(Clinical Immunology)---- Lec # 5

(3)----------Type III H.S. (Immune Complex-Mediated)

Normally, when antibody combines with its specific antigen, **immune complexes are formed**. Normally, they are rapidly removed by the reticuloendothelial system, **BUT ……** Occasionally they **persist** and are **deposited** in tissues, resulting in several disorders and leading to type III H.S.R.

Immune complex-mediated reactions are initiated by Ag-Ab (lgG or lgM) complexes that are formed in the blood vessels & then deposited in tissues. This is followed by complement activation & cellular recruitment including polymorph neutrophil. Inflammation is the main feature of this reaction & the inflammatory response results in:

- Oedema due to fluid accumulation.
- Arythema due to RBC accumulation.
- Induration due to leukocyte infiltration.

Pathogenic mechanism of type III H.S.: Pathogenesis involves interplay of Ag, Ab, complement, & neutrophils.

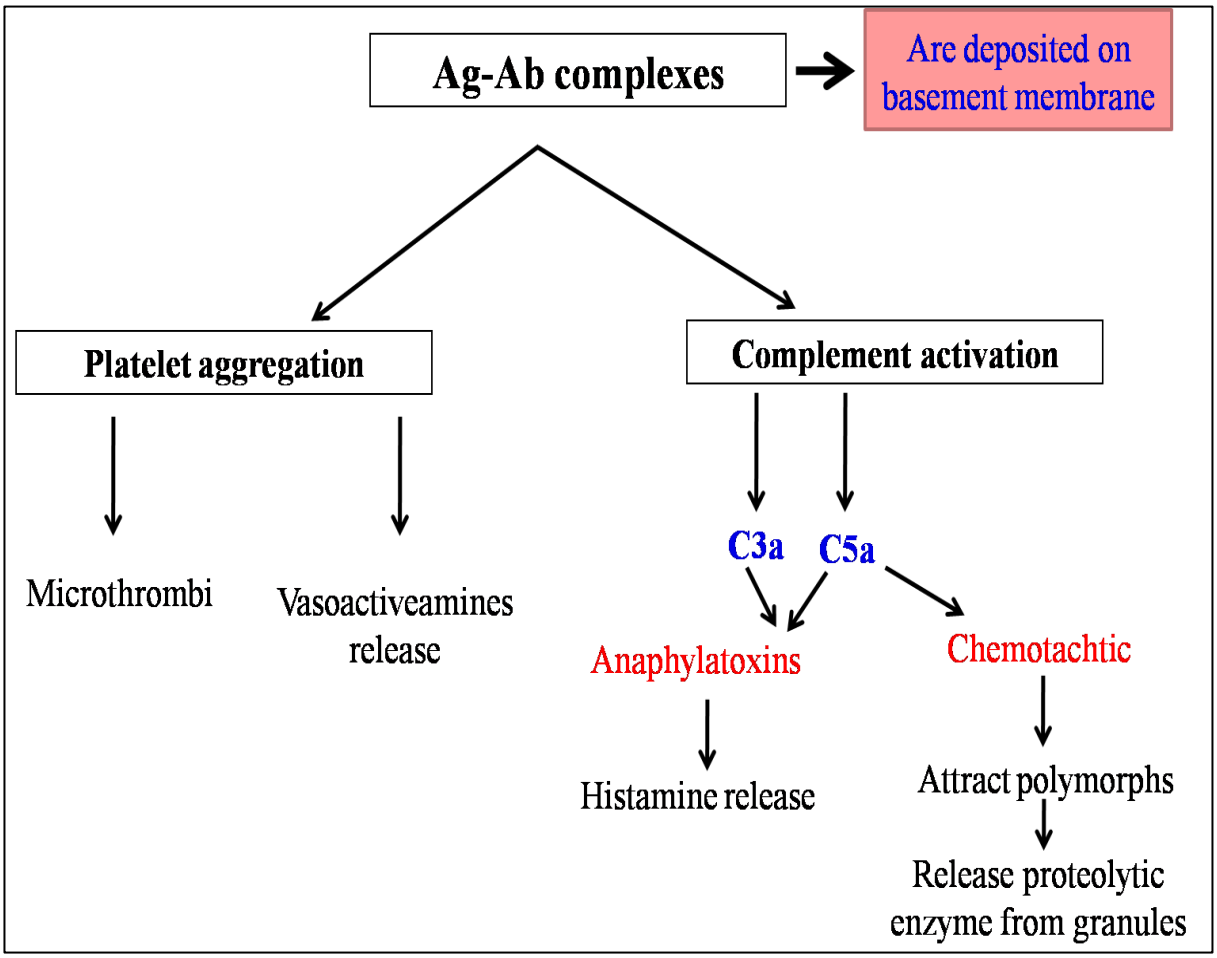
1- Ag-Ab (IgG. IgM) immune complexes are deposited on basement membrane

