HYPERSENSITIVITY

Learning Objectives

- At the end of the session, students will be able to understand:

1. Definition and classification of hypersensitivity

2. Mechanism of Type I – IV hypersensitivity reactions

Immune Response

- Beneficial
- Indifferent
- Injurious
- Tolerance

Hypersensitivity?

- Injurious consequences in sensitized host, following subsequent contact with specific antigen (proteins/ pollen)
- Deals with injurious aspect of heightened & exaggerated immune response→ tissue damage, disease or even death
- Concerned with what happens to host rather than what happens to antigen

Definition

*"Undesirable injurious consequences in **sensitized** host, following subsequent contact with specific antigen"*

OR

" Conditions in which immune responses cause harm to body "

ALLERGY

- Altered state of reactivity to antigen
- Injurious immune response to host- HST, Autoimmunity

Musts for Hypersensitivity

- Contact with allergen
- Sensitizing/priming dose
- Induction of AMI/CMI
- Shocking dose

General Mechanism

- Involves:-
  - Priming/sensitizing dose:
    - *Initial contact with antigen*
    - *Sensitizes appropriate B and T cells*
  - Shocking dose:
    - *Subsequent dose of same antigen*
    - *Abnormal reactions*

General Mechanism Contd.....

Contact with antigen (sensitizing/priming dose)

Subsequent contact (after 2-3 wks, shocking dose)

Hypersensitivity

CLASSIFICATION

- Based on time required to develop clinical reactions on re-exposure:-

- Immediate type (B-cell/antibody mediated):
  - *Anaphylaxis*
  - *Atopy*
  - *Antibody-mediated cell damage*
  - *Arthus phenomenon*
  - *Serum sickness*
- Delayed type (T-cell mediated):
  - *Infection (tuberculin) type*
  - *Contact dermatitis type*

IMMEDIATE HYPERSENSITIVITY	DELAYED HYPERSENSITIVITY
Appears & recedes rapidly	Appears slowly, lasts longer
Induced by antigens or hapten by any route	Induced by antigens or hapten intradermally or with Freund's adjuvant or by skin contact
Antibody mediated	Cell mediated
Passive transfer- with serum	Passive transfer- with T-cells or transfer factor (Not with serum)
Desensitization easy, short lived	Desensitization difficult, long lasting

CLASSIFICATION

- Based on mechanism of pathogenesis (Coombs & Gell classification- 1963):-
- Immediate:
  - *Type I* *IgE mediated*
  - *Type II* *Antibody mediated/Cytotoxic*
  - *Type III* *Immune complex mediated*
- Delayed:
  - *Type IV* *Cell mediated*

TYPE-V HSTR

- Stimulatory type (Jones-Mote Reaction OR Cutaneous Basophil HST)- modification of Type-II HSTR
- Abs recognize & bind to cell surface receptors & disrupts normal function→ leads to cell proliferation & differentiation instead of inhibition/killing
- Ag-Ab reaction enhances activity of affected cell
- e.g. Grave's disease, Myasthenia gravis

HSTRs- Features

Type	Clinical Syndrome	Time	Mediators
Type-I: IgE	Anaphylaxis	Minutes	IgE, histamine, pharmacological agents
	Atopy: respiratory- asthma, eczema, hay fever GI: allergy to shellfish Familial/ genetic predisposition	Minutes	
Type II: Cytolytic & cytotoxic	Ab-mediated damage→ thrombocytopenia→ agranulocytosis, haemolytic anaemia	Variable: hours to day	IgG, IgM, complement
Type III: Immune complex	Arthus reaction	Variable: hours to day	IgG, IgM, complement, leucocytes
	Serum sickness	Days	
Type IV: Delayed HST	Tuberculin test	Hours to days	T-cells, lymphokines, macrophages
	Contact dermatitis	Hours to days	

TYPE-I HYPERSENSITIVITY

- IgE- mediated
- Antibodies fixed to surface of tissue cells (Mast cells, Basophils & Eosinophils) in sensitized individuals
- Antigen combines with **cell fixed antibody**
- Free Abs in circulation- not relevant
- Pharmacologically active substances released & produce reaction
- Two forms:
  - *Anaphylaxis- acute, fatal systemic form*
  - *Atopy- chronic/recurrent, non-fatal local form*

Type-I HSTR: Anaphylaxis

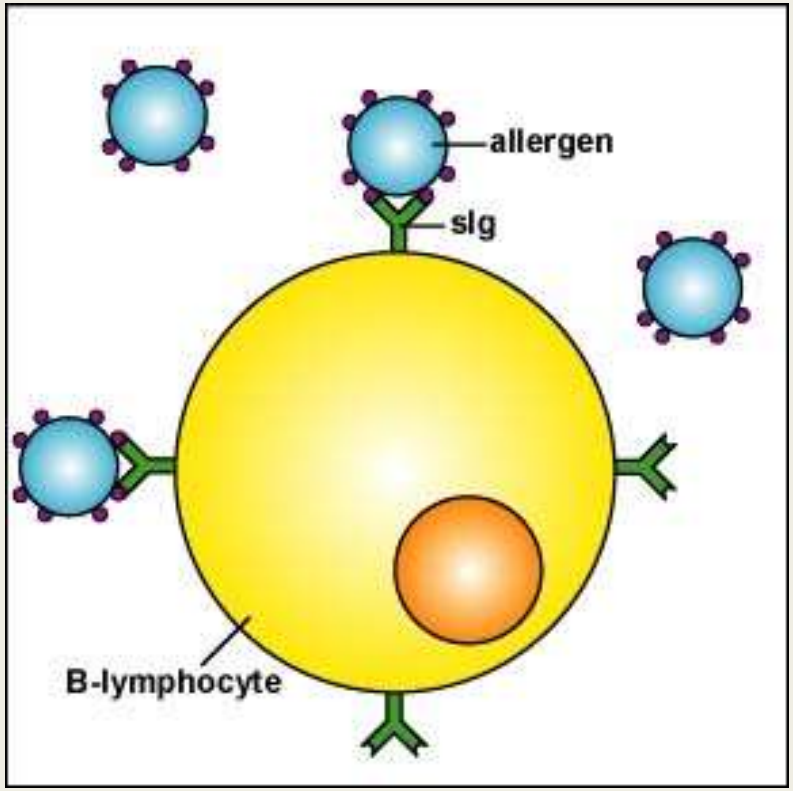
- *Classical Immediate HSTR*

- Most effective- Ag introduced parenterally
- Occur by any route exposure to Ag
- Minute quantities- enough
- Interval of 2-3 wks needed between sensitizing & shocking dose
- Once sensitized- remains so for long time
- Shocking dose most effective by IV route, IP, SC, ID
- Shocking Ag- same or similar to sensitizing Ag

