



HYPERSENSITIVITY

HYPERSENSITIVITY...

- Refers to undesirable (Damaging, discomfort producing, and sometimes fatal reactions produced by the normal immune system.
- Hypersensitivity reactions require a pre-sensitized (Immune) state of the host.



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CLASSIFICATION:

Coombs and Gell classification(1969):

On the basis of mechanism of pathogenesis:

Type 1: Anaphylactic

Type 2: Cytotoxic

Type 3: Immune complex or toxic complex

TYPE 4 : Delayed type

CLASSIFICATION:

On the basis of time required for sensitized host to develop clinical reaction upon re-exposure to the antigen , **SELL(1972)** classified them as-

Immediate reaction

- Appears and recedes rapidly

Delayed reaction

- Appears slowly and lasts longer

TO KNOW...

- **Antigen** - Any substance which, stimulates the production of an antibody with which it reacts specifically and in an observable manner.
- **Hapten** - Substances that are incapable of inducing antibody formation by themselves but can react specifically with antibodies.



TO KNOW...

Antibody-

- Is a protein substance produced as a result of antigenic stimulation.
- Circulating antibodies are immunoglobulins(Igs)of which there are five classes:
IgG,IgA,IgM,IgE and IgD.



General features of Hypersensitivity disorders:

- Both Exogenous and endogenous antigens may elicit hypersensitivity reactions.
- Development of hypersensitivity diseases (both allergic and autoimmune) is often associated with the inheritance of particular susceptible genes. HLA genes and many non-HLA genes have been implicated.
- General principle - Hypersensitivity reflects an imbalance between the effector mechanism of immune responses and the control mechanism that serve to normally limit such responses.

Robbins and Kotran - Pathologic basis of disease - 8th ed.

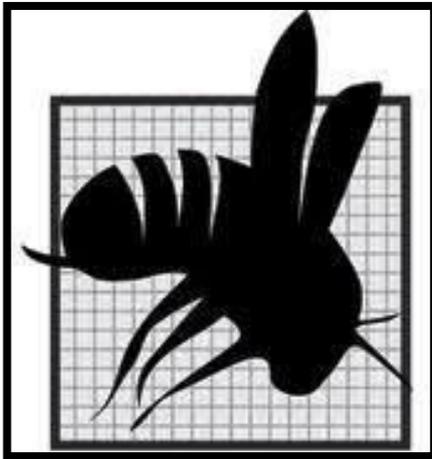
TYPE 1 REACTIONS:

- Classic **immediate** hypersensitivity reaction.
- Occurs **within minutes**.
- These reactions are often called **allergy** and the antigens that elicit them are the **allergens**.
- May occur as **→ Systemic(Anaphylaxis) or Local(Atopy)**.
- Local reactions:
 - **Initial reaction**
 - **Late phase reaction**

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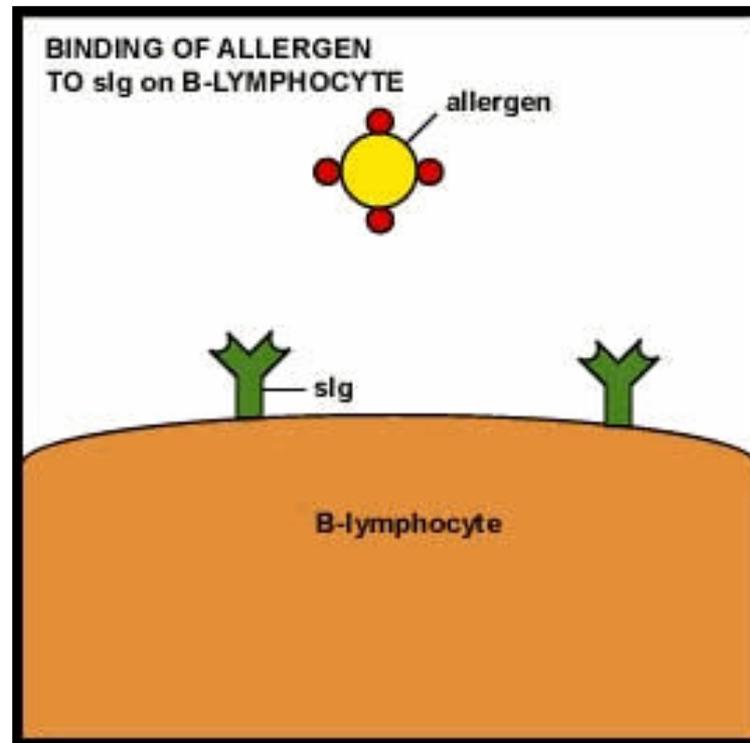
TYPE 1 REACTIONS:

The cause-



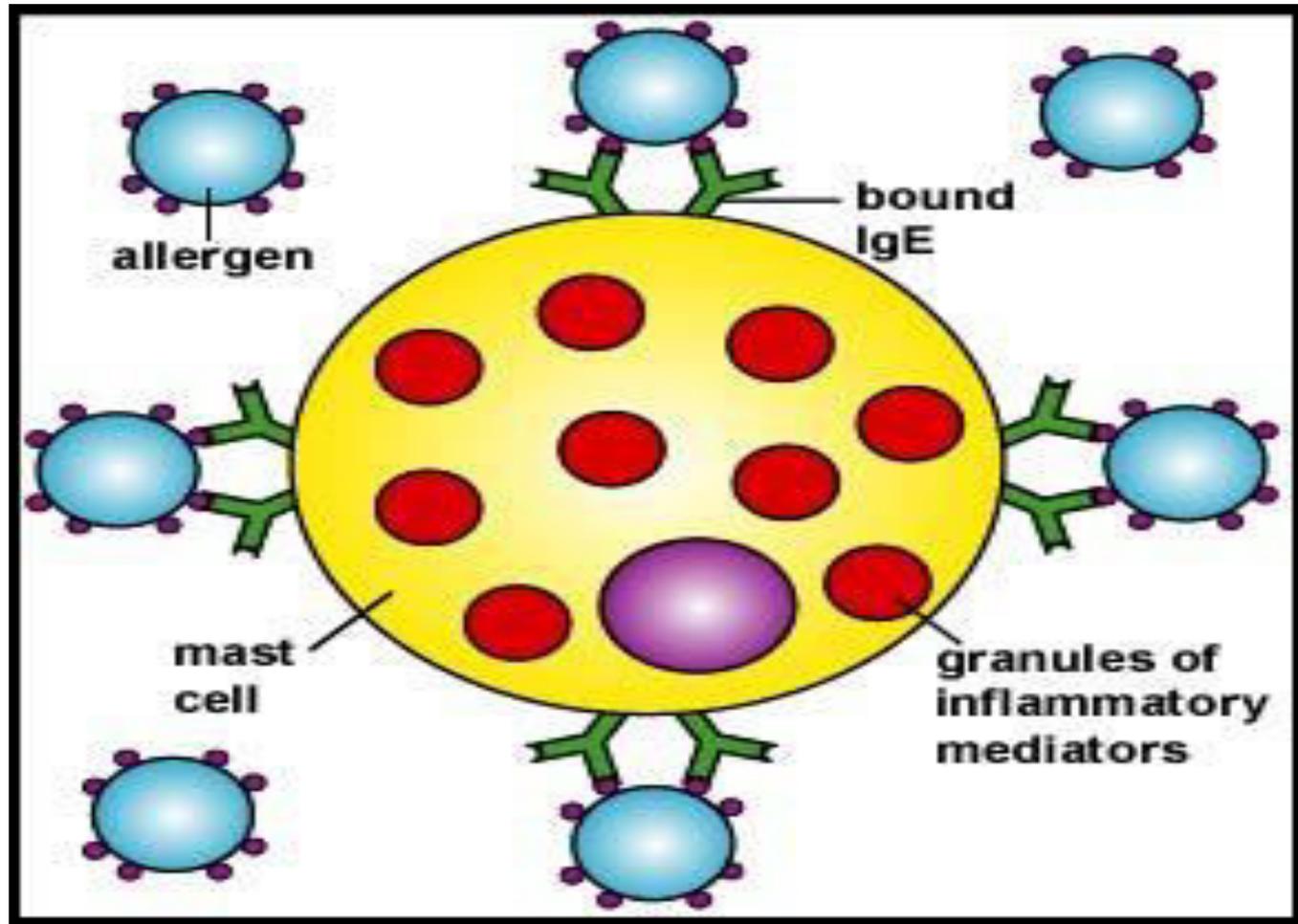
MECHANISM :

