Hypersensitivity Reactions

Objectives

- Difference between hypersensitivity and protective immunity
- Overview of the four major classifications of human hypersensitivity.

1. Type I hypersensitivity – Mechanisms (allergens, IgE, immediate) and clinical overview
2. Type 2, 3, 4 hypersensitivities – Mechanisms and clinical consequences

- Currently practiced vs. novel approaches to clinical management of hypersensitivity

Introduction

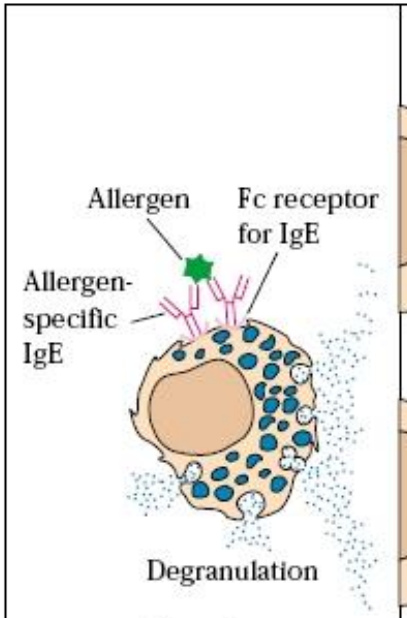
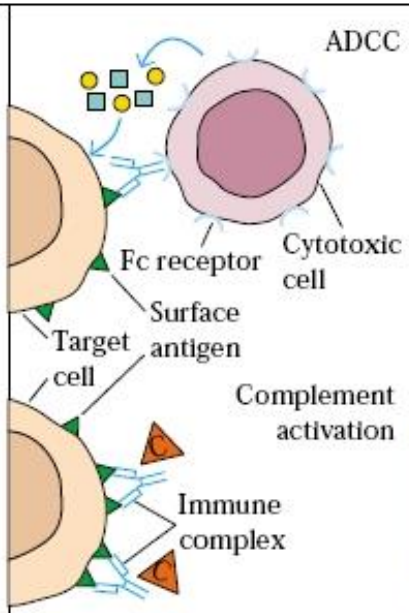
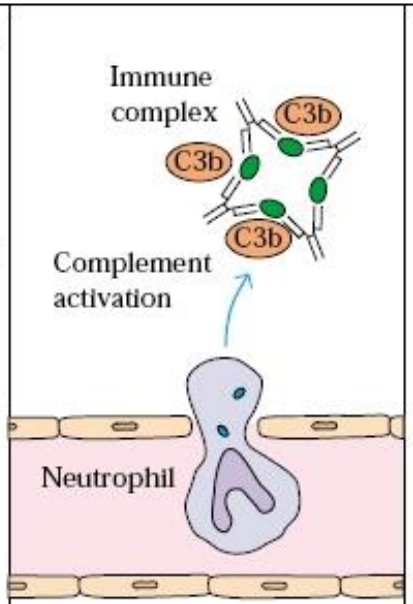
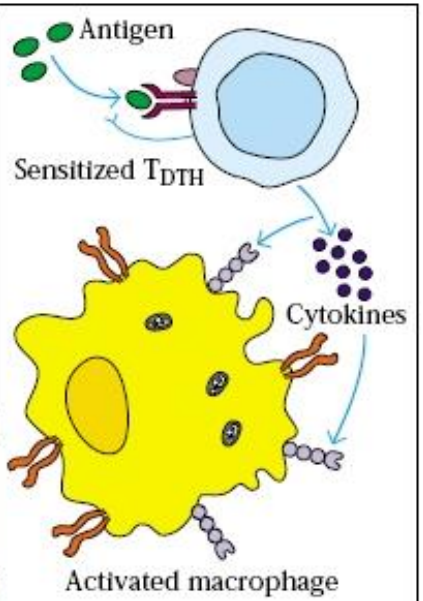
- Hypersensitivity reactions – 'over reaction' of the immune system to harmless environmental antigens
- Hypersensitivity refers to undesirable (damaging, discomfort-producing and sometimes fatal) reactions produced by the normal immune system.
- Hypersensitivity reactions require a pre-sensitized (immune) state of the host.
- Allergen: the antigens that give rise to immediate hypersensitivity

