IMMUNOLOGY

Allergy and Hypersensitivity

Immunosenescence

Immunization

By

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Learning Objectives

- To know about the allergy and hypersensitivity
- To know about the all 4 reactions of hypersensitivity
- To know the status of immunity in both extremes of age
- To know about the vaccination or immunization

Introduction

- Generally the immune system is protective

- Protective mechanisms may result in severe damages to tissues and may lead to death

When?

Severe damages may occur when the immune system responded in *exaggerated or inappropriate form.*

Classification of hypersesitivity

- **Coombs and Gell classification**

1-Type I - immediate (atopic, or anaphylactic)

2-Type II - antibody-dependent

3-Type III - immune complex

4-Type IV - cell-mediated or delayed

Type I - immediate (or atopic, or anaphylactic)

- Type I hypersensitivity is an allergic reaction provoked by re-exposure to a specific antigen.

- Exposure may be by ingestion, inhalation, injection, or direct contact.

- The reaction is mediated by IgE antibodies and produced by the immediate release of histamine, tryptase, arachidonate and derivatives by basophils and mast cells..

- This causes an **inflammatory** response leading to an immediate (within seconds to minutes) reaction.
- The reaction may be either local or systemic. Symptoms vary from mild irritation to sudden death from **anaphylactic shock**.
- Treatment usually involves **epinephrine**, **antihistamines**, and **corticosteroids**

- Type I hypersensitivity is also known as **immediate** or anaphylactic hypersensitivity.

- The reaction may involve skin (urticaria and eczema), eyes (conjunctivitis), nasopharynx (rhinorrhea, rhinitis), bronchopulmonary tissues (asthma) and gastrointestinal tract (gastroenteritis)

- The reaction may cause a range of symptoms from minor inconvenience to death.
- The reaction usually takes 15 - 30 minutes from the time of exposure to the antigen.
- sometimes it may have a delayed onset (10 - 12 hours).

- Immediate hypersensitivity is mediated by **IgE**.
- The primary cellular component in this hypersensitivity is the **mast cell** or **basophil**.
- The reaction is amplified and/or modified by platelets, neutrophils and eosinophils.
- A biopsy of the reaction site demonstrates mainly **mast cells** and **eosinophils**.

Mechanism:

- The mechanism of reaction involves preferential production of IgE, in response to certain antigens (**allergens**).
- IgE has very high affinity for its receptor on mast cells and basophils.
- A subsequent exposure to the same allergen cross links the cell-bound IgE and triggers the release of various pharmacologically active substances

- Mast cells may be triggered by other stimuli such as
  - -Exercise,
  - -Emotional stress
  - -Chemicals (*e.g.*, photographic developing medium, calcium ionophores, codeine, *etc.*),
  - -Anaphylotoxins (*e.g.*, C4a, C3a, C5a, *etc.*).
- These reactions **are not hypersensitivity reactions** although they produce the same symptoms.

Some examples:

- Allergic asthma
- Allergic conjunctivitis
- Allergic rhinitis ("hay fever")
- Anaphylaxis
- Angioedema
- Urticaria (hives)

Type II - antibody-dependent

- **In type II hypersensitivity, the antibodies produced by the immune response bind to antigens on the patient's own cell surfaces.**

- **The antigens recognized in this way may either be intrinsic ("self" antigen, innately part of the patient's cells) or extrinsic (absorbed onto the cells during exposure to some foreign antigen, possibly as part of infection with a pathogen**

- IgG and IgM antibodies bind to these antigens to form complexes that activate the classical pathway of complement activation for eliminating cells presenting foreign antigens (which are usually, but not in this case, pathogens).

- As a result mediators of acute inflammation are generated at the site and membrane attack complexes cause cell lysis and death. The reaction takes hours to a day.

- Type II hypersensitivity is also known as cytotoxic hypersensitivity and may affect a variety of organs and tissues.
- The antigens are normally endogenous, although exogenous chemicals (haptens) which can attach to cell membranes can also lead to type II hypersensitivity.

Examples:

- Drug-induced hemolytic anemia

-Granulocytopenia

-Thrombocytopenia

- The reaction time is minutes to hours.

- Type II hypersensitivity is primarily mediated by antibodies of the IgM or IgG classes and complement

Lab Diagnosis

Diagnostic tests include detection of circulating antibody against the tissues involved and the presence of antibody and complement in the lesion (biopsy) by immunofluorescence

Examples

- Autoimmune haemolytic anaemia
- Pernicious anemia
- Immune thrombocytopenia
- Transfusion reactions
- Hashimoto's thyroiditis
- Graves' disease
- Myasthenia gravis
- Farmer's Lung
- Hemolytic disease of the newborn

Type III - immune complex

In type III hypersensitivity:

- **Soluble immune complexes (aggregations of antigens and IgG and IgM antibodies) form in the blood and are deposited in various tissues (typically the skin, kidney and joints)**