In response to an Antigen(Allergen),more number of specific antibody will be produced.



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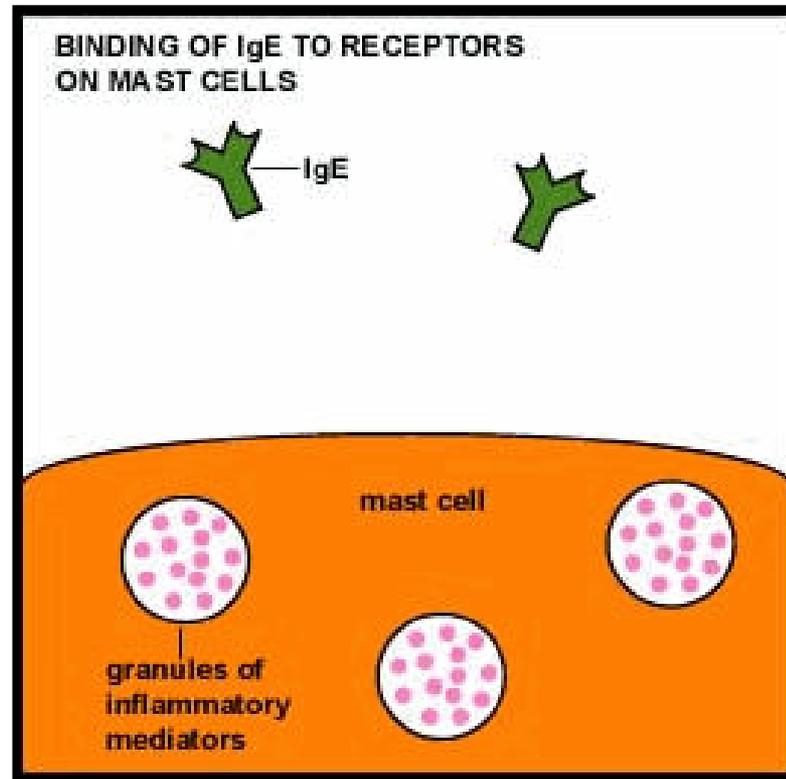
MECHANISM:



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MECHANISM:

Allergic interaction with IgE on the surface of Mast cells triggers the release of inflammatory mediators.

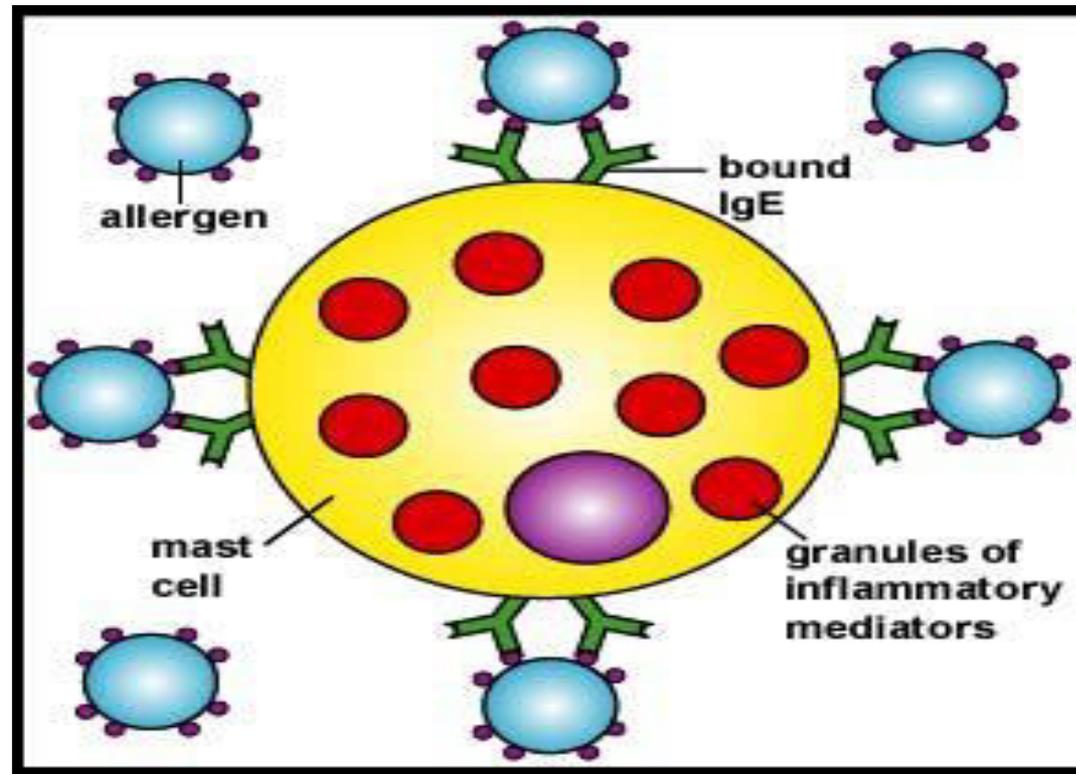


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MECHANISM :

