Hypersensitivities

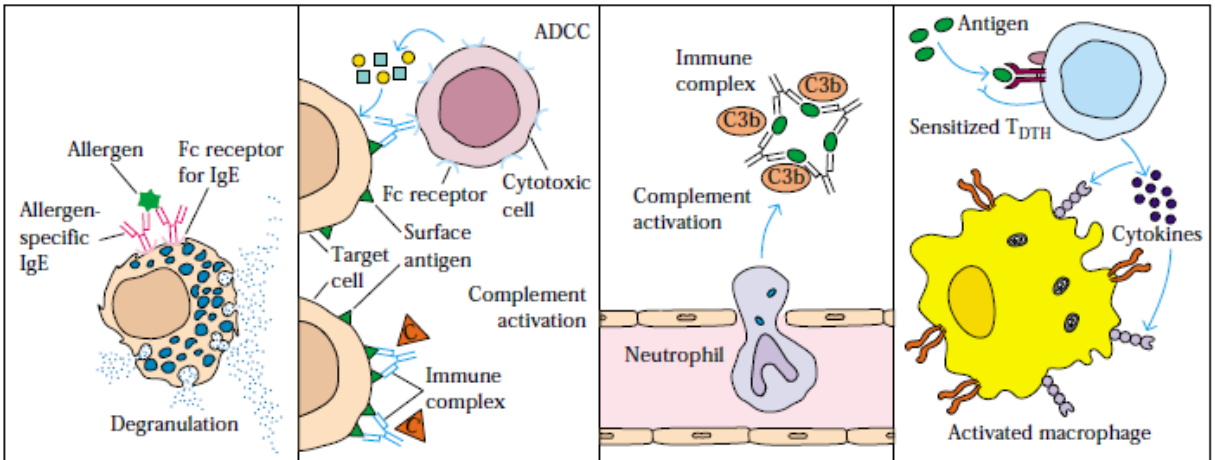
The inflammatory immune response under certain circumstances, however, can have deleterious effects, resulting in significant tissue damage or even death. This inappropriate immune response is termed **hypersensitivity** or **allergy.** Although the word *hypersensitivity* implies an increased response, the response is not always heightened but may, instead, be an inappropriate immune response to an antigen. Hypersensitive reactions may develop in the course of either humoral or cell-mediated responses.

Gell and Coombs Classification

P. G. H. Gell and R. R. A. 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. A fourth type of hypersensitivity depends on reactions within the cell-mediated branch.

1. IgE-mediated (type I)
2. Antibody-mediated (type II)
3. Immune complex–mediated (type III).
4. Delayed-type hypersensitivity, or DTH (type IV)

Each type involves distinct mechanisms, cells, and mediator molecules (Figure 1). Several forms of hypersensitive reaction can be distinguished, reflecting differences in the effector molecules generated in the course of the reaction. In immediate hypersensitive reactions, different antibody isotypes induce different immune effector molecules. IgE antibodies, for example, induce mast-cell degranulation with release of histamine and other biologically active molecules. IgG and IgM antibodies, on the other hand, induce hypersensitive reactions by activating complement. The effector molecules in the complement reactions are the membrane-attack complex and such complement split products as C3a, C4a, and C5a. In delayed-type hypersensitivity reactions, the effector molecules are various cytokines secreted by activated T_H or T_C cells.



Type I	Type II	Type III	Type IV
IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
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 which mediate direct cellular damage
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 include contact dermatitis, tubercular lesions and graft rejection

1. IgE-Mediated (Type I) Hypersensitivity

A type I hypersensitive reaction is induced by certain types of antigens referred to as **allergens,** and has all the hallmarks of a normal humoral response. What distinguishes a type I hypersensitive response from a normal humoral response is that the plasma cells secrete IgE. This class of antibody binds with high affinity to **Fc receptors** on the surface of tissue mast cells and blood basophils. Mast cells and basophils coated by IgE are said to be sensitized. A later exposure to the same allergen cross-links the membrane-bound IgE on sensitized mast cells and basophils, causing **degranulation** of these cells (Figure 2). The pharmacologically active mediators released from the granules act on the surrounding tissues. The principal effects—vasodilation and smooth-muscle contraction—may be either systemic or localized, depending on the extent of mediator release.

