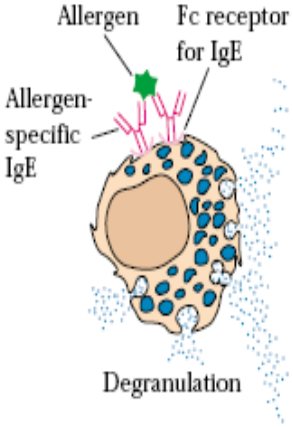
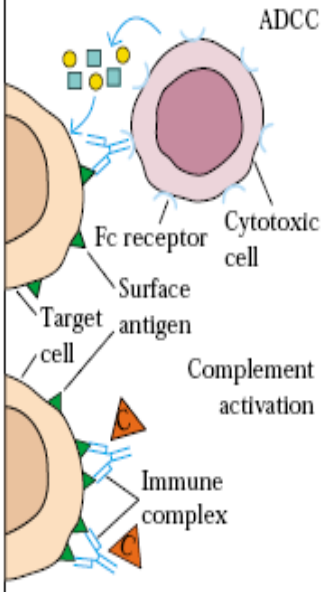
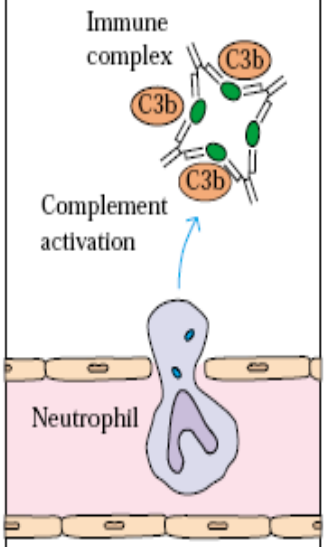
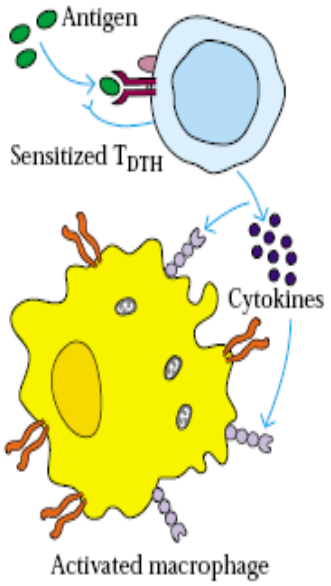
HYPERSENSITIVITY

It may be defined as the exaggerated immune response that causes damage to the individual. It is an increased response to an Ag,, during the process of which the host is damaged. The reactions may develop incourse of either humoral or cell mediated Immune response. **Paul Portier and Charles Richet** were the two French scientists who worked on the violent reactions caused by the stings of Portugeese Man of War Jelly fish. Injection of this toxin to dogs as vaccine failed, instead booster doses caused disasters. Hence they termed these reactions **Anaphylaxis** a word loosely translated from greek to mean the opposite of **Prophylaxis**. They were awarded Nobel Prize in 1913 for this work.

The anaphylactic reactions are mediated by Ab or Ag-Ab complex and the symptoms appears within minutes or hours, hence they are categorized under Immediate Hypersensitivity reactions. If the symptoms appear after days it is named Delayed Type Hypersensitivity. These reactions can also be classified based on the effector molecules generated in the cause of the reaction. In immediate hypersensitivity defferent Ab isotypes induce different immune effector molecules. IgE induces, degranulation of mast cells which are biologically active molecules. IgG and IgM induce hypersensitivity reactions by activating complement, mainly the byproducts C3a, C4a and Ca are generated. In delayed type of Hypersensitivity reactions, cytokines secreted by activated T_H or Tc cells are involved.