Sensitization Phase-

IgE binds to receptors on mast cells and basophils

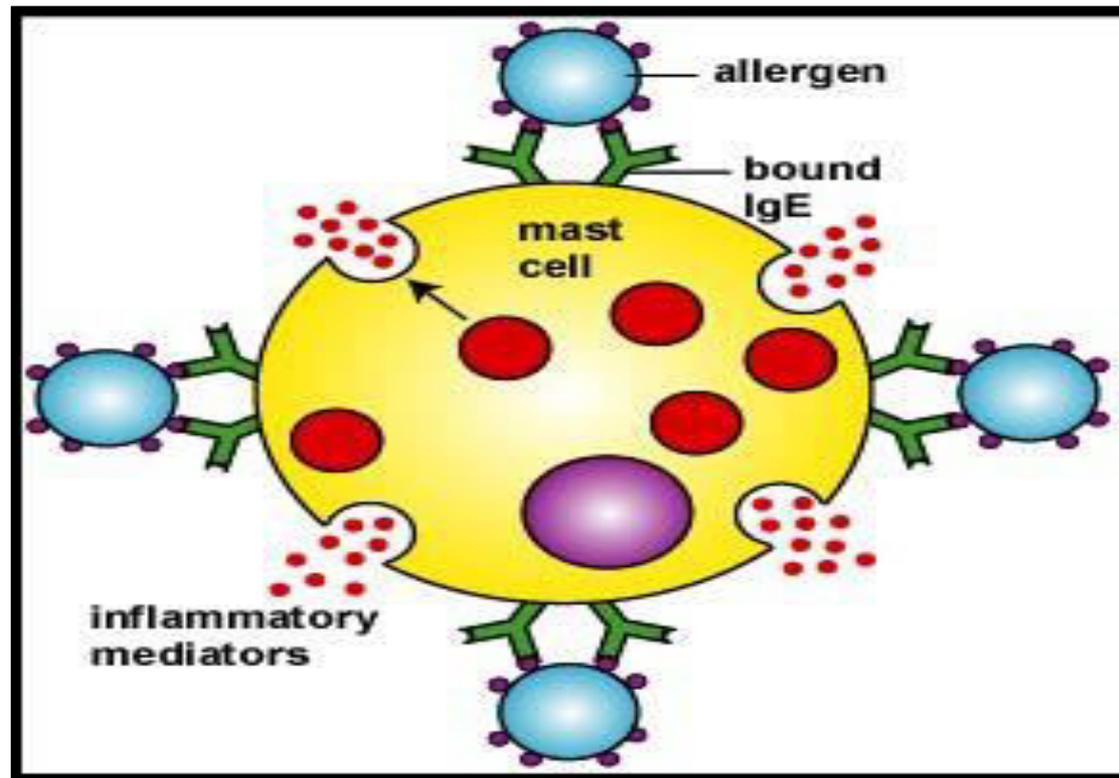


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MECHANISM:

Triggering/Activation phase-

Release of granules and their inflammatory mediators from the mast cell.



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MECHANISM:

Effector Phase-

Effector phase is attributable to the inflammatory mediators released by the mast cell.

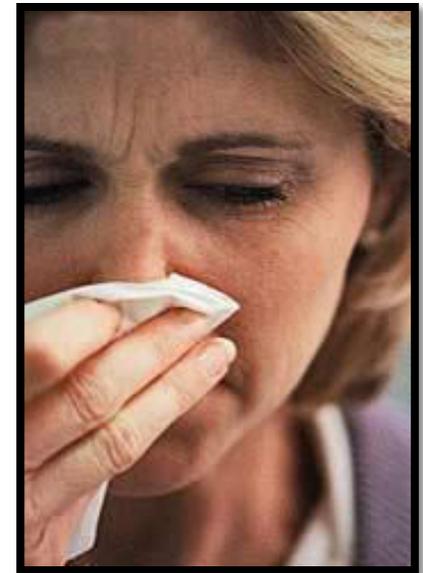
Eczema



Asthma



Rhinitis



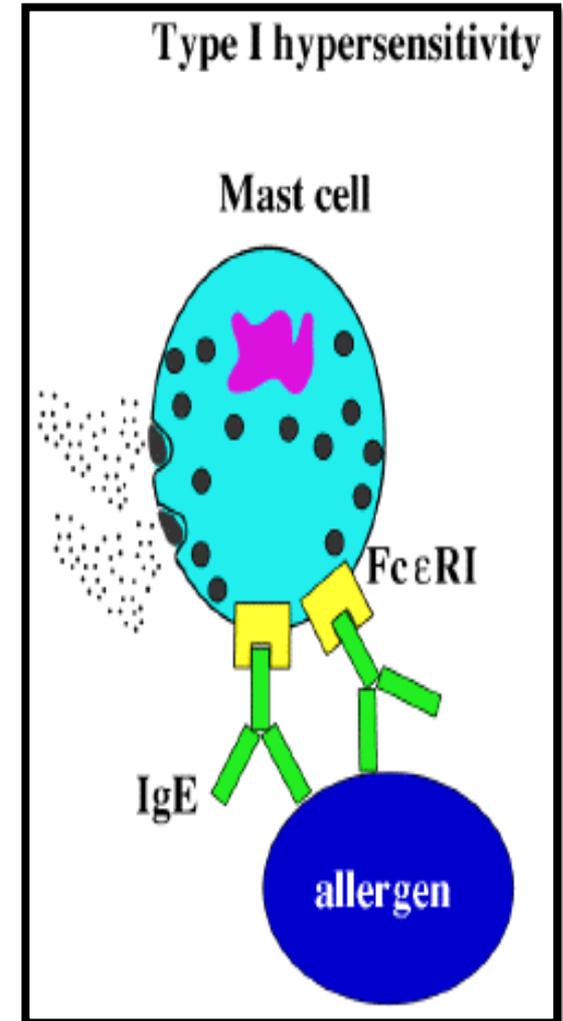
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Drug Hypersensitivity:

when the solution becomes the problem??

- Anti-Microbials especially **penicillin** and **sulfonamides**.
- In many cases, it is not the intact drug but a **metabolic product of it act as hapten** and initiates the reaction.
- Rash, Urticaria, Angioedema, Shock.

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Examples for type 1 reactions:

Anaphylaxis:

- Reactions due to administration of medications.

Atopy:

- Bronchial Asthma
- Allergic dermatitis
- Angioneurotic edema
- Hay fever(Seasonal allergic rhinitis)

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CUTANEOUS ANAPHYLAXIS :

When a small shocking dose of antigen is administered intradermally to a sensitized host, there will be a local wheal and flare response.



PASSIVE CUTANEOUS ANAPHYLAXIS:

Antibody injected intradermally into normal animal-If the antigen along with a dye like Evan's blue is injected IV 4-24 hrs afterwards there will be wheal and flare reaction.

