HYPERSENSITIVITY

INTRODUCTION- HYPERSENSITIVITY

- Antigen when enters into a body it leads to development of immunity or may cause an allergic reaction and results in tissue damage. This undesirable effect of tissue damage is known as ***Hypersensitivity.***
- Antigen antibody reaction may be beneficial by development of immunity (prophylaxis) or harmful to produce hypersensitivity.
- Hypersensitivity is a specific and acquired altered reactivity of the body tissues to a foreign substance (antigen or haptens) producing deleterious effects on the tissues and rendering the host abnormally sensitive to substance which are ordinarily considered innocuous.

CLASSIFICATION OF HYPERSENSITIVITY

- Peter Gell and Robert Coombs (1963) developed a classification system for hypersensitivity reactions.
- This classification consists of four hypersensitivity reactions
  - Type I hypersensitivity (Immediate hypersensitivity; Anaphylaxis)
  - Type II hypersensitivity (Cytotoxic reaction)
  - Type III hypersensitivity (Immune complex disease;Arthus Phenomenon)
  - Type IV hypersensitivity (Cell-mediated;Delayed hypersensitivity).

TYPE I HYPERSENSITIVITY (IMMEDIATE HYPERSENSITIVITYOR IgE MEDIATED HYPERSENSITIVITY)

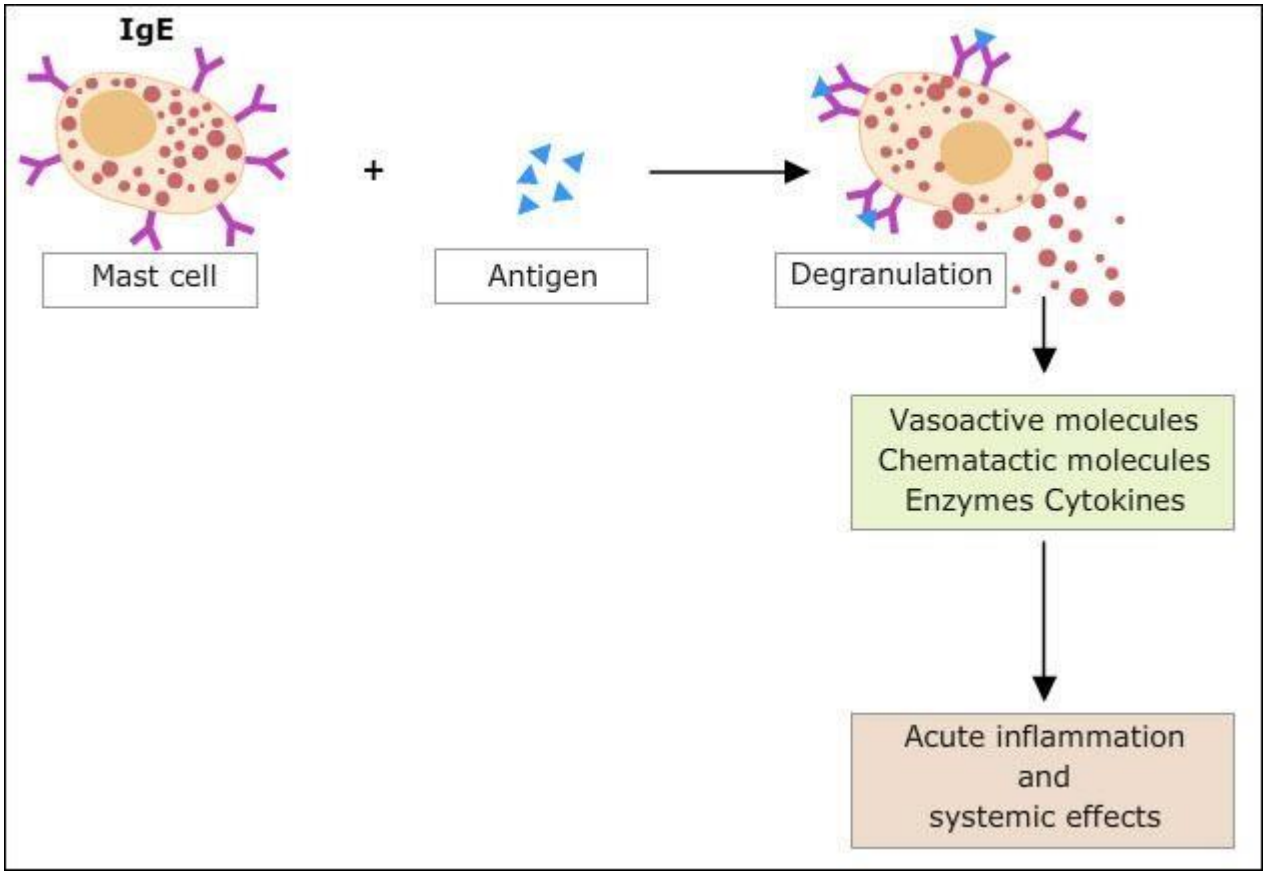
- It is an immediate type of hypersensitivity.
- Type I hypersensitivity are acute inflammatory reactions mediated by IgE bound to mast cells and basophils.
- It is induced by certain types of antigens referred to as *allergens* and is similar to a normal humoral response (The term allergen refers to non-parasitic antigens capable of stimulating Type I hypersensitivity responses in allergic individuals).
- What distinguishes a Type I hypersensitivity response from a normal humoral response is that the plasma cells secretes IgE.
- Though these reactions cause discomfort to the individual, it performs at least two beneficial effects:
- It helps antigen elimination
- Plays an important role in resistance to parasitic worms.