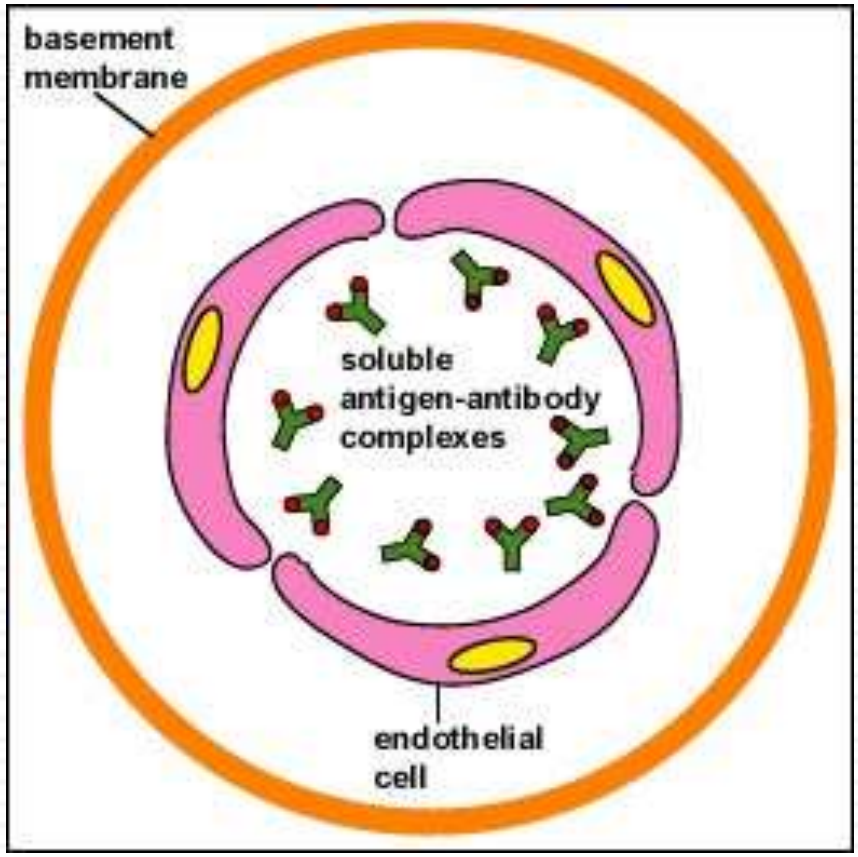
- **This may trigger an immune response according to the classical pathway of complement activation.**
- **The reaction takes hours to days to develop**

- Also known as **immune complex disease**
- occurs when immune complex (Ag-Ab) are not removed from circulation
- These complexes are deposited in various tissues and organs such as:
  - Kidneys
  - Joints
  - Lung
  - Skin

- **Immune complex formation may occur as a result of :**
  - ✓ Autoimmune diseases (RA)
  - ✓ Persistence infection (Viral Hepatitis)
  - ✓ Repeated inhalation of antigenic materials