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DEMONSTRATION OF ATOPIC ANTIGENS-In vitro

SCHUTZ-DALE PHENOMENON:

- Isolated tissue like intestinal or uterine muscle strips from sensitized guinea pigs are kept in Ringer's solution in a bath.
- On addition of specific antigen to the bath, it will contract vigorously.
- This is called as the **SCHUTZ-DALE** phenomenon.
- The reaction is specific and will be elicited only by the antigen to which the animal is sensitive.

DEMONSTRATION OF ATOPIC ANTIGENS-In Vivo

Prausnitz-Kustner reaction:

- Reaginic antibody has an affinity for skin. This is the basis for P-K reaction.
- When serum collected from Kustner (having atopic hypersensitivity to certain species of cooked fish) was injected intracutaneously, into Prausnitz followed 24hrs later by an intracutaneous injection of small quantity of cooked fish antigen into the same site, within a few minutes, wheal and flare reaction occurred.
- Since IgE is homocytotropic, test has to be carried out in man only.

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TYPE 2 REACTION :

•Either IgG or IgM is made against normal self antigens as a result of a failure in immune tolerance or a foreign antigen resembling some molecules on the surface of host cells enters the body .

•IgG or IgM made against that antigen then cross reacts with the host cell surface in any of the following ways:

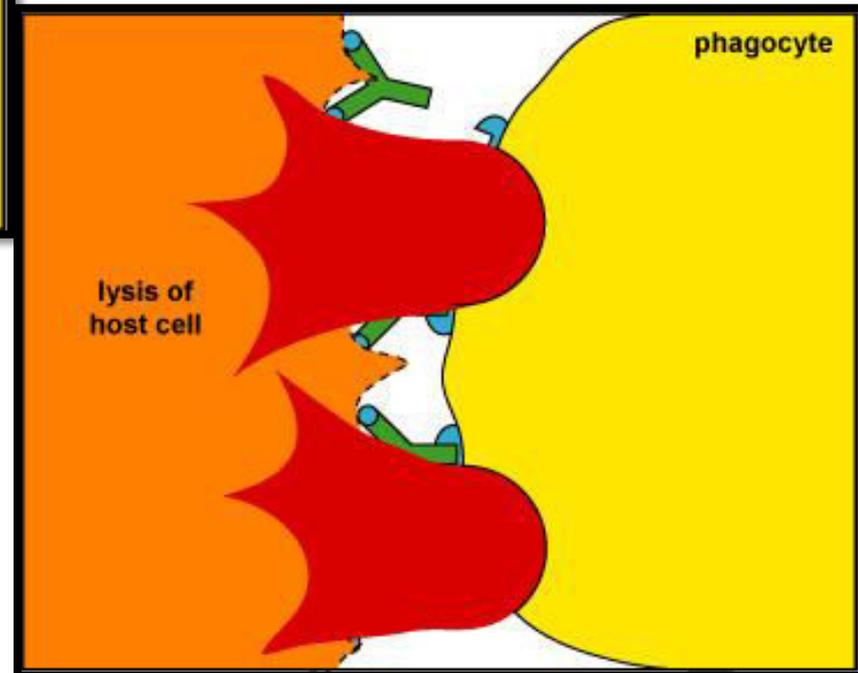
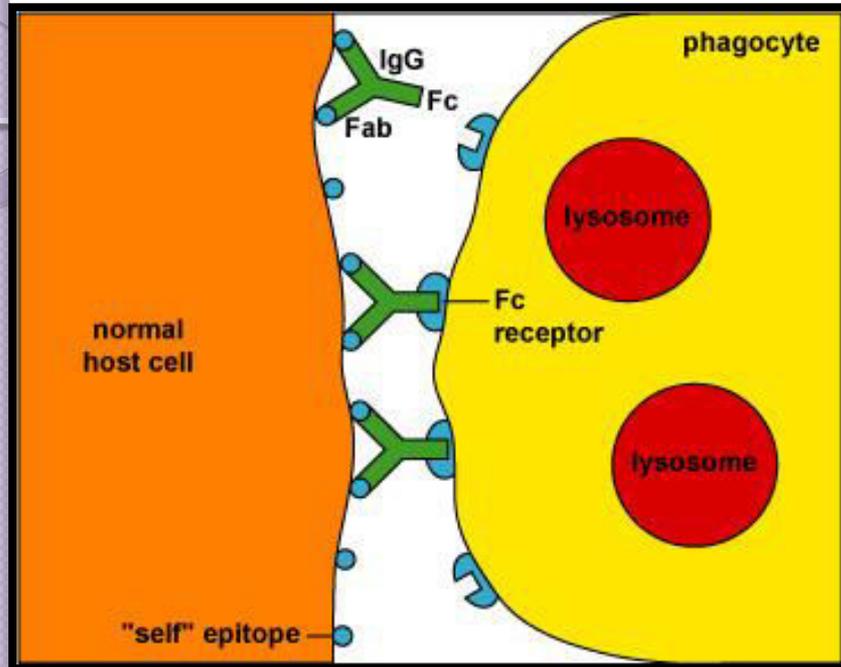
-Opsonization

-MAC Lysis

-ADCC destruction of host cells.

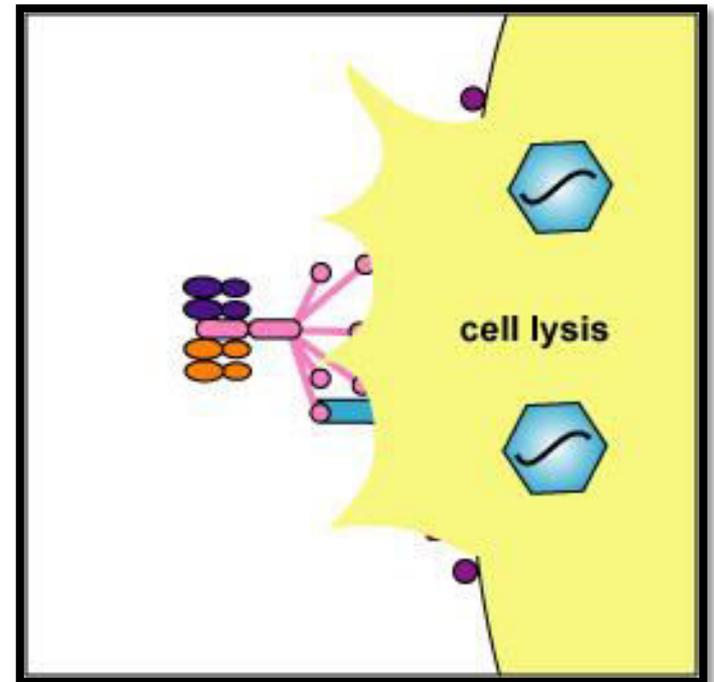
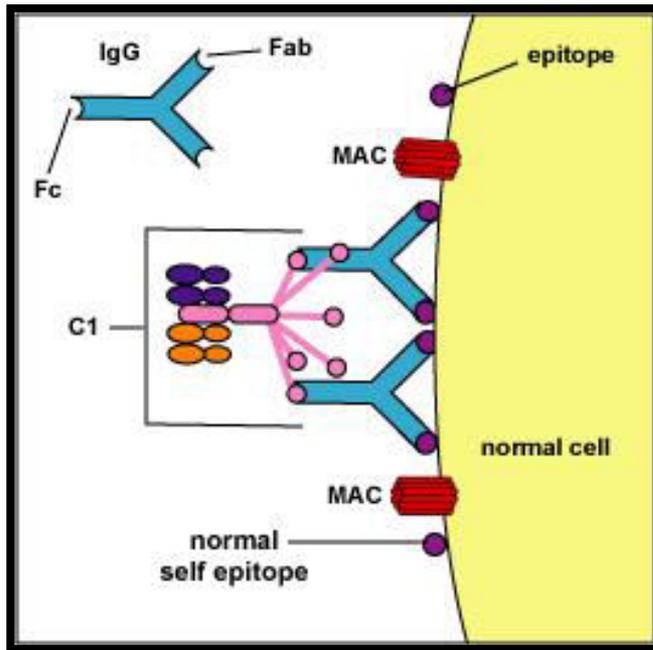
TYPE 2 REACTION :

