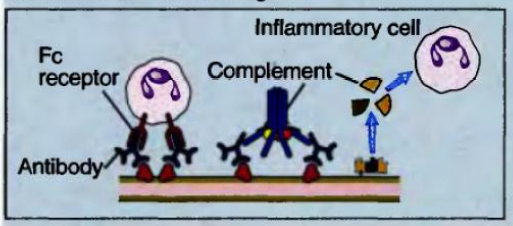
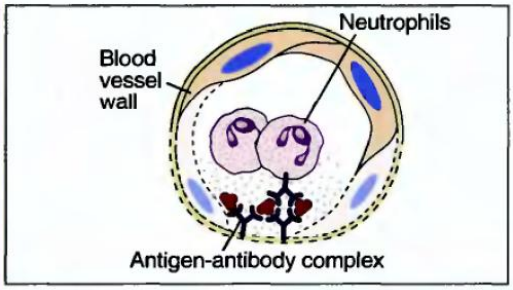
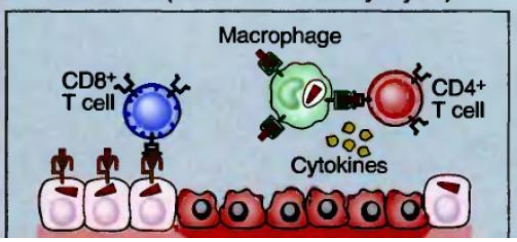
Hyper sensitivity diseases (reactions):

This term is derived from the idea that an immune response to an antigen may result in sensitivity to challenge with that antigen and, therefore, hypersensitivity is a reflection of excessive or aberrant immune responses.

Types of hypersensitivity diseases:

Hypersensitivity diseases are commonly classified on the basis of principal immunologic mechanism that is responsible for tissue injury and disease:

1. Immediate hypersensitivity (type I hypersensitivity): is a type of pathologic reaction that is caused by the release of mediators from mast cells. This reaction is most commonly triggered by production of IgE antibody against environmental antigens and the binding of IgE to mast cells in various tissues.
2. Antibody–mediated hypersensitivity (type II hypersensitivity): Antibodies **other than IgE** directed against **cell or tissue antigens** can damage these cells or tissues or impair their functions.
3. Immune complex diseases (type III hypersensitivity): Antibodies **(other than IgE)**directed against **soluble antigen** may form complexes with the antigens, and these immune complexes may deposit in blood vessels in various tissues and cause inflammation and tissue injury.
4. T cell-mediated diseases (type IV hypersensitivity): result from reaction of T cells against self antigens in tissues.

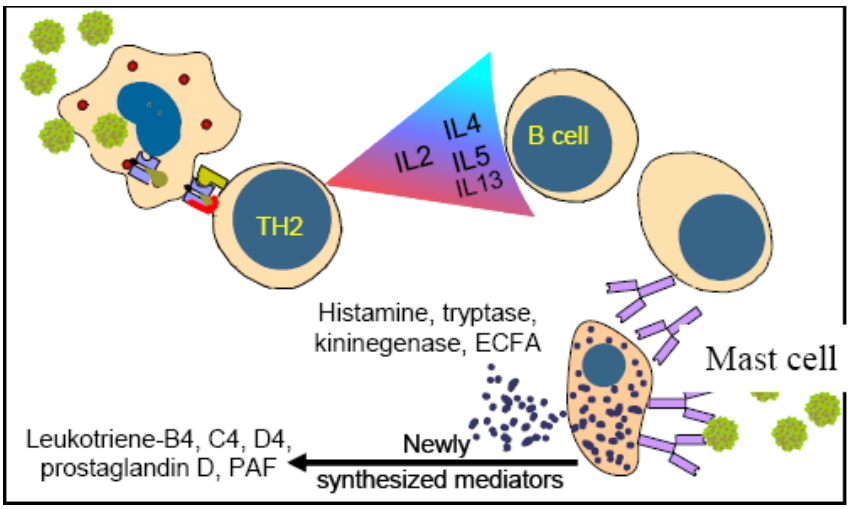
Type of hypersensitivity	Pathologic immune mechanisms	Mechanisms of tissue injury and disease
Immediate hypersensitivity (Type I)	T_H2 cells, IgE antibody, mast cells, eosinophils 	Mast cell–derived mediators (vasoactive amines, lipid mediators, cytokines) Cytokine-mediated inflammation (eosinophils, neutrophils)
Antibody-mediated diseases (Type II)	IgM, IgG antibodies against cell surface or extracellular matrix antigens 	Complement- and Fc receptor–mediated recruitment and activation of leukocytes (neutrophils, macrophages) Opsonization and phagocytosis of cells Abnormalities in cellular function, e.g., hormone receptor signaling
Immune complex–mediated diseases (Type III)	Immune complexes of circulating antigens and IgM or IgG antibodies deposited in vascular basement membrane 	Complement and Fc receptor-mediated recruitment and activation of leukocytes
T cell–mediated diseases (Type IV)	1. $CD4^+$ T cells (delayed-type hypersensitivity) 2. $CD8^+$ CTLs (T cell–mediated cytolysis) 	1. Macrophage activation, cytokine-mediated inflammation 2. Direct target cell lysis, cytokine-mediated inflammation

