Hypersensitivity reactions

In 1964, Gell and Coombs proposed a classification scheme in which hypersensitive reactions are divided into four types. Three types of hypersensitivity occur within the humoral branch and are mediated by antibody or antigen-antibody complexes: IgE-mediated (type I), antibody-mediated (type II), and immune complex– mediated (type III). A fourth type of hypersensitivity depends on reactions within the cell-mediated branch, and is termed delayed-type hypersensitivity, or DTH (type IV).

Hypersensitivity refers to is the term used when an immune response results in inappropriate reactions harmful to the host. Hypersensitivity reactions require a pre-sensitized (immune) state of the host.

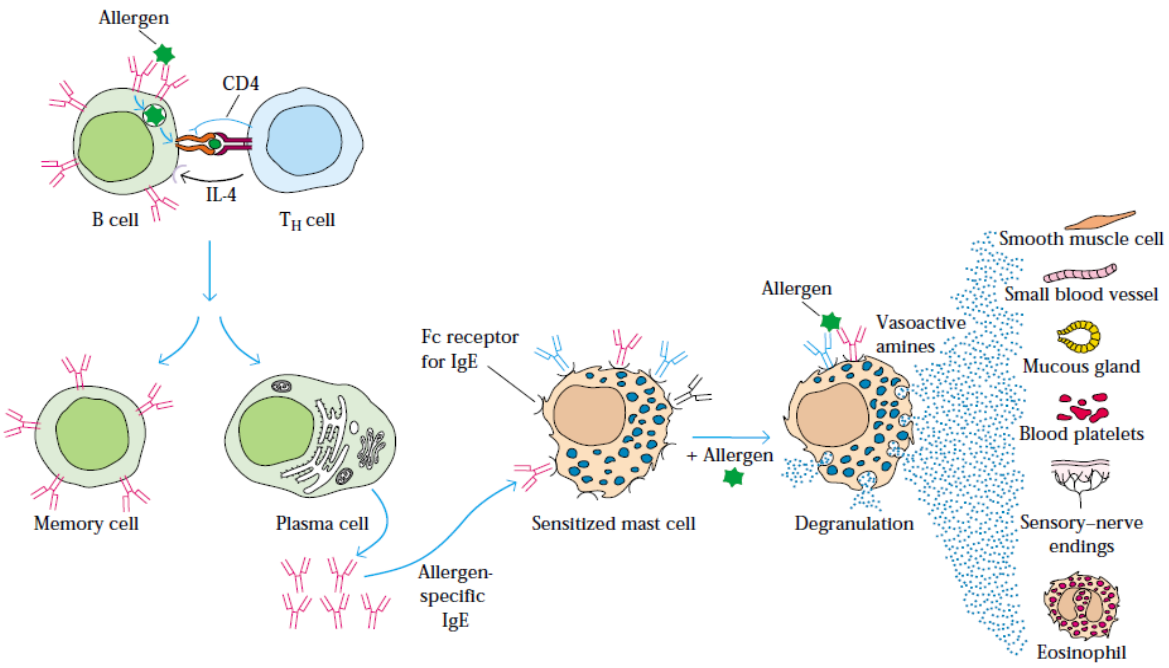
Allergy : was used initially to describe the outcome of the response to an antigen on second exposure for individual sensitized .

Allergen (i.e. allergy generating) which characterise the clinical signs and symptoms an allergic response.

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).

The reaction may cause from minor inconvenience to death. The reaction takes 15-30 minutes from the time of exposure to the antigen. Sometimes the reaction may have a delayed onset (10-12 hours). Immediate hypersensitivity is mediated by IgE. The primary cellular component in this hypersensitivity is mast cell or basophil. The reaction is amplified and/or modified by platelets, neutrophils and eosinophils. The mechanism of reaction involves production of IgE, in response to certain antigens, allergens . IgE has very high affinity for its receptor 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 . Cross-linking of IgE Fc-receptor is important in mast cell triggering. Mast cell degranulation is preceded by increased Ca++ influx.