-Opsonization



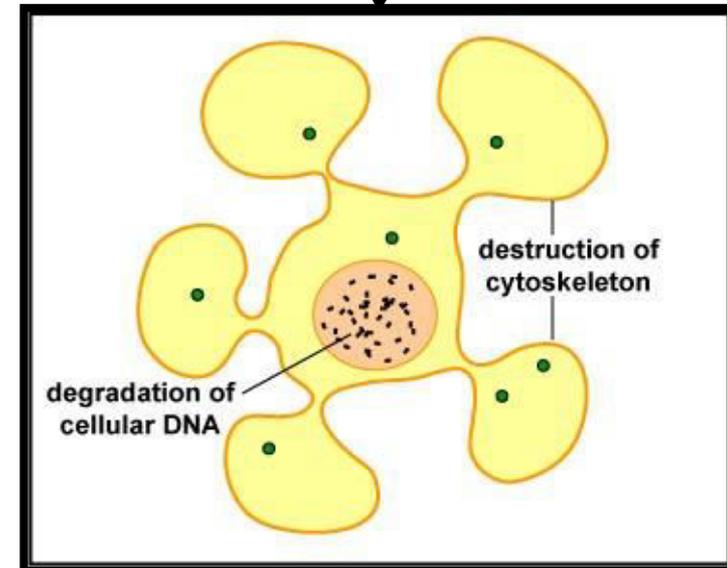
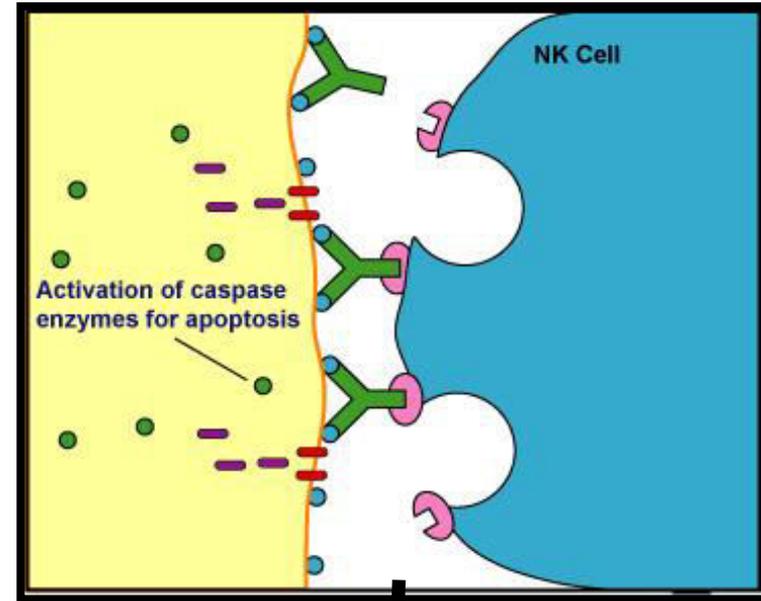
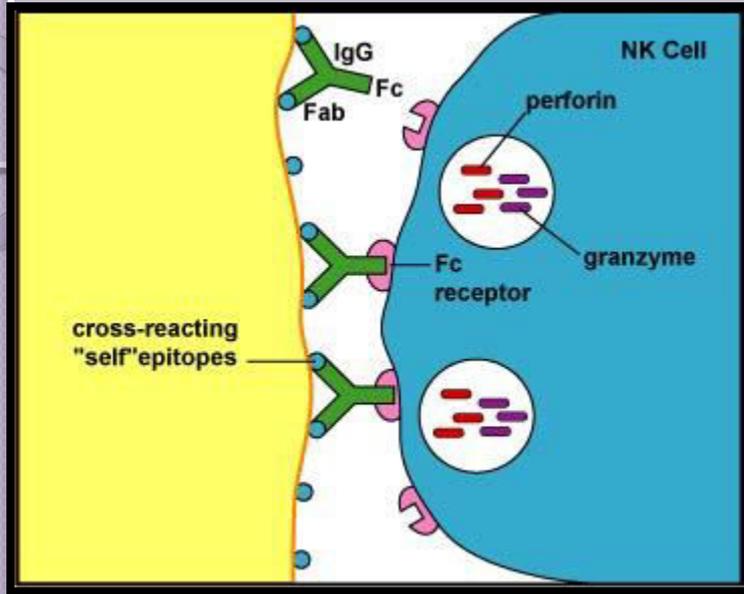
TYPE 2 REACTION :

-MAC lysis



TYPE 2 REACTION :