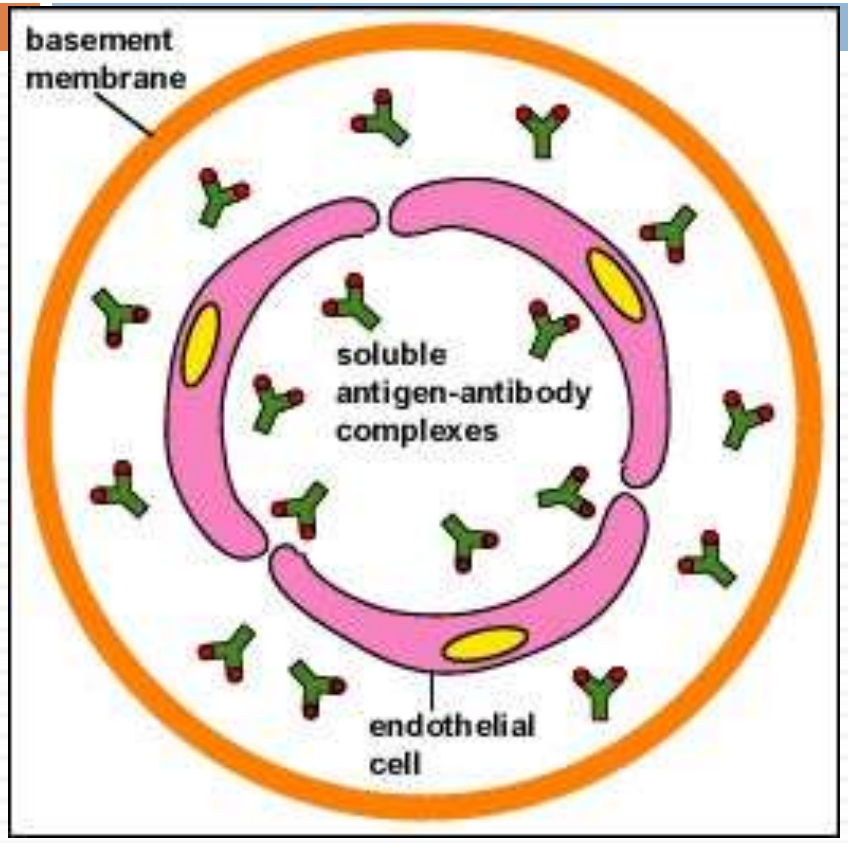
MECHANISM

Step 1



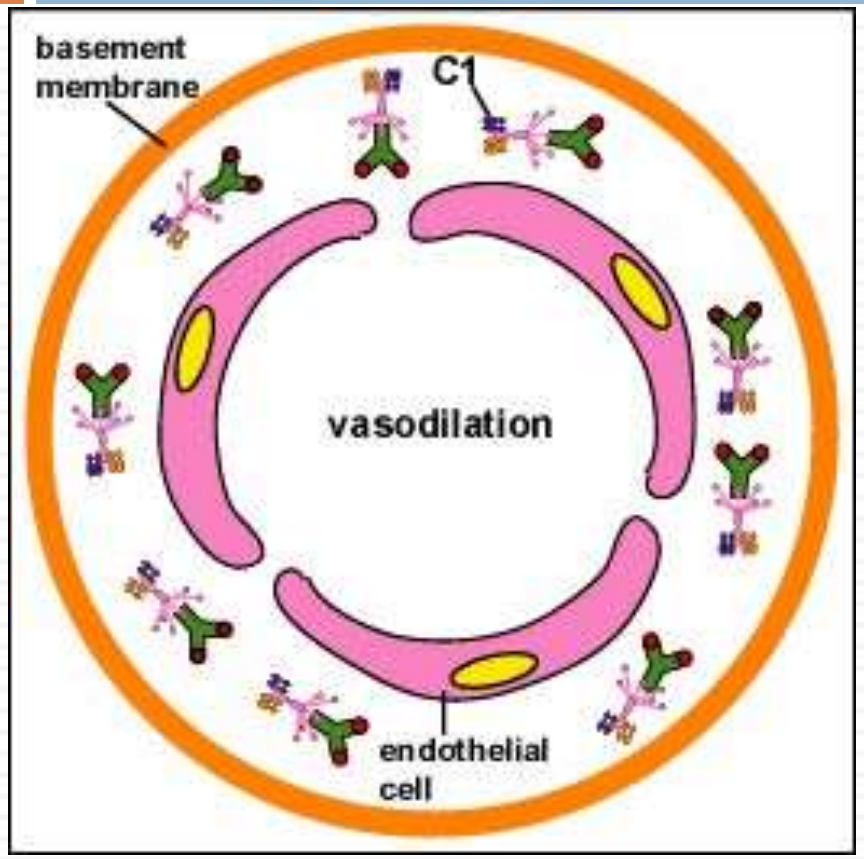
Large quantities of soluble antigen-antibody complexes form in the blood and are not completely removed by macrophages.

Step 2



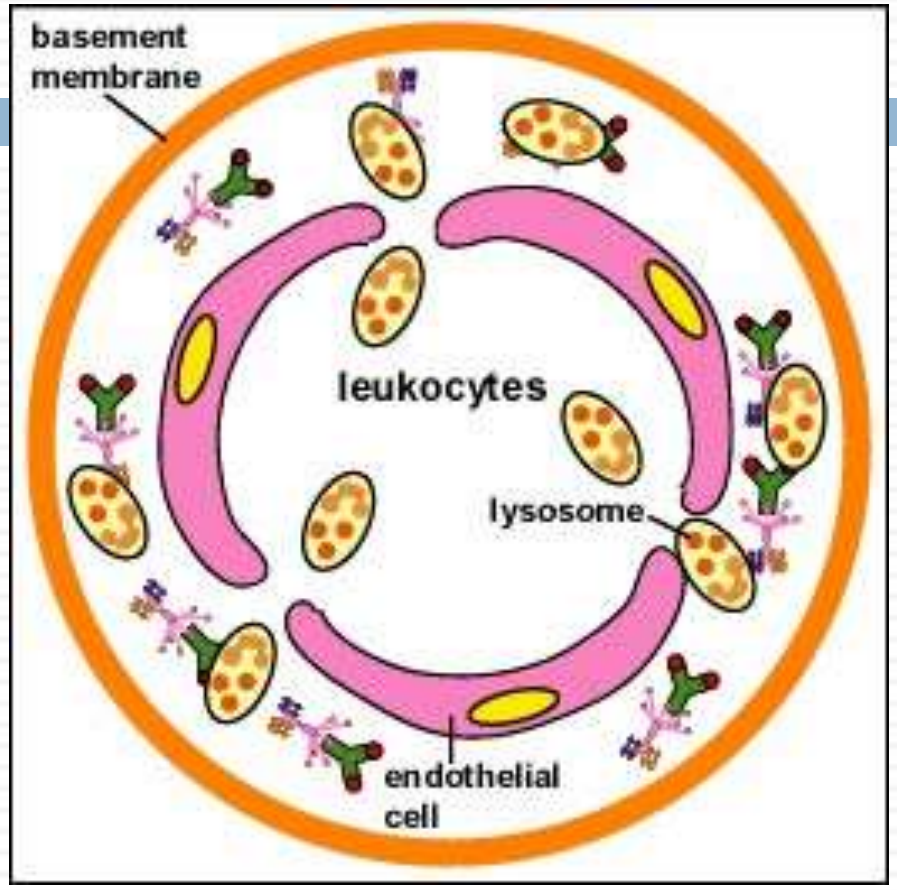
These antigen-antibody complexes lodge in the capillaries between the endothelial cells and the basement membrane.