2- Complement is activated, & C3a & C5a are released. These are anaphylatoxins that cause mast cell degranulation & the release of vasoactiveamines. This increases permeability of vascular endothelium.

C5a is also chemotachtic for neutrophils which then infiltrate the area & release lysosomal enzymes that destroy basement membrane. In addition neurophils have receptors for C3b, move into the area in response to C5a chemotaxin. In the process of attempting to engulf the

immune complexes, these phagocytic cells degranulate & release proteolytic enzymes & other toxic molecules that injured tissues in area.

3- Platelets also interact with immune complexes, this leads to platelet aggregation & microthrombus formation (see Figure below).

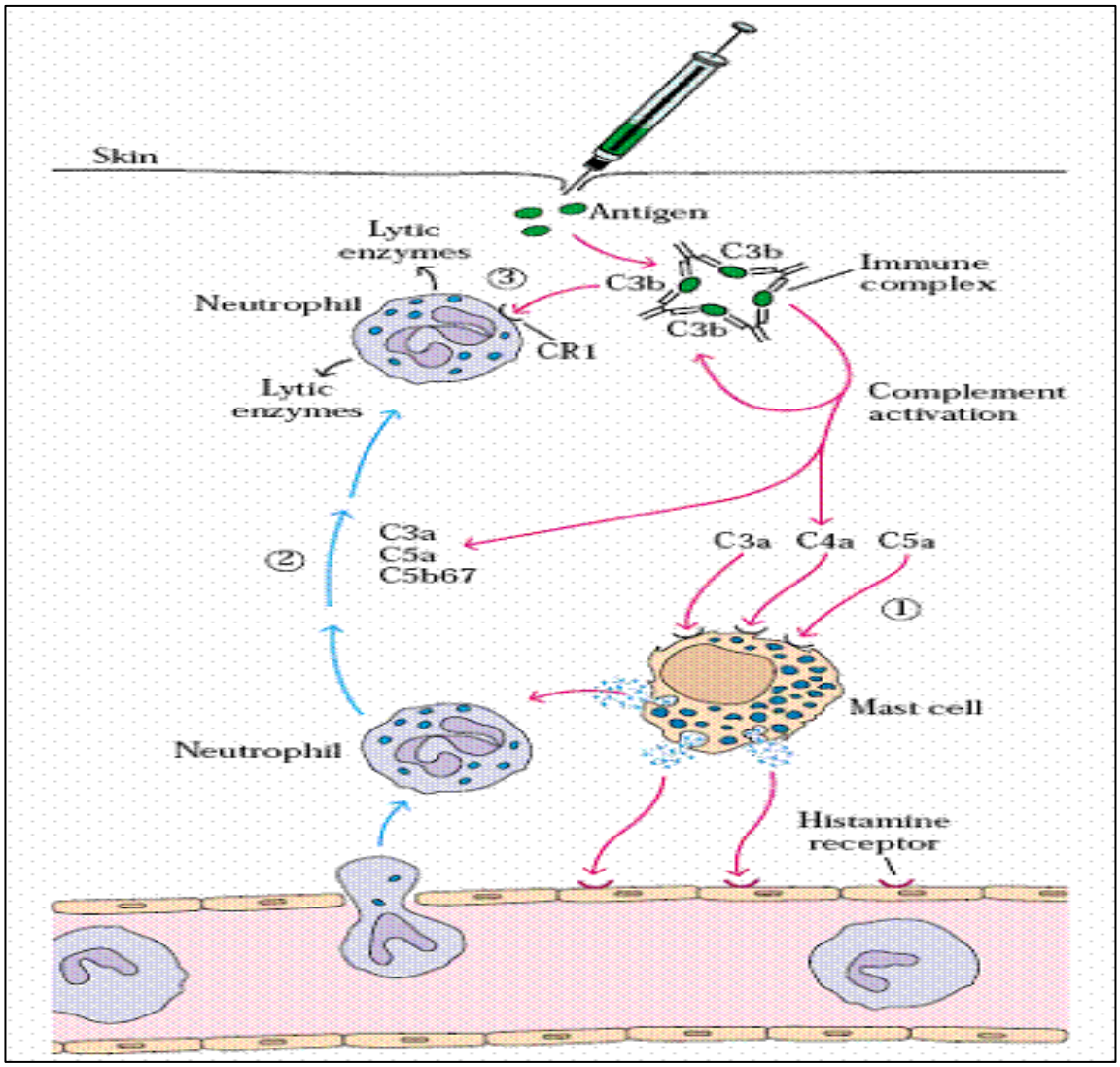


Immune complex mediated type III H.S. is of two types:

1- Local type III H.S. (Arthus reaction)

- It occurs at the zone of Ab access. Immune complexes develop in individuals who have pre-existing Ab to the Ag.