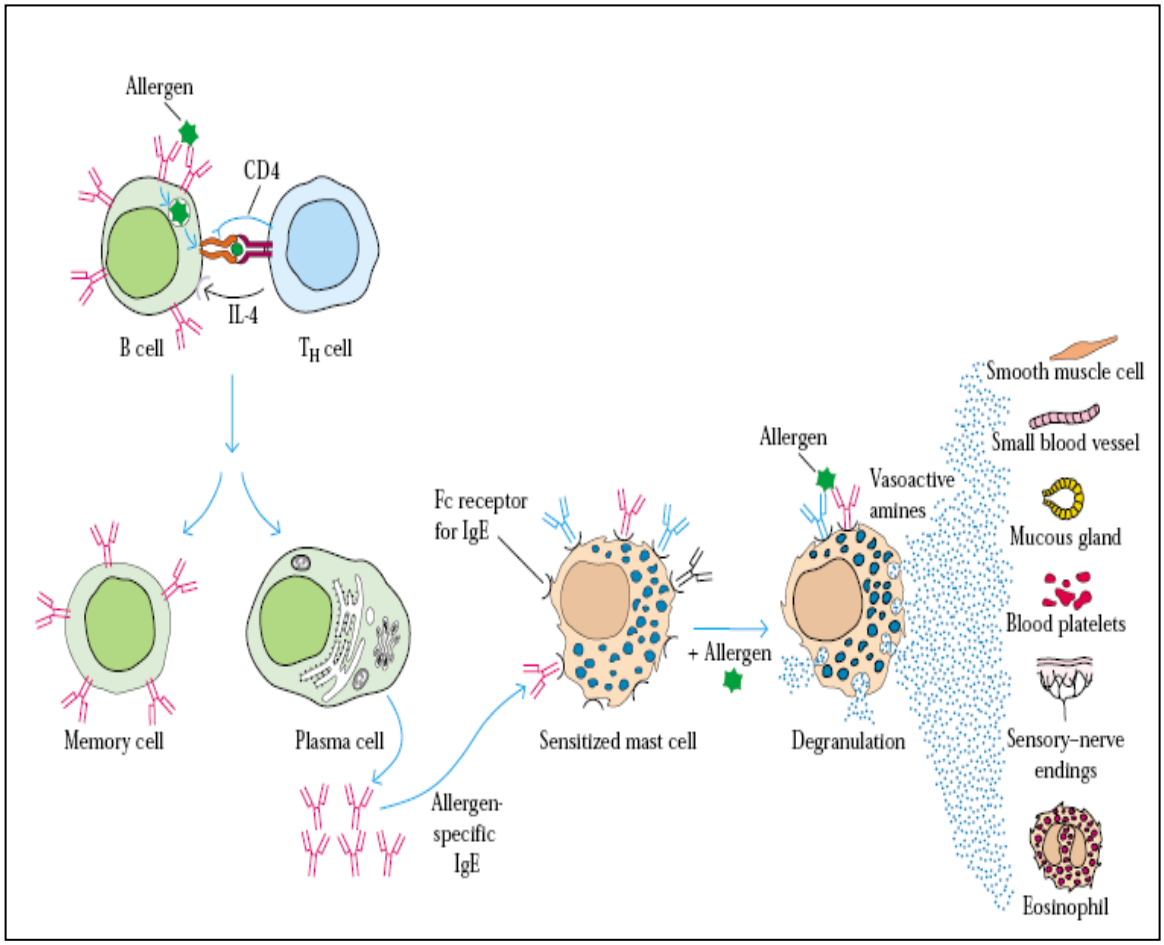
P.G.H.Gell and R.R.A.Coombs proposed a classification mechanism and they classified Hypersensitivity reactions into 4 types.

- IgE mediated (TypeI)
- Ab-meidated (Type II)
- Immune complex mediated (Type III)
- cell mediated delayed type of Hypersensitivity DTH (Type IV).

 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

IgE Mediated (Type I) Hypersensitivity:

The Ag is referred to as allergen. It induces humoral Immune response and plasma cells produce Ab's which are IgE. IgE has receptors on mast cells and basophils. These cells when coated with IgE are said to be sensitized. Later exposure to Ag causes degranulation of these cells. These granules contain pharmacologically active mediators which act on surrounding tissues leading to these effects like vasodialation, smooth muscle contractions, increased mucous secretions and sensitizing nerve endings.



Components which are critical for development for Type I reaction:

1) **Allergen:** Under parasitic infections the serum IgE levels increase. In persons having abnormality called Atopy, some environmental Ag's also induce IgE (non-parasitic induction of IgE production). Atopic individuals suffer from increased level of IgE as well as eosinophils. They are more susceptible to hay fever, eczema, asthma related allergies.