Step 3



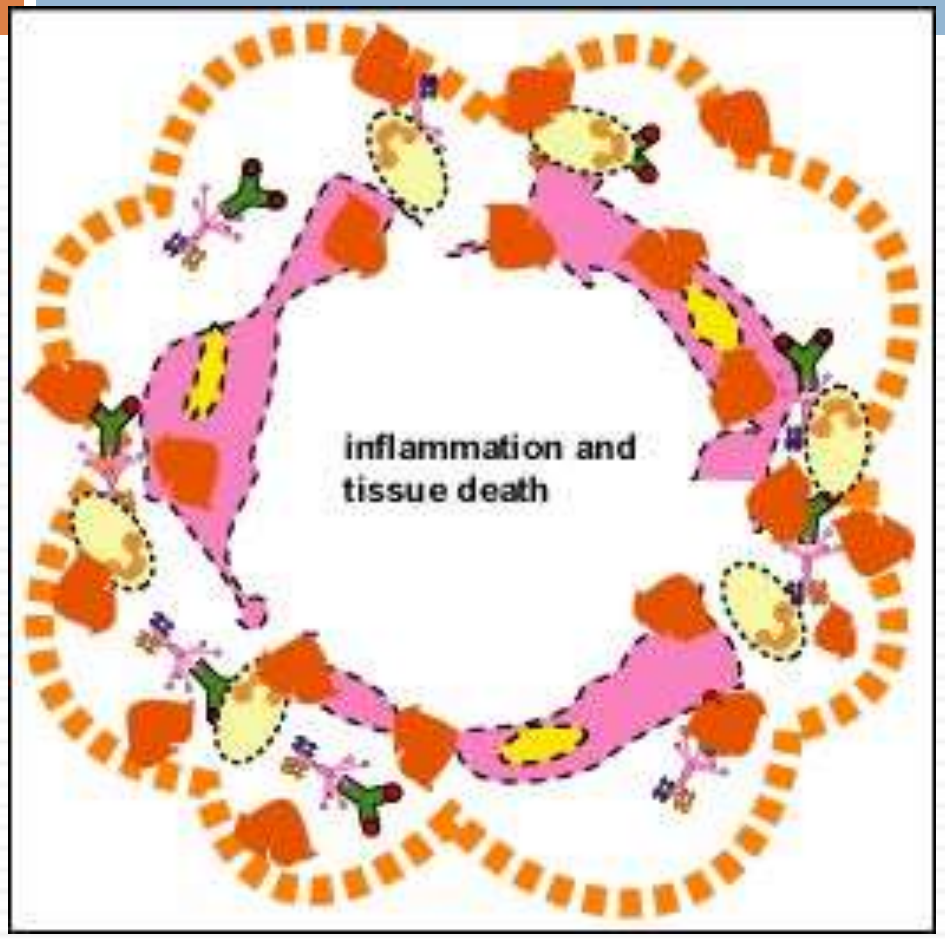
These antigen-antibody complexes activate the classical complement pathway leading to vasodilatation.

Step 4



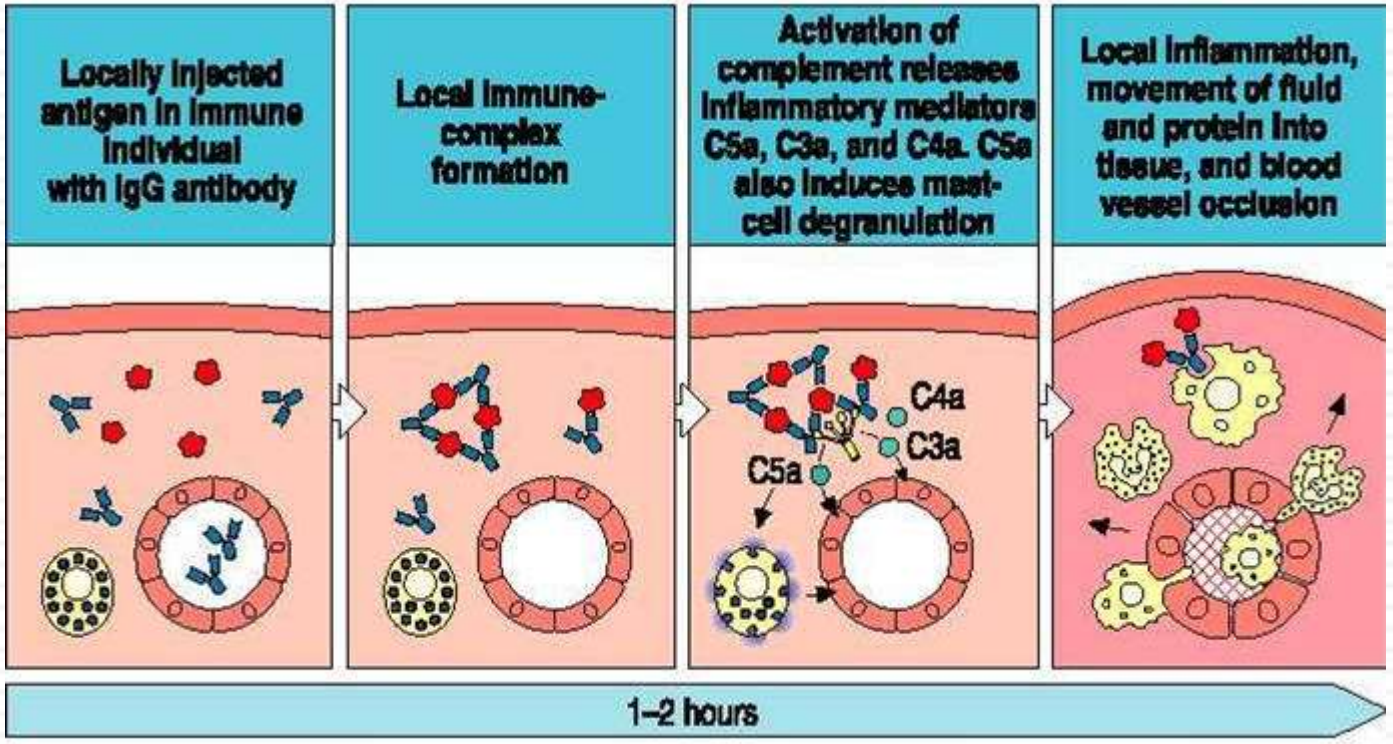
The complement proteins and antigen-antibody complexes attract leukocytes to the area.