Type-I HSTR Mechanism

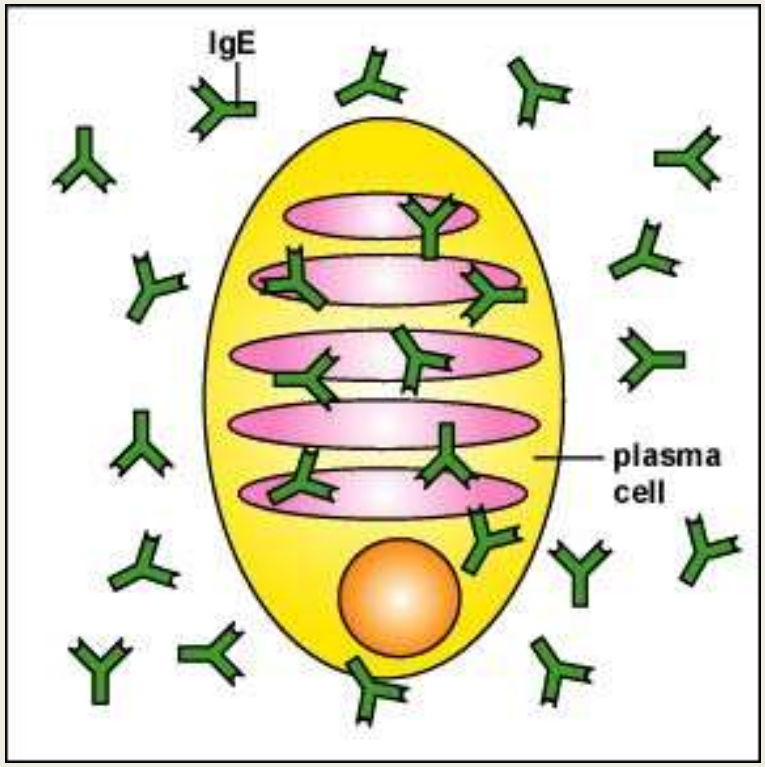
Sensitization

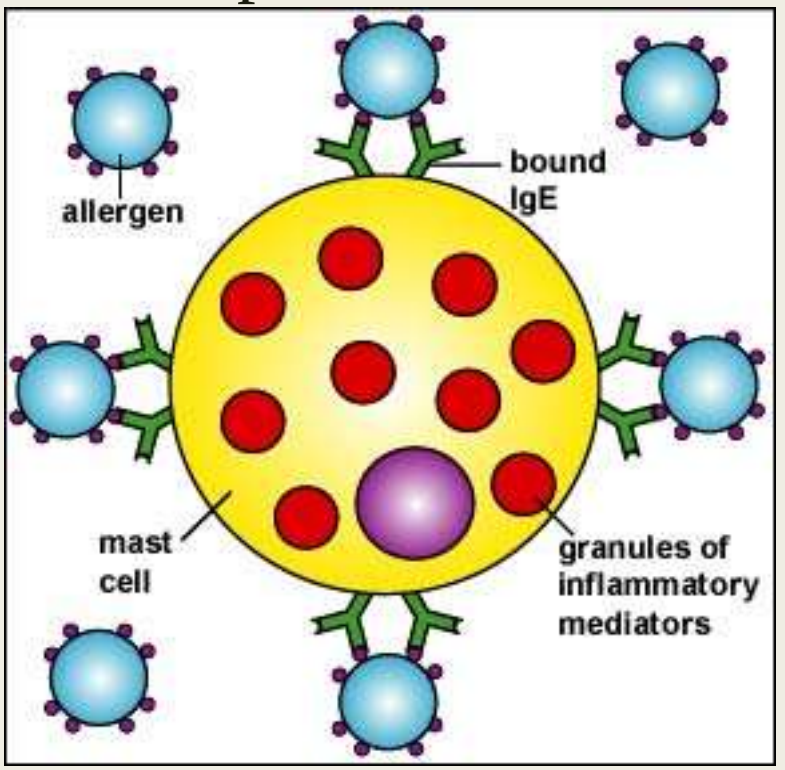
- Allergen enters body
- Recognized by surface-Ig on B-cells
- B-lymphocyte proliferates & differentiates into plasma cells



Type-I HSTR Mechanism

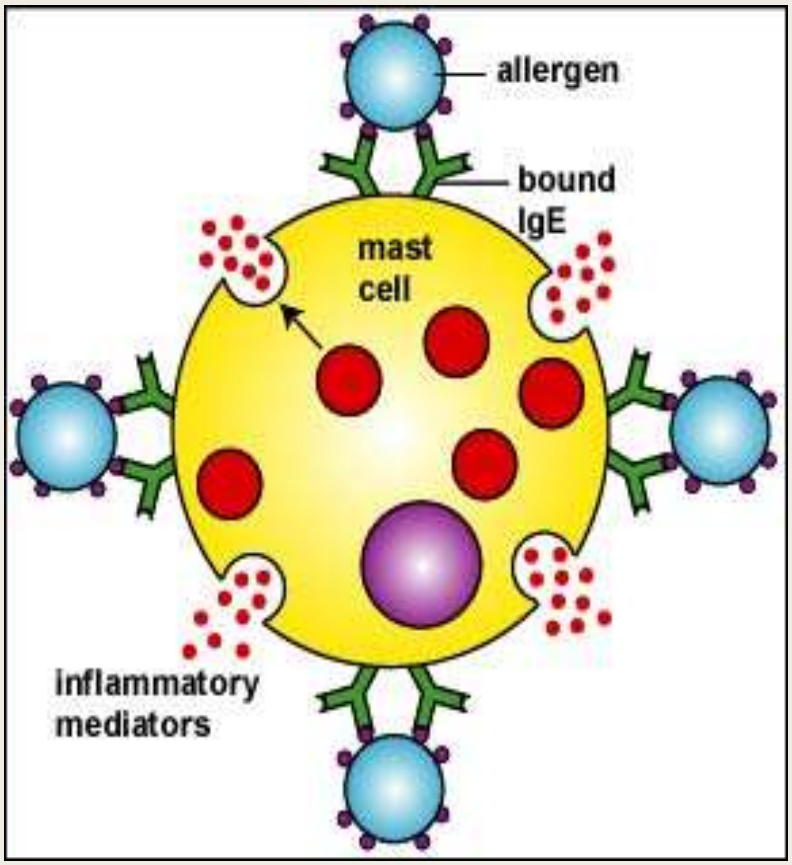
- Plasma cells produce & secrete IgE
- IgE- binds to surface receptors (Fc epsilon) on mast cells & basophils





Type-I HSTR Mechanism

- Subsequent exposure to same allergen causes cross-linking of cell bound IgE on mast cell/ basophil→ leads bridging between adjacent Ab molecules
- Cross-linking increases permeability of cells→ degranulation→ release biologically active substances



Inflammatory mediators bind to receptors on target cells→ leads to symptoms of allergy

Type-I HSTR Mediators

- **Early phase reactions: primary mediators**
  - *Appear within minutes after exposure to antigen*
  - *Mast cells play major role*
  - *Mediated by histamine & other inflammatory mediators*
- **Late phase reactions: secondary mediators**
  - *Begin several hours after exposure to antigen*
  - *Basophils play major role*
  - *Mediated by histamine releasing factor*

Primary Inflammatory Mediators: stored in granules

Molecule	Effects
Histamine, Serotonin	↑Vascular permeability, ↑Smooth muscle contraction
Eosinophil Chemotactic Factor-A	Eosinophil chemotaxis
Neutrophil Chemotactic Factor-A	Neutrophil chemotaxis
Proteases	Bronchial mucus secretion, degradation of blood-vessels & basement membrane

Secondary Inflammatory Mediators:
synthesized *de novo* (newly formed)

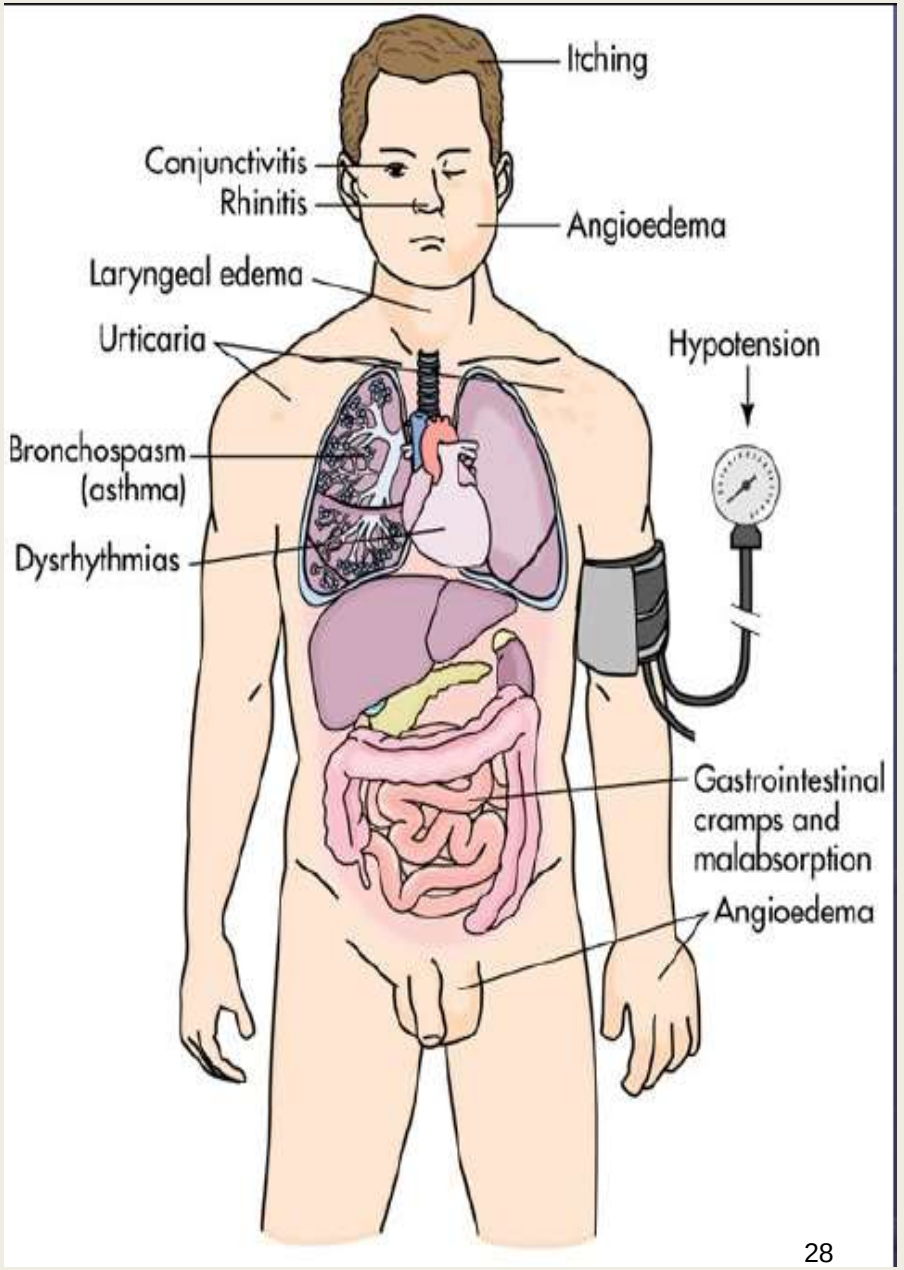
Molecule	Effects
Platelet Activating Factor	Platelet aggregation & degranulation, contraction of smooth muscle
Leukotrienes	↑Vascular permeability, Smooth muscle contraction
Prostaglandins	↑Vasodilatation, Smooth muscle contraction, platelet aggregation
Bradykinin	↑Vascular permeability, Smooth muscle contraction
Cytokines (IL-1, TNF-α)	Numerous effects e.g. Activation of Vascular endothelium, Eosinophil Recruitment and Activation