Most allergic IgE responses occur on the mucous membrane due to any one of the following allergens.

a) Air borne allergens: Plant pollen- from Rye Grass, Rag weed, Birch pollen, Timothy grass pollen etc.
b) Food borne allergens: Nuts, sea food, eggs, peas, milk, beans etc.
c) Insect products: Bee venom, wasp venom, ant venom, cockroach calyx, dust mites.

Most of these allergens are small proteins of molecular weight 15,000 to 40,000da.

2. Reagenic Ab IgE: K.Prausnitz and H.Kustner (1921) proved that the regains does not come under IgA, M or D type. They referred it as IgE after the E antigen of ragweed. It could not be detected due to its low concentration. **S.G.O.Johansson and H.Bennich (1967)** discovered IgE.

3. Mast cells and Basophils: Basophils are granular leucocytes and account to 0.5 to 1% of the circulating WBC. They have granules which stain with basic dyes which have the pharmacologically active mediators. Mast cells are located on all vascularised peripheral tissues, connective tissues mainly near blood and lymphatic vessels. Skin, gastrointestinal tract and respiratory tract contain high concentration of mast cells (10000 mast cells/mm^3 of skin). These are also granulated which have pharmacologically active mediators. They also secrete a variety of cytokines.

4. IgE binding to Fc receptor: Both the mast cells and basophils have receptor for IgE. Crosslinking of IgE by allergen leads to their degranulation. Even a crosslinking chemical, anti-isotype and anti-idiotype antibodies can also cause degranulation. Cross linking of IgE receptors by anti-receptors Abs causes degranualtion. Enhanced calcium ions influx by ionophores, increases membrane permeability for these ions. Calcium if involved in the synthesis of arachidonic acid a precursor for prostaglandins and leukotrienes, which are vasoactive amines. This calcium influx can be inhibited by using drugs like disodium cromoglycate.

5. Pharmacological Agents mediating Type I Reactions: The mediators released by mast cells and basophils act on populations of secondary effector cells like eosinophils, neutrophils, T-lymphocytes, monocytes and platelets. Incase of parasitic infections, the mediators increase vascular permeability, which leads to influx of plasma and inflammatory cells which attack the pathogens.

The primary mediators include, histamines, proteases, eosinophil chemotactic factor, neutrophils chemotactic factor and heparin. The secondary mediators are released after target cell is activated. These include Platelet activation factors, leukotienes, prostaglandins, bradykinins and various cytokines.

{Symptoms of Anaphylaxis: Anaphylaxis is of two types, systemic and localized.

a)Systemic anaphylaxis: This leads to death. Eg: Penicillin sensitized persons die in minutes after giving 2^{nd} dose. Dogs administered with toxin from Portuguese man of war also die. Pigs injected with egg albumin also die.

Reason and events: Animals become restless. Respiration is laboured, bp decreases. Smooth muscles of gastrointestinal tract and urinogenital tract contract leading to defecation and urination. Mediators are responsible for vasodialation and smooth muscle contraction.

Drugs used for cure: Epinephrine: It increases cyclic AMP levels. They counter act the effect of mediators and it blocks mast cell degranulation.

b) Localised anaphylaxis(Atopy): It is localized to a particular organ. Atopy is the tendency to manifest localized anaphylactic reaction and is inherited. This includes

i) Food allergens: food borne allergens lead to degranulation of mast cells lining the gut. These lead to vasodialation and smooth muscle contraction, Ag enter blood stream, which causes asthma, edematous red eruptions. Some develop atopic Urticaria, caused by certain food allergens and drugs. They cause erythematous eruptions and wheal flare response.

ii) Atopic dermatitis (allergic eczema) is an inflammatory disease of skin that is frequently associated with a family history of atopy. The disease is observed most frequently in young children, often developing during infancy. Serum IgE levels are often elevated.

iii)Astham: this is caused due to air borne allergens. Intrinsic asthma is caused due to severe cold or severe exercise. Events include: Mast cells degranulation that effect lower respiratory tract. Contraction of bronchial smooth muscles leads to airway obstruction. Infiltration of neutrophils and eosinophils causes damage to tissues by releasing toxic enzymes, O_2 radicles and cytokines. Asthma can also be due to air borne allergens.