Step 5

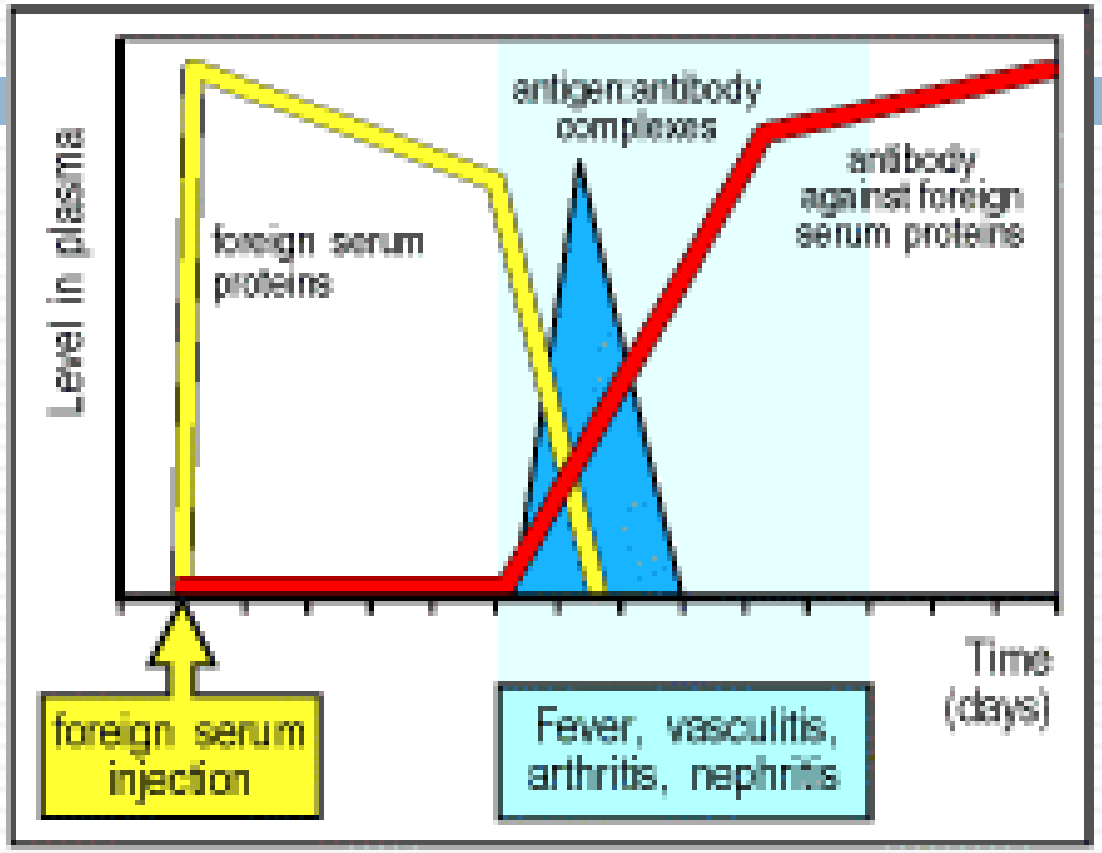


The leukocytes discharge their killing agents and promote massive inflammation. This can lead to tissue death and hemorrhage.

Localized depositions of immune complexes within a tissue cause type III hypersensitivity



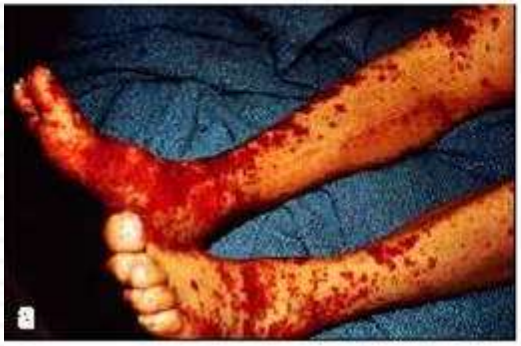
Serum Sickness

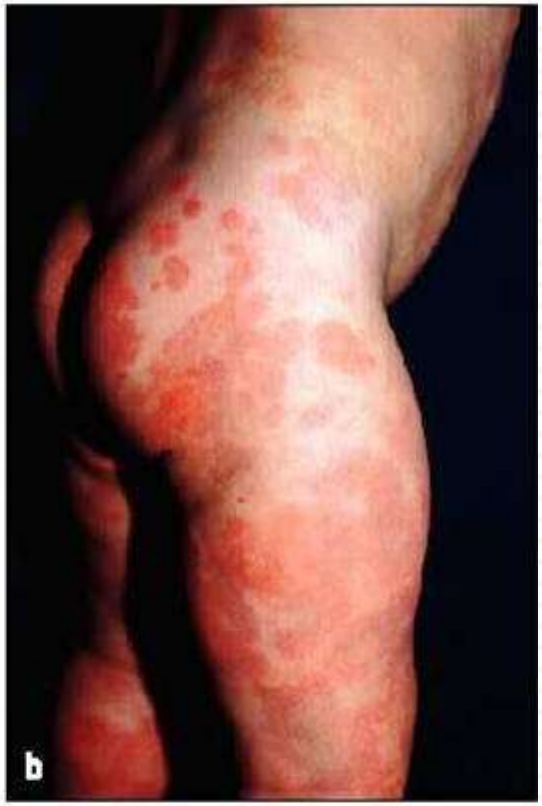


- Is a disease caused by the injection of large doses of a protein antigen into the blood and characterized by the deposition of antigen-antibody complexes in blood vessel walls, especially in the kidneys and joints.