Types of Hypersensitivity Reactions

- There are 4 types of hypersensitivity reactions

1. Type I: classical immediate hypersensitivity
2. Type II: cytotoxic hypersensitivity
3. Type III: immune-complex mediated hypersensitivity
4. Type IV: cell mediated or delayed hypersensitivity

- Types I, II and III are antibody mediated
- Type IV is cell mediated

			
Type I	**Type II**	**Type III**	**Type IV**
IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators	Ab directed against cell surface antigens meditates cell destruction via complement activation or ADCC	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils	Sensitized T_H1 cells release cytokines that activate macrophages or T_C cells which mediate direct cellular damage
Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema	Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia	Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulnephritis, rheumatoid arthritis, and systemic lupus erythematosus	Typical manifestations include contact dermatitis, tubercular lesions and graft rejection

Type I: Immediate hypersensitivity

- An antigen reacts with cell fixed antibody (IgE) leading to release of soluble molecules

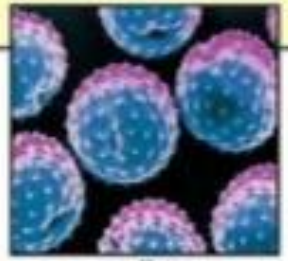
  An antigen (allergen)

  soluble molecules (mediators)
- Soluble molecules cause the manifestation of disease
- Systemic life threatening; anaphylactic shock
- Local atopic allergies; bronchial asthma, hay fever and food allergies

Common sources of allergens

Inhaled materials

Plant pollens
Dander of domesticated animals
Mold spores
Feces of very small animals
e.g., house dust mites


pollen


house dust mite

Injected materials

Insect venoms
Vaccines
Drugs
Therapeutic proteins


wasp


drugs

Ingested materials

Food
Orally administered drugs


peanuts


shellfish

Contacted materials

Plant leaves
Industrial products made from plants
Synthetic chemicals in industrial products
Metals


