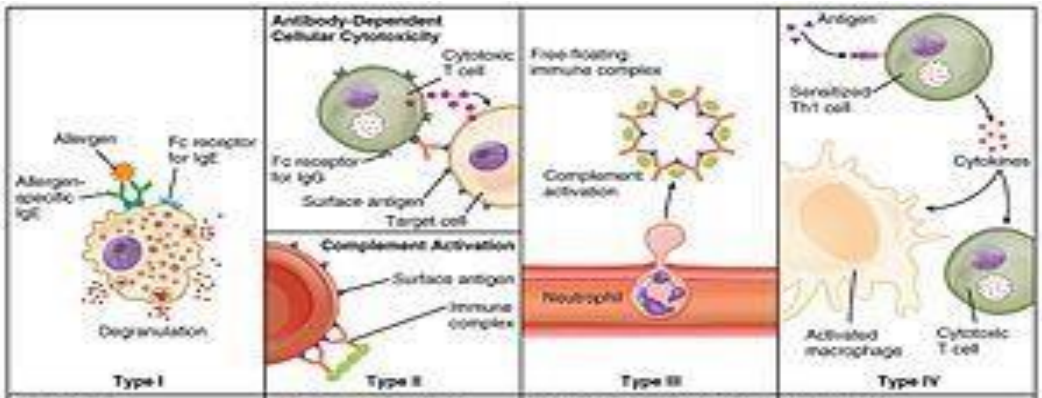
Disorders Associated with the Immune System

Hypersensitivity

The term hypersensitivity refers to an antigenic response that results in undesirable effects. Allergies are a familiar example. Hypersensitivity responses occur in individuals who have been sensitized by previous exposure to an antigen, which in this context is often called an allergen. When a sensitized individual is exposed to that antigen again, the body's immune system reacts to it in a damaging manner. The study of hypersensitivity reactions is called immunopathology. The four principal types of hypersensitivity reactions, summarized in Table 1, are type I (anaphylactic), type II (cytotoxic), type III(immune complex), and type IV(cell-mediated or delayed-type) reactions.



IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
IgE is bound to mast cells via its Fc portion. When an allergen binds to these antibodies, crosslinking of IgE induces degranulation.	Cells are destroyed by bound antibody, either by activation of complement or by a cytotoxic T cell with an Fc receptor for the antibody (ADCC)	Antigen–antibody complexes are deposited in tissues, causing activation of complement, which attracts neutrophils to the site	Th1 cells secrete cytokines, which activate macrophages and cytotoxic T cells and can cause macrophage accumulation at the site
Causes localized and systemic anaphylaxis, seasonal allergies including hay fever, food allergies such as those to shellfish and peanuts, hives, and eczema	Red blood cells destroyed by complement and antibody during a transfusion of mismatched blood type or during erythroblastosis fetalis	Most common forms of immune complex disease are seen in glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus	Most common forms are contact dermatitis, tuberculin reaction, autoimmune diseases such as diabetes mellitus type I, multiple sclerosis, and rheumatoid arthritis

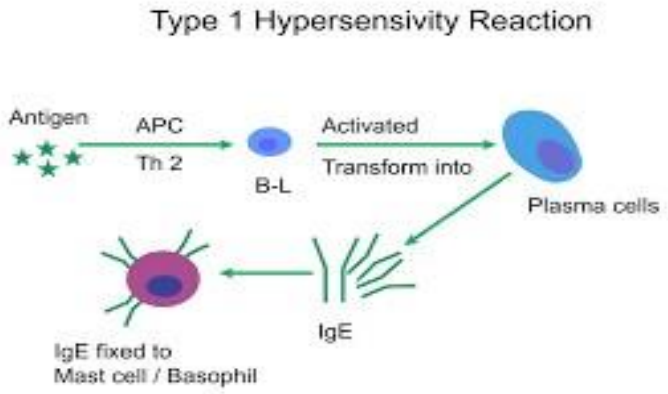
Type I (Anaphylactic) Reactions

Occur **2 to 30 minutes** after a sensitized person is reexposed to an antigen. Anaphylaxis means "the opposite of protected," from the prefix ana-, meaning against, and the Greek phylaxis, meaning protection. Anaphylaxis is an inclusive term for the reactions caused when antigens combine with **IgE** antibodies. Anaphylactic responses can be systemic reactions, producing shock and breathing difficulties that are sometimes fatal. However, they may also be localized reactions, including common allergic conditions such as hay fever, asthma, and hives

(slightly raised, often itchy and reddened areas of the skin).The IgE antibodies produced in response to an antigen (such as insect venom or plant pollen) bind to the surfaces of mast cells and basophils. Both cell types are similar in morphology and in their contribution to allergic reactions. The reaction may involve skin (**urticaria and eczema**), eyes (**conjunctivitis**), nasopharynx (**rhinorrhea, rhinitis**), bronchopulmonary tissues (**asthma)** and gastrointestinal tract (**gastroenteritis**)

Mast cells are especially prevalent in the mucosal and connective tissue of the skin and respiratory tract and in surrounding blood vessels.* Basophils in the bloodstream are recruited to the site of an infection. Mast cells and basophils contain granules of histamine and other chemical mediators.