Serum sickness

Route	Resulting disease	Site of immune-complex deposition
Intravenous (high dose)	Vasculitis	Blood vessel walls
	Nephritis	Renal glomeruli
	Arthritis	Joint spaces
Subcutaneous	Arthus reaction	Perivascular area
Inhaled	Farmer's lung	Alveolar/capillary interface





Systemic Lupus Erythmatosus

- The disease is characterized by the presence of autoantibodies , which form immune complexes with autoantigens and are deposited within the kidney glomeruli

- The resulting type III hypersensitivity is responsible for the glomerulonephritis

  (Inflammation of blood capillary vessels in the glomeruli)

Examples:

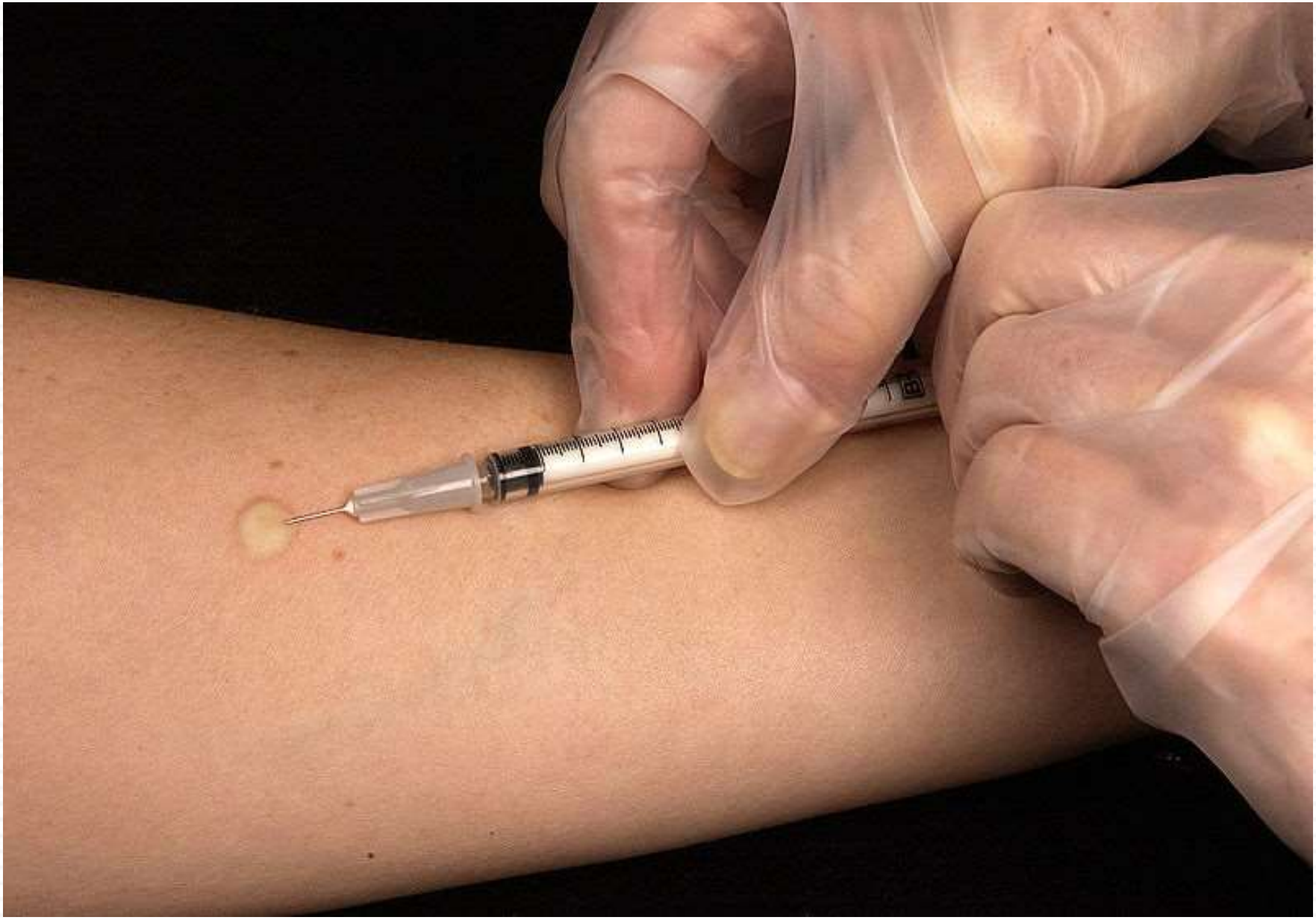
- Immune complex glomerulonephritis
- Rheumatoid arthritis
- Serum sickness
- Subacute bacterial endocarditis
- Symptoms of malaria
- Systemic lupus erythematosus
- Arthus reaction