Mediator	Action	Signs/Symptoms
Histamine	Vasodilatation	Pruritis, edema, wheezing, diarrhea, hypotension
Leukotrienes	Bronchoconstriction	Wheezing
Platelet-activating factor	Bronchoconstriction, vasodilatation	Wheezing, hypotension
C3a, C5a	Smooth muscle contraction, vasodilatation	Wheezing, hypotension
Tryptase	Proteolysis	Edema, smooth muscle contraction

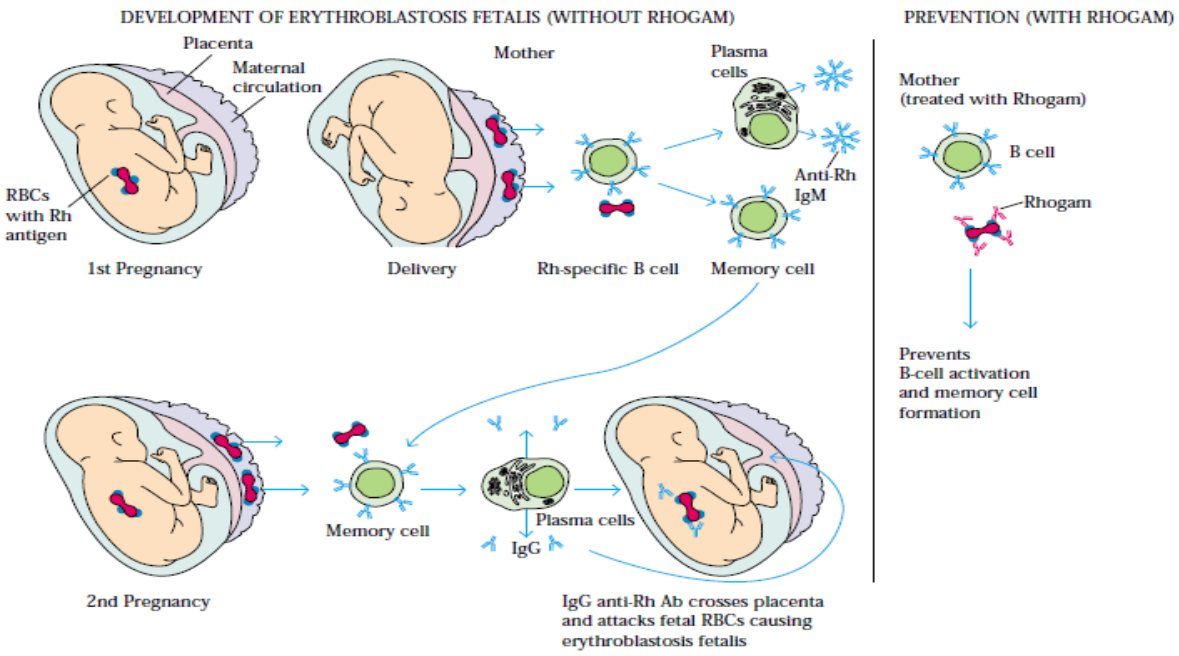
Diagnostic tests for immediate hypersensitivity include skin tests, measurement of total IgE and specific IgE antibodies against the suspected allergens. Total IgE and specific IgE antibodies are measured by a 3 modification of enzyme immunoassay (ELISA). Increased IgE levels are indicative of atopic condition, although IgE may be elevated in some non atopic diseases .

Symptomatic treatment is achieved with antihistamines which block histamine receptors. Chromolyn sodium inhibits mast cell degranulation, probably, by inhibiting Ca++ influx.

Hyposensitization (immunotherapy or desensitization) is another treatment modality which is successful in a number of allergies, particularly to insect venoms and, to some extent, pollens. The mechanism is not clear, but there is a correlation between appearance of IgG (blocking) antibodies and relief from symptoms. specifically inhibit IgE antibodies may play a role.