Mast cells and basophils can have as many as 500,000 sites per cell for IgE attachment. The Fc (stem) region of an IgE antibody can attach to one of these specific receptor sites on such a cell, leaving two antigen-binding sites free. Of course, the attached IgE monomers will not all be specific for the same antigen. But when an antigen encounters two adjacent antibodies of the same appropriate specificity, it can bind to one antigen-binding site on each antibody, bridging the space between them. This bridge triggers the mast cell or basophil to undergo degranulation, a cellular process that releases the granules inside these cells along with the mediators they contain. These mediators cause the unpleasant and damaging effects of an allergic reaction. The best-known mediator, histamine.



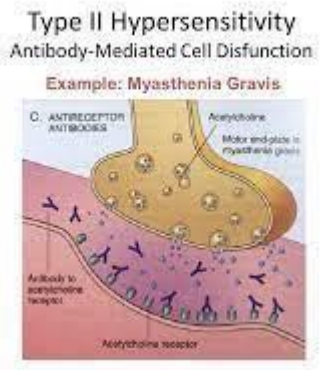
Type II (Cytotoxic) Reactions

Generally involve the activation of complement by the combination of **IgG or IgM** antibodies with an antigenic cell. This activation stimulates complement to lyse the

affected cell, which might be either a foreign cell or a host cell that carries a foreign antigenic determinant (such as a drug) on its surface, the antigens are normally endogenous. Additional cellular damage may be caused within **5 to 8 hours** by the action of macrophages and other cells that attack antibody coated cells. The most familiar cytotoxic hypersensitivity reactions are transfusion reactions, in which red blood cells are destroyed as a result of reacting with circulating antibodies. These reactions involve blood group systems that include the **ABO and Rh antigens** and **Drug-Induced Cytotoxic Reactions**.

Drug-Induced Cytotoxic Reactions

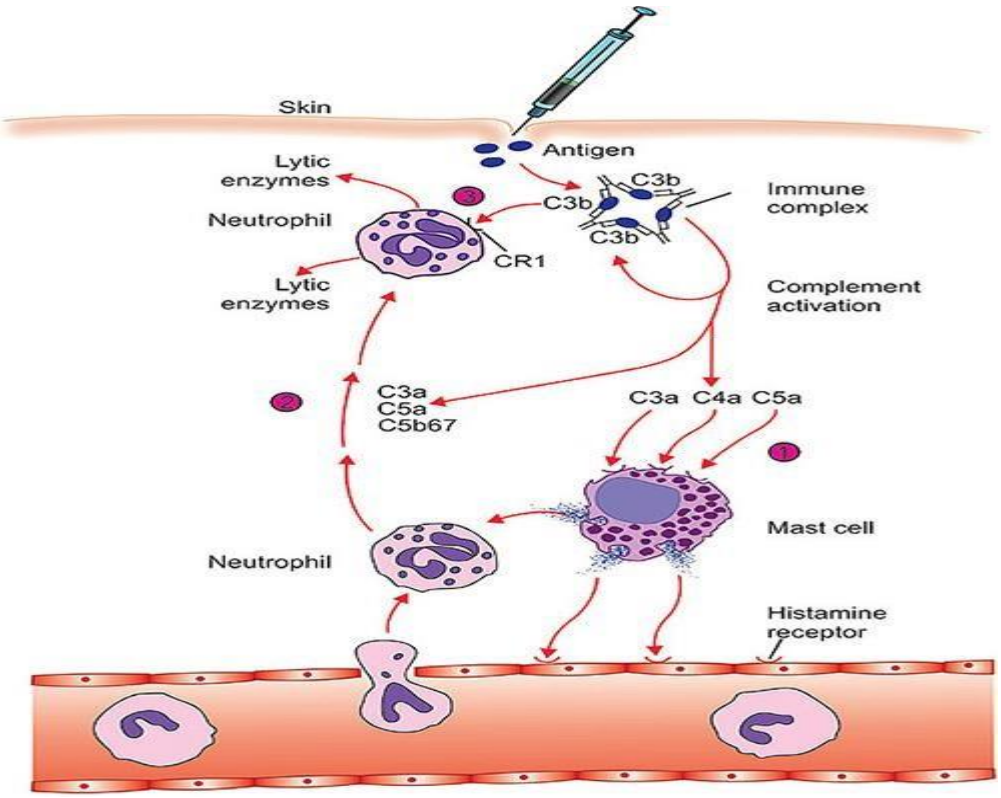
Blood platelets (thrombocytes) are minute cell-like fragments pinched off from megakaryocytes. These key components in blood clots are destroyed by druginduced cytotoxic reactions in the disease called **thrombocytopenic purpura**. The drug molecules are usually haptens because they are too small to be antigenic by themselves. Both antibody and complement are needed for lysis of the platelets. Loss of platelets results in hemorrhages that appear on the skin as purple spots or purpura, which means purple.