poison ivy

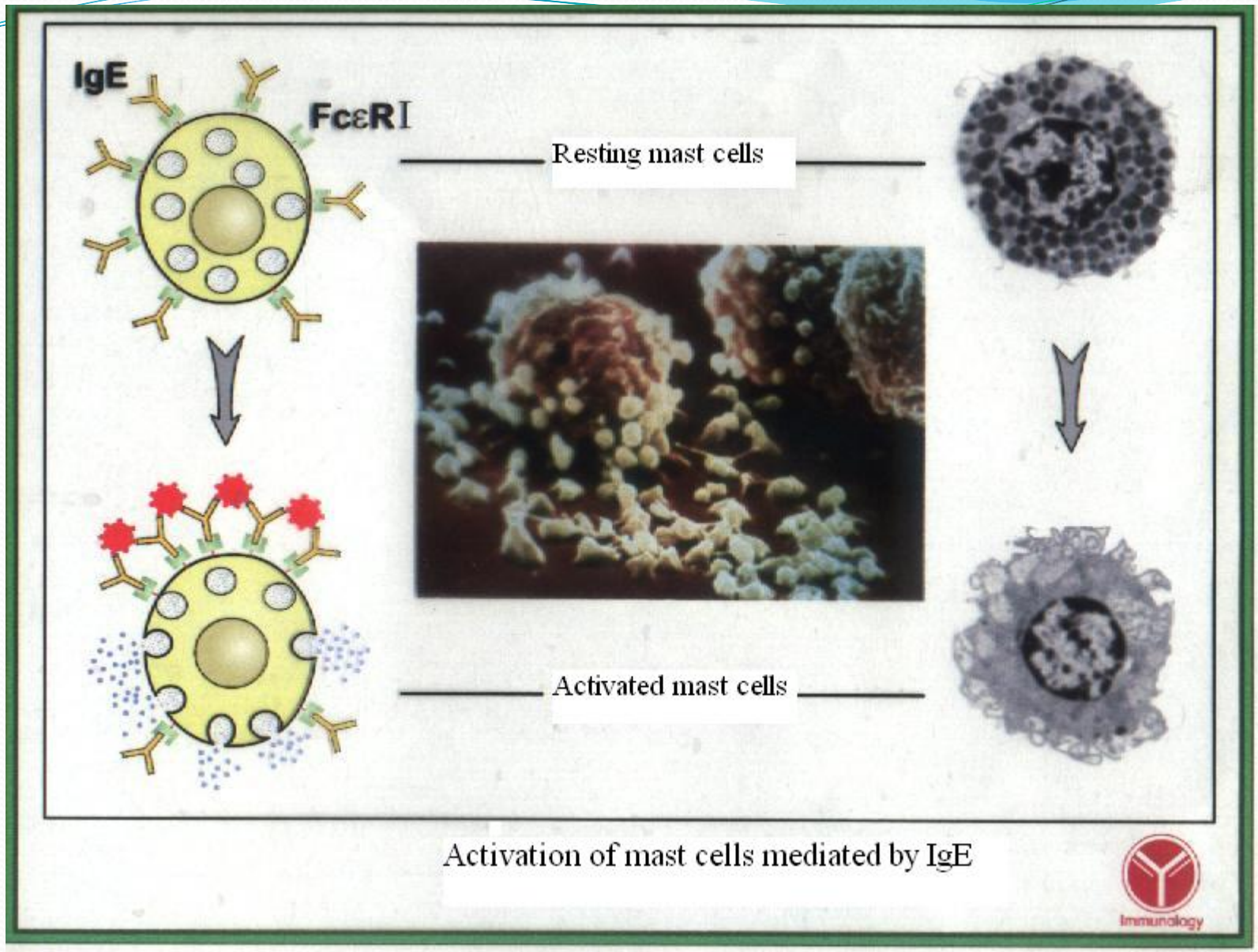

nickel coin

Pathophysiology

- First exposure to allergen: Allergen stimulates formation of antibody (IgE type). Ig E fixes, by its Fc portion to mast cells and basophiles

- Second exposure to the same allergen: It bridges between IgE molecules fixed to mast cells leading to activation and degranulation of mast cells and release of mediators

- Two classes of mediators derived from mast cells:
  1. Preformed mediators stored in granules (histamine)
  2. Newly sensitized mediators: leukotrienes, prostaglandins, platelets activating factor, Cytokines produced by activated mast cells, basophils e.g. TNF, IL3, IL-4, IL-5, IL-13, chemokines
- These mediators cause:
  1. smooth muscle contraction
  2. mucous secretion and bronchial spasm
  3. vasodilatation
  4. vascular permeability and edema



Activation of mast cells mediated by IgE

Anaphylaxis

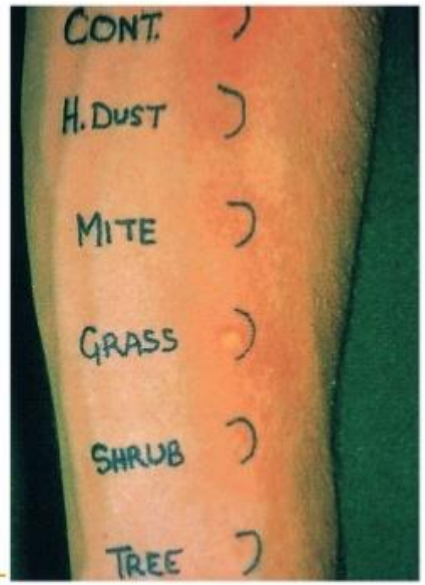
- Systemic form of Type I hypersensitivity
- Exposure to allergen to which a person is previously sensitized
- Allergens:
  1. Drugs: penicillin
  2. Serum injection : anti-diphtheritic or anti-tetanic serum
  3. Anesthesia or insect venom
- Clinical picture: Shock due to sudden decrease of blood pressure, respiratory distress due to bronchospasm, cyanosis, edema, urticaria
- Treatment: corticosteroids injection, epinephrine, antihistamines