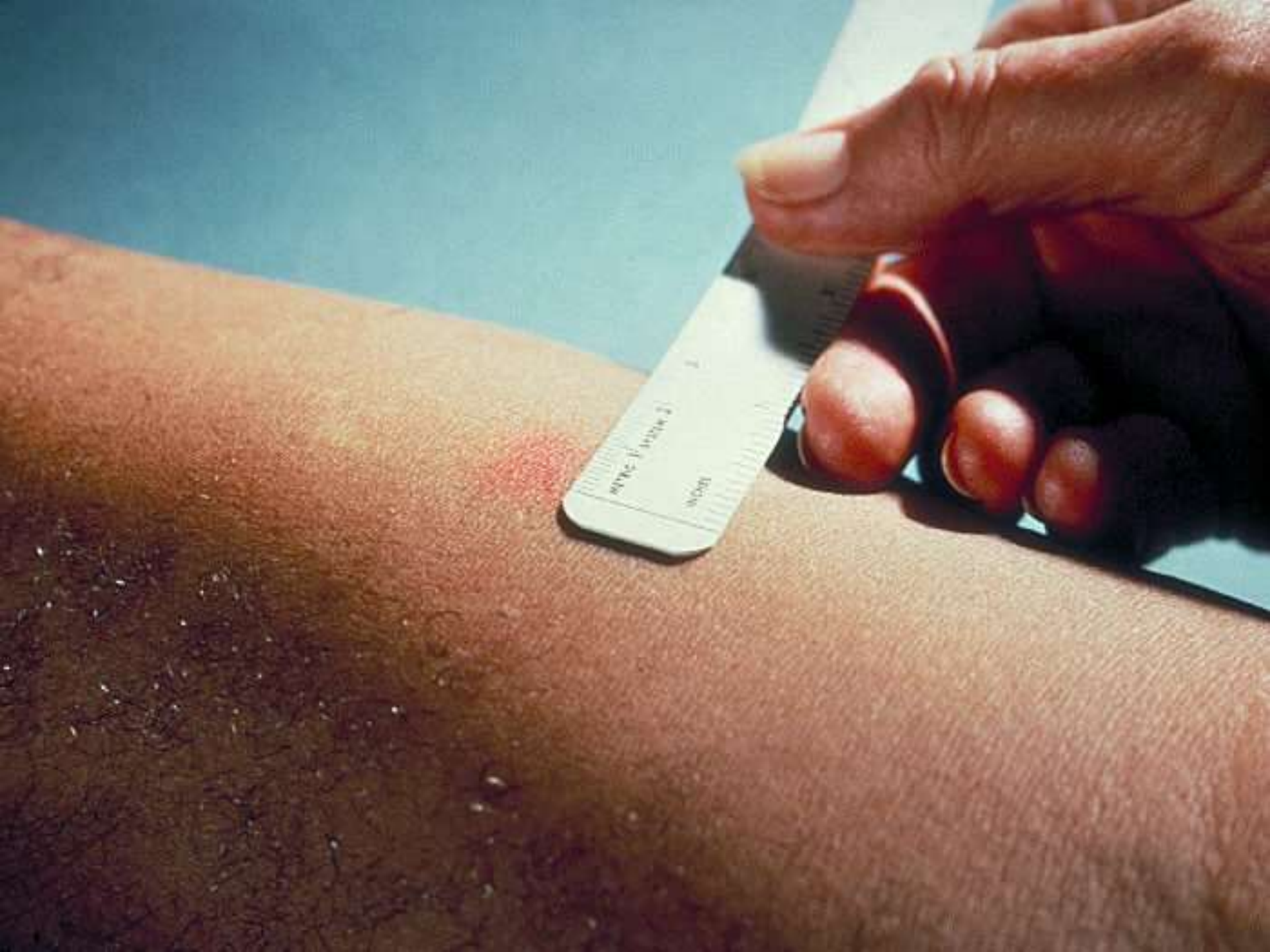
Type IV Hypersensitivity

- Type IV hypersensitivity is often called delayed type as the reaction takes two to three days to develop.

- Unlike the other types, it is not antibody mediated but rather is a type of cell-mediated response.

- Type IV hypersensitivity is also known as **cell mediated** or **delayed type hypersensitivity.**
- The classical example of this hypersensitivity is tuberculin (Montoux) reaction
- Reaction peaks 48 hours after the injection of antigen (PPD or old tuberculin). The lesion is characterized by induration and erythema





- Type IV hypersensitivity is involved in the pathogenesis of many autoimmune and infectious diseases:
  - Tuberculosis
  - Leprosy
  - Blastomycosis
  - Histoplasmosis
  - Toxoplasmosis
  - Leishmaniasis
  - Granulomas due to infections and foreign antigens.

- Another form of delayed hypersensitivity is contact dermatitis (poison ivy (figure 6), chemicals, heavy metals, *etc.*) in which the lesions are more papular

- Type IV hypersensitivity can be classified into three categories depending on the time of onset and clinical and histological presentation

Mechanism:

- The mechanism includes T lymphocytes and monocytes and/or macrophages.
- Cytotoxic T cells (Tc) cause direct damage whereas helper T (TH) cells secrete cytokines which activate cytotoxic T cells, recruit and activate monocytes and macrophages, which cause the bulk of the damage
- The delayed hypersensitivity lesions mainly contain monocytes and a few T cells.

Diagnosis

- Diagnostic tests *in vivo* include delayed cutaneous reaction (e.g. Montoux test)
- In vitro tests for delayed hypersensitivity include mitogenic response, lympho-cytotoxicity and IL-2 production.
- Corticosteroids & other immunosuppressive agents are used in treatment.

Some clinical examples:

- Contact dermatitis (poison ivy rash, for example)
- Temporal arteritis
- Symptoms of leprosy
- Symptoms of tuberculosis
- Transplant rejection