Type III (Immune Complex) Reactions

Involve antibodies against soluble antigens circulating in the serum. In contrast, type II immune reactions are directed against antigens located on cell or tissue surfaces. The **antigen–antibody complexes** are deposited in organs and cause inflammatory damage. 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 the **IgG** class, although **IgM** may also be involved. The antigen may be exogenous (chronic bacterial, viral or parasitic infections), or endogenous (nonorgan specific autoimmunity: e.g., systemic lupus erythematosus, 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. The lesion contains primarily neutrophils and deposits of immune complexes and complement.Macrophages infiltrating in later stages may be involved in the healing process. The affinity of antibody and size of immune complexes are important in production of disease and determining the tissue involved. Diagnosis involves examination of tissue **biopsies** for deposits of immunoglobulin and complement by immunofluorescence microscopy. The presence of immune complexes in serum and depletion in the level of complement are also diagnostic. Polyethylene glycol-mediated turbidity (nephelometry) binding of C1q and Raji cell test are utilized to detect immune complexes. Treatment includes anti-inflammatory agents.

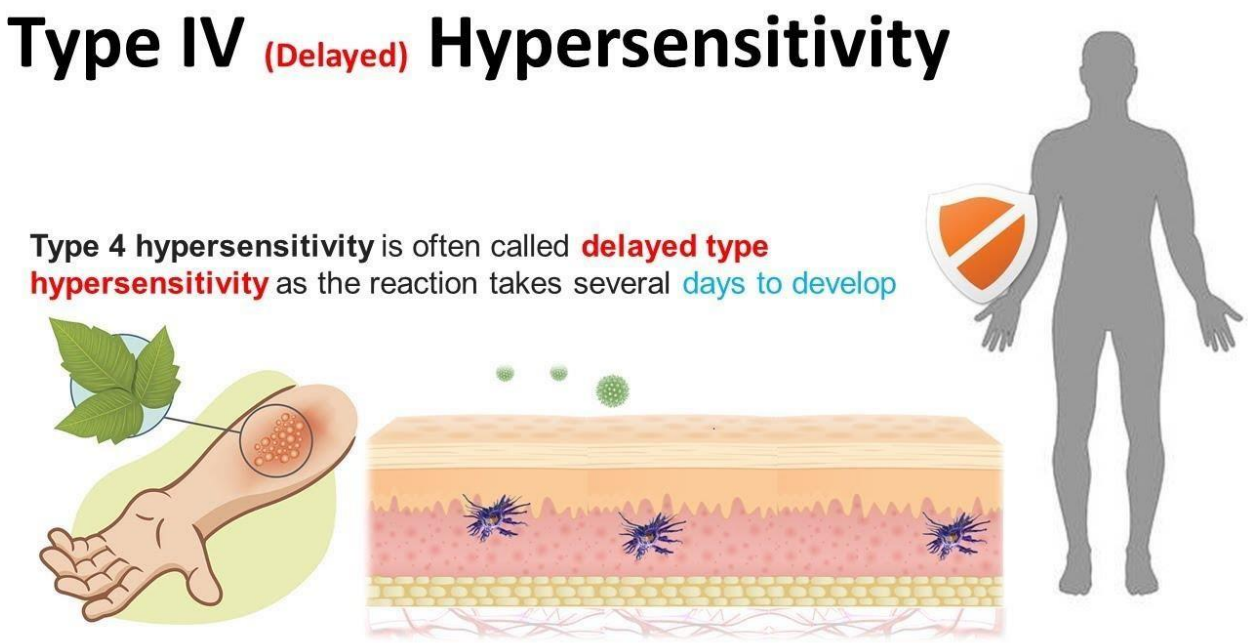


Type IV (Delayed Cell-Mediated) Reactions

Up to this point we have discussed humoral immune responses involving **IgE, IgG, or IgM**. Type IV reactions involve cell mediated immune responses and are caused mainly by **T cells**. Delayed cell-mediated reactions (or delayed hypersensitivity) are not apparent for **a day or more**. A major factor in the delay is the time required for the participating T cells and macrophages to migrate to and accumulate near the foreign antigens. Transplant rejection is most commonly mediated by cytotoxic T lymphocytes (CTLs), but other mechanisms are by antibody-dependent cellmediated cytotoxicity or complement-mediated lysis.

Example: Delayed Cell-Mediated Hypersensitivity Reactions of the Skin (**skin test for tuberculosis**) and **Allergic contact dermatitis**.

Allergic contact dermatitis, another common manifestation of delayed cellmediated hypersensitivity, is usually caused by haptens that combine with proteins (particularly the amino acid lysine) in the skin of some people to produce an immune response. Reactions to poison ivy, cosmetics, and the metals in jewelry (especially nickel) are familiar examples of these allergies.



Comparison of Different Types of hypersensitivity				
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	weal & flare	lysis and necrosis	erythema and edema, necrosis	erythema and induration
histology	basophils and eosinophil	antibody and complement	complement and neutrophils	monocytes and lymphocytes
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