iv) Commonly known as hay fever. Reaction are seen in conjunctiva and nasal mucosa by the air borne allergens. Mast cells degranulation lead to vasodialation. This leads to exudation of conjunctiva, nasal mucosa and upper respiratory tract with sneezing and coughing.**}**

6. Methods for detecting typeI hypersensitivity reactions:

a) RIST

b) RAST

7. Control of hypersensitivity reactions:

i) Avoid contact with Ag.

ii) Desensitization by administering graded doses of allergen.

iii) Hyposensitization- Repeated injections of increasing doses of allergen was found to cause increase in IgG production, when administered subcutaneously. It turns off IgE production, here IgG is called blocking Ag.

iv) Administration of monoclonal Abs against IgE.

v) Stabilizing mast cells using drugs like isoprenaline, which binds to mast cell receptors. Sodium chromoglycate, which stabilizes lysosomal membrane by preventing Ca^{2+} influx.

vi) Blocking histamine receptors by admintering antihistamine drugs which block H_1 and H_2 receptors on target cells.

vii) Blocking release of histamines- Theophylline, is given to asthamic patients orally. It blocks phosphodiesterase which converts cAMP to 5^1-AMP. Therefore cAMP concentration is increased and degranulation is prevented.

<u>TypeII: Antibody Dependent cell mediated cytotoxic hypersensitivity (ADCC)</u>

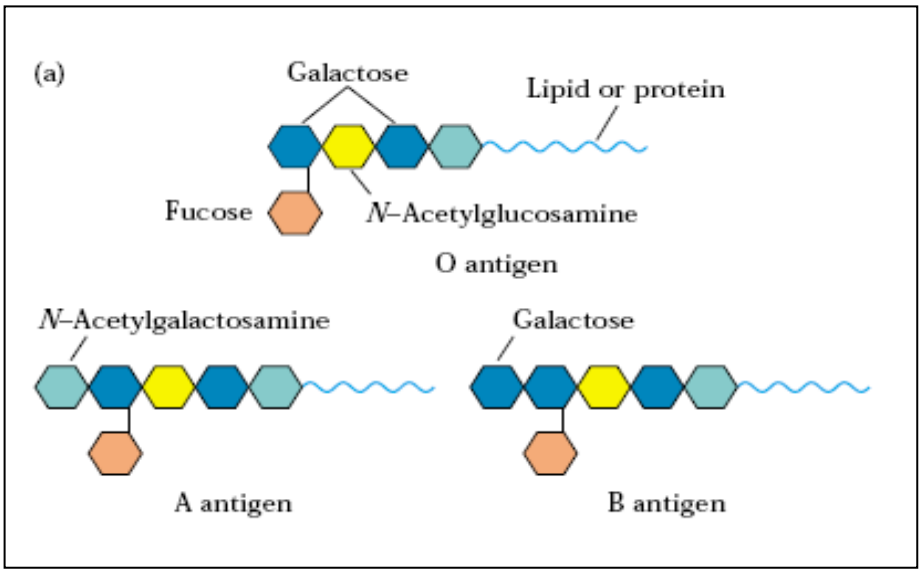
This is caused due to interaction of Ab and cell surface Ags and leads to cytotoxic effects. Cytotoxic cells with receptors for Fc of Ig cause lysis of Ab-bound cell. Some APC have C3b receptors for Ig which promotes their phagocytosis. Examples under this hypersensitivity include, **Agglutination and lysis of RBC** due to mismatched blood groups, **Erythroblastosis foetalis** and **Autoimmune Hemolytic Anaemias.**

I) Isoimmune reactions: These are due to involvement of isoantigens and antibodies.

Isoantigens are the Ags belonging to same species differing in their antigenic properties form one individual to another. Isoimmune reactions are the ractiosn between Ags and Abs belonging to two individual of the same species. These include,

a) Transfusion reactions
b) Erythroblastosis foetalis
c) Transplantation rejection reactions.