ATOPY

- In normal individuals, an IgE response can be elicited by certain carefully designed immunization procedure. But some individuals make IgE continuously and excessively. This condition is called atopy and the individuals are said to be atopic.
- The response is seen mostly against common environmental antigens and has a hereditary correlation.

MECHANISM

- An allergen induces a humoral antibody response and leads to formation of IgE from plasma cells.
- This IgE binds with high affinity Fc receptors on surface of tissue mast cells and 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 sensitised mast cells and basophils causing degranulation of these cells.
- The combination of IgE with antigen on the surface of mast cells also provokes the formation of vasoactive molecules.
- It is these agents both released preformed from the granules and those newly synthesized that generate the characteristic lesions of Type I hypersensitivity.
- Mast cell granules contain histamine and in some species serotonin. Histamine causes smooth muscle contraction in the bronchi, GI tract, uterus and bladder.
- It increases vascular permeability causing fluid accumulation leading to *wheal* formation. It stimulates mucus secretion, lacrimation and salivation.
- Serotonin causes vasoconstriction resulting in the rise in blood pressure. In rats and mice it induces *wheal and flare* reaction.
- Trypsin or chymotrypsin like neutral proteases released can destroy nearby cells and activate the complement C3 and C5 to generate anaphylatoxins.
- Activation of the cycloxygenase pathway and lipoxygenase pathway lead to formation of prostaglandins and leukotrienes respectively (LTC4, LTD4 and LTE4 together were formerly called as slow reacting substances of anaphylaxis or SRS-A).
- Mast cell granules release eosinophil chemotactic factor – A (ECF-A) which accounts for eosinophilia characteristic of Type I hypersensitivity including helminthic infection.
- Various cytokines and heparin are also released due to degranulation. Due to release of heparin, blood from animals experiencing anaphylaxis and dogs with mast cell tumors fail to coagulate.



ROLE OF EOSINOPHILS

- Refer previous notes on eosinophils. Eosinophils are attracted to sites of mast cell degranulation and can degranulate releasing their own mediators.
- Allergy is ***indicated*** by eosinophils. Slight increase in the number of eosinophils is viewed seriously as it indicates allergic reaction.
- Eosinophils have a soothing action because they contain enzymes which nullify histamines, serotonin etc.
- Hence eosinophilia is a favorable reaction.

MANIFESTATION OF TYPE-I REACTIONS

- Manifestations of the reaction depends on
  - *Species variation* - Manifestations vary in different species like guinea pigs, rats, dogs and man, but reaction is specific for any particular species,
  - *Portal of entry* - According to portal of entry Anaphylaxis may be
    - Localized
    - Systemic or Generalized.
- Localized anaphylaxis:
  - Antigenic exposure of a mucosal surface, e.g. Conjunctiva, nasal mucosa or respiratory tract (inhalation) cause conjunctivitis, rhinorrhoea, broanchospasm etc.
  - Cutaneous anaphylaxis results in local swelling or oedema, flare and urticaria.
- Systemic Anaphylaxis:
  - Portal of entry is usually parental (intramuscular or intra venous). Injections: e. g.: - drugs, snake venom, sting of an insect.etc
- Features of Anaphylactic shock

- Acute vasodilatation, pooling of blood and hypotension.
- Increased capillary permeability results in oedema: Laryngeal edema, oliguria.