Atopy

- Local form of type I hypersensitivity
- Exposure to certain allergens that induce production of specific IgE
- Allergens :
  1. Inhalants: dust mite faeces, tree or pollens, mould spor.
  2. Ingestants: milk, egg, fish, choclate
  3. Contactants: wool, nylon, animal fur
  4. Drugs: penicillin, salicylates, anesthesia insect venom
- There is a strong familial predisposition to atopic allergy
- The predisposition is genetically determined
- Allergic rhinitis, allergic asthma, atopic dermatitis are the most common manifestation of atopy. Allergic gastroenteropathy is rare. These manifestation may coexist in the same patients at different times. Atopy can be asymptomatic.

Diagnosis

1. History taking for determining the allergen involved
2. Skin tests: Intradermal injection of battery of different allergens. A wheal and flare (erythema) develop at the site of allergen to which the person is allergic
3. Determination of total serum IgE level
4. Determination of specific IgE levels to the different allergens



Management

1. Avoidance of specific allergen responsible for condition
2. Hyposensitization: Injection of gradually increasing doses of extract of allergen
   - production of IgG blocking antibody which binds allergen and prevent combination with IgE
3. Drug Therapy: corticosteroids injection, epinephrine, antihistamines

Type II: Cytotoxic or Cytolytic Reactions

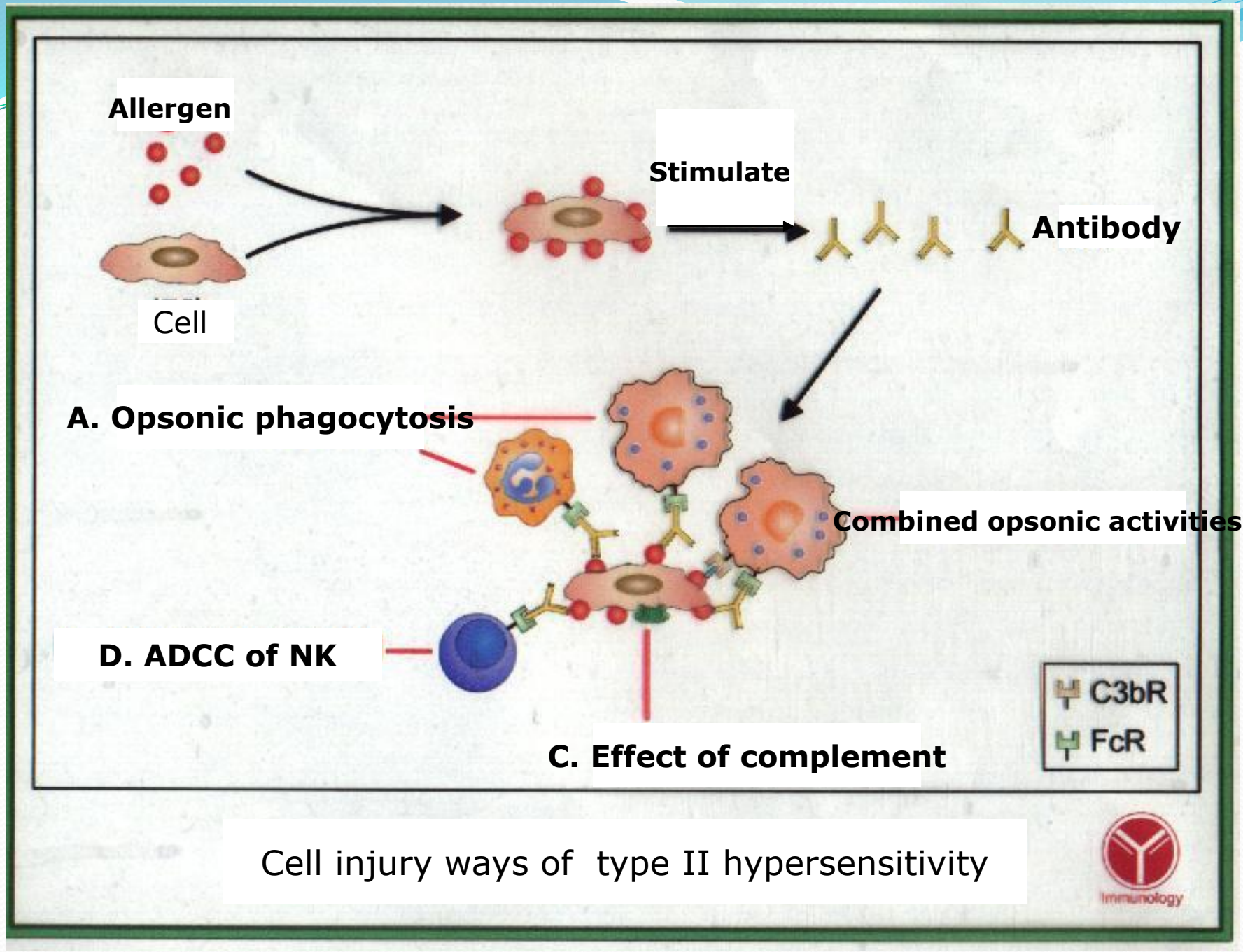
- An antibody (IgG or IgM) reacts with antigen on the cell surface

