Hypersensitivity

Hypersensitivity: Term hypersensitivity refers to the injurious consequences in the sensitised host, following contact with specific antigens. It is a result of an immune reaction. It is an altered state of reactivity to an antigen. In hypersensitivity antigens are of little concern often they are non-injurious or bland substances such as serum proteins.

For induction of hypersensitivity reaction host should have had contact with antigen. Initial contact sensitises the immune system leading to the priming of appropriate B or T lymphocytes this is known as 'Priming/Sensitivity'. Subsequent contact with an allergen causes the manifestation of hypersensitivity is known as a shocking dose.

Classification of Hypersensitivity

Hypersensitivity reaction is classified traditionally into:

1.Immediate Type	a. Anaphylaxis
(Antibody Mediated)	b. Arthus Phenomenon
	c. Antibody Mediated
	d. Atopy.
2.Delayed Type	a. Contact Dermatitis
(Cell Mediated)	b. Tuberculin Type.

Coombs & Gell (1963) classified hypersensitivity reaction:

1.Type I: Anaphylactic Reaction
2.Type II: Cytotoxic/Cell Stimulating
3.Type III: Immune Complex Disease
4.Type IV: Delayed/Cell Mediated

Type I: Hypersensitivity/ Anaphylactic Reaction :(Ana-without; Phylaxis-protection)

Anaphylaxis: A sudden, systemic, severe immediate hypersensitivity reaction resulting from rapid generalized mast cell degranulation.

1. When antigen binds to mast cell-bound IgE and so cross-links two or more FceRI, a series of reactions is triggered that causes the degeneration of the mast cell. Also triggers the production of many different inflammatory mediators and cytokines.
2. Degranulation of the mast cell releases
Vasoactive factors:- Chemotectic factors, Enzymes, Cytokines.
3. Release of the above factors leads to the acute inflammation and systemic effects.

Type II Hypersensitivity

RBC's have characteristic cell surface molecules that can act as antigen. Most red cell surface is either glycoproteins or glycolipids (physiological function of red cell surface antigens is unknown.).The functions of ABO antigens in human beings – Glucose transporter proteins & C in sheep – Amino acid transport & membrane potassium pumps. Normally the antibodies are not formed against the self-antigens i.e., self-red cell surface antigens. But in case of interspecies
blood transfusion, autoimmune disease, etc immune response is stimulated.

- **Blood Transfusion:**
    - Normally the antibodies are not formed against the self-antigens i.e., self-red cell surface antigens. But in blood transfusion from one animal to another genetically dissimilar individual, the antigens on the red cell surface will stimulate an immune response. Resulting in the rapid elimination of transfused red cells as a result of intravascular hemolysis mediated by antibody and complement. And of extravascular destruction resulting from opsonization and clearance by phagocytic cells.
    - Cell destruction mediated by antibodies in this way is classified as type II hypersensitivity reaction.
    - Cross-matching is done to avoid the complications.

- **Autoimmune diseases:** In case of autoimmune anemia and haemolytic diseases
    - anti-erythrocyte antibodies are formed, leads to type II hypersensitivity reaction.

- **Drugs/ Hapten/Free Antigen:** May be absorbed on cell surfaces. Subsequent reaction of the combined antigen or hapten with its corresponding antibodies leads to cell damage (complement mediated lysis of RBC's, leukocytes and platelets).

Blood Group:

Cattle	A, B, C, F, J, L, M, S, Z, T, R'-S'.
Sheep	A, B, C, D, M, R, X.
Pig	A-O.
Horse	A, C, D, K, P, Q, U.
Dog	A, B, C, D, F, J, L, M, N, Tr.
Cat	AB

Because of the complexity of the B system, it is generally impossible to obtain absolutely identical blood from any two unrelated cattle. Indeed it has been suggested that the complexity of the B system is such that there exists sufficient different antigenic combinations to provide a unique identifying character for each bovine in the world.

Type III Hypersensitivity

The formation of an immune complex by the combination of antigen and antibody activates the complement cascade. When complement is activated immune complexes are deposited in tissues, and the generation of chemotactic peptides attracts neutrophils. The neutrophils release free radicals and enzymes into the tissues and cause inflammation and tissue destruction. Lesions generated in this way are classified as type III or immune complex-mediated hypersensitivity reactions.