-ADCC destruction of host cells



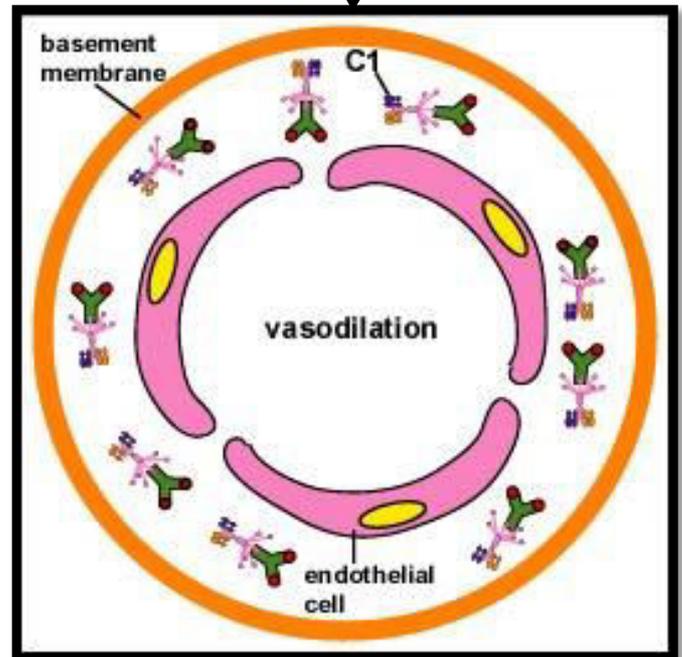
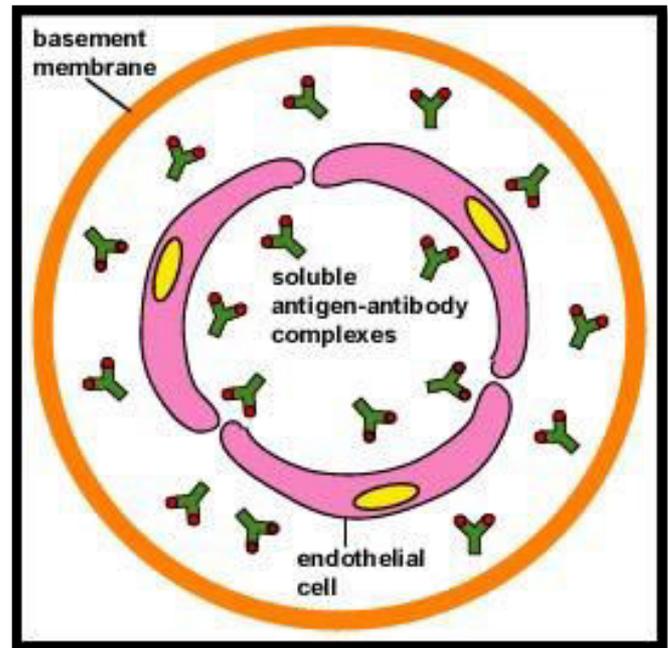
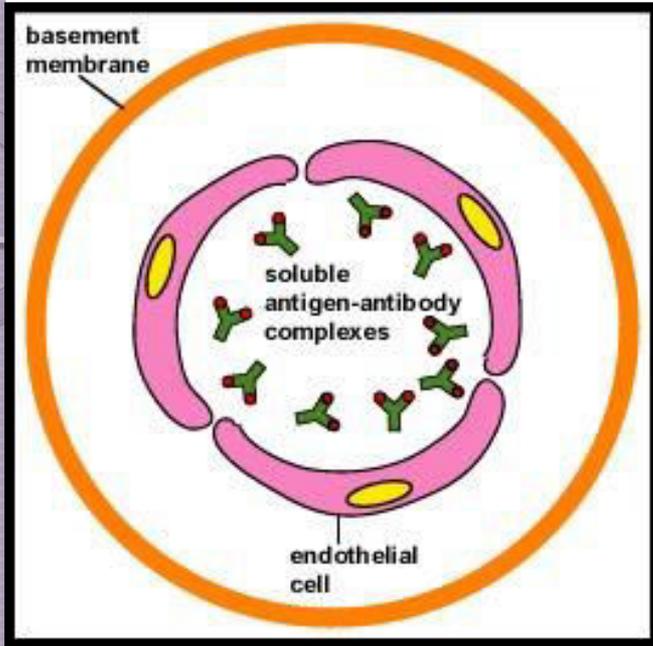
TYPE 2 REACTION :

- The reaction takes about minutes-hours.
- Examples being-
 - Autoimmune hemolytic anaemia, Transfusion reactions, Erythroblastosis fetalis, ITP, Transplant rejection, Drug reactions, Reactions to dental pulp and periapical infections.
 - Myasthenia gravis.
 - Tumour cells, Parasites.

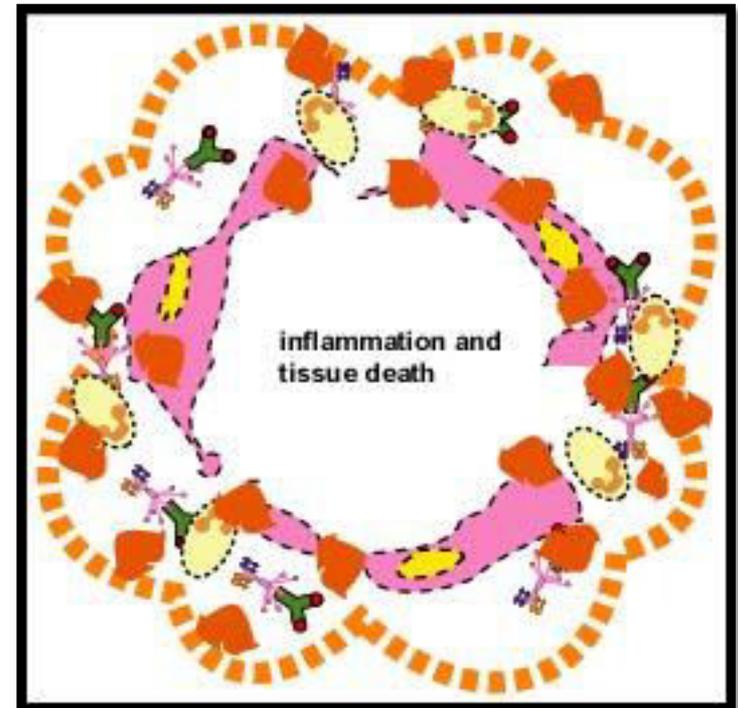
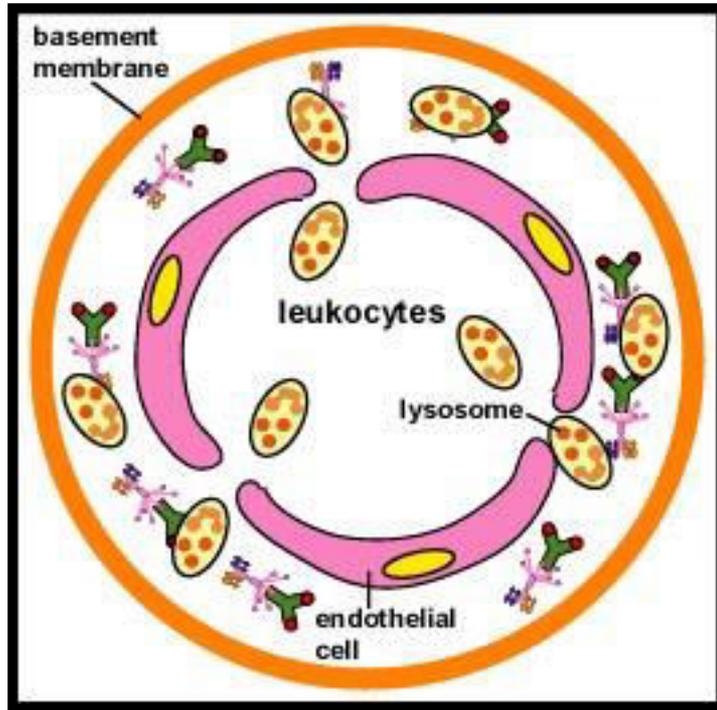
TYPE 3 REACTION:

- Resulting from large quantities of soluble Ag-Ab complexes passing between endothelial cells of the blood vessels and becoming trapped on the surrounding basement membrane.
- The Ag-Ab complexes activate the classical complement pathway .