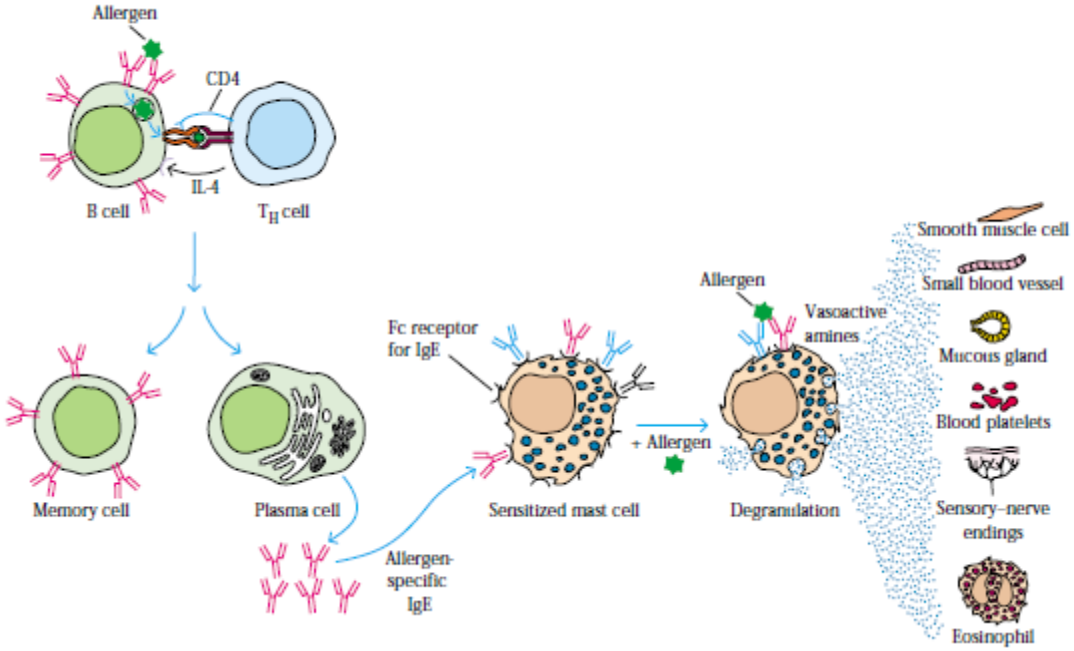


Figure2: General mechanism underlying a type I hypersensitive reaction. Exposure to an allergen activates B cells to form IgE secreting plasma cells. The secreted IgE molecules bind to IgE specific Fc receptors on mast cells and blood basophils. (Many molecules of IgE with various specificities can bind to the IgE-Fc receptor.) Second exposure to the allergen leads to crosslinking of the bound IgE, triggering the release of pharmacologically active mediators, vasoactive amines, from mast cells and basophils. The mediators cause smooth-muscle contraction, increased vascular permeability, and vasodilation.

2. Antibody-Mediated Cytotoxic (Type II) Hypersensitivity

Type II hypersensitive reactions involve antibody-mediated destruction of cells. Antibody can activate the complement system, creating pores in the membrane of a foreign cell (Figure 4), or it can mediate cell destruction by antibody dependent cell-mediated cytotoxicity (ADCC). In this process, cytotoxic cells with Fc receptors bind to the Fc region of antibodies on target cells and promote killing of the cells (see Figure 3). Antibody bound to a foreign cell also can serve as an opsonin, enabling phagocytic cells with Fc or C3b receptors to bind and phagocytose the antibody-coated cell (see Figure 4).

Transfusion Reactions Are Type II Reactions

A large number of proteins and glycoproteins on the membrane of red blood cells are encoded by different genes, each of which has a number of alternative alleles. An individual possessing one allelic form of a blood-group antigen can recognize other allelic forms on transfused blood as foreign and mount an antibody response. In some cases, the antibodies