Arthus reaction: is a skin reaction followed an intradermal or subcutaneous injection of injection in human of experimental animal, with high levels of circulating Abs to Ag. A red, local swelling develops at the site of injection within 4-8 hours & disappears after 10-12 hours. Clearance is by opsonisation through Fc, C3b & C4b receptors on neutrophils & macrophages.



<u>Clinical example on local type III H.S.:</u>

Extrinsic allergic alveolitis (H.S. pneumonitis): it is local type III H.S. to inhalant Ags including:

- Farmer's lung due to inhalation of fungal spores present in dust of moldy hay.
- Pigeon fancier's disease due to inhaled serum protein in dust of dried pigeon feces.
- Allergic bronchopulmonary aspergillosis due to inhalation of spores of fungus aspergillosis.
- Drug induced H.S. pneumonitis → drugs, industrial materials e.g. nitrofurantion, cromolyn… etc.

Clinical features:

- Cough, dyspnea, fever, chills
- 4-8 hours after exposure
- Disappear 18-24 hours

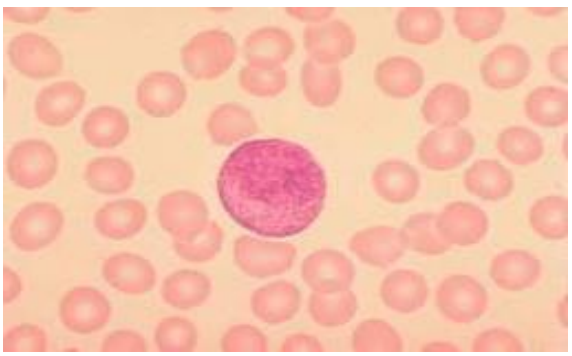
2- <u>Systemic (generalized) type III H.S.:</u>