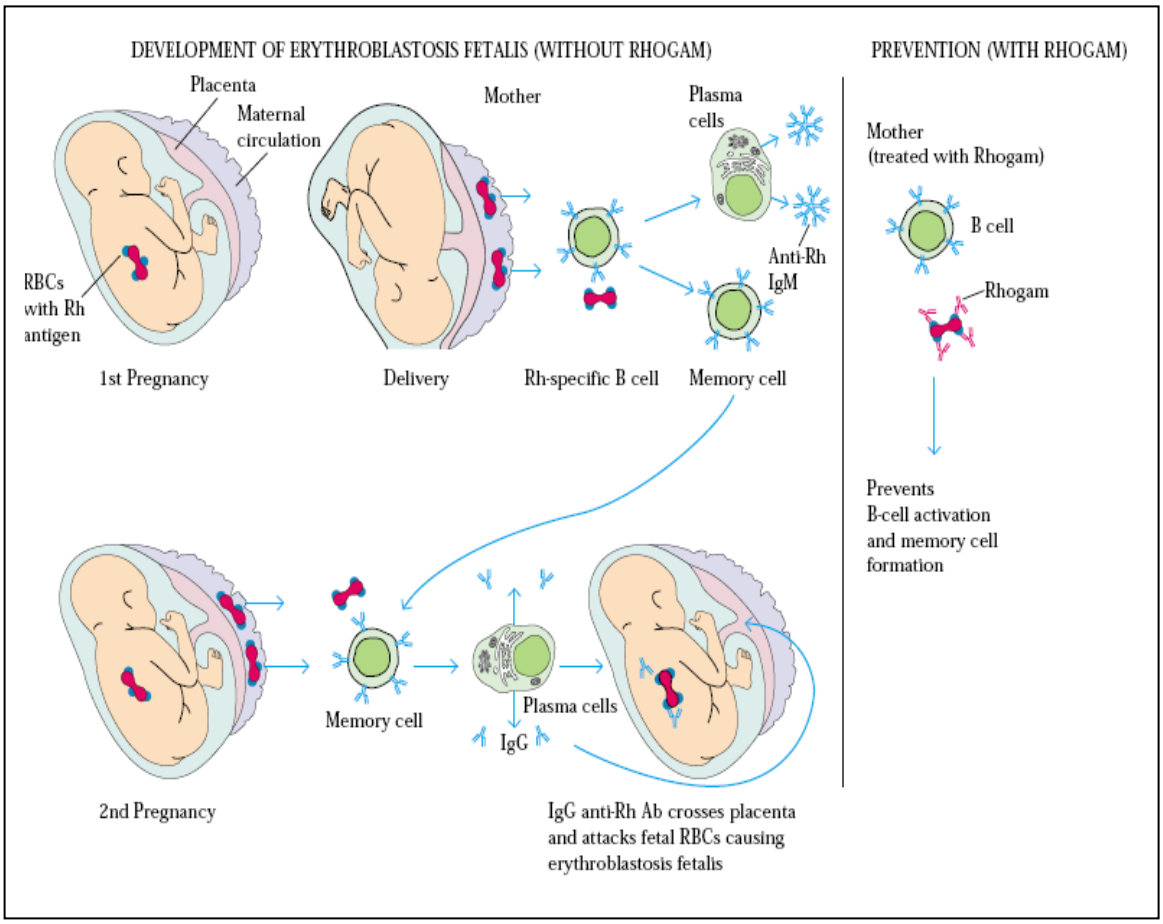
a) Transfusion reaction: Agglutination or lysis of recipient blood due to mismatched blood groups. These groups are identified into 3- A,B and O based on the presence of Ags on RBC. Ag are glycoproteins. The Abs belong to IgM and are called Isohemagglutinins. The structure of epitopes is an given below,



2. Erythroblastosis foetalis: A hemolytic disease caused by the reaction of Rh Ag with RhAb(IgG). Landsteiner (1940) identified this Ag in Rhesus monkey and named it Rh Ag or AgD. Human having this Ag on RBC are called Rh+ and around 93.5% are Rh+. The rest are called Rh-. Rh antibodies do not occur naturally, but are produced when Rh+ blood is given to Rh- person and these can cause hemolysis of RBC.

When a Rh- lady marries an Rh+ man, fetus is Rh+. During delivery of the first child, mixing of blood occurs and Rh^+ Ag having RBC cross placenta, they enter mother who is Rh^- and she develops anti-Rh antibodies. Incase of 2^{nd} baby, these Abs

cross placenta and causes the fetus RBC to lyse. This leads to jaundice in baby and finally death of fetus. This can be prevented by treating mother with RHOGAM (antiRh antibodies) within 72h of first delivery. These prevent sensitization of mother Bcells, therefore it prevents activation of Bcells and therefore memory cells are not formed.



