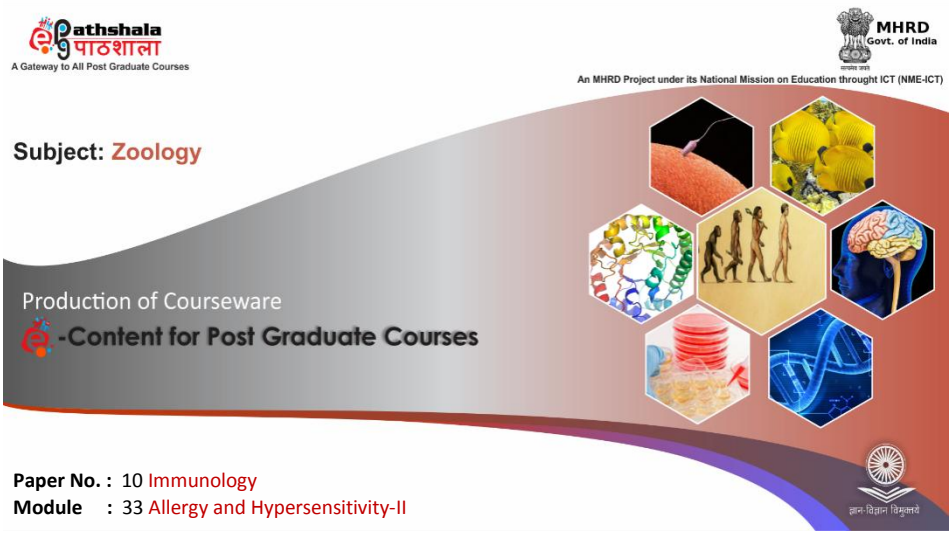

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Description of Module	
Subject Name	ZOOLOGY
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Module Name/Title	Allergy and Hypersensitivity-II
Module ID	33; Allergy and Hypersensitivity-II
Keywords	Delayed type hypersensitivity (DTH), Arthus reaction, Serum Sickness, Plasmapheresis, *Erythroblastosis Fetalis*, Transfusion Reactions

Contents

1. Learning Outcomes

After studying this module, you shall be able to

- **Know:** What are different types of hypersensitive reactions.
- **Learn:** How do these different hypersensitive reactions originate and their effector mechanisms.
- **Identify:** The components causing these reactions, mediators involved and the effects resulted.
- **Analyze:** The beauty of regulated immune response which if becomes dys-regulated or inappropriate can cause deleterious effects to host.

2. Introduction

- Out of the three types of hypersensitive reactions which are included in this module (i.e. type II, III and IV), type II and type III are immediate type hypersensitive reaction whereas type IV is delayed type hypersensitive reaction.
- Except type-IV hypersensitivity which is cell mediated immunity based, rest all hypersensitivity types as per the Gell and Coombs classification are humoral immunity based.
- Type-II hypersensitivity involves death of cells bearing antibody attached to cell surface antigen. It can lyse the cells by complement activation, by induction of phagocytosis or by antibody dependent cell mediated cytotoxicity (ADCC). Examples include blood transfusion reactions, haemolytic disease of newborn through rhesus incompatibility, antibody mediated graft destruction, autoimmune reactions etc.
- Type-III hypersensitive reactions are immune complex mediated complement activation based hypersensitivities. Localized vasodilation and chemotactic neutrophil attraction are elicited by complement split products. The accumulation of immune complexes at the antigen entry site induces localized Arthus reactions whereas circulating immune complex depositing at many sites causes generalized serum sickness. Examples include Farmer's lung and Pigeon fancier's disease.
- Type-IV hypersensitive reactions involve activation of sensitized T_{DTH} cells on secondary contact with antigen which results in secretion of various T_H1 Subtype cytokines and chemokines. These effector molecules help in recruitment and activation of macrophages. It is delayed type hypersensitivity as the onset of reaction takes 24-48 hours in general. Various skin tests e.g. Mantaux test, contact dermatitis etc. are common examples of type-IV hypersensitivity.

3. Type-II Hypersensitivity

Type-II hypersensitive reactions are humoral immunity based immediate type hypersensitive reactions. They involve antibody mediated destruction of target cells. The antibody bound to cell surface antigen can lyse the cell by number of ways such as:

- By activation of complement system which ultimately forms membrane attack complex (MAC) and causes formation of pores in the target cell leading to cell lysis.
- By serving as opsonin, enabling phagocytic cells with Fc or C3b receptors to bind and phagocytose the antibody-coated cell.

- By antibody dependent cell-mediated cytotoxicity (ADCC). In this process, cytotoxic cells promote target cell killing after binding with Fc region of cell surface antibody through their Fc receptors.

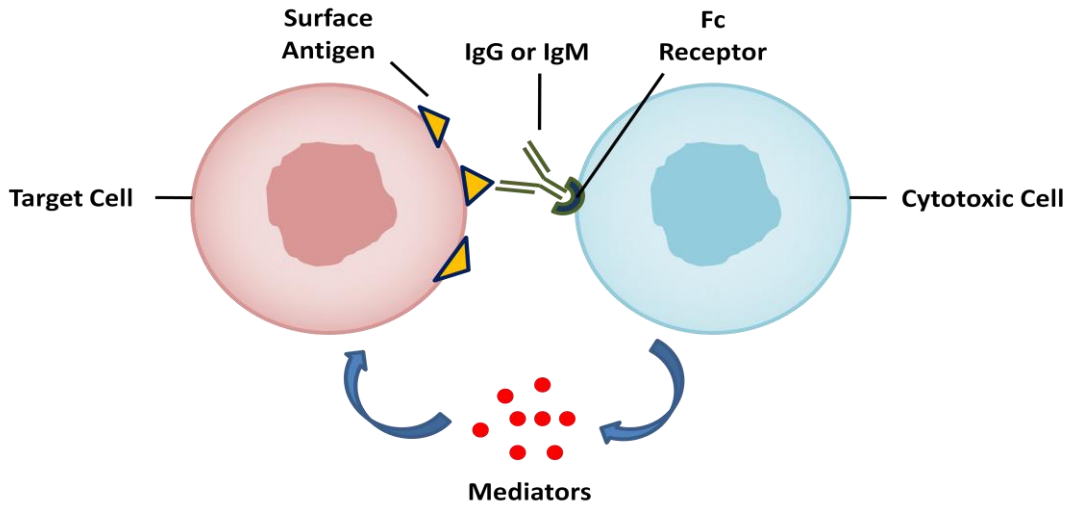

Figure 1: Antibody Mediate Cell Cytotoxicity. Antibody bound to surface antigen on target cell binds to Fc receptors present on cytotoxic cells which upon activation release cytotoxic mediators to kill target cell.
Source: Author

The clinical manifestations of type-II hypersensitivity include Rhesus Incompatibility, Transfusion Reactions, Neonatal Alloimmune Thrombocytopenia, Organ Transplants, Autoimmune Hemolytic Anemia etc. Let us discuss some of these manifestations in detail:

Rhesus Incompatibility/ *Erythroblastosis fetalis*/ Hemolytic disease of newborn:

The rhesus blood grouping system is second most used blood grouping system after ABO type. It was named so after its discovery in the rhesus monkey by Karl Landsteiner and Alexander S. Wiener in 1937. An individual either has or doesn't have the Rh factor or D antigen based on which he is designated as Rh^+ or Rh^-. The clinical consequence of a non-recognized Rh factor i.e. haemolytic transfusion reaction or haemolytic disease of newborn or *erythroblastosis fetalis* was reported by Phillip Levine and Rufus Stetson in 1939.
The 'hemolytic' means destruction of blood cells ('hemo'=blood; 'lysis'=destruction). Similarly, 'erythroblastosis fetalis' means lysis of red blood cells in foetus. These haemolytic conditions are caused due to incompatibility of rhesus factor between mother and developing foetus in mother's womb. When, maternal IgG specific for fetal blood group antigens cross the placenta, they destroy fetal blood cells and cause this disease. It occurs when an Rh^- mother carries an Rh^+ foetus. The Rh^+ foetus expresses the Rh antigen which Rh^- mother does not. The fetal blood cells remain separated from mother's blood by trophoblast layer of placenta during pregnancy. But at the time of delivery, fetal blood from umbilical cord enters the mother's circulation. The Rh or D antigen on these fetal blood cells activate Rh specific B cells in mother which results in the production of Rh specific plasma cells and memory cells in mother. These plasma cells clear the entered fetal Rh+ red blood

cells from maternal circulation but the memory cells create a threat for subsequent pregnancy with Rh+ foetus.

A subsequent pregnancy with Rh+ foetus activates these memory cells which can damage the red blood cells of developing foetus after crossing the placenta. It can cause mild to severe anemia, brain damage and even fatal consequences.

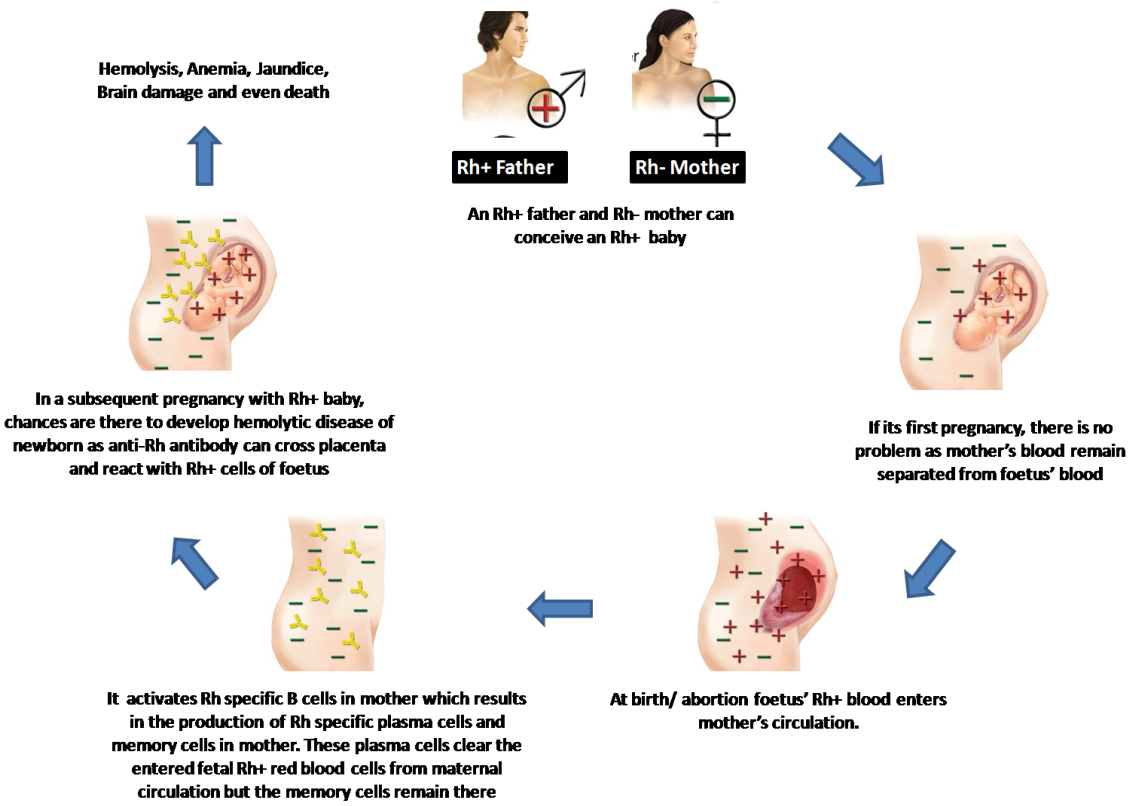

Figure 2: Mechanism of development of haemolytic disease of newborn due to rhesus incompatibility
Source: Author

The subsequent risk of haemolytic disease of newborn can be almost prevented by administering anti Rh antigen antibodies to mother with 24-48 hours of first delivery. These antibodies clear fetal RBCs that have entered the maternal circulation, before they activate B-cells or produce memory cells. These antibodies are called as **Rhogam**. Thus, these antibodies prevent the haemolytic damage to subsequent foetus.

If a woman is detected with haemolytic disease, the treatment is decided on the basis of severity of reaction. If the case is not very severe, the infant is exposed to low dose of UV light to break down the bilirubin to prevent cerebral damage. Also, mother is treated during pregnancy by plasmapheresis. In this technique, a cell separator is used to separate cells and plasma of mother's blood. Since it's the plasma that contains anti Rh antibody, is discarded. The remaining cells are re-infused into mother in fresh plasma solution. In other severe cases, foetus is given an intra-uterine blood exchange

transfusion to replace its Rh+ cells with Rh- cells. Such transfusion reactions are repeated every 10-21 days until delivery.

Value Addition:

Coomb's Test:

- *Coombs test was given by Robin Coombs, Arthur Mourant and Rob Race in 1945.*
- *It is also called as antiglobulin test or AGT.*
- *Coombs test is of direct type or indirect type. Direct Coombs test is used to detect if antibodies or complement proteins are bound to surface of RBCs. The blood sample is collected and cells are separated from plasma. The cells are then incubated with anti-human globulin (the Coombs reagent). The test is confirmed as positive if agglutination of RBCs is seen, which proves that antibody or complement is bound to RBC surface. Indirect Coombs test detects antibodies against RBCs that are present unbound in the patient's serum. In this test, serum is taken from patient's blood and incubated with RBCs of known antigenicity (from other patient blood samples). Agglutination confirms the test to be positive.*
- *Coombs test is used for cross matching before blood transfusions, diagnosis of haemolytic anemia etc.*