The severity and significance of type III hypersensitivity reaction depends on the amount and site of deposition of immune complexes. Two major forms of reaction are recognized :

1. **Local reaction:** Immune complexes are deposited within tissues and can be induced in any tissue to which antigens can gain access.

   Arthus Reaction: If an antigen is injected s/c into an animal that already has antibodies that can precipitate the antigen, an acute inflammatory response will develop at the site of injection within several hours. This is called an Arthus reaction after the scientist who first described it. It starts as erythematous, oedematous swelling, local haemorrhage (eventually), thrombosis, culminating into local tissue destruction.

2. **Circulation**: Large quantities of immune complexes are formed within the circulation & are deposited in the walls of blood vessels. (When antigens are administered intravenously to an immune recipient).

   Serum sickness: Many years ago, when the use of antisera for passive immunization was in its infancy, it was observed that the individuals receiving large doses of equine anti-tetanus serum developed characteristic side effects about 10 days later. Side effects consisted of generalized vasculitis, edema, and urticaria of the skin, lymph node enlargement, joint swelling, and proteinuria. The reaction is of short duration subsiding within a few days and is known as **serum sickness**.

   A similar reaction can be produced experimentally in rabbits by administration of a single dose of antigen. The development of lesions coincides with the formation of large amounts of immune complexes in the circulation as a result of the immune response to circulating antigens.

Type IV Hypersensitivity

When some antigens are injected into the skin of sensitized animals, a slowly developing inflammatory response may occur at the injection of the site. Delayed hypersensitivity of this type is known as **type IV hypersensitivity**.

Cell mediated type of reaction.

Important example of delayed type of hypersensitivity reaction is the **tuberculin reaction**: a skin reaction in an animal with tuberculosis as a result of an intradermal injection of tuberculin.

Tuberculin Test:

Tuberculin is the name given to extracts of *Mycobacterium tuberculosis, Mycobacterium bovis,* or *Mycobacterium avium*. PPD-Purified Protein Derivative is prepared by growing organisms in synthetic medium, killing them with steam and filtering. And is precipitated with tricholoroacetic acid, washed and finally resuspended in buffer ready for use.

When tuberculin is injected into the skin of normal animal there is no significant response. On the other hand, if it is injected into an animal sensitized by infection with mycobacteria, a delayed type of hypersensitivity response will occur.

Following intradermal injection with tuberculin into a sensitized animal, red, indurated (hard) swelling slowly develops at the injection site. The inflammation begins between 12-24 hrs reaches its greatest intensity by 24-72 hours and may persist for several weeks. Resulting into tissue destruction and necrosis at the site of injection.

Tuberculin reaction is immunologically specific inflammatory reaction mediated by T cells.

Pathological consequences: Tubercle formation, allergic contact dermatitis.
Other similar tests : , Jhonin test, Brucellin test, Mallein test.

Tuberculin

Tuberculin is a protein substance (*purified protein derivative*) from the tuberculosis-causing bacillus, *Mycobacterium tuberculosis,* first discovered and extracted by Robert Koch in 1890. When the test is positive, a region of swelling 10 mm (0.4 inch) or greater in diameter, usually accompanied by redness, occurs within 48 hours at the site of injection. A positive reaction indicates that the individual was previously exposed to the tubercle bacillus, but it does not necessarily indicate that active clinical tuberculosis is present, or ever existed.

Shortly thereafter, the diagnostic capabilities of the material were recognized through its use in animals. In 1934, Seibert and Glenn, prepared the first batch of a much more purified preparation, which they termed *purified protein derivative* (PPD). The most prevalent antigenic proteins in PPD are now known to be the bacterial heat shock proteins (or chaperonins) GroES, GroEL2, HspX, and DnaK. The antigen is prepared in liquid form containing the detergent Tween 80 to decrease adsorption of protein to the glass of the vial. The standard intermediate tuberculin test consists of the intradermal injection (Mantoux method) of 0.1 mL of material, which contains 5 *tuberculin units* (TU).

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