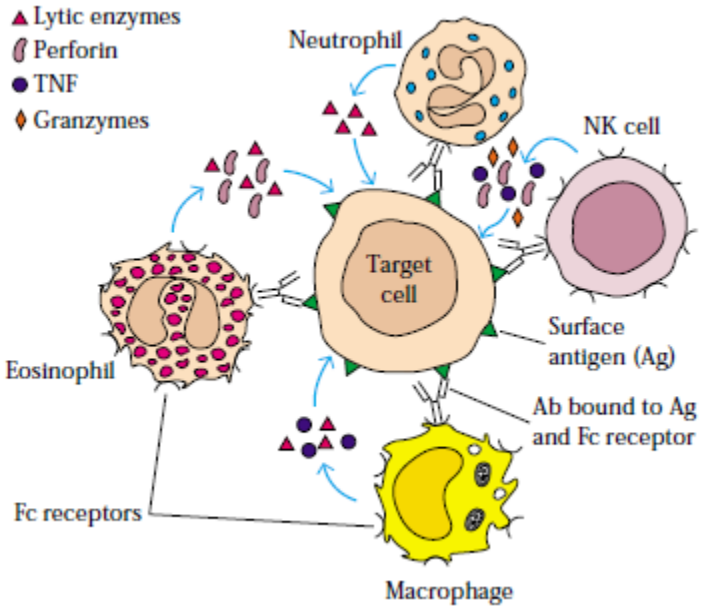


Figure 3. Antibody-dependent cell-mediated cytotoxicity (ADCC). Nonspecific cytotoxic cells are directed to specific target cells by binding to the Fc region of antibody bound to surface antigens on the target cells. Various substances (e.g., lytic enzymes, TNF, perforin, granzymes) secreted by the nonspecific cytotoxic cells then mediate target cell destruction.

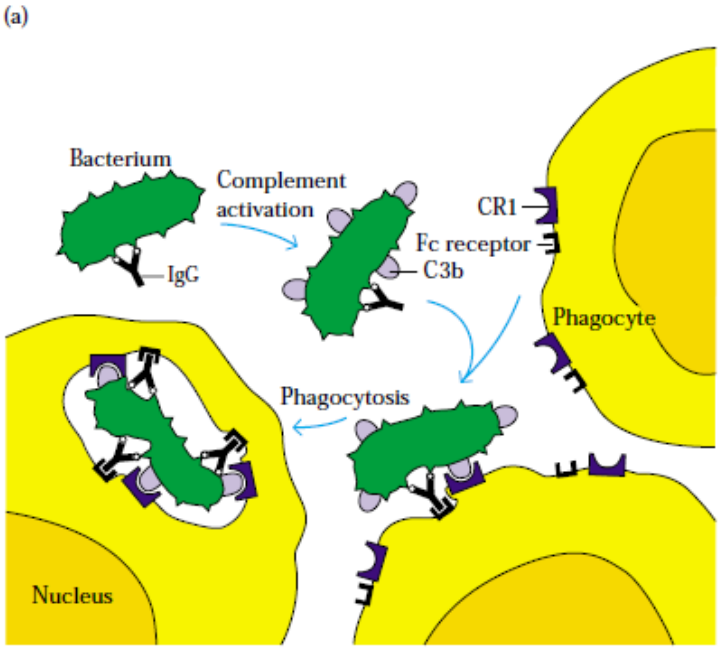
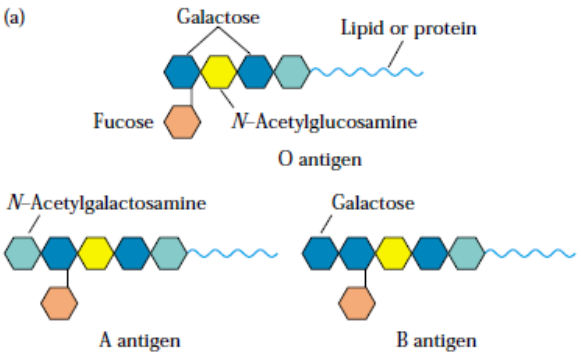


Figure 4: Schematic representation of the roles of C3b and antibody in opsonization

have already been induced by natural exposure to similar antigenic determinants on a variety of microorganisms present in the normal flora of the gut. This is the case with the ABO blood-group antigens (Figure 5). Antibodies to the A, B, and O antigens, called isohemagglutinins, are usually of the IgM class. An individual with blood type A, for example, recognizes B-like epitopes on intestinal microorganisms and produces isohemagglutinins to the B-like epitopes. This same individual does not respond to A-like epitopes on the same intestinal microorganisms because these A-like epitopes are too similar to self and a state of self-tolerance to these epitopes should exist (Figure 5b).