3. Transplantation Rejection Reaction: A transplantation can result in Ab production due to HLA Ags. These Abs are cytotoxic to graft tissues. The damaged tissues are attacked by phagocytic and lymphoid cells. Platelets are also involved in such rejection reaction.

II Autoimmune reactions: These reactions are brought by Ag-Ab of the same individual. The antigens are autoantigens. Some familiar examples of this reaction are,

- **a.** Autoimmune haemolytic anaemia
- **b.** Autoimmune thrombocytopaenia purpura
- **c.** Autoimmune thyroiditis

d. Autoimmune glomerulo nephritis

The mechanism of all cytotoxic reactions can be due to:

a. Phagocytosis
b. Lysis
c. Killing by cytotoxic killer cells.

Type III: Immune Complex Mediated Hypersensitivity: This reaction is brought about by Ag-Ab ccomplexes. When enormous amount of Ag enter body, it leads to production of high concentration of Abs and both these come together to form insoluble precipitates. These complexes get attached to minute blood capillaries in the regions of glomerulus, synovium, skin, choroids plexus and respiratory tract. They cause tissue damage due to complement activation. The Abs involved are IgG and IgM. These hypersensitivities are caused due to repeated exposure to infectious microorganisms or due to repeated contact with environmental agents. Eg: Arthus reaction, Serum sickness.

Mechanism: It involves following steps(Figure)

-Immune complexes activate complement system(Classical pathway)

-During activation anaphylotoxins and chemotoxins are produced.

-C3a, C4a and C5a are anaphylotoxins, which trigger degranulation of mast cells.

-Histamines released bind to blood capillaries and finally result in vasodialation, which inturn leads to increased diapedesis of mast cells and neutrophils.

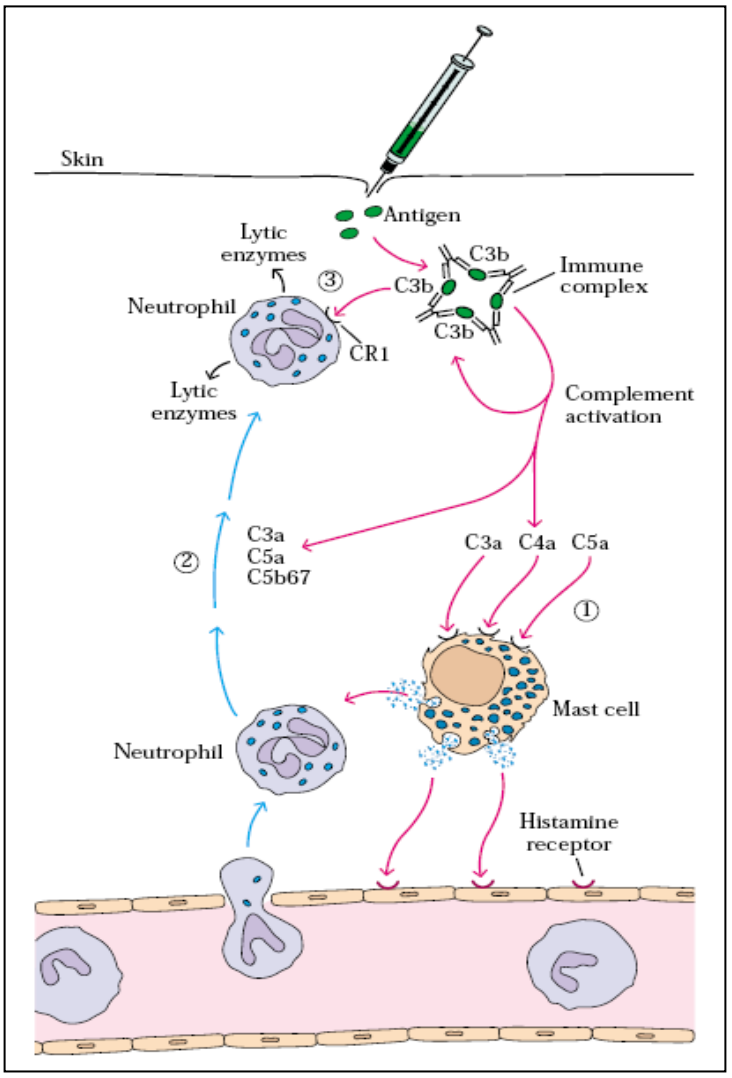
-The chemotoxins C3a, C5a, C5b, C6 and C7 acts as neutrophil chemotactic factors

-The neutrophils release lytic enzymes and try to phagocytose the C3b coated immune complexes.