- Spasm of smooth muscles cause respiratory distress, bronchospasm and cyanosis
- Death from circulatory failure.

ACUTE ANAPHYLAXIS

- In cattle acute anaphylaxis is due to pulmonary hypertension.
- This is due to constriction of pulmonary veins leading to pulmonary oedema and severe dyspnoea.
- The smooth muscle of the bladder and intestine contract causing urination, defecation and bloting.
- The main mediators are serotonin (histamine is much less), kinins and leukotrienes.
- Heparin released from mast cells does not allow blood coagulation.

CLINICAL TYPE-I HYPERSENSITIVITY REACTIONS

- Milk Allergy
- Food allergy
- Atopic dermatitis
- Drug or vaccine hypersensitivity
- Allergies to parasite etc.

Milk allergy

- Jersey cattle may become allergic to the α casein of their own milk which is synthesized in the udder and if milking is delayed the increased intramammary pressure forced the protein into blood stream. This results into anaphylactic reaction, urticaria and death.

Food allergy

- Certain ingested protein (eggs, fish, dairy products, beef etc) are not fully absorbed and the peptide antigen reach mast cells within few minutes which results in pruritic skin reaction (papules and erythematous) and also vomiting and diarrhea. This type of reactions is common in dogs and cats.

Atopic dermatitis

- It is a chronic multifactorial syndrome with inflammation and itching reaction on the skin. Commonly it is due environmental allergy due to dust, pollens, molds, animal dander etc and observed in dogs, cats, horses and goats. Initially there may be diffused erythema, licking and scratching results in hair loss, papules, scaling and crusting. Some dogs may develop otitis externa.

Allergies to vaccines or drugs

- Allergies have been recorded to killed foot and mouth disease, rabies and CBPP vaccines. Penicillin allergy may be induced in animals either by therapeutic exposure or by ingestion of penicillin contaminated milk. The penicillin molecule is degraded in vivo into penicilloyl group. This binds to proteins and provokes an immune response.

Allergies to parasites

- Allergies reported to tapeworms, fly bites, mites etc. Responses to Demodex mites and components of flea saliva may cause Type IV hypersensitivity.

DIAGNOSIS OF TYPE - I HYPERSENSITIVITY REACTION

- Skin test
  - Hypersensitive animal is given an intradermal injection of diluted antigen intradermally, this provokes local inflammation. Vasoreactive molecules are released within minutes to produce redness (erythrema) because of capillary dilation, a circumscribed edema (wheal) is produced due to increase vascular permeability. This *wheal and flare* response to antigen reaches maximum within 30 minutes and then fades within a few hours.
  - The site of injection is examined for local inflammatory reaction.
- Passive cutaneous anaphylaxis
  - Diluted test serum is injected at different sites into skin of a normal animal.
  - After 24-48 hours, antigen solution is administered intravenously.
  - In positive cases, injection site shows an immediate inflammatory reaction.

- Serology
  - Serological methods of measuring the level of specific IgE in body fluids are radioallergosorbent test (RAST), Western blot and ELISA.

TREATMENT

- The allergen should be avoided.
- *Desensitization therapy* - Small amounts of dilute aqueous solutions of antigen are administered. First injection contains only a small quantity of allergen. Over a period of weeks, dose is increased. Dogs and cats respond well to this therapy but horses do not.
- Corticosteroid is commonly used to reduce irritation and inflammation in acute allergic response. This Inhibits production of prostaglandins and leukotrienes and is useful for treatment of long term Type I hypersensitivity reactions. But

main side effects are immunosuppression and increased susceptibility to infection.

- The β agonist like epinephrine, isoprenaline, sulbutamol; αantagonists like methoxamine and phenylephrine are extensively used. Epinephrine is the most important drug used to treat anaphylaxis.
- Antihistaminic (pharmalogical blocking- as they mimic the struck of active mediators) can be used to a lesser extent

INTRODUCTION- TYPE II HYPERSENSITIVITY

- It is generally called as antibody (IgG or IgM) mediated cytolytic or ctyotoxic reaction.
- The antibodies, mainly (IgG or IgM) can cause tissue injury by recruiting and activating the inflammatory cells and the complement system.
- The antibodies interact with complement and the effector cells via their Fc regions and thus the antibody acts as a bridge between antigen and the effector cells resulting in lysis of cells.
- Complex of bound antigen, antibody and complement lead to the production of enzymes, which damage the cell membrane causing osmotic changes andeventual lysis.
- It can destroy cells by ADCC (Antibody Dependent Cell Mediated Cytotoxicity)and also act as opsonin thereby facilitating phagocytosis.