Type I Hypersensitivity

It is also known as **immediate** or **anaphylactic** hypersensitivity. The reaction may involve skin (urticaria and eczema), eyes (conjunctivitis), nasopharynx (rhinorrhea, rhinitis), bronchopulmonary tissues (asthma) and gastrointestinal tract (gastroenteritis).

Clinical syndrome	Clinical and pathologic manifestations
Allergic rhinitis, sinusitis (hay fever)	Increased mucus secretion; inflammation of upper airways, sinuses
Food allergies	Increased peristalsis due to contraction of intestinal muscles
Bronchial asthma	Bronchial hyper-responsiveness caused by smooth muscle contraction; inflammation and tissue injury caused by late phase reaction
Anaphylaxis (may be caused by drugs, bee sting, food)	Fall in blood pressure (shock) caused by vascular dilatation; airway obstruction due to laryngeal edema

The type I hypersensitivity reaction may cause from minor inconvenience to death. The reaction takes 15-30 minutes from the time of exposure to the antigen **(allergens)**. Sometimes the reaction may have a delayed onset (10-12 hours).



The precise mechanism as to why some individuals are more prone to type-I hypersensitivity is not clear. However, it has been shown that such individuals preferentially produce more of TH2 cells that secrete IL-4, IL-5 and IL-13 which in turn favor IgE class switch. IgE has very high affinity for its receptor (Fcε; CD23) on mast cells and basophils. A subsequent exposure to the same allergen cross links the cell-bound IgE and triggers the release of various pharmacologically active substances (Figure 1). Cross-linking of IgE Fc-receptor is important in mast cell triggering. Mast cell degranulation is preceded by increased **Ca++ influx**,

which is a crucial process; ionophores which increase cytoplasmic Ca++ also promote degranulation of mast cells, whereas, agents which deplete cytoplasmic Ca++ suppress degranulation.

TABLE 15-3 Principal mediators involved in type I hypersensitivity

Mediator	Effects
	PRIMARY
Histamine, heparin	Increased vascular permeability; smooth muscle contraction
Serotonin (rodents)	Increased vascular permeability; smooth muscle contraction
Eosinophil chemotactic factor (ECF-A)	Eosinophil chemotaxis
Neutrophil chemotactic factor (NCF-A)	Neutrophil chemotaxis
Proteases (tryptase, chymase)	Bronchial mucus secretion; degradation of blood vessel basement membrane; generation of complement split products
	SECONDARY
Platelet-activating factor	Platelet aggregation and degranulation; contraction of pulmonary smooth muscles
Leukotrienes (slow reactive substance of anaphylaxis, SRS-A)	Increased vascular permeability; contraction of pulmonary smooth muscles
Prostaglandins	Vasodilation; contraction of pulmonary smooth muscles; platelet aggregation
Bradykinin	Increased vascular permeability; smooth muscle contraction
Cytokines	
IL-1 and TNF-α	Systemic anaphylaxis; increased expression of CAMs on venular endothelial cells
IL-4 and IL-13	Increased IgE production
IL-3, IL-5, IL-6, IL-10, TGF-β, and GM-CSF	Various effects (see Table 12-1)

Table 15-3
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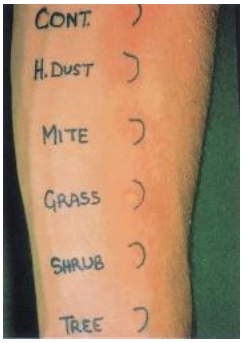
Diagnosis:

1. skin tests (prick and intradermal) resulting in wheal and flare reaction.
2. Radioimmunosorbent test (RIST) can quantify nanogram amounts of total serum IgE
3. Radioallergosorbent test (RAST) can quantify nanogram amounts of serum IgE specific for a particular allergen

Increased IgE levels are indicative of atopic condition, although IgE may be elevated in some non atopic diseases (*e.g.*, myelomas, helminthic infection, *etc.*).