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. Antibodies to other blood-group antigens (Rh, Kidd, Kell, and Duffy) lead to delayed hemolytic transfusion. The reactions develop between 2 and 6 days and antibodies are usually of the IgG class. The transfused blood induces clonal selection and production of IgG against a variety of blood-group membrane antigens, most commonly Rh, Kidd, Kell, and Duffy.



(b)

Genotype	Blood–group phenotype	Antigens on erythrocytes (*agglutinins*)	Serum antibodies (*isohemagglutinins*)
AA or AO	A	A	Anti–B
BB or BO	B	B	Anti–A
AB	AB	A and B	None
OO	O	None	Anti–A and anti–B

Figure 5: ABO blood group. (a) Structure of terminal sugars, which constitute the distinguishing epitopes, in the A, B, and O blood antigens. (b) ABO genotypes and corresponding phenotypes, agglutinins, and isohemagglutinins.

Hemolytic Disease of the Newborn Is Caused by Type II Reactions

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. During pregnancy, fetal red blood cells are separated from the mother's circulation by a layer of cells in the placenta called the trophoblast. During her 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.

The secreted IgM antibody clears the Rh^+ fetal red cells from the mother's circulation, but the memory cells remain, a threat to any subsequent pregnancy with an Rh^+ fetus. 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 (Figure 6). Mild to severe anemia can develop in the fetus, sometimes with fatal consequences. In addition, conversion of hemoglobin to bilirubin can present an additional threat to the newborn because the lipid-soluble bilirubin may accumulate in the brain and cause brain damage.

Treatment

Hemolytic disease of the newborn caused by Rh incompatibility in a subsequent pregnancy can be almost entirely prevented by administering antibodies against the Rh antigen to the mother within 24–48 h after the first delivery. These antibodies, called **Rhogam,** bind to any fetal red blood cells that enter the mother's circulation at the time of delivery and facilitate their clearance before B-cell activation and ensuing memory-cell production can take place. In a subsequent pregnancy with an Rh^+ fetus, a mother who has been treated with Rhogam is unlikely to produce IgG anti-Rh antibodies; thus, the fetus is protected from the damage that would occur when these antibodies crossed the placenta.

For a severe reaction, the fetus can be given an intrauterine blood-exchange transfusion to replace fetal Rh^+ red blood cells with Rh^- cells. These transfusions are given every 10–21 days until delivery. In less severe cases, a blood-exchange transfusion is not given until after birth,

primarily to remove bilirubin; the infant is also exposed to low levels of UV light to break down the bilirubin and prevent cerebral damage. The mother can also be treated during the pregnancy by **plasmapheresis.** In this procedure, a cell separation machine is used to separate the mother's blood into two fractions, cells and plasma. The plasma containing the anti-Rh antibody is discarded, and the cells are reinfused into the mother in an albumin or fresh-plasma solution.

The majority of cases (65%) of hemolytic disease of the newborn have minor consequences and are caused by ABO blood-group incompatibility between the mother and fetus. Type A or B fetuses carried by type O mothers most commonly develop these reactions. A type O mother is most likely to develop IgG antibody to the A or B blood-group antigens either through natural exposure or through exposure to fetal blood-group A or B antigens in successive pregnancies.