BLOOD TRASFUSION REACTIONS

- The antigens found on the surface of red blood cells are called blood group antigens.
- Most of the blood group antigens are cell membrane components. But there are also soluble molecules passively adsorbed into red cell surfaces.
- Animals can make antibodies against foreign blood group antigens even though they may never have been exposed to foreign red cells.
- These natural antibodies are derived not from prior contact with foreign red cells but from exposure to similar or identical epitopes (heterophile antigen) seen in nature.
- Many blood group antigens are also common structural components of a wide range of microorganisms, protozoa, helminthes etc.
- During blood transfusion, there will not be any immune response if the donor RBCs are identical to that of the recipient. But if the recipient possesses natural antibodies (of the IgM type) to donor red cell antigens, they will be attacked immediately. This may cause agglutination, hemolysis or opsonisation and phagocytosis.
- Agglutination of erythrocytes caused by haemagglutin (antibodies) from another individual of the same species is called *isohaemagglutination*. These antibodies are called as isohaemagglutinins and are usually of the IgM type.
- In the absence of natural antibodies, foreign antigen on the transfused RBCs will stimulate an immune response in the recipient. The transfused cells then circulate for a period before antibodies (of the IgG type) are produced and immune elimination occurs. A second transfusion with identical foreign cells results in immediate destruction. The rapid destruction of large number of foreign RBCs can lead to serious pathological Type II hypersensitive reaction.
- The severity of the reaction depends on the volume of blood transfused. There

will be hemolysis, complement activation, anaphylatoxin release, mast cell degranulation and release of vasoactive agents. The animals show signs of sympathetic activity like sweating, salivation, lacrimation, diarrhea and vomiting. In the second stage there is hypertension, cardiac arrhythmias and increased heart and respiratory rates.

- Transfusion reactions can be prevented by *cross matching*. Donor RBCs are mixed with recipient serum and incubated at 37 ° C for 30 minutes. If the red cells are lysed or agglutinated by the recipient's serum, then no transfusion should be attempted with those cells.

HEMOLYTIC DISEASE OF NEWBORN

- Female animals may become sensitized to fetal RBCs leaked into their blood stream through the placenta during pregnancy.
- In such females, these anti-red cell antibodies may then be concentrated in their colostrum.
- When the newborn suckles, these colostral antibodies are absorbed through the intestinal wall and so reach its circulation.
- These antibodies directed against the blood group antigens of the newborn cause rapid destruction of its red blood cells. The resulting disease is called *hemolytic disease of newborn (HDN) or neonatal isoerythrolysis*.
- For HDN to occur, four conditions should be satisfied.
    - The young animal must inherit a red cell antigen from its sire that is not present in its mother.
    - The mother must be sensitized to this antigen
    - The mother's response to this antigen may be boosted by transplacental hemorrhage in late gestation
    - The young animal must ingest colostrum containing high titred antibody to its red blood cells.

BLOOD GROUPS

- *Cattle* - 11 blood group systems. B and J are important. HDN is rare in calves. It may result from vaccination against anaplasmosis or babesiosis. If it occurs death is due to disseminated intravascular coagulation (DIC).
- *Sheep* - 6 blood group systems.
- *Pigs* - 16 systems, HDN can occur due to use of hog cholera vaccine containing pig blood;
- *Horses* – 7 systems, HDN only a problem in foals born to mares that had many foals previously.
- *Dogs* – 8 systems, DEA (Dog Erythrocyte Antigen) 1.1, 1.2, 3, 4...etc;

- *Cats* – only one blood group system. HDN is rare.
- *Chicken* – 12 blood group systems. A haemolytic disease may be artificially produced in chicken embryos by vaccinating the hen with cock red cells.