TYPE 3 REACTION :



TYPE 3 REACTION :



TYPE 3 REACTION :

•Two types:

-**Localized** : Arthus reaction

-**Generalized**: Serum sickness.

Examples:

Arthus - Injection of ATS, farmer's lung.

Serum sickness-Steven Jhonson

syndrome, SLE, Sjogren's

syndrome, Glomerulonephritis, Goodpasture's

syndrome, arthritis, uveitis.

Robbins and Kotran-Pathologic basis of disease-8th ed

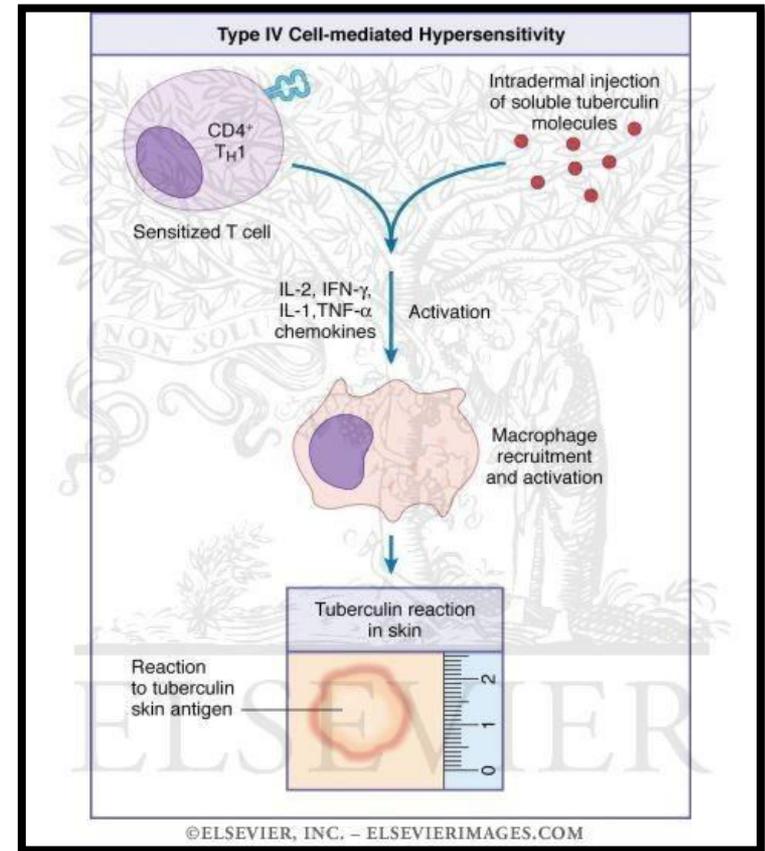
TYPE 4 REACTION:

- It is a delayed type of hypersensitivity.
- Cell-mediated rather than antibody mediated.
- Here, the T-8 lymphocytes become sensitized to an antigen and differentiate into cytotoxic T-Lymphocytes(CTL's) while effector T-4 lymphocytes become sensitized to an antigen and produce cytokines.
- Two types:
 - Tuberculin type
 - Contact dermatitis type(Poison Ivy, Penicillin, Chemicals like nickel, chromium).
- Examples-tuberculin reaction(Mantoux test), Typhoid, contact dermatitis, Transplant rejection.

Textbook of microbiology-Panicker, 7th ed.

TYPE 4 REACTION-DELAYED TYPE:

- Small dose of tuberculin is injected intra-dermally in an individual sensitized
- ↓
- An inflammation sets within 48-72 hrs.
- ↓
- In unsensitized individual, the tuberculin injection provides no response.
- ↓
- Thus, useful for identifying tubercle bacilli

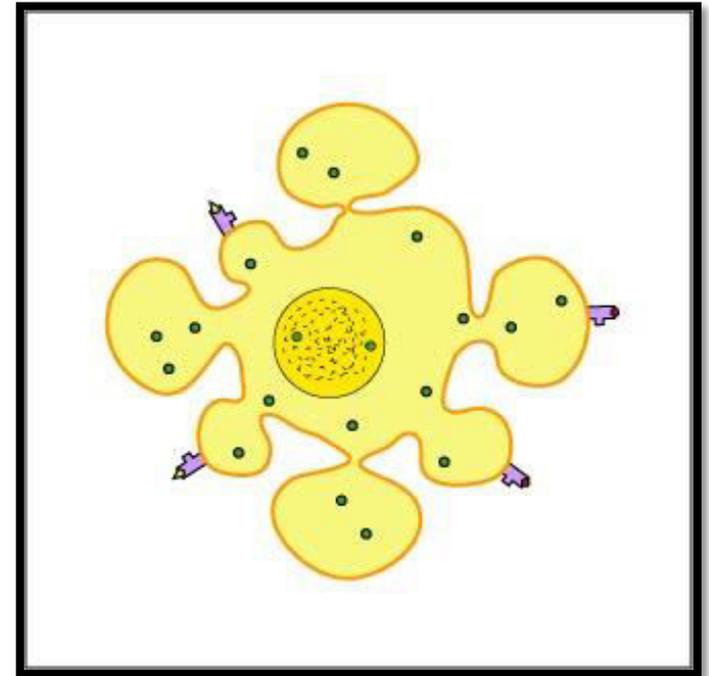
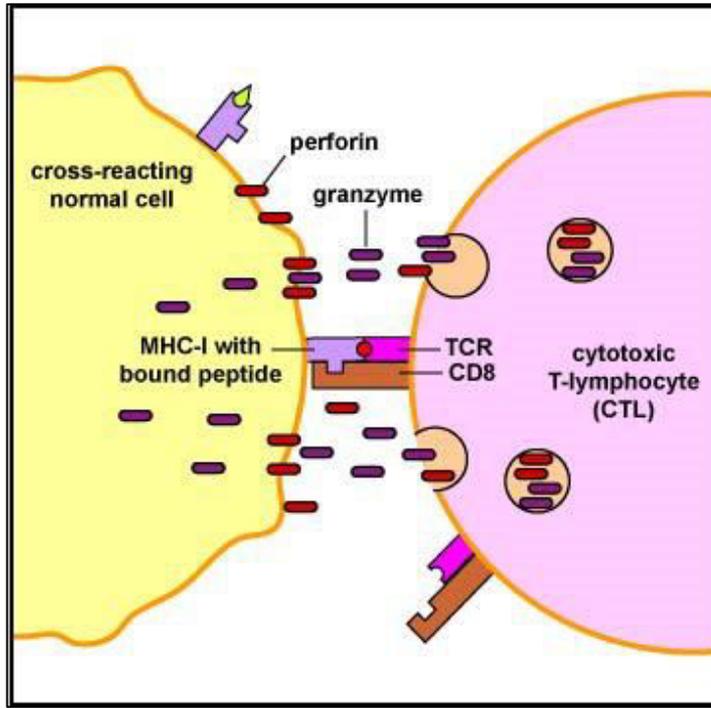