- This antigen may be part of cell membrane or circulating antigen (or hapten) that attaches to cell membrane

Mechanism of Cytolysis

- Cell lysis results due to :

1. Complement fixation to antigen antibody complex on cell surface. The activated complement will lead to cell lysis
2. Phagocytosis is enhanced by the antibody (opsinin) bound to cell antigen leading to opsonization of the target cell
3. Antibody depended cellular cytotoxicity (ADCC):
   - Antibody coated cells
   - Cells most active in ADCC are: NK, macrophages, neutrophils and eosinophils



Cell injury ways of type II hypersensitivity

Clinical Conditions

1. Transfusion reaction due to ABO incompatibility
2. Rh-incompatability (Haemolytic disease of the newborn)
3. Autoimmune diseases:
   - e.g. SLE, autoimmune haemolytic anaemia, idiopathic thrombocytopenic purpura, myasthenia gravis, nephrotoxic nephritis, Hashimoto's thyroiditis, Graves's disease

6- Drug reaction (type II):

- Penicillin may attach as haptens to RBCs and induce antibodies which are cytotoxic for the cell-drug complex leading to haemolysis
- Quinine may attach to platelets and the antibodies cause platelets destruction and thrombocytopenic purpura

Type III: Immune Complex Mediated Reaction

- When antibodies (IgG or IgM) 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