Anaphylactoid Reaction

- Resembles anaphylactic shock
- Clinical resemblance- same chemical mediators participating in both
- Caused by IV injection of heavy metal salts, trypsin, peptone, starch & polysaccharide
- Not mediated by Abs (no immunological basis, non-specific mechanism)
- Activate alternate complement pathway with release of anaphylatoxins

Type-I HSTR

- Humans –
  - *Itching of scalp & tongue, flushing of skin, difficulty in breathing, nausea, vomiting, diarrhea, acute hypotension, loss of consciousness, death (rare)*
  - *Causes*
    - Serum therapy, antibiotics, insect stings
  - *Treatment- Adrenalin*



Cutaneous Anaphylaxis

- Small shocking dose, given ID to sensitized host- local wheal & flare reaction (local anaphylaxis)
- Used for
  - *Testing for hypersensitivity*
  - *Identification of allergens for atopy*
- Precautions- Keep adrenalin injection ready to combat severe fatal reaction

Passive Cutaneous Anaphylaxis

- In vivo method- detection of Ab (Ovary-1952)
- Ab injected intradermally→ Ag with dye (Evans blue) injected IV 4-24hrs afterwards→ immediate blue coloration at site of ID injection d/t vasodilatation & increased permeability (wheal & flare reaction)
- Detect human IgG (heterocytropic Ab) & not IgE (homocytotropic)

Anaphylaxis in vitro

- Isolated tissues (intestinal/ uterine muscle strips) from sensitized G.pig

↓

Held in Ringer's solution

↓

Addition of specific Ag

↓

Vigorous contraction of tissues

ATOPY (Out of place/ Strangeness)

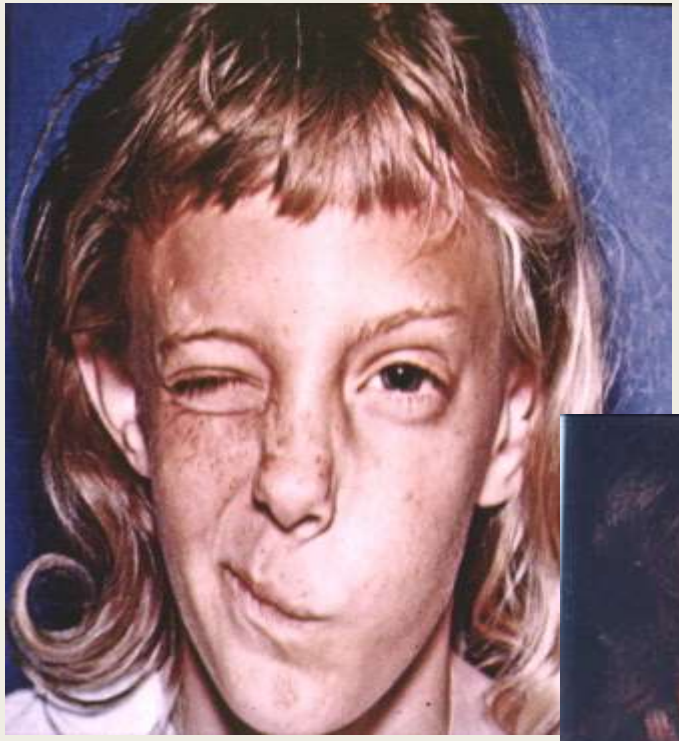
- Familial HST- genetically determined, linked to MHC genotypes
- Occur spontaneously
- Ags involved- pollens, dust, food (mushroom, prawn), drug (penicillin, sulphonamides)
- Ags induce IgE Abs (reagin Abs)
- Reaction- at site of entry of Ag
- Artificial induction of atopy- difficult, atopens poor Ags

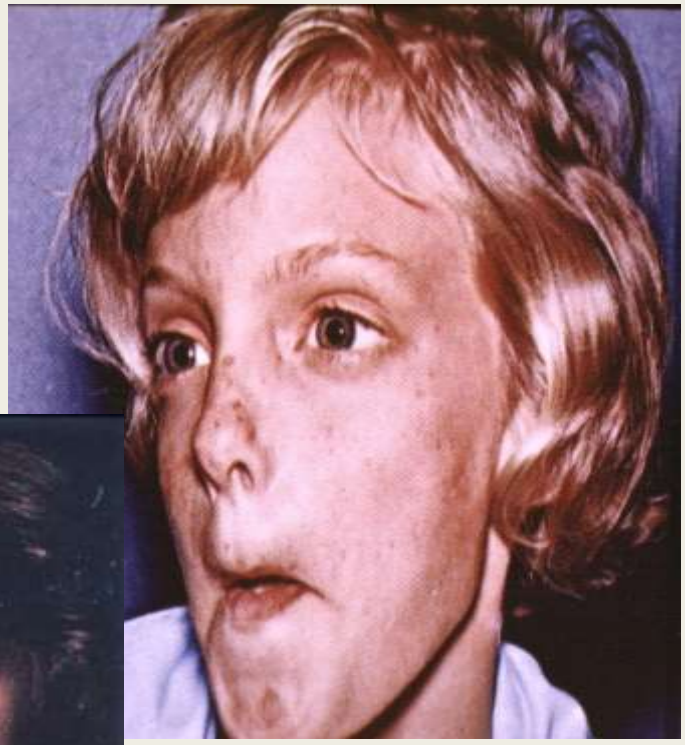
ATOPY

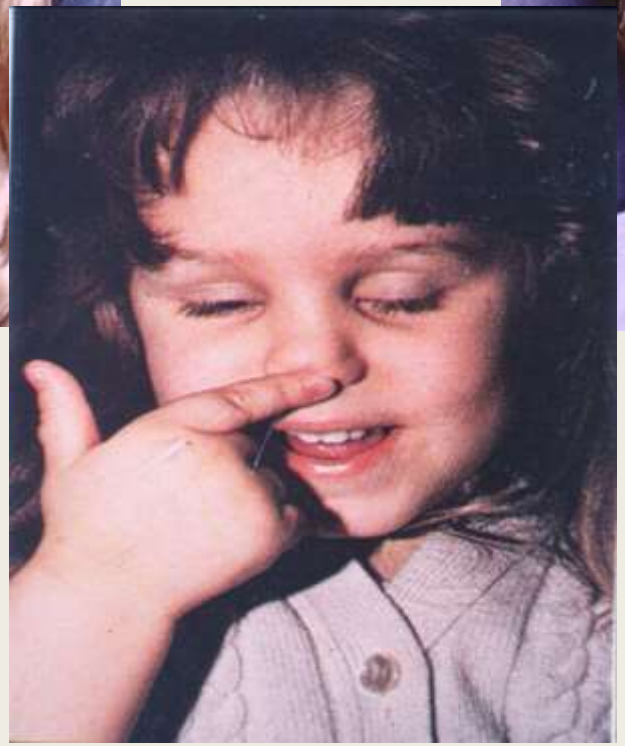
- Atopic sensitivity- overproduction of IgE, associated with IgA deficiency
- Inhalant & ingestant Ags- dealt by IgA, lining respiratory & intestinal mucosa
- IgA deficiency- massive stimulation of IgE forming cells→ overproduction of IgE
- Symptoms- release of pharmacologically active substances
- Clinical expression- portal of entry of Ag