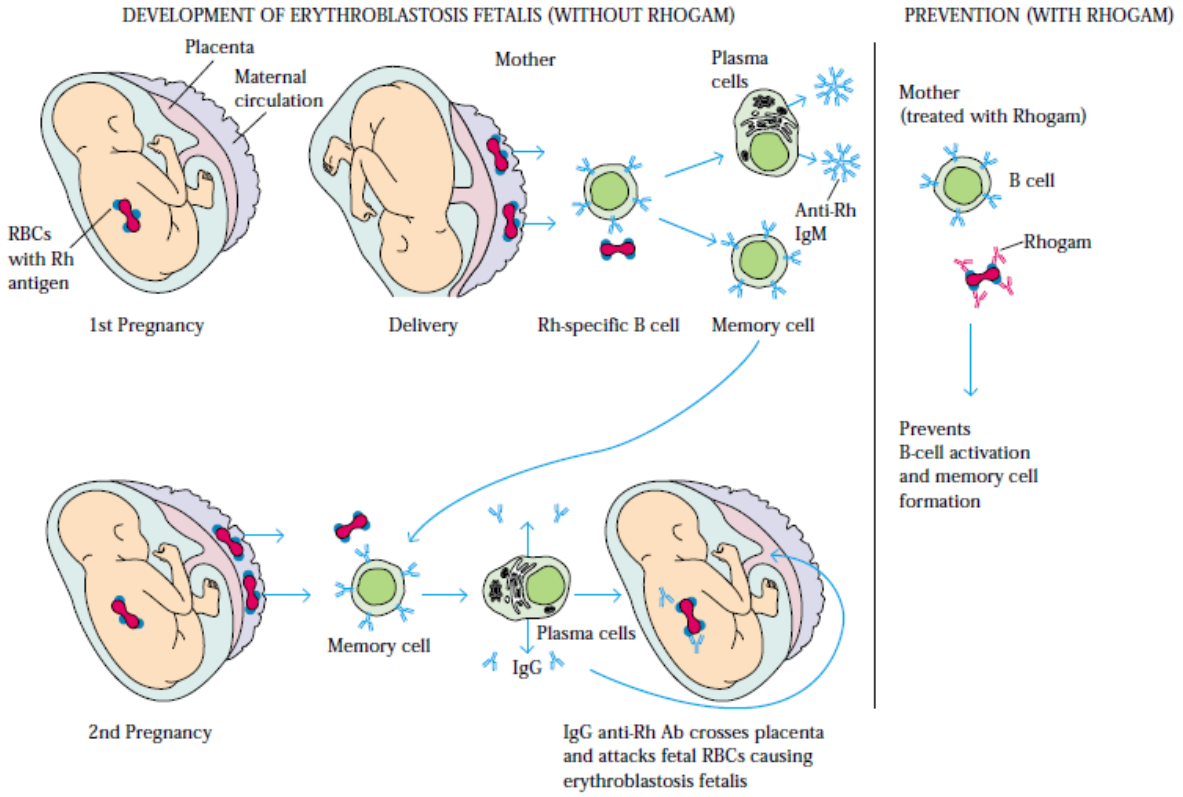


Figure 5. Development of erythroblastosis fetalis (hemolytic disease of the newborn) caused when an Rh$^-$ mother carries an Rh$^+$ fetus (*left*), and effect of treatment with anti-Rh antibody, or Rhogam (*right*).

3. Immune Complex–Mediated (Type III) Hypersensitivity

The reaction of antibody with antigen generates immune complexes. Generally this complexing of antigen with antibody facilitates the clearance of antigen by phagocytic cells. In some cases, however, large amounts of immune complexes can lead to tissue-damaging type III hypersensitive reactions. The magnitude of the reaction depends on the quantity of immune complexes as well as their distribution within the body. When the complexes are deposited in tissue very near the site of antigen entry, a **localized** reaction develops. When the complexes are formed in the blood, a reaction can develop **wherever the complexes** are deposited.

In particular, complex deposition is frequently observed on blood-vessel walls, in the synovial membrane of joints, on the glomerular basement membrane of the kidney, and on the choroid plexus of the brain. The deposition of these complexes initiates a reaction that results in the recruitment of neutrophils to the site. The tissue there is injured as a consequence of granular release from the neutrophil. Type III hypersensitive reactions develop when immune complexes activate the complement system's array of immune effector molecules. As explained in Complement system, the C3a, C4a, and C5a complement split products are anaphylatoxins that cause localized mast-cell degranulation and consequent increase in local vascular permeability. C3a, C5a, and C5b67 are also chemotactic factors for neutrophils, which can accumulate in large numbers at the site of immune-complex deposition. Larger immune complexes are deposited on the basement membrane of blood vessel walls or kidney glomeruli, whereas smaller complexes may pass through the basement membrane and be deposited in the subepithelium. The type of lesion that results depends on the site of deposition of the complexes.

Much of the tissue damage in type III reactions stems from release of lytic enzymes by neutrophils as they attempt to phagocytose immune complexes. The C3b complement component acts as an opsonin, coating immune complexes. A neutrophil binds to a C3b-coated immune complex by means of the type I complement receptor, which is specific for C3b. Because the complex is deposited on the basement membrane surface, phagocytosis is impeded, so that lytic enzymes are released during the unsuccessful attempts of the neutrophil to ingest the adhering immune complex. Further activation of the membrane-attack mechanism of the complement

system can also contribute to the destruction of tissue. In addition, the activation of complement can induce aggregation of platelets, and the resulting release of clotting factors can lead to formation of microthrombi.