Type II Hypersensitivity

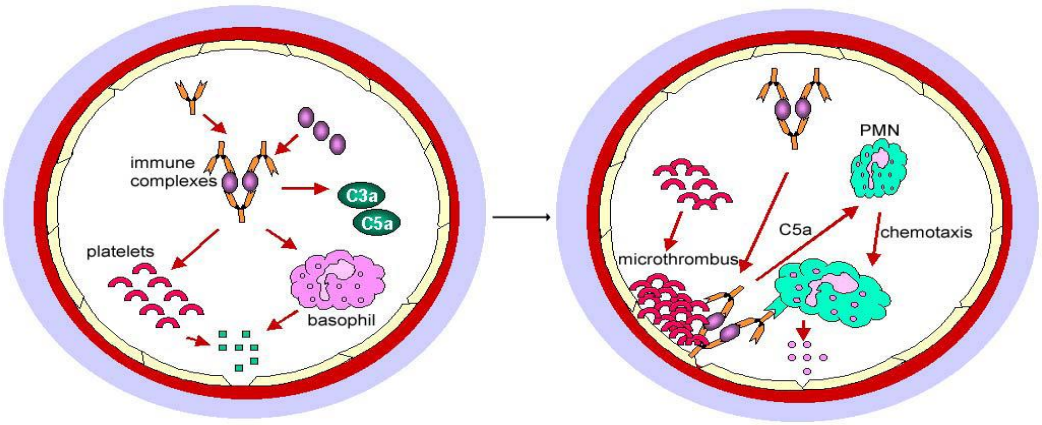
It is also known as cytotoxic hypersensitivity , and may affect a variety of organs and tissues. The antigens are normally endogenous, although exogenous chemicals (haptens) which can attach to cell membranes can also lead to type II hypersensitivity. Drug-induced hemolytic anemia, granulocytopenia and thrombocytopenia are such examples. The reaction time is minutes to hours. It is primarily mediated by antibodies of IgM or IgG class and complement . It can mediate cell destruction by antibody dependent cell-mediated cytotoxicity (ADCC).Phagocytes and K cells may also play a role (ADCC). The lesion contains antibody, complement and neutrophils. **During first pregnancy with an Rh+ fetus, an Rh– woman is usually not exposed to enough fetal red blood cells to activate her Rh-specific B cells. At the time of delivery, however, separation of the placenta from the uterine wall allows larger amounts of fetal umbilical-cord blood to enter the mother's circulation. These fetal red blood cells activate Rh-specific B cells, resulting in production of Rh-specific plasma cells and memory B cells in the mother. Activation of these memory cells in a subsequent pregnancy results in the formation of IgG anti-Rh antibodies, which cross the placenta and damage the fetal red blood cells . In addition, because the lipid-soluble bilirubin may accumulate in the brain and cause brain damage. Hemolytic disease of the newborn caused by Rh incompatibility in a subsequent pregnancy can be almost entirely prevented by antibodies against the Rh antigen to the mother within 24–48 h after the first delivery. These antibodies, called Rhogam.**



Type III Hypersensitivity

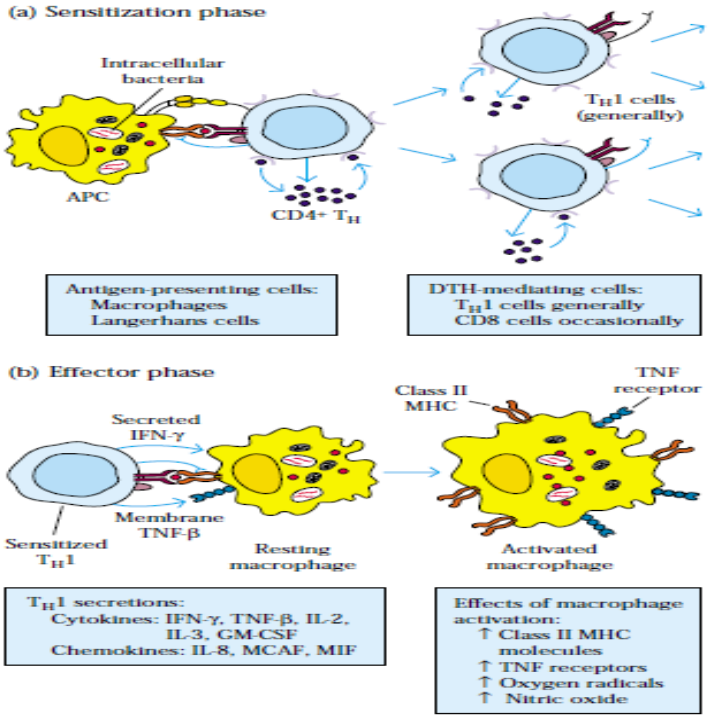
It is also known as immune complex hypersensitivity. The reaction may be general (e.g., serum sickness) or may involve individual organs including skin (e.g., systemic lupus erythematosus, Arthus reaction), kidneys (e.g., lupus nephritis), lungs (e.g., aspergillosis), blood vessels (e.g., polyarteritis), joints (e.g., rheumatoid arthritis) or other organs. This reaction may be the pathogenic mechanism of diseases caused by many microorganisms.