TYPE-II HYPERSENSITIVITY REACTIONS TO DRUGS

- Red cells may be destroyed by three mechanisms in drug induced hypersensitivity.
  - The drug and antibody may combine and directly activate complement and red blood cells are destroyed in a bystanded effect as activated complement components bind to nearby cells.
  - Some drugs may adsorb on to the red cells. Since these cells are then modified, they may be recognized as foreign and eliminated by an immune response. Drugs like Penicillin, Quinine, L- DOPA, Aminosalicylic acid modify RBC and make them as non-self, resulting in autoimmune response and haemolysis.
  - Drugs like cephalosporin may modify red cell membrane and they adsorb antibody and then removed by phagocytic cells.
  - Sulfonamides , phenylbutazone , aminopyrine and chloramphenicol modify granulocytes resuting in granulocytosis or granulocytopaenia.
  - Sulfonamides , phenylbutazone and chloramphenicol causes thrombocytopaenia.

TYPE-II HYPERSENSITIVITY REACTIONS TO INFECTIOUSAGENTS

- In infections caused by Equine infectious anemia virus, protozoa like Trypanosomes, Anaplasma and Babesia, the organisms are adsorbed onto the red cells and alter them.
- They are regarded as foreign and they are either lysed by antibody and complement or phagocytosed by mononuclear phagocytes.This results in severe anemia.

TYPE III AND TYPE IV HYPERSENSITIVITY AND AUTO IMMUNITY

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TYPE III HYPERSENSITIVITY

Introduction

- It is a type of antibody mediated hypersensitivity reaction characterized by
  - Deposition of antigen (usually soluble antigen) -antibody complex in the tissues (particularly on the vascular endothelial surface
  - Complement activation
  - Massive infiltration of polymorphs, release of vasoactive molecules , inflammation and tissue destruction.
- Two types of reactions are recognized
  - Local - Arthus phenomenon
  - Systemic - Serum sickness

ARTHUS REACTION

- If an antigen is injected subcutaneously into an animal that already has precipitating antibodies, then acute inflammation will develop at the injection site within several hours. This is called ***Arthus reaction***.
- It starts as an erythematous, edematous swelling, eventually local hemorrhage and thrombosis occur and, if severe, end in local tissue destruction.
- The antibodies involved in Arthus reaction must be both precipitating and complement activating and are usually of the IgG class.
- A reversed Arthus reaction can be produced if antibodies are given intradermally to an animal with a high level of circulating antigen. Eosinophil infiltration is not a significant feature of this type of hypersensitivity.
- The immune complexes are deposited between and beneath vascular endothelial cells.
- A reversed Arthus reaction can be produced if antibodies are given intradermally to an animal with a high level of circulating antigen, which results in similar reaction.
- A passive Arthus reaction can be produced by giving antibody intravenously and antigen intradermally.
- Reverse passive Arthus reaction can be produced by giving antigen intravenously and antibody intradermally.
- Examples
    - Blue eye
    - Hypersensitivity pneumonitis

BLUE EYE

- This condition is seen in a small proportion of dogs that have been either infected or vaccinated with live canine adenovirus type I.
- Lesion in blue eye is an anterior uveitis leading to corneal edema and opacity.
- The cornea is infilterated by neutrophils and virus-antibody complexes can be detected.
- Reaction develops 1-3 weeks after onset of infection and usually resolves spontaneously.

HYPERSENSITIVITY PNEUMONITIS

- Type III hypersensitivity reactions may occur in lungs when sensitized animals inhale antigens.
- ***Example:*** Cattle fed moldy hay (when hay is stored in damp, thermophilic actinomycetes will grow) for long periods, can become sensitized to spores of *Saccharopolyspora rectivirgula (Micropolyspora faeni)* .
- Eventually, when spores are inhaled, antibodies formed against spore antigen will form immune complexes resulting in complement activation and interstitial pneumonia.
- A hypersensitivity pneumonitis seen in farmer's chronically exposed to *S. rectivirgula* spores is called *farmer's lung (Hay sickness* is a condition seen in horses which is similar to farmer's lung).
- A similar condition arising from exposure to dust from pigeon faeces is called as *pigeon breeder's lung*.
- Other conditions are *mushroom grower's lung, librarian's lung etc.*

SERUM SICKNESS

- When large amounts of antigen enter blood and bind to antibody, circulating immune complexes are formed. If the antigen is in excess, small complexes form which are not cleared from the system.
- They are deposited in the walls of blood vessels, especially medium sized arteries and in vessels where there is a physiological outflow of fluid such as gomeruli, synovia and the choroids plexus and can cause tissue damaging Type III reactions.
- Such kind of reaction were observed in individuals administered with large doses of hyperimmune serum (eg: antitetanus serum) from a foreign species and is known as ***serum sickness***.
- The symptoms are generalized vasculitis with erythema, edema and urticaria of the skin, neutropenia, lymph node enlargement, joint swelling and proteinuria. The reaction is of short duration subsiding in a few days' time.

