Antibody mediated or 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, 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. 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. (Please note that the antibody type involved here is mostly IgM or IgG). Hence, these above mentioned processes, which are usually protective in nature as they aid in killing of pathogens, can become destructive if antibodies generated are against tissue or cell surface antigens.

Major examples of this type of hypersensitivity are,

- **Transfusion Reactions**- (Please go through content of blood transfusion reactions provided to you in the practical of blood group determination). In summary, blood transfusion reactions can occur if incompatible blood is transfused. For eg, if a type A individual is transfused with blood containing type B cells, a **transfusion reaction** occurs in which the anti-B isohemagglutinins (b) 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. 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. Typical symptoms include fever, chills, nausea, clotting within blood vessels, pain in the lower back, and hemoglobin in the urine. Delayed hemolytic transfusion reactions generally occur in individuals who have received repeated transfusions of ABO-compatible blood that is incompatible for other blood groupantigens. The reactions develop between 2-6 days after transfusion, reflecting the secondary nature of these reactions. 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. Symptoms include fever, low hemoglobin, increased bilirubin, mild jaundice, and anemia.

- **Hemolytic diseases in infants**- 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. 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, which 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. Activation of these memory cells in a subsequent Rh- pregnancy results in the formation of IgG anti-Rh antibodies, which cross the placenta and damage the fetal red blood cells. Mild to severe anemia can develop in the fetus, sometimes with fatal consequences. In addition, conversion of hemoglobin to bilirubin which is lipid-soluble andb may accumulate in the brain and cause brain damage.

The disease can be 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 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.

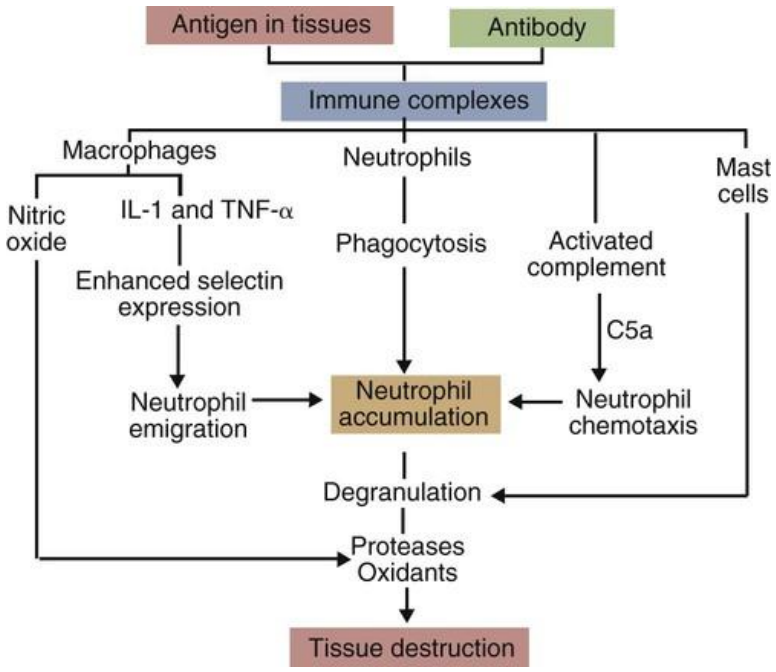
The disease can be detected by testing maternal serum at intervals during pregnancy for antibodies to the Rh antigen. A rise in the titer of these antibodies as pregnancy progresses indicates that the mother has been exposed to Rh antigens and is producing increasing amounts of antibody.