4. HLA typing: There are genetic predisposition for atopic diseases and there is evidence for HLA (A2) association.



Treatment:

1. Antihistamines that block histamine receptors.
2. Immunotherapy: includes;

a) IgG antibodies against the Fc portions of IgE that binds to mast cells has been approved for treatment of certain allergies, as it can block mast cell sensitization.

b) Hyposensitization: repeated administration of increases doses of allergens. Such repeated introduction of allergen by subcutaneous injections appears to cause a shift toward IgG production or to induce T-cell–mediated suppression (possibly by a shift to the TH1 subset and IFN-γ production) that turns off the IgE response. In this situation, the IgG antibody is referred to as *blocking antibody* because it competes for the allergen, binds to it, and forms a complex that can be removed by phagocytosis; as a result, the allergen is not available to crosslink the fixed IgE on the mast-cell membranes, and allergic symptoms decrease

Type II Hypersensitivity

It is also known as **cytotoxic hypersensitivity** and may affect a variety of organs and tissues. The antigens are normally endogenous, although exogenous chemicals (haptens) that can attach to cell membranes can also lead to type II hypersensitivity. The reaction time is minutes to hours. It is mediated, primarily, by antibodies of IgM or IgG class and complement. Phagocytes and NK cells may also play a role.

Diagnosis:

1. Detection of circulating antibody against tissues involved
2. The presence of antibody and complement in the lesion (biopsy) by immunofluorescence.

Treatment:
Anti-inflammatory and immunosuppressive agents.

Examples of type II hypersensitivity reaction include:

1. **Transfusion reaction**

If a type A individual is transfused with blood containing type B cells, a **transfusion reaction** occurs in which the anti-B isohemagglutinins bind to the B blood cells and mediate their destruction by means of complement-mediated lysis The clinical manifestations of transfusion reactions result from massive intravascular hemolysis of the transfused red blood cells by antibody plus complement. These manifestations may be either immediate or delayed. Reactions that begin immediately are most commonly associated with ABO blood-group incompatibilities, which lead to complement mediated lysis triggered by the IgM isohemagglutinins. Within hours, free hemoglobin can be detected in the plasma; it is filtered through the kidneys, resulting in hemoglobinuria. Some of the hemoglobin gets converted to bilirubin, which at high levels is toxic.
Delayed hemolytic transfusion reactions generally occur in individuals who have received repeated transfusions of ABO-compatible blood that is incompatible for other blood group antigens. The reactions develop between 2 and 6 days after transfusion, reflecting the secondary nature of these reactions. The transfused blood induces clonal selection and production of IgG against a variety of blood-group membrane antigens. The predominant isotype involved in these reactions is IgG, which is less effective than IgM in activating complement. For this reason, complement-mediated lysis of the transfused red blood cells is incomplete, and many of the transfused cells are destroyed at extravascular sites by agglutination, opsonization, and subsequent phagocytosis by macrophages.

2. **Hemolytic disease of newborn**

Hemolytic disease of the newborn develops when maternal IgG antibodies specific for fetal blood-group antigens cross the placenta and destroy fetal red blood cells. The consequences of such transfer can be minor, serious, or lethal. Severe hemolytic disease of the newborn, called **erythroblastosis fetalis,** most commonly develops when an Rh+ fetus

expresses an **Rh antigen** on its blood cells that the Rh– mother does not express.

A rise in the titer of these antibodies as pregnancy progresses indicates that the mother has been exposed to Rh antigens and is producing increasing amounts of antibody. The presence of maternal IgG on the surface of fetal red blood cells can be detected by a Coombs test.

3. **Drug-induced hemolytic anemia, are such examples**.