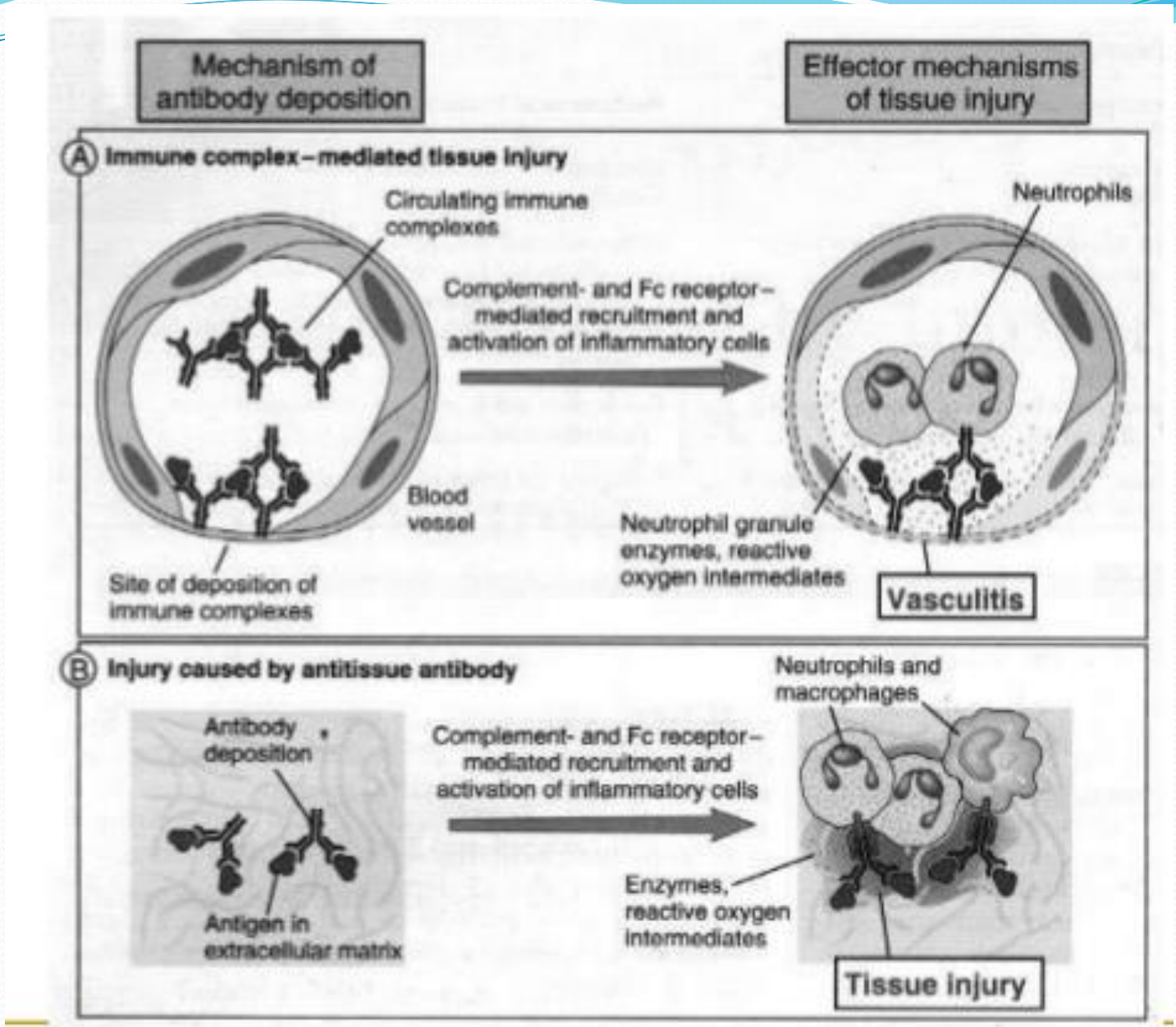
Mechanism Of Tissue Injury

- Immune complexes trigger inflammatory processes:

1. Immune complexes ----activate the complement------ release anaphylatoxins C3a, C5a----- stimulate degranulation of basophiles and mast cells-------release histamine -----Histamine increase 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 inflammatory process
3. Platelets are aggregated with two consequences

a- release of histamine

b- form of microthrombi which lead to ischemia

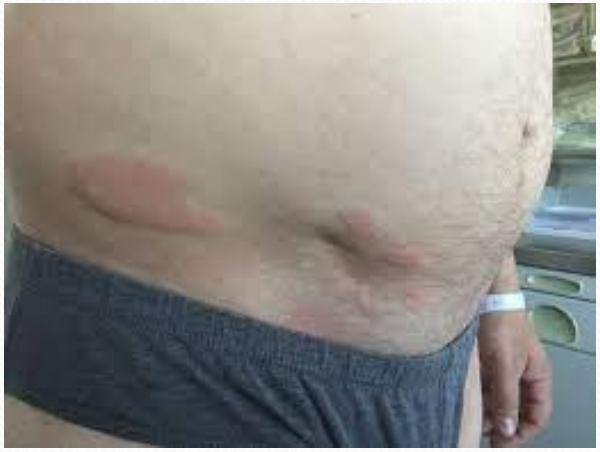

Mechanism of antibody deposition
Effector mechanisms of tissue injury
A Immune complex–mediated tissue injury
Circulating immune complexes
Complement- and Fc receptor–mediated recruitment and activation of inflammatory cells
Neutrophils
Blood vessel
Neutrophil granule enzymes, reactive oxygen intermediates
Site of deposition of immune complexes
Vasculitis
B Injury caused by antitissue antibody
Antibody deposition
Complement- and Fc receptor–mediated recruitment and activation of inflammatory cells
Neutrophils and macrophages
Enzymes, reactive oxygen intermediates
Antigen in extracellular matrix
Tissue injury

