

بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِیْمِ



Type III Hypersensitivity

Immune complex reaction

Type III: Immune Complex Mediated Reaction

- *When **antibodies** (Ig G or Ig M) and **antigen** coexist **immune complexes** are formed
- *Immune complexes are **removed** by **reticuloendoth. syst.**
- *Some **immune complexes** **escape phagocytosis**
- ***Immune complexes** **deposited** in tissues on the basement membrane of blood vessels and cause **tissue injury**

Mechanism Of Tissue Injury

Immune complexes trigger inflammatory processes:

- 1) Immune complexes **activate** the complement **release** anaphylatoxins C_{3a}, C_{5a}
stimulate degranulation of basophiles and mast cells **release** histamine
Histamine **↑** vascular permeability and help deposition of immune complexes
- 2) Neutrophils are attracted to the site by immune complexes and release lysosomal enzymes which damage tissues and intensify the inflammat. Pro.
- 3) Platelets are aggregated with two consequences
 - a- release of histamine
 - b- form of microthrombi which lead to ischemia

Clinical conditions of Type III Hypersensitivity

Diseases produced by immune complexes are those in which antigens persists without being eliminated as:

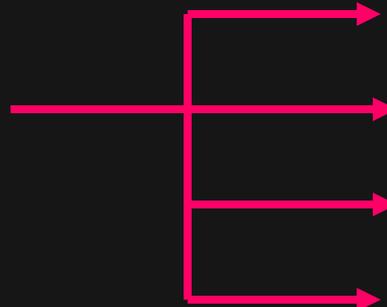
- a- Repeated exposure to extrinsic antigen
- b- injection of large amounts of antigens
- c- Persistent infections
- d- Autoimmunity to self components

1- Arthus Reaction

* This is a local immune complex deposition phenomenon
e.g. **diabetic patients receiving insulin subcutaneously**

* Local reactions in the form of  edema
erythema
necrosis

* Immune complexes **deposited**  in small blood vessels

leading to  vasculitis
microthrombi formation
vascular occlusion
necrosis

2- Serum Sickness

- * A systemic immune complex phenomenon
- * Injection of large doses of foreign serum
- * Antigen is slowly cleared from circulation
- * Immune complexes are deposited in various sites

- * **10 days after injection**
 - fever
 - urticaria
 - arthralgia
 - lymphadenopathy
 - splenomegaly
 - glomerulonephritis

- e.g. treatment with**
 - antidiphtheritic serum
 - penicillin
 - sulphonamides

3- Post-streptococcal glomerulonephritis

glomerulitis associated with infective endocarditis

4- Hypersensitive pneumonitis (farmer lung)

immune complexes deposition in lung after repeated inhalation of dust , mold spores

5- Endogenous antigen antibody complexes

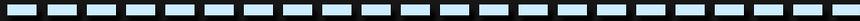
involved in autoimmune diseases

e.g. **SLE, rheumatoid arthritis**

Clinical types of hypersensitivity III in animals

■ Local type III

- There are some diseases in the domestic animals in which type III reactions play a major role.
- **1-Blue-eye**
- Blue-eye is a condition in a small proportion of dogs that have been either infected or vaccinated with live canine adenovirus type-1



- **2-hypersensitivity pneumonitis**
- Animal lung----- inhalation of Ag
- Examples:
- Cattle housed during winter and exposed to dust from hay (thermophilic actinomyces will grow)
- (Micropolyspora faeni spores)
- Chronic obstructive pulmonary disease (COPD) in horses (hay dust).



- **In man we also have**
- A-farmer's lung (M.faeni)
- B-pigeon breeder's lung (pigeon feces).
- C-mushroom grower's disease (spores from soil).
- D-librarian's lung (dust from old books)



- **3-staphylococcal hypersensitivity**
- Staphylococcal hypersensitivity is a pruritic pustular dermatitis of dogs. Skin testing suggested the involvement of type I, III, and IV. But type III may be predominant in some cases.

Generalized type III hypersensitivity

- Serum sickness (result from passive immunization).
- The disease can be induced experimentally in rabbits and the anima develop a glomerulonephritis and arteritis.

OTHER IMMUNE COMPLEXES

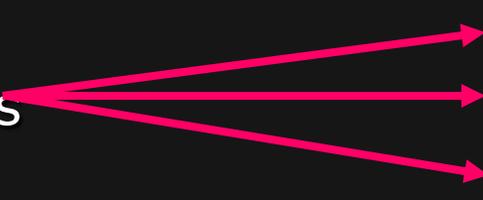
- **1-Purpura Hemorrhagic**
- Occur in horses recovered from an acute streptococcal infection (*Streptococcus equi*).
- **2-Dietary hypersensitivity**
- In case of feeding the very young calves with soy protein causing hypersensitivity and loss of weight.

- **3-Polyarthrititis**
- Immune complexes can be readily found in the blood and synovial fluid of animals with rheumatoid arthritis.
- **4-Drug hypersensitivity:**
- Similar to that of type II
- -anemia
- Thrombocytopenia
- -granulocytopenia.