Certain antibiotics (e.g., penicillin, cephalosporin, and streptomycin) can absorb nonspecifically to proteins on RBC membranes, forming a complex similar to a hapten-carrier complex. In some patients, such drug-protein complexes induce formation of antibodies, which then bind to the adsorbed drug on red blood cells, inducing complement mediated lysis and thus progressive anemia. When the drug is withdrawn, the hemolytic anemia disappears

Type III Hypersensitivity

Also known as (**immune complex hypersensitivity)**. It is mediated by the deposition of antigen–antibody complexes. The complexes fix complement to release the anaphylatoxin products C3a and C5a. These induce the release of vasoactive amines from basophils, and chemotactic factors that attract platelets and other inflammatory cells, especially neutrophils.

Examples:

1. **Arthus reaction**, named after its discoverer.

Injection of an antigen intradermally or subcutaneously into an animal that has high levels circulating antibody specific for that antigen leads to formation of localized immune complexes, which mediate an acute Arthus reaction within 4–8 h (Figure 16-15).Microscopic examination of the tissue reveals neutrophils adhering to the vascular endothelium and then migrating into the tissues at the site of immune complex deposition. As the reaction develops, localized tissue and vascular damage results in an accumulation of fluid (edema) and red blood cells (erythema) at the site.The severity of the reaction can vary from mild swelling and redness to tissue necrosis

2. **Serum sickness** is a systemic type of type III hypersensitivity.

It was most frequently caused by multiple injections of antiserum such as antipneumococcal or antidiphtheria in the era before antibiotics became available. Antibodies against the foreign serum proteins developed and immune complexes caused inflammation in the joints and skin and the glomeruli of the kidney.

3. **systemic lupus erythematosus (SLE)**:

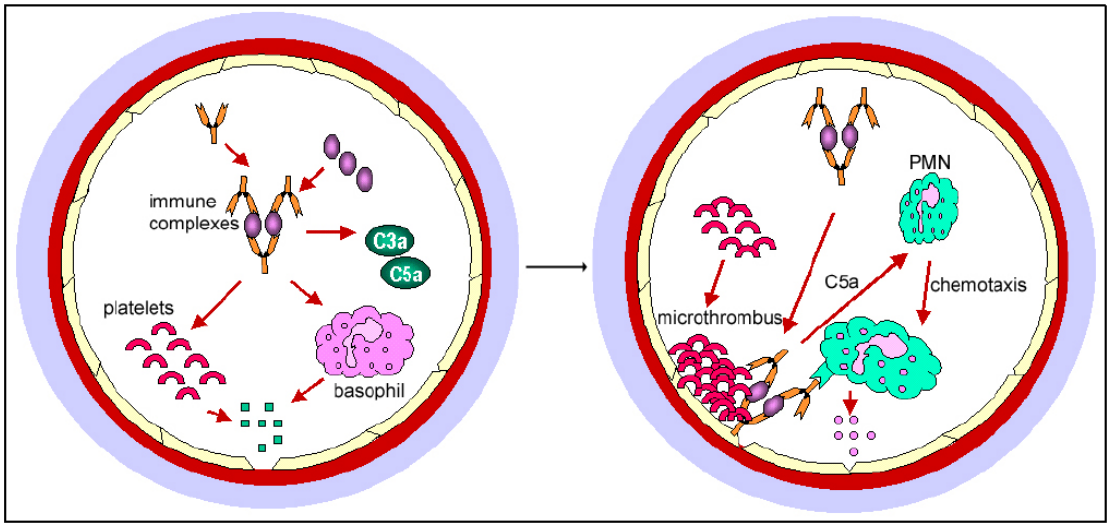
Is a systemic autoimmune diseases, especially. In this disease antibodies are formed to many antigens, including nuclear proteins and single- and double-stranded DNA. The autoantibodies cause nephritis due the deposition of complexes in the basement membrane of the glomeruli and vasculitis, thrombosis and pleurititis.

Intrapulmonary Arthus-type reactions induced by bacterial spores, fungi, or dried fecal proteins can also cause pneumonitis or alveolitis. These reactions are known by a variety of common names reflecting the source of the antigen. For example, “farmer’s lung” develops after inhalation of thermophilic actinomycetes from moldy hay, and “pigeon fancier’s disease” results from inhalation of a serum protein in dust derived from dried pigeon feces.

Diagnosis:

1. Examination of tissue biopsies for deposits of Ig and complement by immunofluorescence.
2. Presence of immune complexes in serum and depletion in complement level are also diagnostic.

Treatment: anti-inflammatory agents.