Clinical conditions of Type III Hypersensitivity

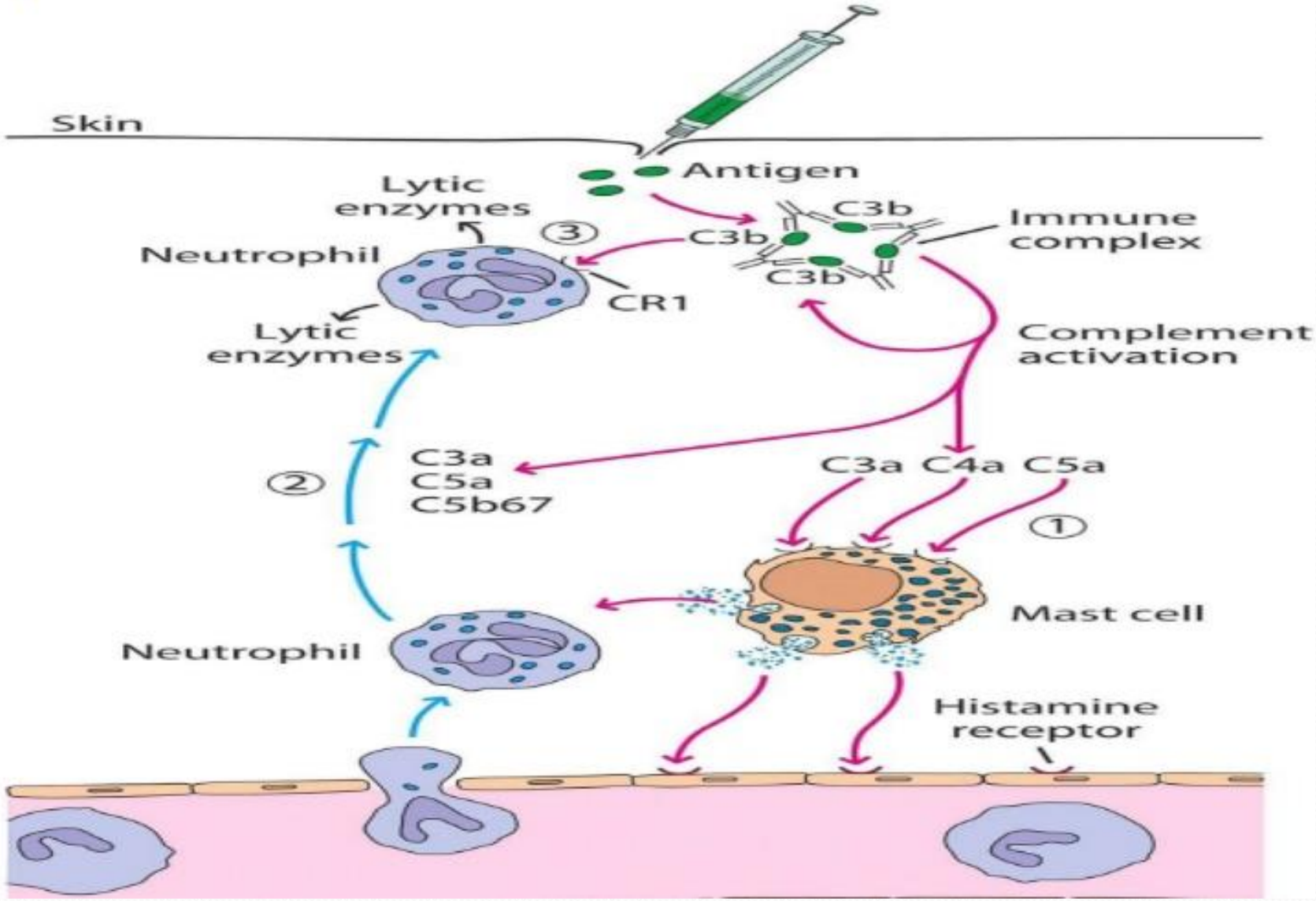
1- Arthus Reaction

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

1. Local reactions in the form of edema erythema necrosis
2. Immune complexes deposited in small blood vessels Leading to:
   - vasculitis
   - microthrombi formation
   - vascular occlusion
   - necrosis