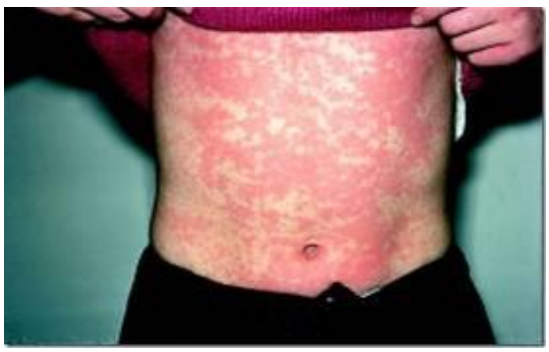
- It occurs at the zone of Ag excess
- It follows injection of large doses of Ag, then the Ag-Ab complexes are of small size molecules which activate complement inefficiently and then these complexes diffuse through the blood & accumulate on:
  - **a-** Basement membrane of capillaries & large blood vessels causing vasculitis & arteritis.
  - **b-** Glomerular basement membrane causing glomerular nephritis
  - **c-** Synovial membrane causing arthritis

Clinical examples on systemic type III:

1- Serum sickness:

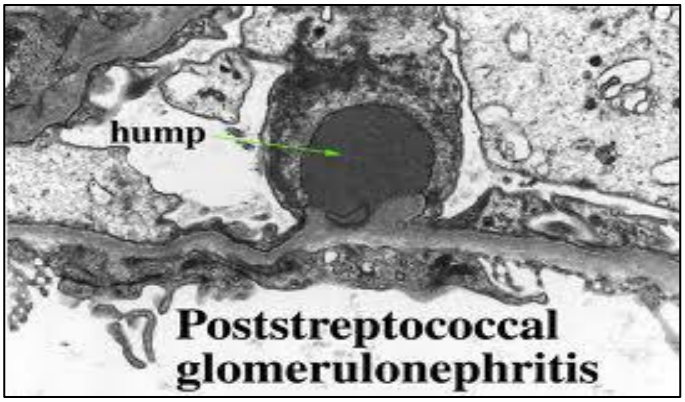
It is a complication of serum therapy following injection of massive doses of foreign protein in human like injection of horse anti-diphtheria serum or horse anti-tetanus serum.

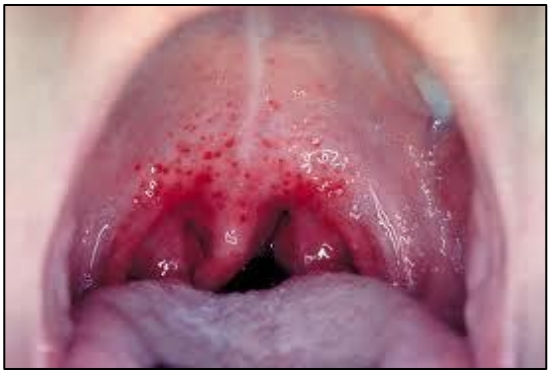




2- Post-streptococcal glomerular nephritis:

Following streptococcal pharyngitis, immune complexes are deposited in glomerular basement membrane leading to protein uria & hematuria.





(4)----------Type IV hypersensitivity: Cell mediated (delayed) H.S.

- Inflammatory reaction occurs as a result of interaction between actively sensitized T-Lymphocytes & specific Ag.
- The reaction is mediated by:
  a- Lymphokines (CD4+→ Th1 → TDTH)
  b- Cytotoxicity (CD8+→ TC)
- It is a delayed type reaction because it takes 24-72 hours to develop.
- The complement & antibodies play no role in this reaction.
- Delayed type H.S. is a major immune response to intracellular microbes, including:
  a- Bacteria → mycobacterium T.B. , mycobacterium leprae
  b- Viruses → measles, chicken pox, herpes
  c- Parasite → *Leishmania* species
  d- Fungal → *C. albicans, C. neoformans, H. capsulatum.*

Mechanism of delayed type H.S.:

Antigens that induce type 4 H.S. tend to activate Th lymphocytes of Th1 subset, which are often referred to as TDTH cells.

The activated Th1 cells secret INF-γ, TNF-β, IL2 GM-CSF…etc.

These cytokines lead to the recruitment of large number of monocytes from the blood & to their activation when they become macrophages in tissues.