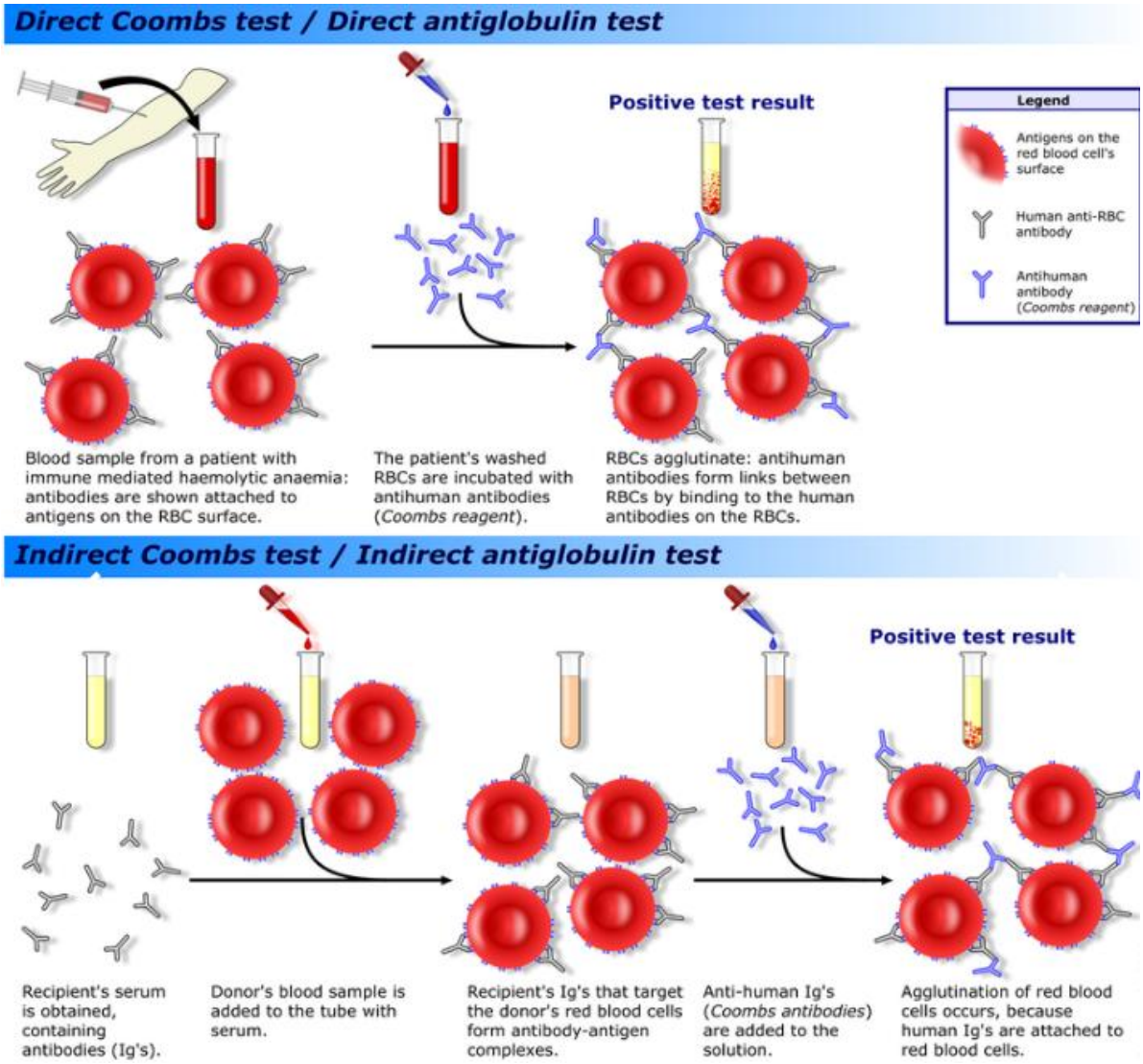

Figure 3: Procedure of direct and indirect Coombs test

Source: https://en.m.wikipedia.org/wiki/Coombs

Plasmapheresis:

Plasmapheresis (means, taking away plasma) is a medical procedure to remove, treat and return of blood plasma from circulation. Michael Rubinstein used this technique for the first time in 1959 to treat thrombotic thrombocytopenic purpura. This technique is used as therapy against autoimmune disorders, erythroblastosis fetalis etc. A generalized depiction of plasmapheresis technique is shown in figure 4.

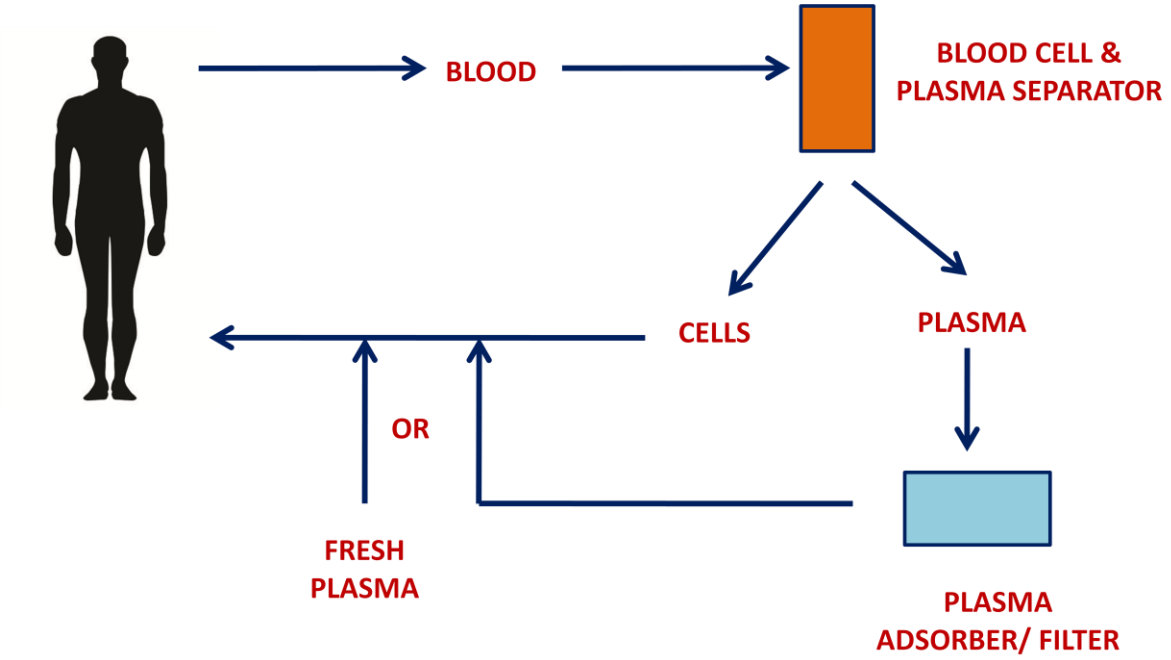

Figure 4: Plasmapheresis technique, which involves collection of blood from the patient, its separation into cells and plasma, absorbtion or filtration of plasma, mixing of filtered or fresh plasma with cells and transfusion back to the patient.

Source: Author

Other type-II hypersensitivity related disorders are:

ABO incompatibility between mother and foetus:

In most of the cases, the haemolytic disease of newborn has minor consequences. These are because of ABO incompatibility between mother and foetus instead of Rh incompatibility. An O blood group mother carrying A or B blood group foetus usually develops anti-A or anti-B IgG antibody. It can lead to fetal anemia but its mild only. It can cause bilirubin accumulation leading to jaundice. Exposure to low dose of UV is generally used to treat infant that breaks the bilirubin and avoids brain damage. For more severe cases, blood exchange transfusion may also be required.

Induction of Hemolytic anemia by drugs:

The non-specific adsorption of some antibiotics (e.g. penicillin, streptomycin, cephaliosporin etc.) to proteins present on RBC membranes forms a complex similar to hepten-carrier complex. These complexes induce antibody generation which further bind to adsorbed antibiotics and activate complement mediated lysis and haemolytic anemia. Such a haemolytic anemia disappears with withdrawal of drugs/ antibiotics.

Neonatal alloimmune thrombocytopenia:

In this disease, the foetus has a decreased platelet/ thrombocyte count. The platelet antigens are inherited from both mother and father. But there are chances that a mother has no platelet antigens of

its own and the child in mother's womb has got the platelet antigen from father. In such cases, it causes neonatal alloimmune thrombocytopenia because of maternal antibodies specific for platelet antigens coming from father.