-These lead to oedamatous and haemorrhagic lesions.

Exmple1; Arthrus reaction

This was observed by arthrus. It is produced upon intradermal injection of substances like horse serum, egg albumin etc. They induce IgG formation which activates complement. During activation anaphylotoxins are produced which trigger degranulation of mast cells to release vasoactive amines. Finally it results in erythema, haemorrhage and necrosis. Symptoms appear in 2 to 8h after injection and Persist for about 12 to 24h.



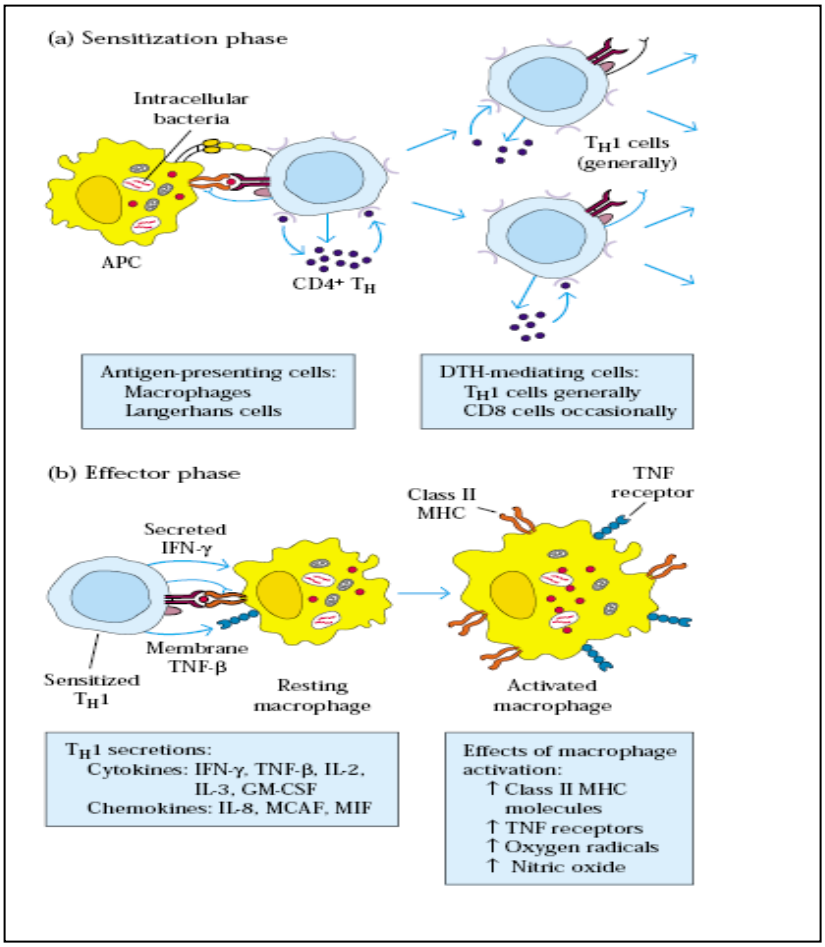
Example 2: Serum sickness:

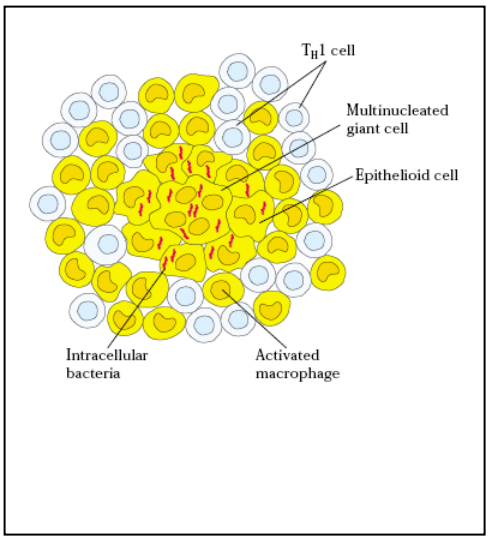
Caused due to injection of enourmous amounts of antisera like ATS or antidiphtheria serum. It was discovered by Von Pirquet and Schick. IgG is the predominant Ab that activated complement and results in the formation of anaphylotoxins and chemotoxins.