The activated macrophages phagocytose the Ag & release active O2 metabolites & lytic enzymes, some of which leak out of the cells & damage the surrounding tissue.

CTL (Cytotoxic T-Lymphocyte):

Plays a critical role in the host-cell mediated immune response against viral infection, graft rejection… etc

The interaction between CTL & target cells involves:

1- Adhesion & recognition
2- Delivery of a "lethal hit"
3- Death of target cell

Clinical examples on delayed type H.S.:

Tuberculin skin test (TT):

- **Positive TT** indicates the presence of specifically sensitized T-lymph.
- **Principles:**
    a- PPD (purified protein derivatives)→standerized to tu (Todd units)
    b- I.D. injection of 5-250 Tu
    c- Positive response → 48-72hrs >10 mm (erythema & induration)

d- Negative skin test:

1- No T.B. infection

2- Presence of Energy due to:

**Overwhelming infection

**Immunosuppressive illness

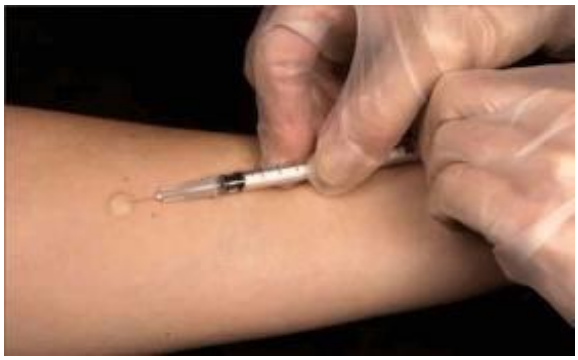
e.g. sarcoidosis, AIDS, Hodgkin's disease.

Positive tuberculin (Mantoux) test indicates:

1- An unapparent (subclinical) infection

2- Past history dis.

3- Previous immunization



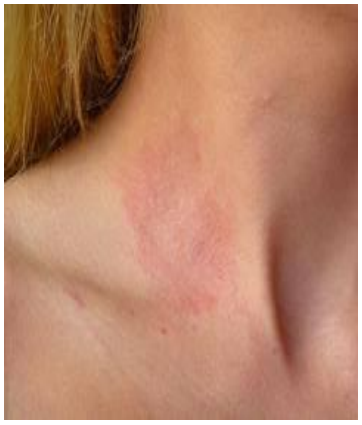
Allergic contact dermatitis:

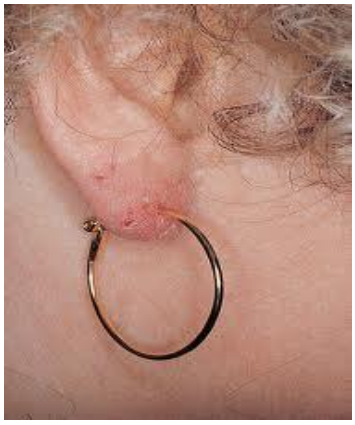
- Due to contact with sensitizing substances or Ag:
  a- Topically applied drugs (neomycin)
  b- Cosmetics, nickel & chromate (costume jewelry)
  c- Dyes, rubber compounds, preservatives… etc

- The antigenic components of these substances can attach to host proteins & serve as haptens, & then act as T-cell stimulating Ag.

- Immunological features:
  a- T-cell mediated eczematous disease
  b- Characterized by 48hrs delayed eczematous response to the epicutaneous application of Ag.

- **Clinical features:**
  - a- Acute from→ erythema, oedema, vesiculation
  - b- Chronic from→ scaling
- The site of lesion is a clue for diagnosis:
  - a- Ear lobes→ earring
  - b- Around neck→ neck lacer
  - c- Wrist→ watch, bracelets, bands





Diagnosis:

- History
- Distribution of lesion
- In vivo diagnosis → patch test

Patch test:

A low dose of suspected Ag is placed on a patch of the patient's skin.

Eczema may develop 48-72 hrs later, indicative of type IV H.S.