  Conjunctivitis, rhinitis, GIT symptoms, dermatitis
- T/t- specific desensitisation (hyposensitisation)

Type-I HSTR- Common Allergy

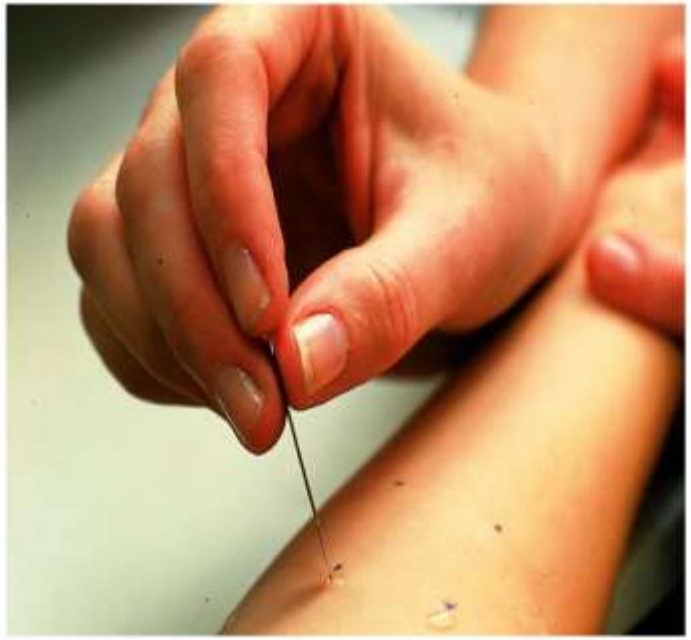






Type-I HSTR- Detection

- Skin test
- Conjunctival test
- ELISA
- Radioallergosorbent assay (RAST)
- Radioimmunosorbent test (RIST)



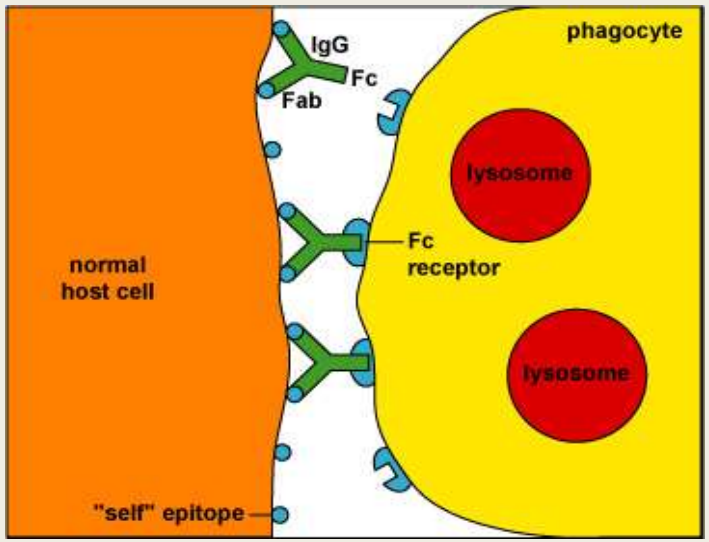
TYPE-II HYPERSENSITIVITY

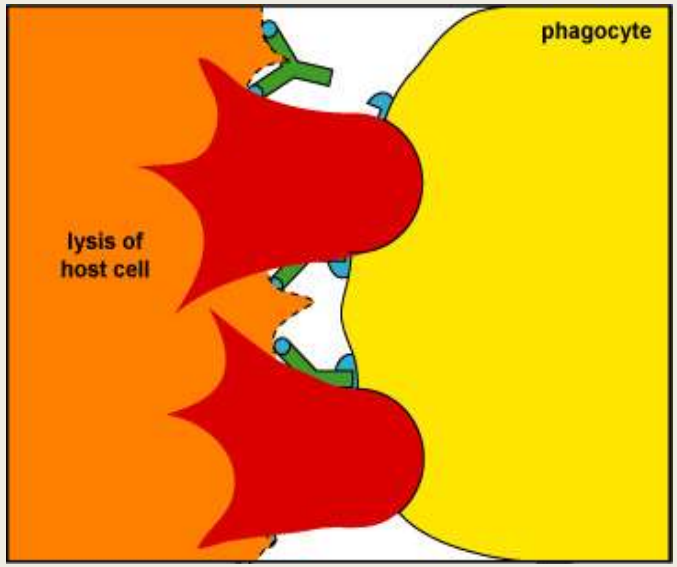
Type-II HSTR

- Cytotoxic or cell stimulating hypersensitivity
- IgG or IgM (rarely)- made against normal self-Ag or foreign Ags resembling some molecule on surface of host cells
- Binding of antibodies to surface of host cells leads to:
  - *Opsonization*
  - *Membrane Attack Complex (MAC) lysis of the cells*
  - *ADCC destruction of the host cells*

Type-II HSTR Opsonization

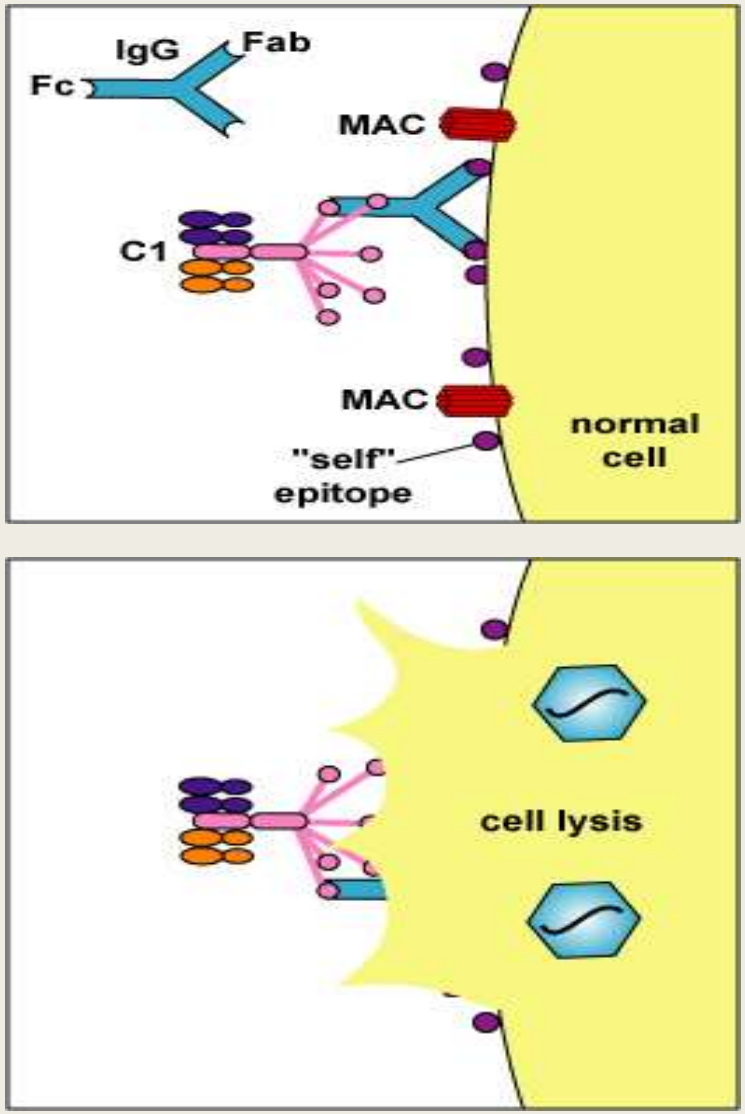
- Fab of IgG reacts with epitopes on host cell membrane
- Phagocytes bind to Fc portion of IgG
- Phagocytes discharge lysosomes→ cell lysis





Type-II HSTR MAC-lysis

- IgG or IgM reacts with epitopes on host cell membrane
- Activates classical complement pathway
- Membrane Attack Complex (MAC) causes lysis of cell



Type-II HSTR ADCC-lysis

- NK cells bind to Fc portion of Abs that have bound to epitopes of cells recognized as non-self e.g. infected cells & tumor cells