Generally such a thrombocytopenia is mild and remains asymptomatic. But in some cases hemorrhage and particularly intracranial hemorrhage can occur which can cause death.

Transfusion reaction:

The red blood cells (RBCs) have a number of proteins and glycoproteins on their membranes. These proteins/ glycoproteins are encoded by different genes, each of which has various alleles. If a person having a particular allelic form of blood group antigen is transfused with blood having different allelic form on its RBCs, they are considered as foreign or non-self and an antibody response is generated.

Let us consider the ABO blood grouping system first to understand these transfusion reactions. ABO blood groups are distinguished on the basis of difference in terminal sugars that constitute the distinguishing epitopes in A, B and O antigens. The antigenic groups A and B are derived from H substance by the action of glycosyltransferases encoded by A or B gene respectively. The structure of these terminal sugars is shown in figure 5 below:

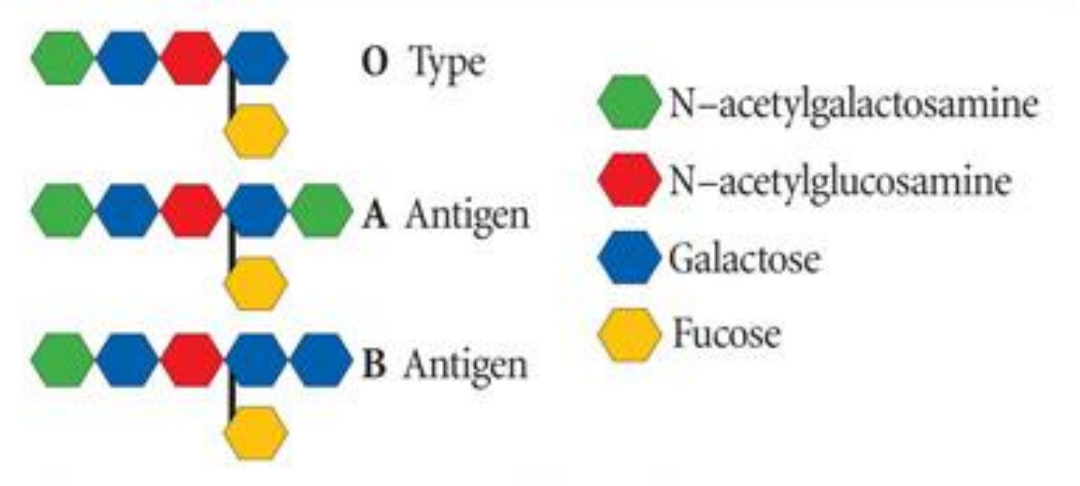

Figure 5: Difference in structures of A, B and H antigen present on surface of blood RBCs

Source: Author

A person having A antigen on its RBCs (i.e. A agglutinins) recognizes B-like epitopes on intestinal microorganisms and generates antibodies to B-like epitopes. These antibodies against A, B and O antigens are called as isohemagglutinins. Similarly, a person with B antigen on its RBCs (i.e. B agglutinins) recognizes A-like epitopes on intestinal microorganisms and generates antibodies to A-like epitopes. An O blood group individual has no surface antigen on RBCs, whereas AB blood group individual has both the A and B surface antigen. The blood groups in ABO blood grouping system are shown below in the table…along with their agglutinins and isohemagglutinins:

Blood Group or Phenotype	Genotype	Agglutinin or antigen on RBC surface	Isohemagglutinin or serum antibody
A	AA or AO	A	Anti-B
B	BB or BO	B	Anti-A
O	O	None	Anti-A and Anti-B
AB	AB	A and B	None

Table 1: Phenotypes, genotypes, agglutinins and isohemagglutinins of ABO blood grouping system

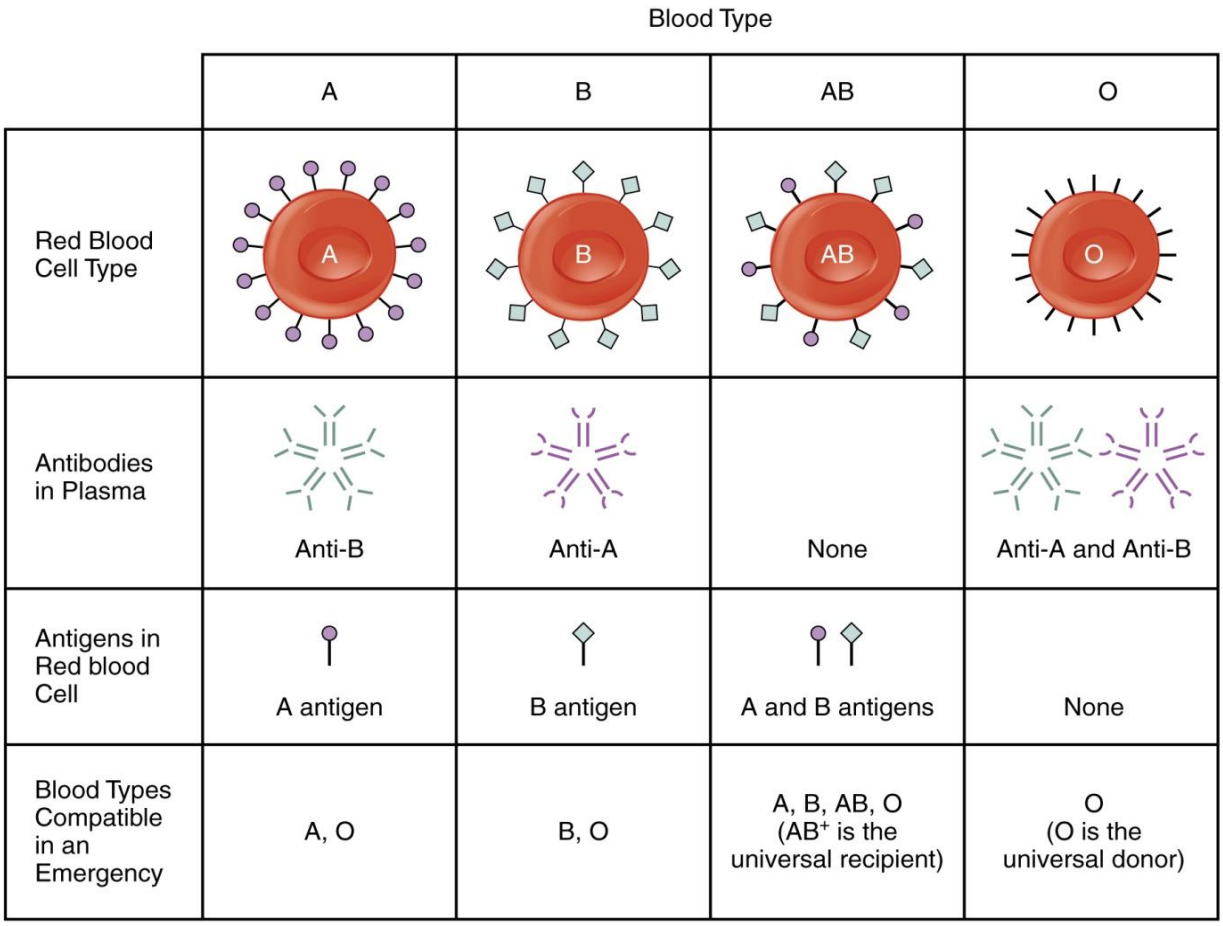

Figure 6: Characteristic properties of different blood group RBCs

Source:
http://biowiki.ucdavis.edu/TextMaps/OpenStax_Anatomy_and_Physiology/Unit_4%3A_Fluids_and_Transport/18%3A_The_Cardiovascular_System%3A_Blood/18.6%3A_Blood_Typing

The blood group is detected on the basis of agglutination of RBCs by mixing blood of the individual with anti-A, anti-B and anti-D antibodies (A, B for A and B antigen and D for Rh factor). For example, the image below represents A^+ blood group as the anti-A and anti-D antibodies agglutinated the RBCs, which confirmed the presence of A and D surface antigens respectively.