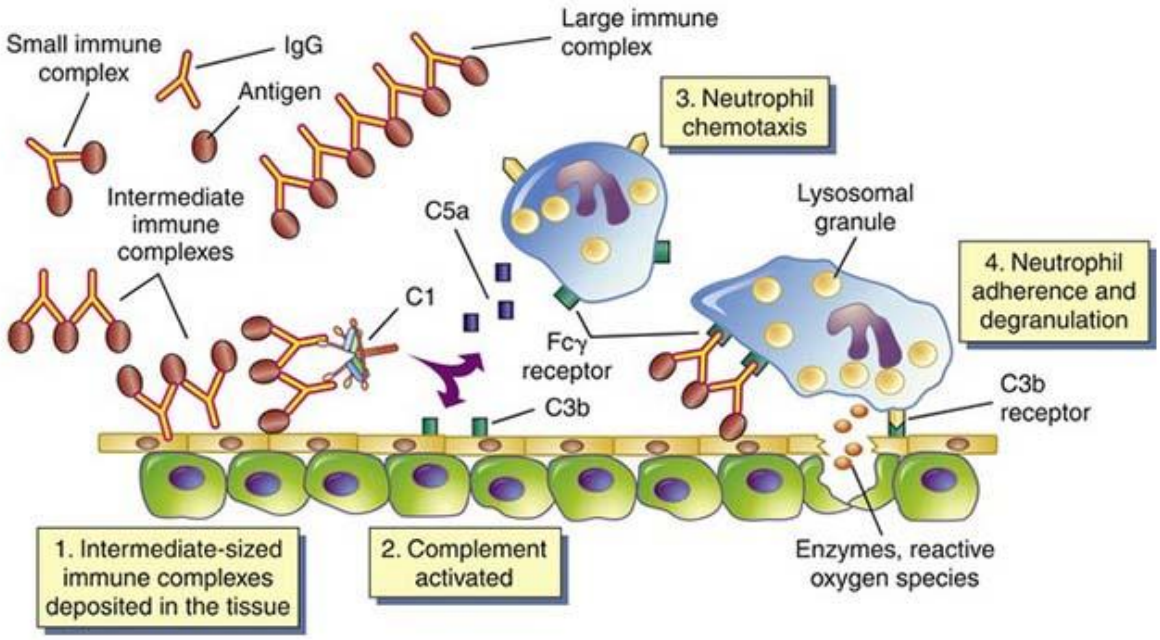
Upon detection, the treatment depends on the severity of the reaction. For a severe reaction, the fetus can be given an intrauterine blood-exchange transfusion to replace fetal Rh+ red blood cells with Rh– cells. These transfusions are given every 10–21 days until delivery. In less severe cases, a blood-exchange 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.

- **Drug induced haemolytic anemia**- Certain antibiotics (e.g., penicillin, cephalosporin, and streptomycin) can adsorb non specifically onto 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 progressive anemia. When the drug is withdrawn, the hemolytic anemia disappears.

Immune complex or 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 and distribution of immune complexes in the body. When the complexes get 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. 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. This initiates a reaction that results in the recruitment of neutrophils to the site and tissue damage due to release of lytic contents of the granules. Immune complexes can also activate the complement system's array of immune effector molecules. Anaphylatoxins (C3a, C5a, and C5b67) released cause localized mast-cell degranulation and consequent increase in local vascular permeability. They 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. All, lead to extensive tissue damage. Type III reactions are also referred to as **Arthus reactions**.





Localised Type III Reaction- Injection of an antigen intradermally or subcutaneously into an animal that has high levels of circulating antibody specific for that antigen leads to formation of localized immune complexes, which mediate an acute Arthus reaction within 4–8 h. Neutrophils adher 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. After an insect bite, a sensitive individual may have a rapid, localized type I reaction at the site. Often, some 4–8 h later, a typical Arthus reaction also develops at the site, with pronounced erythema and edema. Pulmonary Arthus reactions induced by bacterial spores, fungi, or dried fecal proteins can also cause pneumonitis or alveolitis.