- Once bound to Fc portion of Ab, NK cell→ lyse cell with pore-forming proteins (perforins) & proteolytic enzymes (granzymes)

Type-II HSTR Examples

- AB and Rh blood group reactions
- Autoimmune diseases:
  - *Rheumatic fever*
  - *Idiopathic thrombocytopenia*
  - *Myasthenia gravis*
  - *Graves' disease*
  - *Multiple sclerosis*
- Drug reactions
- Early transplant rejections

Type-II HSTR Demonstration

- Direct Coombs test
- Agglutination
- CFT
- Precipitation
- Immunofluorescence

TYPE-III HYPERSENSITIVITY

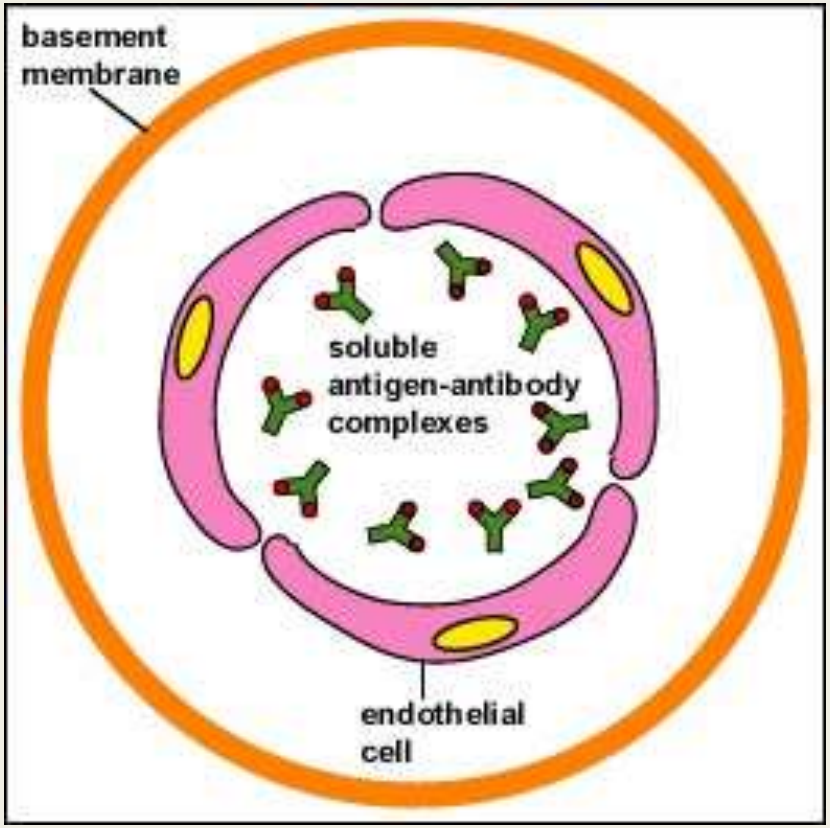
Type-III Hypersensitivity

- Immune complex or toxic complex mediated HST
- Soluble Ag-Ab complexes- deposited in organs & cause inflammatory damage
- Damage- caused by activation of complement, platelets, phagocytes

Type-III HSTR Mechanism

STEP-1

- Large quantities of soluble Ag-Ab complexes formed in blood
- Not completely removed by macrophages



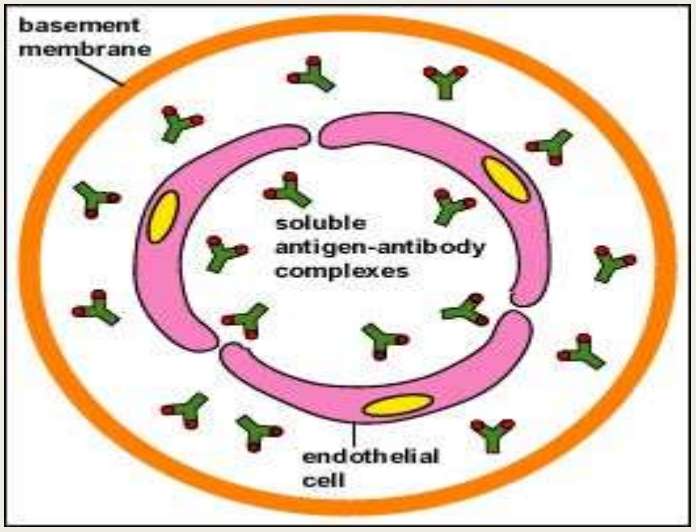
Type-III HSTR Mechanism

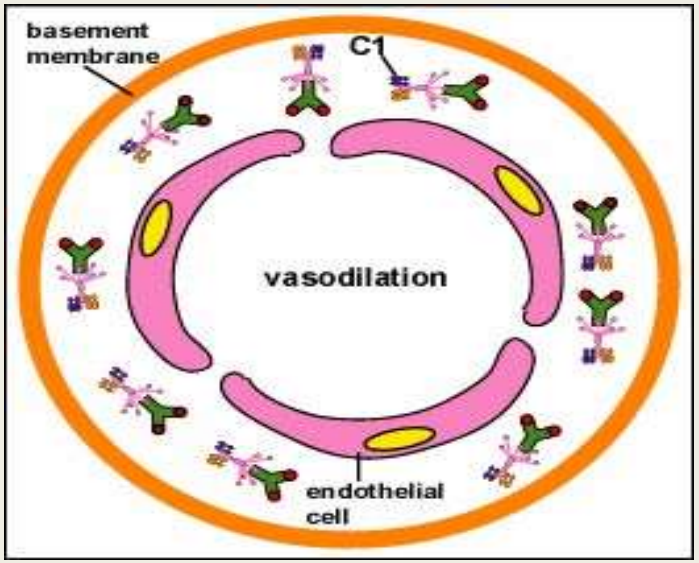
STEP-2

Ag-Ab complexes lodge in capillaries between endothelial cells & basement membrane

STEP-3

Ag-Ab complexes activate classical complement pathway vasodilatation





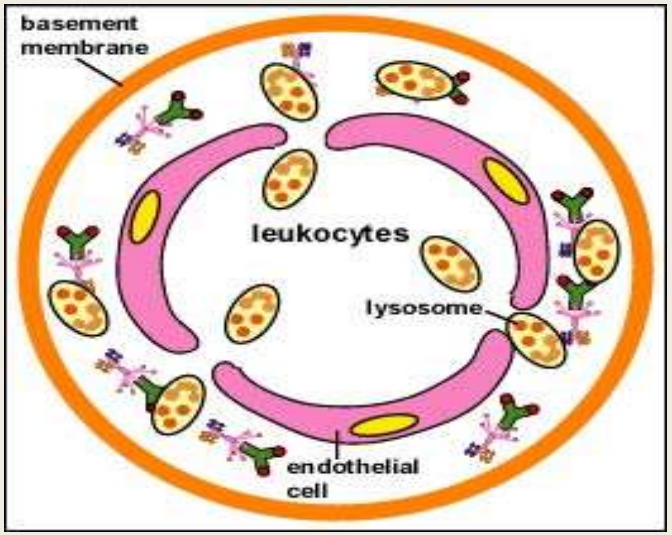
Type-III HSTR Mechanism

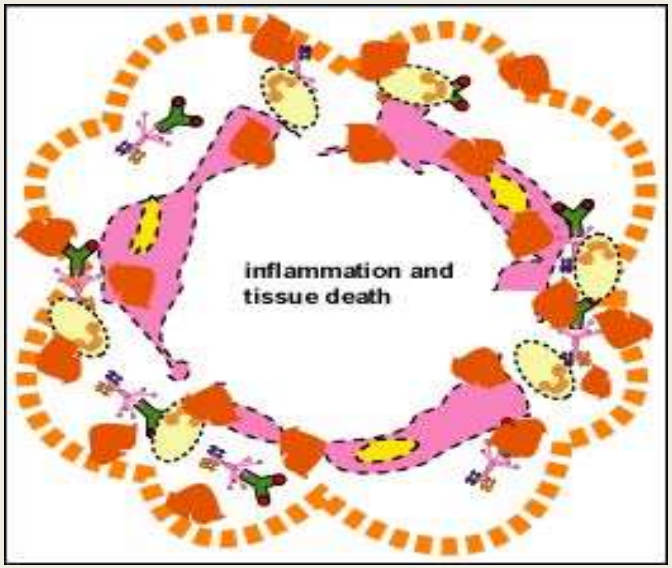
STEP-4

Complement proteins and Ag-Ab complexes attract leukocytes to area

STEP-5

Leukocytes discharge killing Agents & promote massive inflammation→ tissue death & hemorrhage