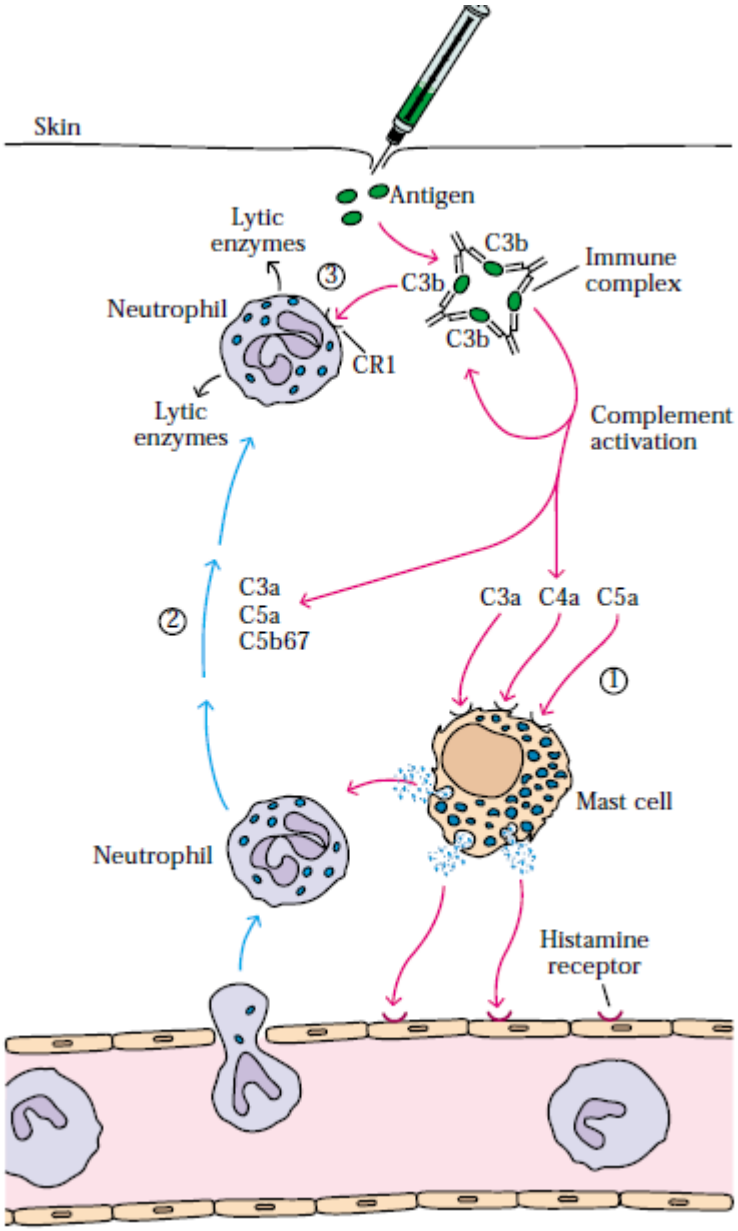


Figure 6: Development of a type III hypersensitive reaction. Complement activation initiated by immune complexes (classical pathway) produces complement intermediates that (1) mediate mast-cell degranulation, (2) chemotactically attract neutrophils, and (3) stimulate release of lytic enzymes from neutrophils trying to phagocytose C3b-coated immune complexes.

Examples:

- "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.

- Serum sickness
- Autoimmune Diseases

  Systemic lupus erythematosus

  Rheumatoid arthritis
- Infectious Diseases

  Poststreptococcal glomerulonephritis

4. Type IV or Delayed-Type Hypersensitivity (DTH)

When some subpopulations of activated TH cells encounter certain types of antigens, they secrete cytokines that induce a localized inflammatory reaction called delayed-type hypersensitivity (DTH). The reaction is characterized by large influxes of nonspecific inflammatory cells, in particular, macrophages. This type of reaction was first described in 1890 by Robert Koch, who observed that individuals infected with *Mycobacterium tuberculosis* developed a localized inflammatory response when injected intradermally with a filtrate derived from a mycobacterial culture. He called this localized skin reaction a “tuberculin reaction.” The hallmarks of a type IV reaction are the delay in time required for the reaction to develop and the recruitment of macrophages as opposed to neutrophils, as found in a type III reaction.