Arthus Reaction



2- Serum Sickness

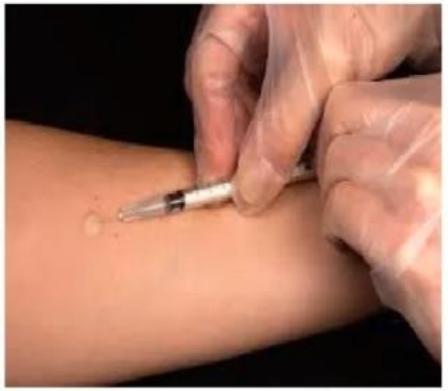
- A systemic immune complex phenomenon
- Injection of large doses of foreign serum
- Antigen is slowly cleared from circulation
- Immune complexes are deposited in various sites
- e.g. treatment with
  - antidiphtheritic serum
  - penicillin
  - sulphonamides
- 10 days after injection
  - fever
  - urticaria
  - arthralgia
  - lymphadenopathy
  - spleenomegaly
  - glomerulonephritis

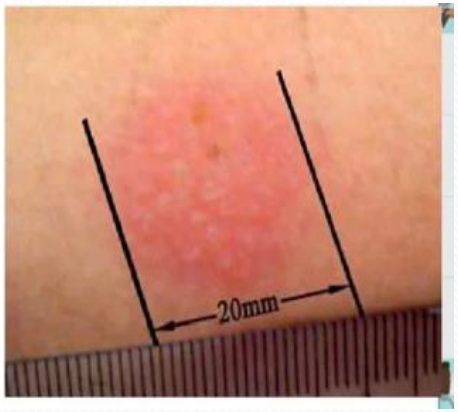
3- Post-streptococcal glomerulonephritis: glomerulitis associated with infective endocarditis

Type IV: Cell Mediated Delayed Type Hypersensitivity

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

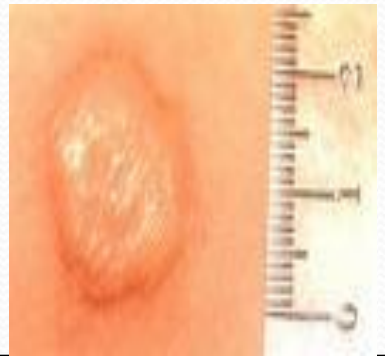
- No histamine or chemically related substances are released from cells
- The classical example of this hypersensitivity is tuberculin test which peaks 48 hours after the injection of antigen (PPD or old tuberculin). The lesion is characterized by induration and erythema.
- Granulomas due to infections and foreign bodies is type VI reaction





1. Tuberculin –Type Hypersensitivity

- When PPD is injected intradermally in sensitized person
- Local indurated area appearsat injection site (48-72 hs)
- Indurations due to accumulation of macrophages and lymphocytes
- Similar reactions observed in diseases e.g. brucellosis, lepromin test in leprosy



2. Granulomatous lesions

- In chronic diseases : TB, Leprosy, schistosomiases
- Intracellular organisms resist destruction by macrophag.
- Persistent antigen in tissues stimulate local DTH reaction
- Continuous release of cytokines leads to accumulation of macrophages which give rise to epitheloidal and giant cell granuloma

3. Contact Dermatitis

- Contact of skin with chemical substances or drugs e.g. poison, hair dyes, cosmetics, soaps, neomycin
- These substances enter skin in small molecules
- They are haptens that attached to body proteins, form immunogenic substances
- DTH reaction to these immunogenic subst. lead to: inflammtory reaction of skin in
  - eczyma
  - rash
  - vesicular eruption

5- Insulin dependant diabetes mellitus: T-cells invade the pancreatic islets and specifically destroy insulin secreting beta cells