TYPE 4 REACTION -CELLULAR CYTOTOXICITY:

- Mediated by cytotoxic T cells that cause direct tissue injury.
- Here, recognition of the cell surface antigen by a T-cell receptor will bring the T-cell into close contact with the target cell.
- This triggers release of perforins and granzymes-
Apoptosis.

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Levinson 11th ed.

MECHANISM:



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SHWARTZMAN REACTION:

•Schwartzman (1928), described that if a culture filtrate of *S.typhi* is injected **intra-dermally** in a rabbit and **24-hrs later**, by the same filtrate **I.V.**, a **haemorrhagic necrotic lesion** develops at the site of **intra-dermal injection**.

Textbook of microbiology-Panicker, 7th ed.



Well done Gell and
Coombs!!!!But this
is not the end.....

Type 5 Hypersensitivity reaction: Stimulatory type:

An additional type that is sometimes used as a distinction from Type 2. Instead of binding to cell surface components, the antibodies recognize and bind to the cell surface receptors, which either prevents the intended ligand binding with the receptor or mimics the effects of the ligand, thus impairing cell signalling.

Examples : Myasthenia Gravis and Grave's disease.

Textbook of medical physiology - Sembulingam - 3rd edition

Type 5 Hypersensitivity reaction: Stimulatory type

Grave's disease:

- Normally TSH combines with surface receptors of thyroid cells and causes synthesis and secretion of hormones.
- The secretion of hormones can be increased by thyroid stimulating antibodies (TSAB) produced by plasma cells. The excess secretion of thyroid hormone results in grave's disease.

Textbook of medical physiology - Sembulingam - 3rd edition.

Type 5 Hypersensitivity reaction: Stimulatory type

Myasthenia Gravis :

- Characterized by weakness, easy fatigability and paralysis of skeletal muscles.
- In some, IgG autoantibodies are produced which may bind with the receptor proteins for acetylcholine in the neuromuscular junction.
- This prevents neuromuscular transmission since Ach released from axon terminal cannot execute the actions due to the preoccupation of the receptors.

Textbook of medical physiology - Sembulingam - 3rd edition

ALLERGY SKIN PRICK OR SCRATCH TEST

•Most common-Place allergen on the skin(Usually forearm, upperarm or back), and then scratching or pricking the skin so that the allergen is introduced under the skin surface.



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ALLERGY SKIN PRICK OR SCRATCH TEST

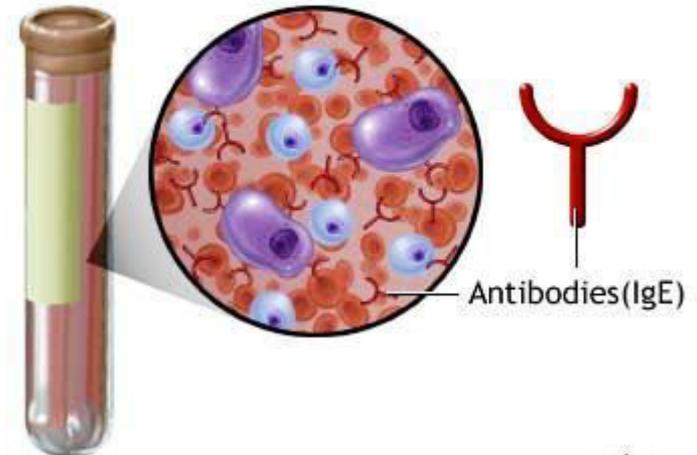
- Skin is observed for swelling and redness at the site.
- Several suspected allergens can be tested at the same time - results within 20 minutes.
- Measures specific IgE attached to cells in the skin important in allergies called mast cells.



BLOOD TEST-RAST(RADIOALLERGOSORBENT)

- Measures the level of allergy antibody, IgE produced when your blood is mixed with a series of allergens in the laboratory.
- If allergic to a substance- IgE level may increase in the blood.
- Indication- skin problems like eczema, long standing medications that cannot be stopped or preference.

The blood test measures the levels of allergy antibody, or IgE, produced when your blood is mixed with a series of allergens in a laboratory



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USE OR ELIMINATION TESTS:

- Suspected items are eliminated and/or introduced while the person is observed for response to the substance.
- Used to check for food or medication allergies.

EYELID :

- Occasionally, the suspected allergen is dissolved and dropped onto the conjunctiva, as a means of testing for allergies.

REACTION TO PHYSICAL STIMULI:

Heat, cold or another stimulant is applied and the patient is observed to see if they have an allergic response.

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MANAGEMENT:

- Avoid the specific allergen.
- The most appropriate medication depends upon the type and severity of symptoms.
- Medications:
 - Anti-Histamines.
 - Corticosteroids.
 - Leukotriene inhibitors.
- Allergy shots(Immunotherapy): Regular injections of the allergen are given, with each dose slightly larger than the previous dose. This keeps our body from over reacting to the allergen.

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MANAGEMENT: Anaphylaxis

First line of treatment-

- **Adrenaline:** 0.1 to 0.3 ml S.C. - Maybe repeated upto 3 times at intervals of over 20 minutes. I.V adrenaline 0.1 ml in 10ml saline is allowed only in the terminal stage.
- **Tourniquet:** is placed proximal to the site of injection or sting - It should be released for 1 or 2 minutes every 10 minutes.
- **Oxygen :** Given by inhalation or nasal catheter.
- **Anti-Histamines:** H1 antagonists to be given parenterally or orally for 48 hrs.
- **Corticosteroids** - Hydrocortisone upto 200 mg I.V, is used immediately, to be followed by 4-6 hrs doses in moderately severe reactions.

Cont...

MANAGEMENT: Anaphylaxis

Second line of treatment-

- I.V fluids to maintain systolic blood pressure.
- Vasopressors, Nor adrenaline, Adrenaline, Dopamine may be tried if I.V. fluids are not effective.
- Intubation and tracheostomy.
- Supportive therapy : using anti-histamines, bronchodilators, vitamins and fluids.

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REFERANCE

- Robbins and Kotran-Pathologic basis of disease-8th ed
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THANK YOU