Serum sickness appears in 7 to 12days after injection of serum.

Type IV Cell Mediated Delayed Type Hypersensitivity: This is caused by the interaction between Ag and sensitized T cells. The reactions lead to inflammatory reaction and causes tissue damage. Symptoms appear in 24 to 72 h. It can be transferred from one person to another by transferring sensitized T cells. The lymphokines released by activated T cells lead to this reaction. The Ag include, infectious pathogens like bacteria, viruses, fungi and parasites. It is also caused by contact with nickel salts of ornamental jewels, neomycin ointment etc. Tuberculin reaction, contact dermatitis, leprosy, small pox, measles, herpes, leishmaniasis, schistosomiasis etc.

Mechanism: It involves to phases, sensitization phase and effector phase. T cells after receiving Ag through APCs become activated. This involves formation of some sensitized cells. Sensitized T cells when they come into contact with Ag for second time, release soluble proteins called lymphokines, which activate macrophages to kill the intracellular tubercule bacilli by phagocytosis. Increased phagocytic activity causes nonspecific cell destruction. Prolonged DTH leads to visible granulomatous reaction resulting in multinucleate giant cells, which lead to tissue damage and necrosis.





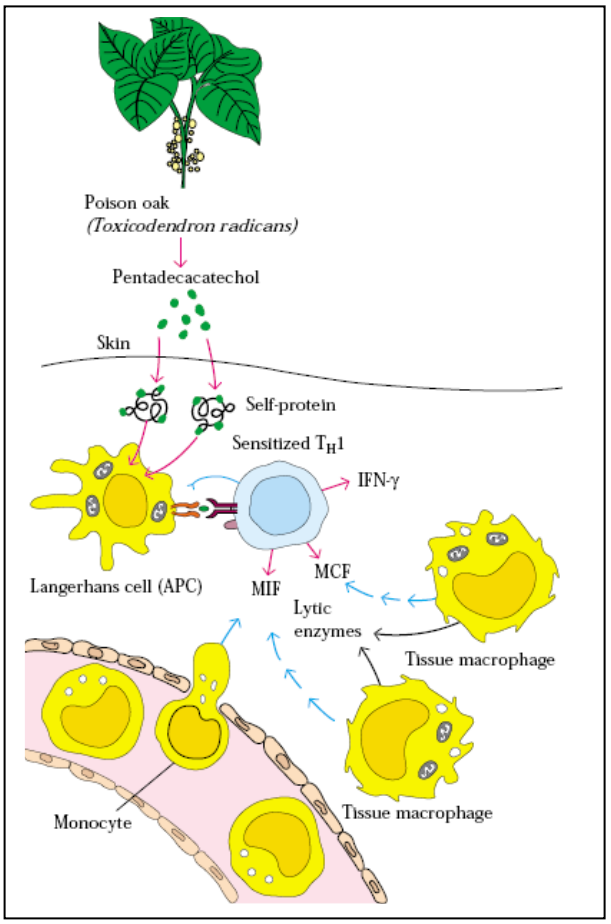
Contact dermatitis:

It leads to inflammation of skin when a person is exposed to material which is allergic to him.

Eg: Cosmetics, insecticides, rubber, leather good Jewellery etc are the allergens.

Pentadeca catechol is an allergen from the leaves of the poison oak, Toxicodendron radicum leaves. When rubbed on skin, it binds to self proteins.

The Langerhan cells take up the complex, process and present the antigenic part to T_H^1 cells. These cells release cytokines which increase infiltration of macrophages to the area. This leads to non-specific damage of the effected area by the macrophages.



Important question:

1. Define hypersensitivity? Explain the phenomenon with examples. -6
2. Write a brief account on type I hypersensitivity. -6
3. Write a detailed account on DTH. -8

All the 4 reactions are to be practiced.