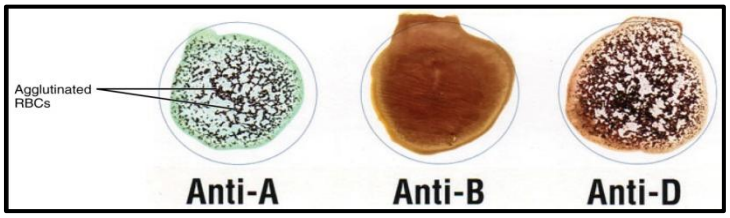

Figure 7: ABO type blood group testing using antisera against A, B and D antigens

Source:
http://biowiki.ucdavis.edu/TextMaps/OpenStax_Anatomy_and_Physiology/Unit_4%3A_Fluids_and_Transport/18%3A_The_Cardiovascular_System%3A_Blood/18.6%3A_Blood_Typing

If a person is transfused with blood having surface antigens on RBCs different from its own blood RBCs, a transfusion reaction takes place. The clinical manifestations of transfusion reaction involves antibody and complement mediated intravascular hemolysis of RBCs of transfused blood.

There can be immediate or delayed transfusion reactions. Immediate transfusion reactions arise due to ABO incompatibilities whereas delayed transfusion reaction result due to ABO-compatible but other blood group incompatibility. In immediate types, hemoglobinuria i.e. release of haemoglobin in urine is detected within few hours of transfusion. Fever, chills, clotting and nausea are other common symptoms. Some of the haemoglobin gets converted to bilitubin also, which is highly toxic at high levels. The predominant isotype in immediate type transfusion reactions is IgM which is very effective in complement activation. In delayed type transfusion reactions, symptoms appear after 2 to 6 days of blood transfusion. Common blood group antigens known to cause delayed transfusion reactions are Kidd, Duffy, Kell etc. Isotype involved in these reactions is IgG which is not as effective as IgM in complement mediated cell lysis. Thus, there is incomplete complement mediated lysis of transfused blood cells in delayed transfusion reactions. Symptoms include fever, low haemoglobin, anemia, jaundice etc. Since RBC destruction occurs at extravascular sites, there is no free haemoglobin detection in delayed transfusion reactions. The best strategy to avoid these reactions is to cross-match the donor and recipient's blood.

4. Type-III Hypersensitivity

Type-III hypersensitive reactions are humoral immunity based immediate type hypersensitive reactions. They involve antigen-antibody complex or immune complex mediated complement activation with ensuing inflammatory response mediated by neutrophil infiltration.

In general, the antibodies complex with antigens and facilitate the clearance of this antigen-antibody complex by phagocytes. But, if there is accumulation of such immune complexes, it leads to type-III hypersensitive reactions. The strength of type-III hypersensitivity depends on site and amount of immune complexes. The common sites of deposition of immune complexes are: Synovial membrane of joints, Walls of blood vessels, choroid plexus of brain and glomerular basement membrane of kidney.

With the accumulation of immune complexes at a particular site, complement proteins get activated. The split products of complement proteins i.e. C3a, C4a and C5a act as anaphylatoxins. These

anaphylatoxic molecules increase the vascular permeability and cause mast cell degranulation . Some of these products i.e. C3a, C5a and C5b67 act as chemotactic factors for extravasation and accumulation of neutrophils at the site of immune complex deposition. These neutrophils release lytic enzymes as they are unable to phagocytose the immune complexes deposited on basement membranes. C3b acts as an opsonin for binding of neutrohils. Aggregation of platelets and complement mediated tissue damage are other mechanisms involved in type-III hypersensitive reactions.

Type-III hypersensitive reactions can be localized or generalized.

Localized type-III hypersensitive reactions:

An intradermal or subcutaneous injection to an individual having circulating antibodies specific for injected antigen at high level leads to formation of immune complex which are localized and in high number. It leads to local Arthus reaction within 4-8 hours. The tissue with Arthus reaction shows adherence of neutrophils to vascular endothelium and then their migration to tissues at the site of immune complex deposition. It leads to localized vascular and tissue damage with edema and erythema. These Arthus reactions are known with various names, usually depending on source of antigen e.g. 'Pigeon Fancier's Disease' is named so because it results from inhalation of serum protein in dust derived from dried pigeon fecal matter. Similarly, 'Farmer's lung' results from inhalation of thermophilic actinomycetes from mouldy hay.

A diagrammatic depiction of mechanism of a local Arthus reaction is shown below in figure 8.

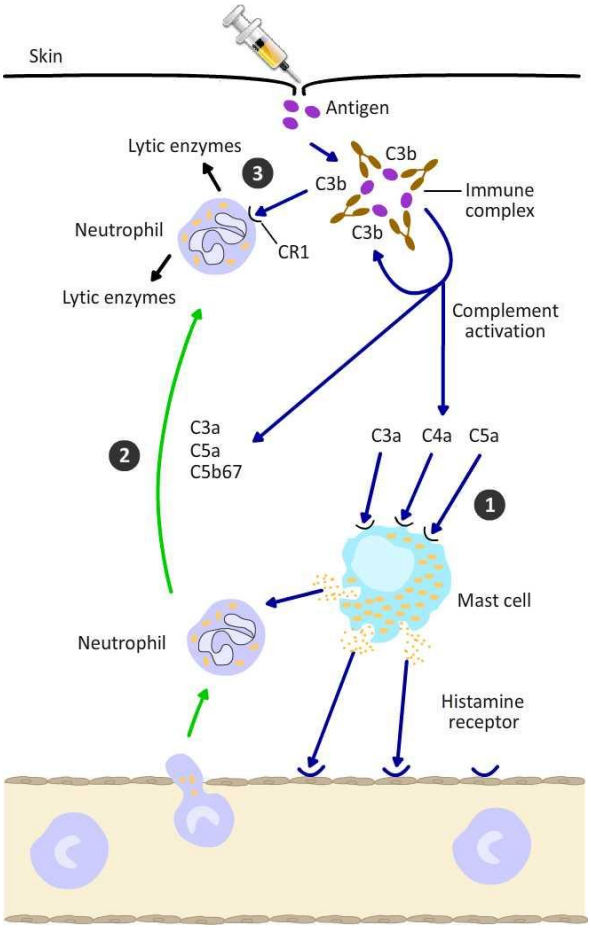

Figure 8: Mechanism of development of a localized Arthus reaction

Source: Author

Value addition:

Arhus reaction was discovered by ***Nicolas Maurice Arthus*** *in 1903. He observed that repeated subcutaneous injection of horse serum into rabbit resulted in edema and slow absorption of serum. Further injection led to gangrene eventually*

Generalized type-III hypersensitive reaction:

Circulating immune complexes in blood arising due to large amount of antigen entered and bound with antibody in blood, give rise to generalized type-III hypersensitive reactions. The clinical manifestations of generalized type-III hypersensitive reactions are called as **'Serum Sickness'** which includes vasculitis, fever, erythema & edema, weakness, arthritis, glomerulonephritis and lymphadenopathy etc. Though the immune complexes may deposit at various sites but generally they accumulate more at the sites where filteration of plasma occurs i.e. kidney, arteries and synovial joints. That is the reason why serum sickness shows high incidence of glomerulonephritis, vasculitis and arthritis respectively.