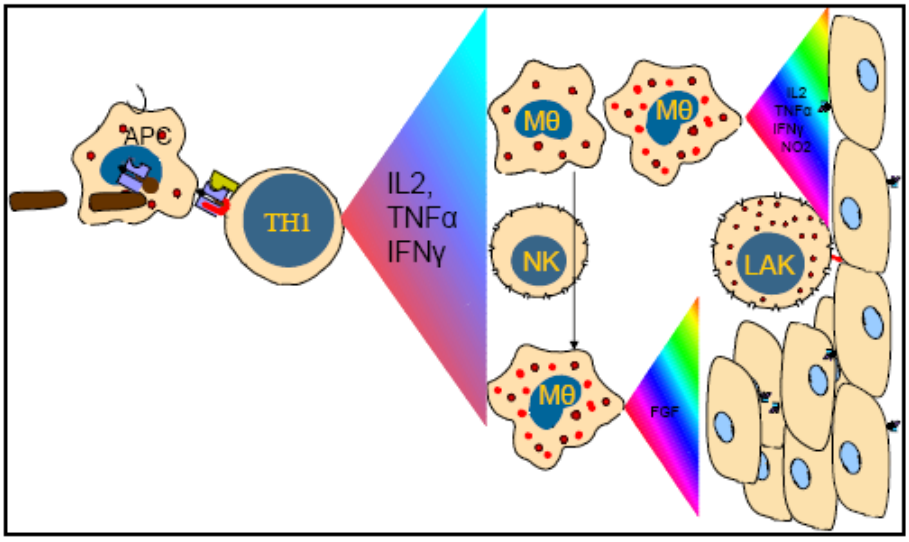
Type IV Hypersensitivity

It is also known as **cell mediated** or **delayed type hypersensitivity**. The classical example of this hypersensitivity is **tuberculin** (**Montoux**) reaction that peaks 48 hours after the injection of antigen (PPD or old tuberculin). The lesion is characterized by induration and erythema.

Type IV hypersensitivity is involved in the pathogenesis of many autoimmune and infectious diseases (tuberculosis, leprosy, blastomycosis, histoplasmosis, toxoplasmosis, leishmaniasis, *etc.*) and granulomas due to infections and foreign antigens. Another form of delayed hypersensitivity is **contact dermatitis** (poison ivy, chemicals, heavy metals, *etc.*) in which the lesions are more papular. Type IV hypersensitivity can be classified into three categories depending on the time of onset and clinical and histological presentation.

type	reaction time	clinical appearance	histology	antigen and site
contact	48-72 hr	eczema	lymphocytes, followed by macrophages; edema of epidermis	epidermal (organic chemicals, poison ivy, heavy metals, *etc.*)
tuberculin	48-72 hr	local induration	lymphocytes, monocytes, macrophages	intradermal (tuberculin, lepromin, *etc.*)
granuloma	21-28 days	hardening	macrophages, epitheloid and giant cells, fibrosis	persistent antigen or foreign body presence (tuberculosis, leprosy, *etc.*)

Mechanisms of damage in delayed hypersensitivity include T lymphocytes and monocytes and/or macrophages. The pathogenesis is triggered primarily by helper T (TH1) cells that secrete cytokines that activate and recruit macrophages, which cause the bulk of the damage.



Major lymphokines involved in delayed hypersensitivity reaction include monocyte chemotactic factor, interleukin-2, interferon-γ, TNF α, *etc.*

Diagnosis:
Delayed cutaneous reaction (*e.g.* Montoux test) and patch test (for contact dermatitis).

Treatment: Corticosteroids and other immunosuppressive agents

Comparative summary of all four types of hypersensitivity reactions

characteristics	type-I (anaphylactic)	type-II (cytotoxic)	type-III (immune complex	type-IV (delayed type)
antibody	IgE	IgG, IgM	IgG, IgM	None
antigen	exogenous	cell surface	soluble	tissues & organs
response time	15-30 minutes	minutes-hours	3-8 hours	48-72 hours
appearance	wheal & flare	lysis and necrosis	erythema and edema, necrosis	erythema and induration
histology	basophils and eosinophil	antibody and complement	complement and neutrophils	macrophages and T cells
transferred with	antibody	antibody	antibody	T-cells
examples	allergic asthma, hay fever	erythroblastosis fetalis, Goodpasture's nephritis	SLE, farmer's lung disease	tuberculin test, poison ivy, granuloma