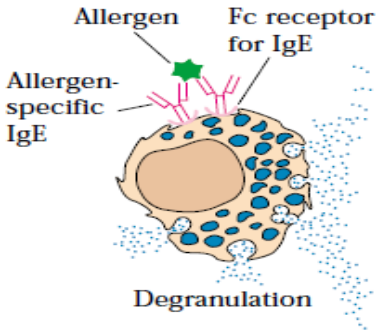
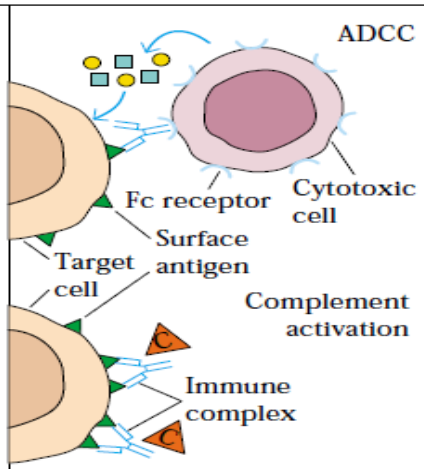
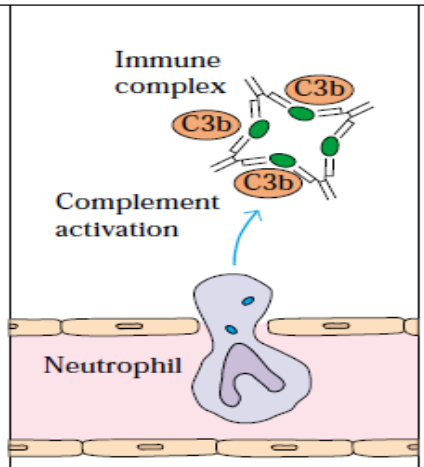
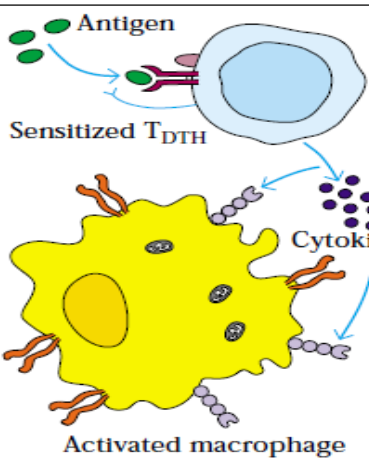
The reaction may take 3-10 hours after exposure to the antigen (as in Arthus reaction). It is mediated by soluble immune complexes. They are mostly of IgG class, although IgM may also be involved. The antigen may be exogenous (chronic bacterial, viral or parasitic infections), or endogenous (non-organ specific autoimmunity: e.g., systemic lupus eythematosus, SLE). The antigen is soluble and not attached to the organ involved. Primary components are soluble immune complexes and complement (C3a, 4a and 5a). The damage is caused by platelets and neutrophils .



Type IV Hypersensitivity

It is also known as **cell mediated** or **delayed type hypersensitivity**. The classical example of this hypersensitivity is **tuberculin** (**Montoux**) reaction which peaks 48 hours after the injection of antigen . 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 I	**Type II**	**Type III**	**Type IV**
IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivit
Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators	Ab directed against cell surface antigens meditates cell destruction via complement activation or ADCC	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils	Sensitized T_H1 cells release cytokines that activate macrophages or T_C cells whic mediate direct cellular damag
Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema	Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia	Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulnephritis, rheumatoid arthritis, and systemic lupus erythematosus	Typical manifestations includ contact dermatitis, tubercular lesions and graft rejection