Serum sickness is not the only pathogenesis because of immune complex mediated type-III hypersensitive reactions. The other common conditions are:
Infectious diseases e.g. Meningitis, Hepatitis, Trypanosomiasis etc.
Drug induced e.g. Penicillin and Sulfonamides etc.
Autoimmune disorders e.g. Rheumatoid arthritis, Systemic lupus erythematosus, Goodpasture's syndrome etc.

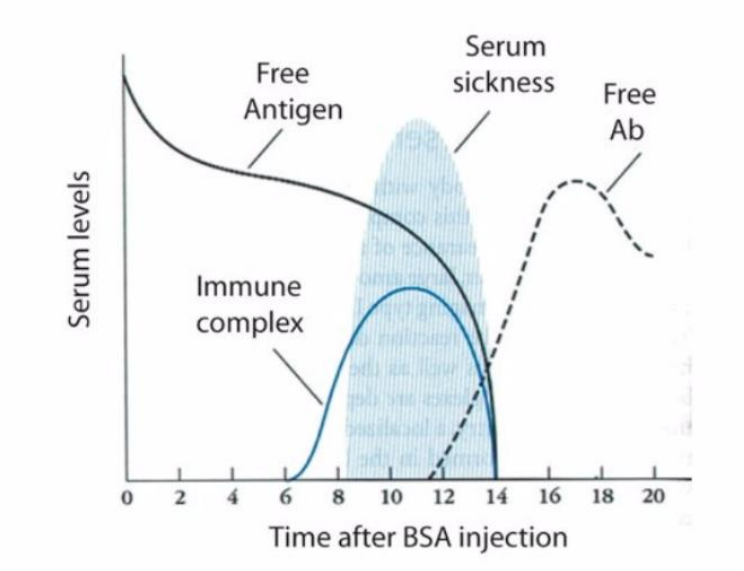

Figure 9: Graphical representation to show correlation between immune complex formation and development of serum sickness symptoms. Injection of large dose of Bovine Serum Albumin (BSA) in rabbit leads to formation of antibodies and subsequent immune complex formation. The symptoms of serum sickness coincide with peak of immune complex formation. With clearance of these immune complexes, free circulating antibodies are left and serum sickness symptoms subside.

Source: Modified from Kuby's Immunology 4th ed. by R. A. Goldsby, T. J. Kindt and B. A. Osborne

5. Type-IV hypersensitivity

- Type-IV hypersensitive reactions are cell mediated immunity based, delayed type hypersensitive reactions.
- As compared to immediate type reactions, delayed hypersensitive reactions take 48-72 hours to develop and instead of neutrophils, macrophages are the major components which are infiltrated at the site of inflammation.
- It was first described by Robert Koch in 1890.
- A simplified general overview of mechanism of type-IV hypersensitive reaction can be shown as:

Entry of Antigen

↓

Activation of sensitized T_{DTH} cells (Generally T_H1 subpopulation, but some T_c cells are also involved)

↓

Release of cytokines i.e. Interleukin-2 (IL-2), Interferon gamma (IFN-γ), tumor necrosis factor-β (TNF-β) and macrophage inhibition factor (MIF)

↓

Infiltration and activation of macrophages with increased phagocytic activity and increased concentration of lytic enzymes

↓

Localized tissue destruction with lytic enzymes i.e. type-IV hypersensitivity.

Type-IV hypersensitivity is important to fight intracellular parasites and bacteria as they cannot be accessed by circulating antibodies. Thus, the phagocytic activity and lytic enzyme mediated destruction of infected cells is required to protect the host from such infections. But a heightened response may lead to non-specific tissue destruction at the site of infection. The continued presence of pathogen with ineffective defense process leads to chronic DTH reaction. For example, lung cavitation in *Mycobacterium tuberculosis* infection and granulomatous skin lesions in *Mycobacterium leprae* infection are results of chronin DTH reactions.

Detection of DTH response or type-IV hypersensitivity:

The presence of T_{DTH} cells which have been sensitized earlier with an antigen can be detected by reaction to an intradermal injection of the same antigen. A characteristic skin lesion develops at the site of injection in a positive test which indicates the individual has a sensitized T_{DTH} population for that particular antigen. For example, the Mantaux test or Tuberculin test or Purified Protein Derivative (PPD) test is done to test whether the individual has been exposed to *Mycobacterium tuberculosis*. In this test, PPD (a protein derived from cell wall) is injected intradermally and observed for development of firm, swollen, red lesion on skin after 48-72 hours. Development of such a skin lesion indicates that the person has been exposed to *Mycobacterium tuberculosis.* Though, it cannot be concluded whether the person was exposed to pathogenic form of *Mycobacterium tuberculosis* or the vaccine.

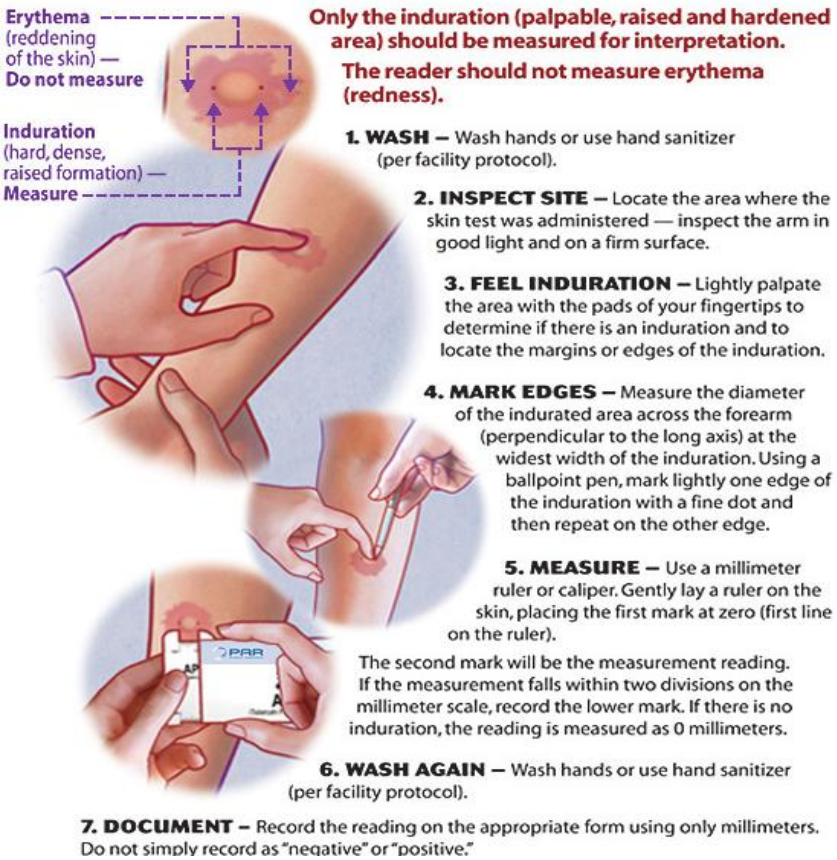

Figure 9: Procedure for PPD skin test/ Mantaux test

Source: http://www.parsterileproducts.com/products/products/aplisol/administer-read-interpret.php