TYPE IV HYPERSENSITIVITY

Introduction

- Delayed Type Hypersensitivity (DTH) reactions are classified as Type IV hypersensitivity and results from interaction between the injected antigen, antigen presenting cells and T cells (cell mediated).
- These reactions is not induced by circulating bodies but by the sensitized T cells which on contact with specific antigen release lymphokines and exert biological effects on lymphocytes, inflammatory cells and tissue cells.

- DTH cannot be passively transfer by serum but can be done with lymphocytes. Two types of DTH are recognized (i) Tuberculin (injection) type and (ii) contact dermatitis type.
- *Example:* Tuberculin reaction – the skin reaction in an animal that results from an intradermal injection of tuberculin which is an antigenic extract from the tubercle bacillus.

THE TUBERCULIN REACTION

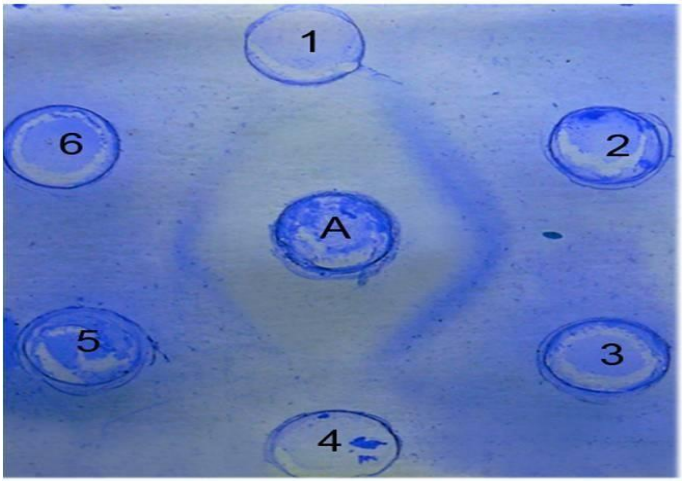
- Tuberculin is used to test/identify animals suffering from tuberculosis.
- Tuberculin is the extracts of *Mycobacterium tuberculosis, M. bovis* or *M. avium.*
- Several types of tuberculin are used. The most predominant is purified protein derivative (PPD) tuberculin prepared by growing organisms in synthetic medium, killing them with steam and filtering.
- The PPD tuberculin is precipitated from this filtrate with trichloracetic acid, washed and finally resuspended in buffer for use. Its antigenic component is thought to be heat shock protein 65 (HSP 65).
- When tuberculin is injected intradermally into a sensitized animal, a red indurated (hard) swelling slowly develops at the injection site. The inflammation begins between 12 and 24 hours, reaches its greatest intensity by 24 to 72 hours and may persist for several weeks before gradually fading.
- T cells mediate the tuberculin reaction. When an animal is *invaded by M. tuberculosis*, the organisms are readily phagocytosed by macrophages. Some of this antigen is presented to Th1 cells, triggers an immune response and generates memory cells. These long lived memory T cells are able to respond to *mycobacterial antigen* entering the body by any route.
- In a sensitized animal, on intradermal injection, the Langerhans cells take up antigen to draining lymph node and present to memory T cells and that attract TH1 effector cells.
- Circulating TH1 cells recognize the antigen, become activated and accumulate around the antigen deposit, secrete biologically active substances like IFN- g and IL-2, serotonin, IL-8 and lymphotactin (a chemotactic for lymphocytes) etc. This causes infiltration and attracts more T cells (CD 4+ and CD 8+).
- Macrophages accumulated in the lesion ingest and eventually destroy the antigen.

THE TUBERCULIN REACTIONS IN CATTLE

- Skin testing for identifying animals that have or have had tuberculosis can be done by
  - Single intradermal testing (SID)
  - Comparative test
  - Short thermal test
  - Stormont test

SINGLE INTRADERMAL TEST (SID)

- 0.05 ml of PPD tuberculin from *Mycobacterium tuberculosis* or *M. bovis* is injected intradermally into one anal fold.
- After 72 to 96 hours a comparison is made between injected and uninjected folds and a positive reaction consists of a diffuse hard lump.
- The injection can also be given into the mucocutaneous junction of the vulva and side of neck. In latter case, it is more sensitive but restraint of the animal is difficult.