Type IV
Cell Mediated
Delayed Type Hypersensitivity

Type IV: Cell Mediated Delayed Type Hypersensitivity

mechanism

- * 1- T-cells cause tissue injury by  triggering DTH reactions by TH1 or directly killing target cells by CD8
- * 2-TH1 and CD8 T cells secrete cytokines (IFN- γ and TNF)
- * 3- Cytokines 
 - attract lymphocytes
 - activate macrophages
 - induce inflammation
- * 4-Tissue damage results from products of activated macrophages

Tuberculin –Type Hypersensitivity

Mechanisms:

*1- When **tuberculin antigen(PPD)** intradermally in **sensitized** person

PPD=Purified Protein Derivative

*2- Local **indurated area** appears **injection site** (48-72 hs)

*3- Indurations due to **accumulation** Of:
macrophages and lymphocytes

* Similar reactions observed in diseases
e.g. **brucellosis, lepromin test in leprosy, Frei's test in lymphogranuloma venereum**

Type IV Hypersensitivity Clinical Conditions

A-Granulomatous lesions

Examples:

* **In chronic diseases** : T.B., Leprosy, schistosomiasis

Mechanisms:

- *1- **Intracellular organisms resist destruction** by macrophage.
- *2- **Persistent antigen** in tissues **stimulate local DTH** reaction
- * 3-Continuous **release of cytokines** leads to **accumulation of macrophages** which give rise to **epithelial and giant cell granuloma**

B-Contact Dermatitis

Examples:

- * **Contact of skin** with **chemical** substances or **drugs**
e.g. poison, hair dyes, cosmetics, soaps, neomycin

Mechanisms:

- *1- These substances **enter skin** in small molecules
- * 2-They are **haptens** that **attached** to body **proteins**, form **immunogenic substances**
- *3- **DTH reaction** to these **immunogenic** subst. lead to:





C- Auto immune diseases and graft rejection are due to in part to delayed hypersensitivity reactions

D- Insulin dependent diabetes mellitus

T-cells invade the pancreatic islets and specifically destroy insulin secreting beta cells

Tuberculin Reaction In Animals

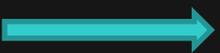
- **Tuberculin:** is the name given to extracts of *Mycobacterium tuberculosis*, *M. bovis*, or *M. avium* used to skin test animals in order to identify those with tuberculosis.
- **PPD:** Purified Protein Derivative tuberculin.
- This PPD is prepared by growing organisms in synthetic medium, killing them with steam, and filtering.

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- The PPD tuberculin is precipitated from this filtrate with trichloroacetic acid, washed, and finally resuspended in buffer ready for use. Its major antigenic component is probably a heat shock protein (HSP65).

Mechanism

- PPD injected into the skin of:
- Normal animal  no significant response.
- Sensitized animal (TB infected)  DTH is developed (a red indurated swelling slowly develops at the injection site).
- The inflammation begins between 12 and 24 hrs, reaches its greatest intensity by 24-72 hrs and may persist for several weeks before gradually fading.

Tuberculin reactions in cattle

- This do detected TB infected animals
- Skin testing of cattle may be performed in several ways:
- **1-single intradermal (SID) test.**
- **0.05 ml of PPD is injected into one anal fold  72-96 hrs and compare it with un injected folds.**



- **Advantage:** simple
- **Disadvantages:**
 - a-cannot distinguish between tuberculosis and infection with other mycobacteria (M.avium, M.paratuberculosis and Nocardia.
 - b-False positive results due to vaccination or M. faeni.
 - c-False negative in animals:
 - with advanced tuberculosis
 - With very early infection
 - That calved within the preceding 4-6 wks.
 - Very old cows
 - Tested within the preceding 1 to 10 wks.



2-Comparative

- The comparative test, for example, involves intradermal inoculation of both avian and bovine tuberculins
- And examined 72 hrs later and compared:
- If the swelling observed on avium PPD= +ve for *M.avium* or *M.paratuberculosis*.
- If the swelling observed on tuberculosis PPD= +ve for *M.bovis* or *M.tuberculosis*.

3-Short thermal

- In which a large volume of tuberculin solution is given subcutaneously and animal is examined for a rise in temperature between 4-8 hrs later.
- PPD → T cells → cytokines →
macrophage → IL-1 causes
increase in body temp.

4-Stormont

- The Stormont test relies on the increased sensitivity of a test site, which occurs after a single injection.
- It is performed by giving two doses of tuberculin at the same injection site 7 days apart.

Tuberculin Reaction In Other Animals

- In pig and dog the best test is a SID test given in the skin behind the ear.
- In cat the short thermal test is the best.
- In sheep and goats the antigen is usually given in anal fold.
- Horses appear to be unusually sensitive to tuberculin, and the dose used must be reduced accordingly.
- In birds, good reactions may be obtained by inoculating tuberculin into the wattle or wing web.

JOHNIN REACTIONS

- DTH in animals infected with *M. paratuberculosis*.
- Johnin Ag .Intradermal injection
- +ve like SID
- Or
- False -ve

Best alternative of Johnin

- Johnin A.g $\xrightarrow{\text{IV}}$ measure animal temperature $\xrightarrow{\quad}$ a rise in temp. of 1C or a neutrophilia after 6hrs is considered a positive result.
- These tests are probably of limited usefulness in individual animals but may be used for the identification of infected herds.

Other skin tests

- **Brucellin** : a filtrate of a 20-day broth culture, and brucellegen, a nucleoprotein extract.
- **Mullein** : in horses with glanders (*Pseudomonas mallei*). It is a skin test used in either a short thermal or an ophthalmic test by dropping the Ag solution into an eye leads to conjunctivitis.

- **Histoplasmin** : is used in histoplasmosis.
- **Coccidioidin** : is used coccidioidomycosis
- **Toxoplasmin** : is used in toxoplasmosis.
- **Note** :the last two tests are not specific and may induce Ab formation in uninfected animals to become serologically positive.

Thanks