Type-III HSTR

- Arthus reaction-
  - Local manifestation
- Serum sickness-
  - Systemic form, self limited

Type-III HSTR

- Arthus reaction:-

- Localized area of tissue necrosis due to vasculitis resulting from acute immune complex deposition

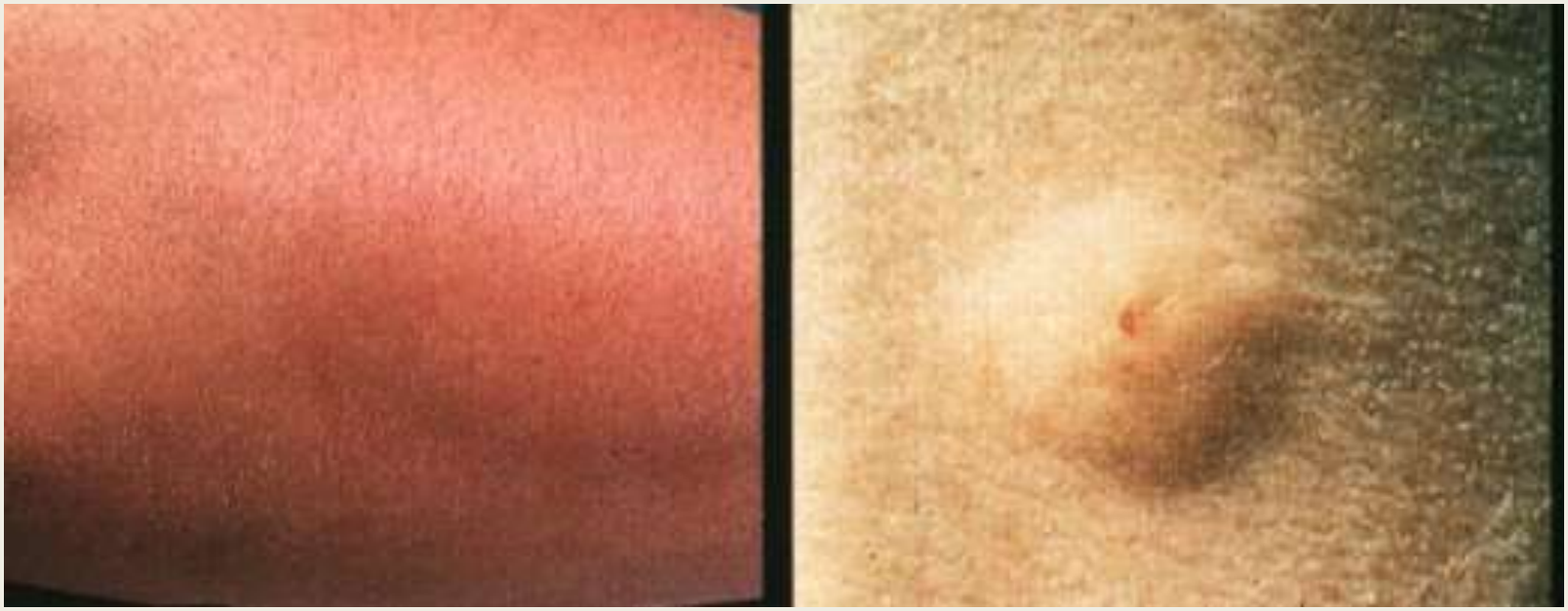
- E.g. Farmer's lung

  Pigeon fancier's disease

Arthus reaction & Wheal & flare reaction

Arthus reaction
Type-III

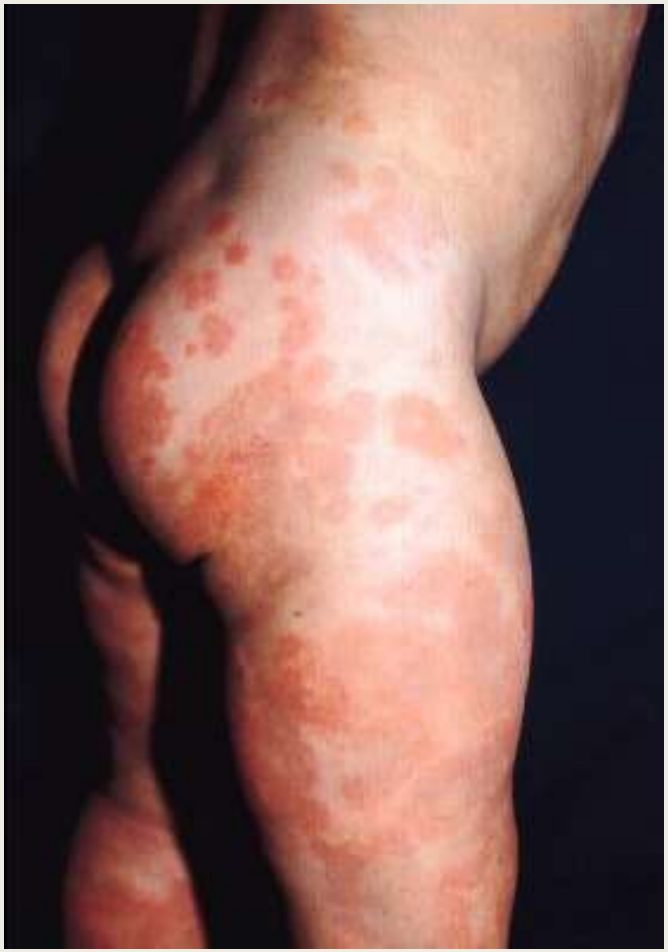
Wheal & flare reaction
Type-I

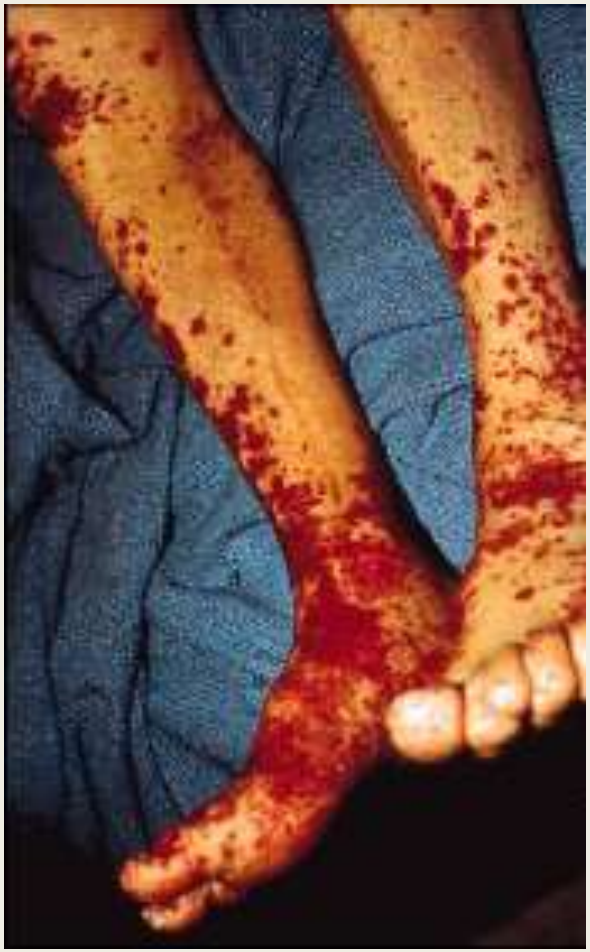


Type-III HSTR Serum sickness

- Single dose of high concentration of foreign serum
- Presence of sufficient quantities of soluble Ag in circulation→ antigen excess
- Soluble Ag-Ab complexes- poorly cleared
- Major pathology- complex deposition
- Deposited immune complexes trigger neutrophils to damage surrounding endothelium and basement membranes
- Complexes- deposited in skin, kidney and joints, e.g. arthritis and glomerulonephritis
- e.g. SLE, RA, drug allergies, PSGN, tumors

Serum sickness





TYPE-IV HYPERSENSITIVITY

Type-IV Hypersensitivity

- Delayed or cell mediated hypersensitivity
- Ag activates specifically sensitized CD_4 & CD_8 T-cells→ secretion of lymphokines
- Cannot transferred via serum (by T-cells or transfer factor)
- Appears slowly in 24-48hours
- Important host defense mechanism
- e.g. *Granulomatous lesions of M. leprae*
  Lung cavitations in M. tuberculosis