- *Advantage:* simple test.
- *Disadvantages*
    - Cannot distinguish infection by other mycobacteria such as *M. avium* or *M. paratuberculosis* or Nocardia.
    - False positive results may be due to exposure to *M. phlei.*
    - False negative in advanced tuberculosis, early infection, in animals calved within the preceding 4-6 weeks, very old cows and in animals tested within the preceding 1-10 weeks.

COMPARATIVE TEST

- Injection of both avian and bovine tuberculin at side of neck at separate sites.
- Examined after 72 hours.
- If avian tuberculin site shows the greatest reaction, animal is considered to be infected with *M. avium* or *M. paratuberculosis*.
- If *M. bovis* site is showing more reaction, animal infected with *M. tuberculosis* or *M. bovis*.
- This test done when avian tuberculosis or Johne 's disease is prevalent.
- PPD from *M. bovis* more specific in cattle as it gives less cross reaction with *M. avium*.
- Advantage: More specific than SID.
- Disadvantage: more complex

SHORT THERMAL TEST

- Large volume of tuberculin solution is given subcutaneously and animal is examined for rise in temperature between 4 and 8 hours later (tuberculin acts on T cells that then release cytokines that stimulate macrophages to release IL-1).
- Used in post partum animals and infected animals.
- Advantage: High efficiency.
- Disadvantage: time consuming, may cause anaphylaxis

STORMONT TEST

- Performed by giving two injections on the same site 7 days apart.
- Relies on the increased sensitivity of a test site that occurs after a single injection. Used in post-partum animals and advanced cases.
- Advantage: Very sensitive and accurate
- Disadvantage: Three visits required, may sensitize the animal.

TUBERCULIN REACTIONS IN OTHER ANIMALS

- Pigs and cats positive for a short period only after infection hence this test is unreliable.
- In pigs and dogs, the SID performed in the *skin behind the ear*.
- In cats, short thermal test is the best.
- For, Sheep and goats the test is done in the anal fold but results are unreliable.
- Horses are unusually sensitive to tuberculin so a lesser dose is used. But there is no correlation between test results and actual condition.
- In birds, good reaction is obtained and the test is done in the wattle or wing web.

Animal	Test	Site
Pigs and dog	SID	Skin behind the ear.
Cats	Short thermal test	Subcutaneous
Sheep and goats	SID	Anal fold Not reliable
Horses	SID	Not reliable
Birds	SID	Wattle or wing web.

JOHNIN REACTION

- Animals infected with *Mycobacterium avium var. paratuberculosis* may develop a delayed hypersensitivity reaction following intradermal inoculation of an extract of this organism called *johnin*.
- But negative results are obtained in clinical infection. In such cases, intravenous johnin test is done.
- Johnin given intravenously and temperature noted at intervals.
- A rise in temperature of 1 ° C or a neutrophilia after 6 hours is considered positive.
- This test is used for identification of infected herds.

OTHER SKIN TESTS

- For diagnosis of brucellosis (*Brucella abortus*), *brucellin*- a filtrate of a 20-day old broth culture and *brucellergen* – a nucleoprotein extract are used but they produce antibody and can not be used where eradication is monitored by serological tests.
- *Mallein (culture filtrate)*, used for diagnosis of Glanders caused by *Burkholderia mallei* in horses. Short thermal test or ophthalmic test can be done.
- Antigen dropped to eye show transient conjunctivitis in positive cases.
- In the intrapalpebral test, antigen injected into skin of lower eyelid and positive reactions are indicated by swelling and ophthalmia.
- Skin testing also used for detection of histoplasmosis *(using histoplasmin),* coccidioidomycosis *(using coccidioidin)* toxoplasmosis *(using toxoplasmin)* and leprosy *(Lepromin or leprosin).*

Disease	Reagent
Brucellosis	Brucellin (Filtrate of a 20-day old broth culture)
Glanders	Mallein (Extract from *Burkholderia mallei* culture)
Histoplasmosis	Histoplasmin
Coccidioidomycosis	Coccidioidin
Toxoplasmosis	Toxoplasmin
Leprosy	Lepromin

DISEASES CAUSED BY DELAYED TYPE HYPERSENSITIVITY

Allergic Contact Dermatitis

- Type IV hypersensitivity reaction results due to exposure of skin to some chemicals, oils of poison ivy plant, insecticides etc.