Generalized Type III Reaction- When large amounts of antigen enter the bloodstream and bind to antibody, small sized circulating immune complexes can form which are not easily cleared by the phagocytic cells. They can cause tissue- damaging type III reactions wherever they get deposited. Historically, generalized type III reactions are observed after the administration of antitoxins containing foreign serum, such as horse anti tetanus or anti diphtheria serum. The recipient of a foreign antiserum develops antibodies specific for the foreign serum proteins; these antibodies then form circulating immune complexes with the foreign serum antigens. Typically, within days or weeks after exposure to foreign serum antigens, an individual begins to manifest a combination of symptoms that are called **serum sickness** and include fever, weakness, generalized vasculitis (rashes) with edema and erythema, lymphadenopathy, arthritis, and sometimes glomerulonephritis. The sites of deposition vary but, in general, complexes accumulate in tissues where filtration of plasma occurs. This explains the high incidence of glomerulonephritis (complex deposition in the kidney) and vasculitis (deposition in the arteries) and arthritis (deposition in the synovial joints) caused by serum sickness. (In general the term **itis** means inflammation, so when used as a suffix, it means inflammation of that particular tissue. For eg, vascul-itis means inflammation in the vascular membrane of vessels). A number of autoimmune diseases such

as lupus, rheumatoid arthritis etc stem from circulating complexes of antibody with self-proteins. Complexes of antibody with various bacterial, viral, and parasitic antigens for eg, hepatitis, malarial antigens etc, have been shown to induce a variety of type III hypersensitive reactions.

Delayed Type Reaction or Type IV Hypersensitivity

This reaction is characterized by large influxes of nonspecific inflammatory cells, in particular, macrophages. Moreover, DTH is caused by cellular components of the system, as opposed to humoural i.e antibodies, as for the other three hypersensitivities. **Robert Koch**, first 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." Later, as it became apparent that a variety of other antigens could induce this response, its name was changed to delayed-type or type IV hypersensitivity in reference to the delayed onset of the reaction and to the tissue damage (hypersensitivity) that is often associated with it.

Development of a Type IV response is as follows,

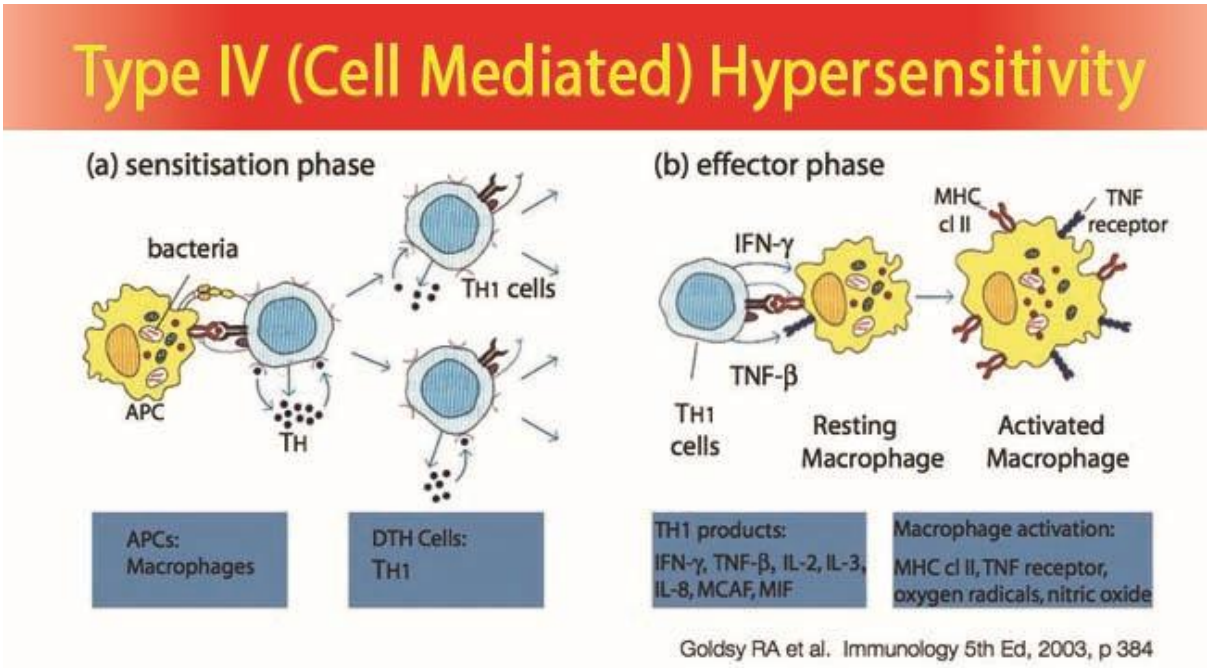
- The development of the DTH response begins with an initial sensitization phase of 1–2 weeks after primary contact with an antigen. During this period, TH cells are activated and clonally expanded by antigen presented together with the requisite class II MHC molecule on an appropriate antigen presenting cell, specifically macrophages and Langerhans cells, a type of dendritic cells found in the epidermis. In some species, including humans, the vascular endothelial cells express class II MHC molecules and also function as APCs in the development of the DTH response. Generally, the T cells activated during the sensitization phase are CD4+, primarily of the TH1 subtype, but in a few cases CD8+ cells have also been shown to induce a DTH response.