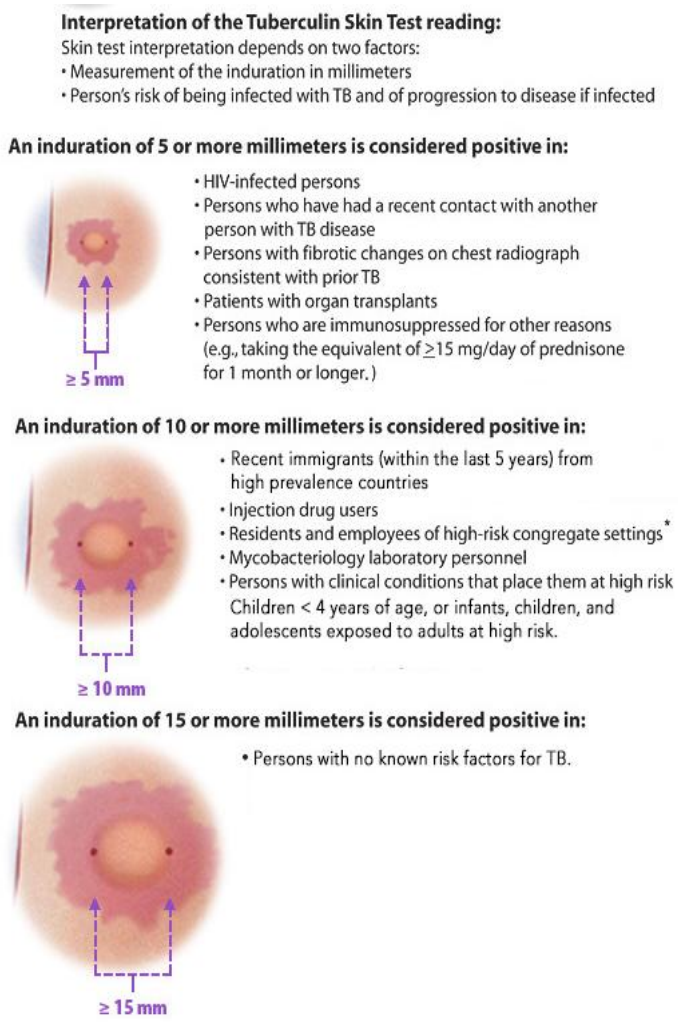

Figure 10: Reading of PPD test result/ induration size

Source: http://www.parsterileproducts.com/products/products/aplisol/administer-read-interpret.php

Similarly, other skin tests for detection of previous exposure of microbe causing leprosy and coccidiomycosis are done with lepromin and coccidiodin as test antigens respectively. Also the AIDS progression can be detected by monitoring decreased skin reactivity to any of various antigens (haptens or antigens). As AIDS progresses, $CD4^{+}T_{H}$ cell population decreases, decreasing T_{DTH} cells mediated type-IV hypersensitive response.

Contact dermatitis arising due to contact with chemicals like formaldehyde, trinitrophenol, turpentine, nickel etc.; cosmetics like hair dyes; plants like poison oak and poison ivy are mediated by type-IV hypersensitive reactions. The mechanism involves:

Complex formation of these antigens with skin proteins

↓

Internalization of these complex by skin antigen presenting cells (i.e. Langerhans cells)

↓

Processing and presentation of these antigens with class II MHC molecules

↓

Activation of sensitized T_{DTH} cells

<u>An example of type-IV hypersensitivity generated due to poison oak is represented below</u>:

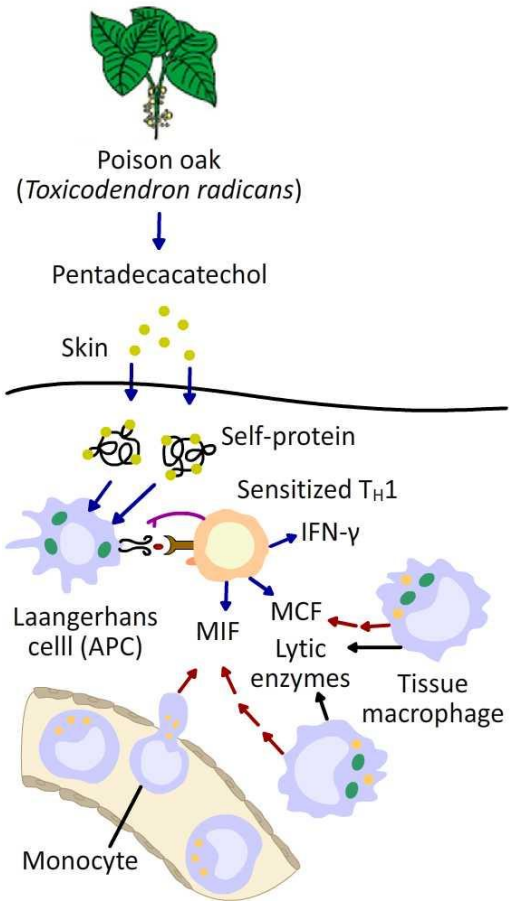

Figure 11: Contact dermatitis by poison oak: An example of type-IV hypersensitivity

Source: Author

Phases of DTH response:

DTH response is divided into an initial sensitization phase and an effector phse. Sensitization phase lsts for 1-2 weeks after primary contact with antigen. In this phase T_H cells undergo activation and clonal expansion by antigen presented with MHC-II molecules on antigen presenting cells (APCs). Langerhans cells and macrophages are primary APCs involved in this response. The T cells involved in this phase are $CD4^+$ T_H1 subpopulation mainly but some $CD8^+$ Tc cells have also been shown to induce DTH response. T_{DTH} denotes activated T_H cells (or some Tc cells) only but named so to denote their function in DTH response.

Effector phase is induced with subsequent exposure of antigen. In this phase sensitized T_{DTH} cells secrete a number of cytokines which recruit and activate macrophages and other non-specific inflammatory cells to site of inflammation. Since it takes time for cytokines to induce localized influx of immune cells, the DTH response shows a delayed onset and becomes apparent after 24-48 hours of secondary contact with antigen.

In cases where antigen is not cleared easily, a granulomatous reaction develops which can damage host tissues a well. In granulomatous reaction, continuous activation of macrophages leads to adherence of these cells to form an epitheloid shape or multi-nucleated giant cell after fusion. Such giant cells displace the normal cells and create a palpable nodule. High amount of lytic enzymes released by these cells cause tissue damage or even necrosis.