Infection Allergy

- Associated with some of the fungal, viral and chronic bacterial diseases.

Jones-Mote Hypersensitivity

- A type of reactivity very similar to delayed type hypersensitivity observed in man and animals.
- It is characterized by inflammation and basophils infiltration immediately under the epidermis followed by injection with an antigen in the skin.

TOLERANCE

- A number of mechnisms exist to protect an individual from potentially self-reactive lymphocytes; these are given the general term tolerance. A primary mechanism termed central tolerance deletes T- or B- cell clones before the cells are allowed to mature if they possess receptors that recognize self-antigens with greater affinity.
- Central tolerance occurs in the primary lymphoid organs, bone marrow and thymus. However, there are certain lymphocyte clones which are not deleted in the primary lymphoid organs, there are additional safe guards to limit their activity by the peripheral tolerance, which render lymphocytes inactive in the secondary lymphoid organs.
- Peripheral tolerance can be defined as the inactivation of self-reactive T cells or B cells in the periphery, rendering themincapable of responding to self.

AUTO IMMUNITY

Introduction

- Self-antigens are not immunogenic.
- Autoimmunity is a condition in which the body produces antibodies and T cell responses against elements of its own tissues (autoantigens).
- In other words, tissue compounds of the body behave as auto antigens and initiate immune response to produce autoantibodies and T cell response.
- The individuals lose the ability to distinguish between *self* and *non-self*.
- Auto immunity literally means *protection to self* but actually means *injury to self*.
- Ehrlich (1901) observed that goats produce antibodies to erythrocytes receive from other goats and postulated *horror autotoxicus*.
- Auto immune reaction can result
    - From a normal immune response to an abnormal or unusual antigen
    - As a result of abnormal immune response to normal antigen.

BREAKDOWN OF IMMUNE TOLERENCE TO SELF ANTIGEN(AUTOIMMUNITY)

Antigen hidden or sequestrated in cells or tissues

- Some body proteins remain hidden or sequestrated from immunologically competent cells. So, they are not recognized as 'self' by the immune system.
- When such protein escape into the circulation (due to trauma or infection), they behave as antigens, induce immune response and produce tissue damage.
- *Examples:*
    - *Lens protein:* usually isolated or sequestrated from immune system during development. Due to trauma to the eye, lens protein may escape into circulation, produce autoantibody and cause immunologic damage to the eye (sympathetic ophthalmia).
    - *Hepatitis:* In chronic hepatiis in dogs, autoantibodies are produced against liver membrane proteins.

Antigen formed by molecular changes

- Body tissues or cells undergo antigenic alteration due to physical, chemical or biological influences. Such neoantigen elicit immune response.
- *Examples:*
- Immunoconglutinins(IKs): IKs are antoantobodies produced against complement components like C_2, C_3 and C_4. The new epitopes are exposed during complement activation and form IKs. The lecel of IKs in serum reflects the amount of complement activation.

Molecular Mimicry (Cross reacting antigen)

- Molecular mimicry or sharing of epitopes between an infectious agents or parasites and body tissue specific antigen results in autoimmunity and tissue damage.
- *Example: Trypanosoma cruzi* contain antigen that cross react with mammalian neurons and heart muscle results in nervous and heart disease.

PRIMARY IMMUNODEFICIENCIES

- As a result of genetic mutations, defects may develop in the immune system resulting in immunodeficiency.
- Defects in innate immunity include deficiencies in phagocytosis and intracellular killing leading to increased susceptibility to bacterial diseases. Eg. Bovine leukocyte adhesion deficiency.
- Defects in T cell function generally predispose an animal to overwhelming virus infections.
- Defects in B cell functions predispose animals to overwhelming bacterial diseases.
- Combined immunodeficiencies are most severe since affected animals lack resistance to all infectious agents.

SECONDARY IMMUNODEFICIENCY

- Immunodeficiencies included by some known cause are not uncommon in domestic animals.
- The most important cause of immunosuppression are viral infections. In order to survive within a host, viruses may causeprofound immunodeficiency either by infecting and killing lymphocytes or by causing them to become cancerous.
- Other major causes of immunodeficiencies include stress, malnutritions, mycotoxins and old age etc.