TYPE-IV HSTR

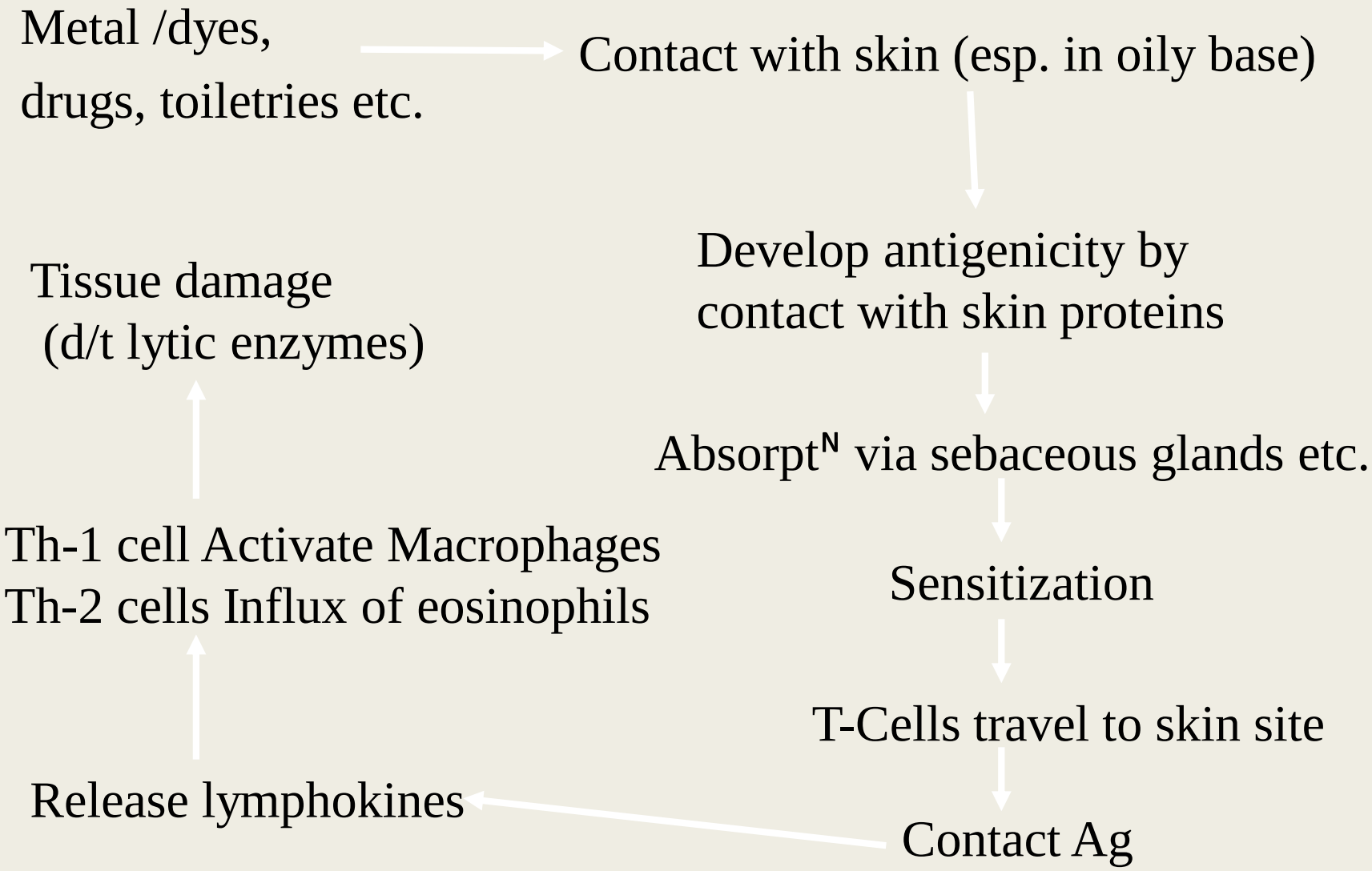
Two Types:-

1. Tuberculin (infection) type
2. Contact dermatitis type

Type-IV HSTR Tuberculin type

- Small dose of tuberculin/ PPD injected ID in sensitized individual
- Inflammatory reaction- in 48 to 72 hrs
- Un-sensitized individual- No reaction
- Demonstrated in case of viruses, bacteria, parasites, fungi (esp. intracellular)

Type-IV HSTR- Contact dermatitis

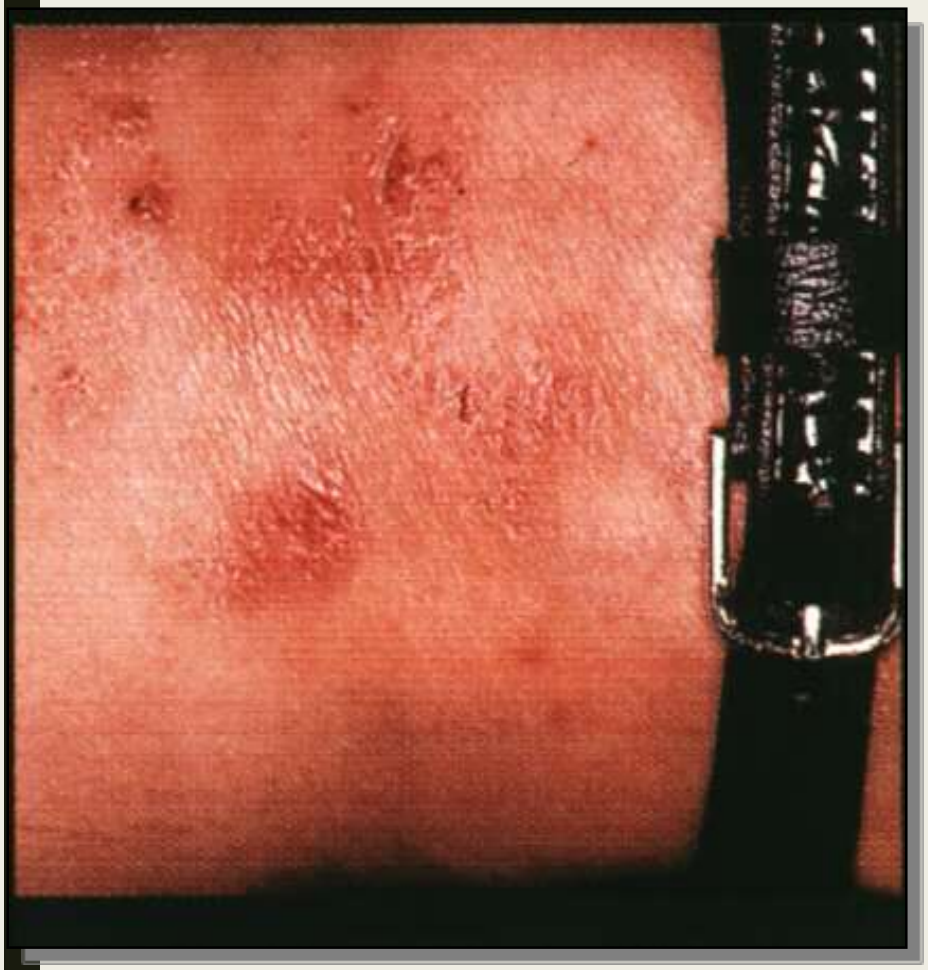


Type-IV HSTR- Granulomatous Type

- Serious type
- Develop over period of 21-28 days
- Granuloma formation d/t aggregation & proliferation of macrophages
- e.g. leprosy, tuberculosis

- ***TYPE-IV HSTR:- in chronic infections e.g. leprosy. TB, leishmaniasis, candidiasis, HSV infection etc***