- A subsequent exposure to the antigen induces the effector phase of the DTH response, where TH1 cells secrete a variety of cytokines that recruit and activate macrophages and other nonspecific inflammatory cells. A DTH response normally does not become apparent until an average of 24 h after the second contact with the antigen; the response generally peaks 48–72 h after second contact. The delayed onset of this response reflects the time required for the cytokines to induce localized influxes of macrophages and their activation. Once a DTH response begins, a complex interplay of nonspecific cells and mediators is set in motion that can result in tremendous amplification. By the time the DTH response is fully developed, only about 5% of the participating cells are antigen-specific TH1 cells; the remainder are macrophages and other nonspecific cells.

- Macrophages are the principal effector cells of the DTH response, Activated macrophages exhibit increased levels of phagocytosis and an increased ability to kill microorganisms through various cytotoxic mediators, for eg IL-3,GM-CSF, IFN-ɤ and TNF-α and β etc. In addition, activated macrophages express increased levels of class

II MHC molecules and cell-adhesion molecules and therefore function more effectively as antigen-presenting cells. The heightened phagocytic activity and the buildup of lytic enzymes from macrophages in the area of infection lead to nonspecific destruction of cells, and thus of the intracellular pathogen. Generally, the pathogen is cleared rapidly with little tissue damage. However, in some cases, especially if the antigen is not easily cleared, a prolonged DTH response can itself become destructive to the host as the intense inflammatory response develops into a visible granulomatous reaction. A granuloma develops when continuous activation of macrophages induces the macrophages to adhere closely to one another, assuming an epithelioid shape and sometimes fusing to form multinucleated giant cells, which destroy surrounding tissue. The response can damage blood vessels leading to extensive tissue necrosis.

- 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.



Delayed-type hypersensitivity (DTH)
(e.g. tuberculin skin test)

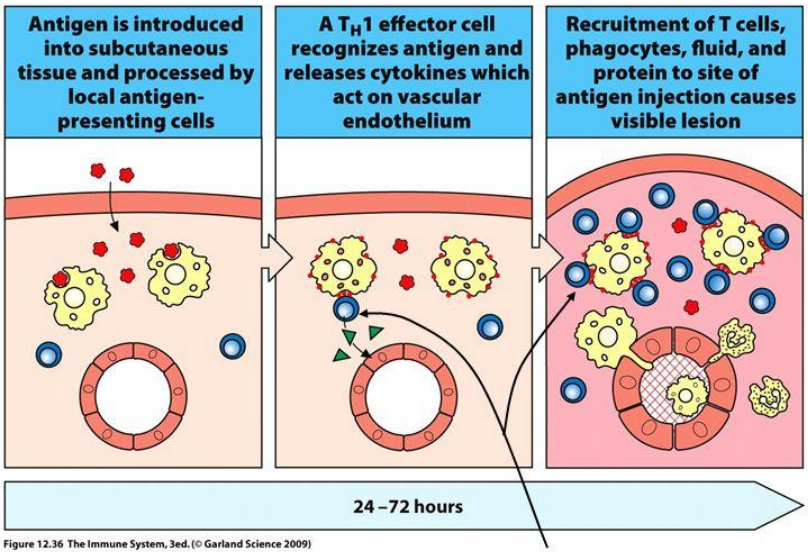


Figure 12.36 The Immune System, 3ed. (© Garland Science 2009)

T_H1 from a previous immunization (memory)