Many contact-dermatitis reactions, including the responses to formaldehyde, trinitrophenol, nickel, turpentine, and active agents in various cosmetics and hair dyes, poison oak, and poison ivy, are mediated by TH1 cells. In the reaction to poison oak, for example, a pentadecacatechol compound from the leaves of the plant forms a complex with skin proteins.When TH cells react with this compound appropriately displayed by local antigen-presenting cells, they differentiate into sensitized TH1 cells. A subsequent exposure to pentadecacatechol will elicit activation of TH1 cells and induce cytokine production (Figure 6). Approximately 48–72 h after the second exposure, the secreted cytokines cause macrophages to accumulate at the site. Activation of these macrophages and release of lytic enzymes result in the redness and pustules that characterize a reaction to poison oak.

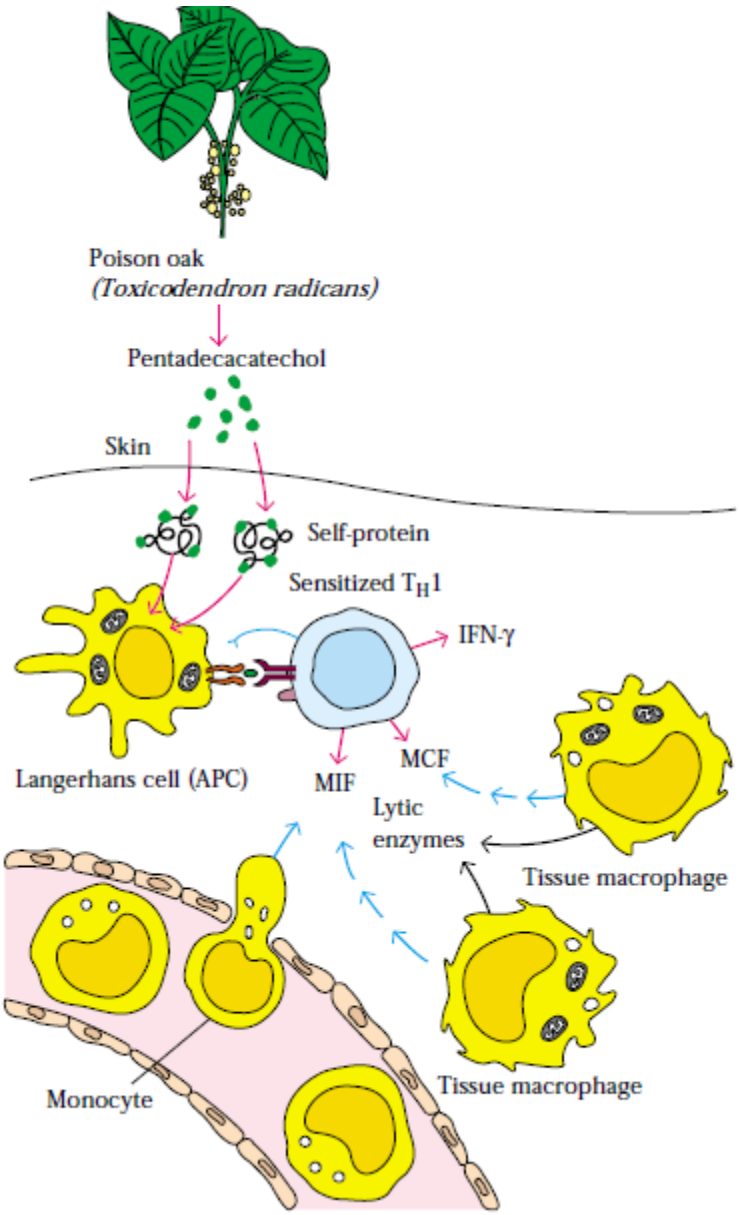


Figure 6: Development of delayed-type hypersensitivity reaction after a second exposure to poison oak. Cytokines such as IFN-γ, macrophage-chemotactic factor (MCF), and migration-inhibition factor (MIF) released from sensitized T_H1 cells mediate this reaction. Tissue damage results from lytic enzymes released from activated macrophages.