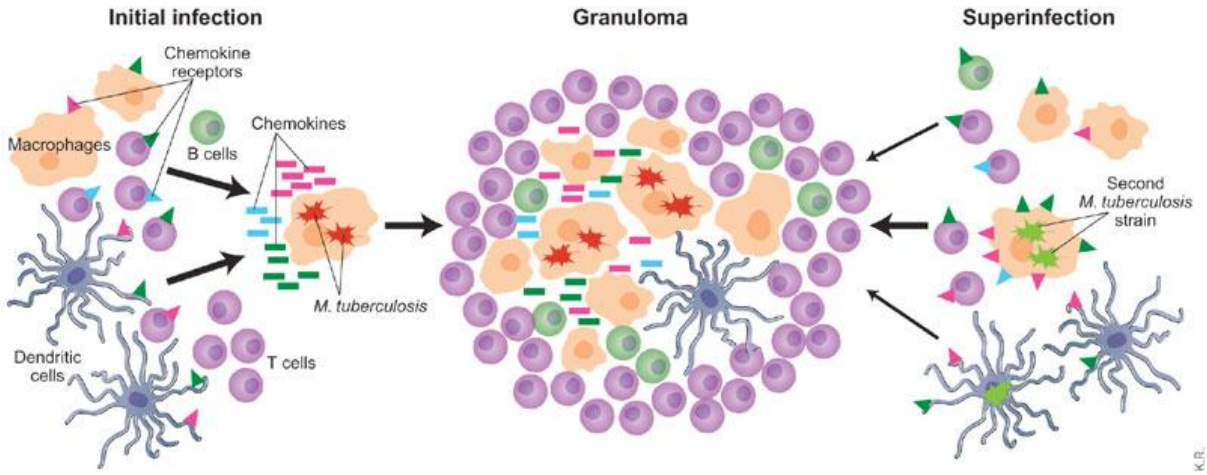

Figure 12: Granuloma formation due to chronic DTH reaction

Source: http://www.nature.com/ni/journal/v5/n8/fig_tab/ni0804-778_F1.html

An overview of phases of DTH response is shown below in figure 13:

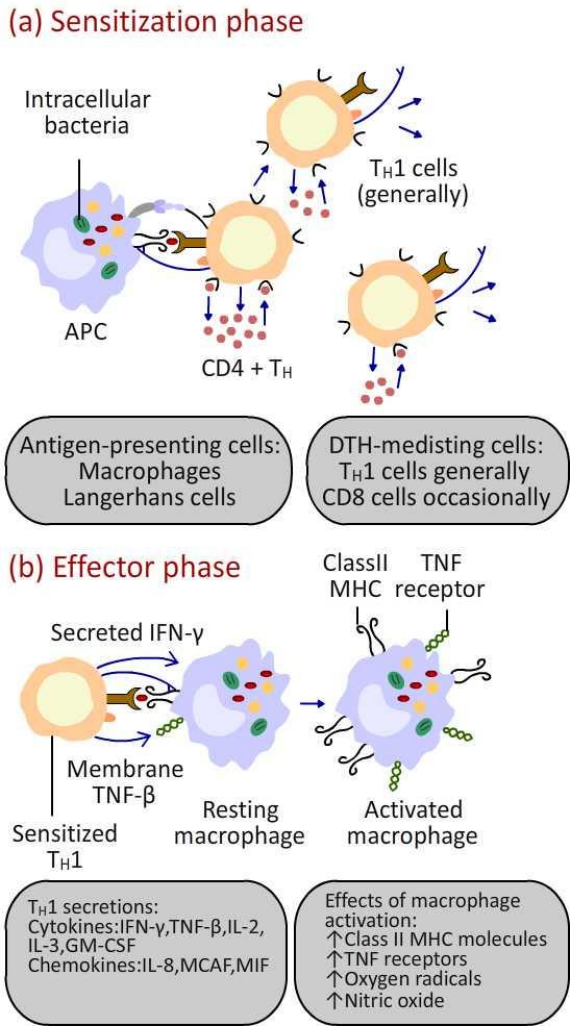

Figure 13: Development of a DTH response

Source: Author

Cytokines and chemokines involved in DTH response:

The profile of cytokines observed in DTH response indicates that T_{DTH} cells are primarily TH1 subset only. The cytokines involved in DTH response are:
IL2: Amplifies the population of cytokine producing T cells
IL-3 and GM-CSF: Inducers of localized hematopoiesis of granulocyte-monocyte lineage.
IFN-γ and TNF-β: Facilitate extravasation of monocytes and macrophages

Chemokines Involved:
Monocyte chemotactic and activating factor (MCAF): Chemotactctic recruitment of monocyte to site of inflammation is performed by MCAF.

Migration inhibition factor (MIF): It prevents further migration of monocytes beyond the site of inflammation.

Common Inducers of Type-IV Hypersensitivity:

Type	Examples
Intracellular Bacteria:	Mycobacterium tuberculosis, Mycobacterium leprae, Brucella abortus etc.
Intracellular Parasites:	Leishmania sp.
Intracellular Viruses:	Herpes simplex virus, Measles, Variola etc.
Intracellular Fungi:	Candida albicans, Histoplams capsulatum etc.
Contact Antigens:	Hair dyes, Poison Oak, Poison Ivy etc.

Table 2: Common type-IV hypersensitivity inducer classes with examples

6. Summary

- As per the Gell and Coombs classification, all hypersensitivities can be classified in four groups i.e. type I, II, III and IV. Type I, II and III are humoral immunity based hypersensitivities which shows their symptoms in hours and hence termed as immediate type. On the other hand type-IV is cell mediated immunity based hypersensitivity which takes days to weeks to show its symptoms and thus called as delayed type hypersensitivity (DTH).
- Type II hypersensitivity is antibody dependent hypersensitivity. The antibodies bound to the surface antigens on target cells can lyse the target cells by either complement activation, by promoting phagocytosis or by antibody dependent cell mediated cytotoxicity (ADCC).
- The clinical manifestations of type-II hypersensitivity include Rhesus Incompatibility, Transfusion Reactions, Neonatal Alloimmune Thrombocytopenia, Organ Transplants, Autoimmune Hemolytic Anemia etc.
- Coombs test is primary used to detect type-II hypersensitivity in haemolytic disease of newborn and transfusion reactions etc.
- Type-III hypersensitive reactions are humoral immunity based immediate type hypersensitive reactions. They involve antigen-antibody complex or immune complex mediated complement activation with ensuing inflammatory response mediated by neutrophil infilteration.
- Type-III hypersensitive reactions can be localized or generalized. Localized type III hypersensitivity leads to local **Arthus reaction** (Described by **Nicolas Maurice Arthus** in 1903) within 4-8 hours. The symptoms include edema and erythema. Examples are: 'Pigeon Fancier's Disease' and 'Farmer's lung'
- Generalized type-III hypersensitive reaction includes **'Serum Sickness'** which shows vasculitis, fever, erythema & edema, weakness, arthritis, glomerulonephritis and lymphadenopathy
- Type-IV hypersensitive reactions are cell mediated immunity based, delayed type hypersensitive reactions. As compared to immediate type reactions, delayed hypersensitive reactions take 48-72 hours to develop and instead of neutrophils, macrophages are the major components which are infiltrated at the site of inflammation. It was first described by Robert Koch in 1890. Type-IV

hypersensitivity involves activation of sensitized T_{DTH} cells, release of cytokines, infiltration and activation of macrophages with increased phagocytic activity and increased concentration of lytic enzymes.

- Type-IV hypersensitivity involves two phases i.e. sensitization phase (activation and clonal expansion of TH cells) and effector phase (release of mediators to cause effector functions). Various intracellular pathogens and contact antigens are known to cause type-IV hypersensitive reactions.