Contact Dermatitis Reaction



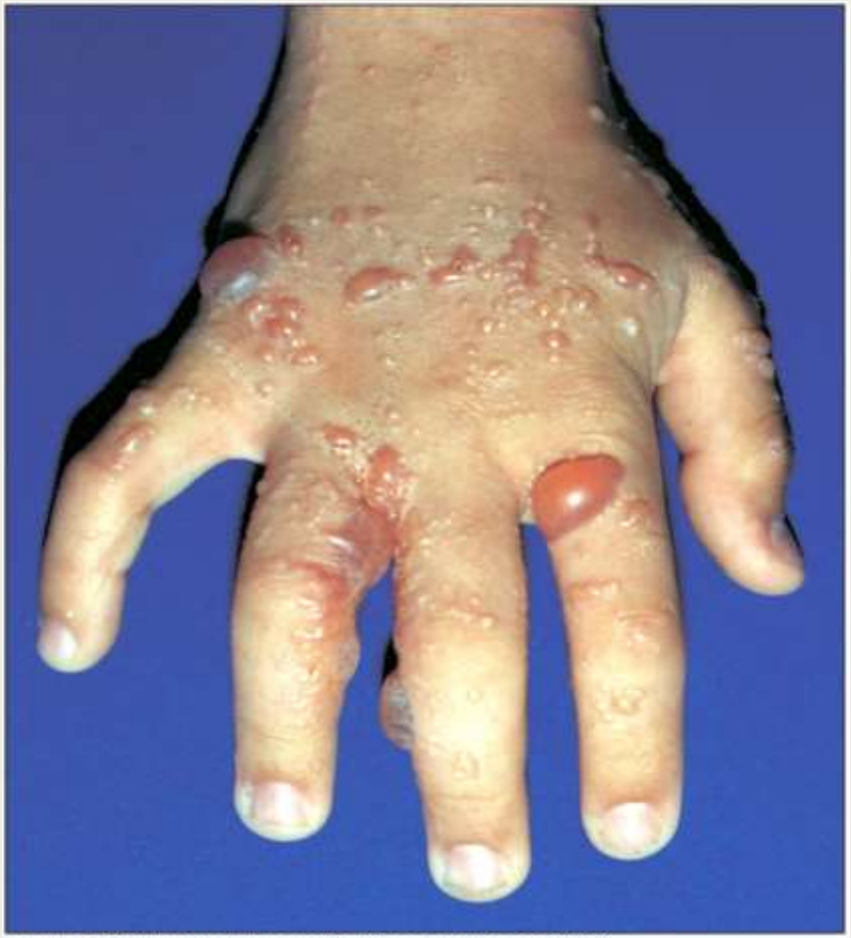
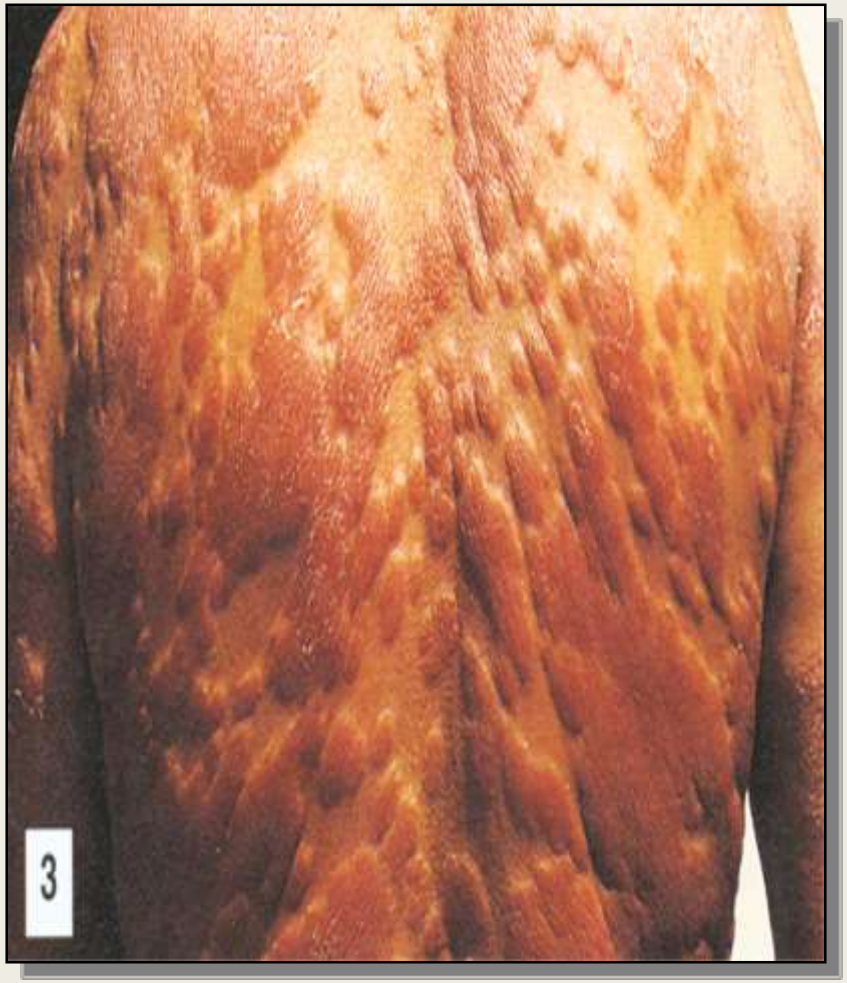
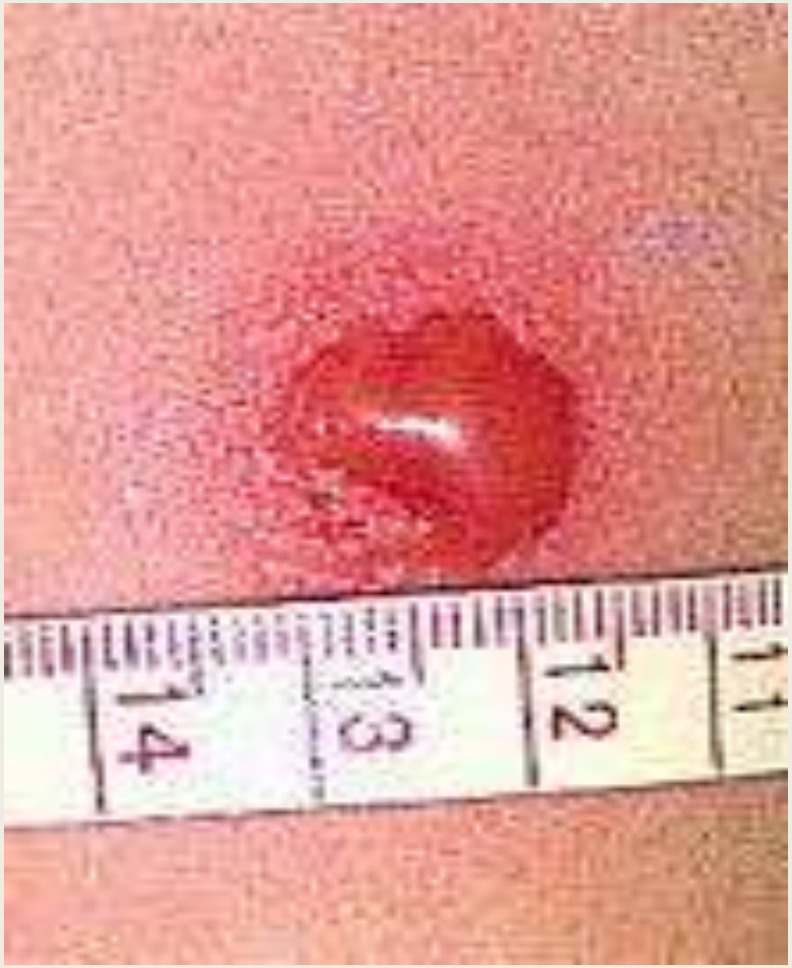


Figure 12-28 Immunobiology, 6/e. (© Garland Science 2005)

Granuloma- Leprosy patient





Shwartzman Reaction

- Not immune response
- Superficial resemblance to HSTR
- Specialized type of intravascular coagulation precipitated by endotoxin
- e.g. fulminating meningococcal septicemia (Waterhouse-Friderichsen syndrome), septic shock syndrome-Gram neg. septicemia accompanied by ARDS

SUMMARY

	Type I	Type II	Type III	Type IV
Immune response	Humoral	Humoral	Humoral	Cellular
Immediate / Delayed	Immediate	Immediate	Immediate	Delayed
Duration	2-30 mins	5-8 hrs	2-8 hrs	24-72 hrs
Antigen	Soluble	Cell surface bound	Soluble	Soluble/ bound
Mediator	IgE	IgG	Ag-Ab complex	T(DTH) cells

	Type I	Type II	Type III	Type IV
Effector mechanism	Mast cell degranulatN	ADCC Complement mediated cytotoxicity	Complement activation & inflammatory response	Macrophage activation leads to phagocytosis/ cell cytotoxicity
Desensitization	Easy but short lasting	Easy but short lasting	Easy but short lasting	Difficult but sustained
Manifestations	Anaphylaxis Asthma, Atopic dermatitis	Transfusion reaction, Rh-incompatibility, hemolytic anemia	Arthus reaction, serum sickness, glomerulonephritis Rheumatoid arthritis	Tuberculin test, granuloma formation, contact dermatitis