The hypersensitivity reactions

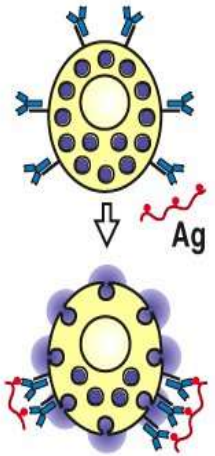
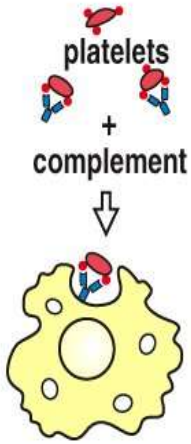
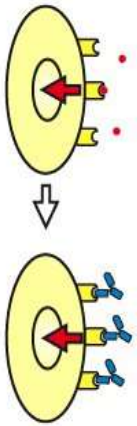
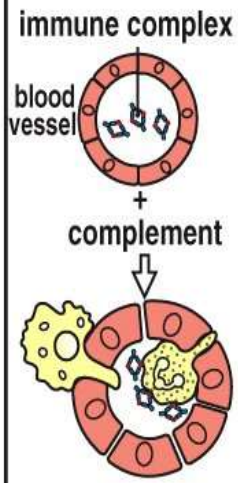
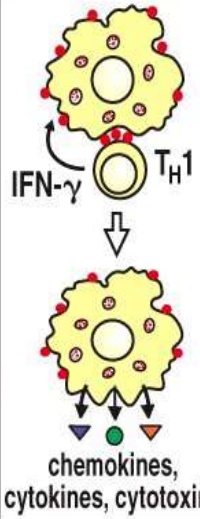
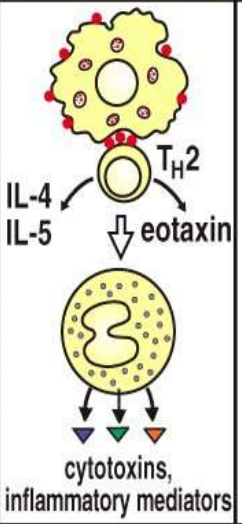
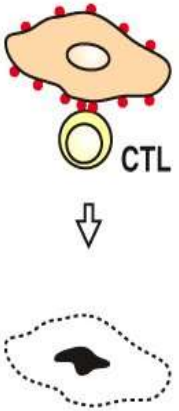
	Type I	Type II		Type III	Type IV		
Immune reactant	IgE	IgG		IgG	T_H1 cells	T_H2 cells	CTL
Antigen	Soluble antigen	Cell- or matrix-associated antigen	Cell-surface receptor	Soluble antigen	Soluble antigen	Soluble antigen	Cell-associated antigen
Effector mechanism	Mast-cell activation	Complement, FcR^+ cells (phagocytes, NK cells)	Antibody alters signaling	Complement, Phagocytes	Macrophage activation	IgE production, Eosinophil activation, Mastocytosis	Cytotoxicity
							
Example of hypersensitivity reaction	Allergic rhinitis, asthma, systemic anaphylaxis	Some drug allergies (eg, penicillin)	Chronic urticaria (antibody against FCεR1α)	Serum sickness, Arthus reaction	Contact dermatitis, tuberculin reaction	Chronic asthma, chronic allergic rhinitis	Contact dermatitis

Figure 12-2 Immunobiology, 6/e. (© Garland Science 2005)

IMMUNOSENESCENCE

(effect of ageing on immunity)

WHAT IS IMMUNOSENESCENCE?

- **Immunosenescence** refers to the gradual deterioration of the immune system brought on by natural ageing process.
- Progressive deterioration in the ability to respond to infections.
- This age-associated immune deficiency is common and found in both long and short-living species as a function of their age relative to life expectancy.

- Immunosenescence is not a random deteriorative phenomenon, rather it appears to inversely repeat an evolutionary pattern.

- Immunosenescence can also be sometimes happen as the result of the continuous unavoidable exposure to a variety of antigens such as viruses and bacteria.

New born

Confounding variables

- Pace of ageing
- Spectrum of `young-old (>65y) to extremely old (>95y)
- Survivor bias
- Institutionalisation
- Physical fitness

CONSEQUENCES OF AGING

- Atrophy of the thymus.
- Changes in the innate immunity
- Changes in the function of both B and T cells.
- Changes in both the total numbers and subsets of lymphocytes
- Changes in the patterns of secretion of cytokines and growth factors.
- Disruption of intracellular signaling.

IMPACT OF ADVANCING AGE ON INNATE IMMUNITY

Aged phagocytes include a reduced expression of Toll-like receptors on macrophages.

There is a decline in the phagocytic capacity and reduced superoxide anion production (ROS) in macrophages and neutrophils in the aged.

Activation of neutrophils by formyl-methionyl-leucyl-phenylalanine (fMLP) is impaired in old compared to young , linked to a reduction of intracellular Ca^{2+}mobilization.

INFLAMM-AGEING

Ageing is associated with the increased production of pro-inflammatory cytokines(IL-1 and $TNF-\alpha$) by macrophages and fibroblasts.

For example.

Elevated levels of these mediators are responsible for the age-associated diseases such as diabetes, osteoporosis and atherosclerosis hence called Inflammatory Pathogenesis.

The emerging evidence suggests that the balance between pro- and anti-inflammatory cytokines(IL-4, IL-6, IL-10, IL-11, and IL-13).

Natural Killer cells:

- Impaired NK-cell cytotoxicity and reduced production of cytokines and chemokines by activated NK cells.

- Expansion of different NK-cell subsets because there are reports that in the elderly there is an increased proportion of the $CD56^-$ NK-cell subset compared to more abundant $CD56^+$ NK-cell subset.

Cellular Immunity in the Elderly

- Altered T cell phenotype
  - ↓ naïve T cells; ↑ memory T cells
- Reduced T cell responses
  - ↓ response to TCR stimulation
  - ↓ T cell proliferation
  - ↓ expression of IL2-R
  - ↓ IL2 production

Ginaldi et al 1999

IMPAIRED B CELL DEVELOPMENT

HSC in the bone marrow give rise to early B cells through common lymphocyte precursors.

These common lymphocyte precursors become Pro-B cells in the bone marrow by immunoglobulin heavy-chain gene rearrangements and subsequently differentiate into Pre-B cells.

Transition to Pro-B cell and Pre-B cell stages are dependent upon the activity of recombination activating gene (*RAG1* and *RAG2*).

TWO MECAHNISMS RESPONSIBLE FOR IMPAIRMENT

1) Decreased production of long-term immunoglobulin-producing B lymphocytes because of intrinsic and micro-environmental defects in bone marrow.

(2) The loss of immunoglobulin diversity and affinity. Reduced activity of transcription factors like E2A and *Pax-5*.

THYMIC INVOLUTION

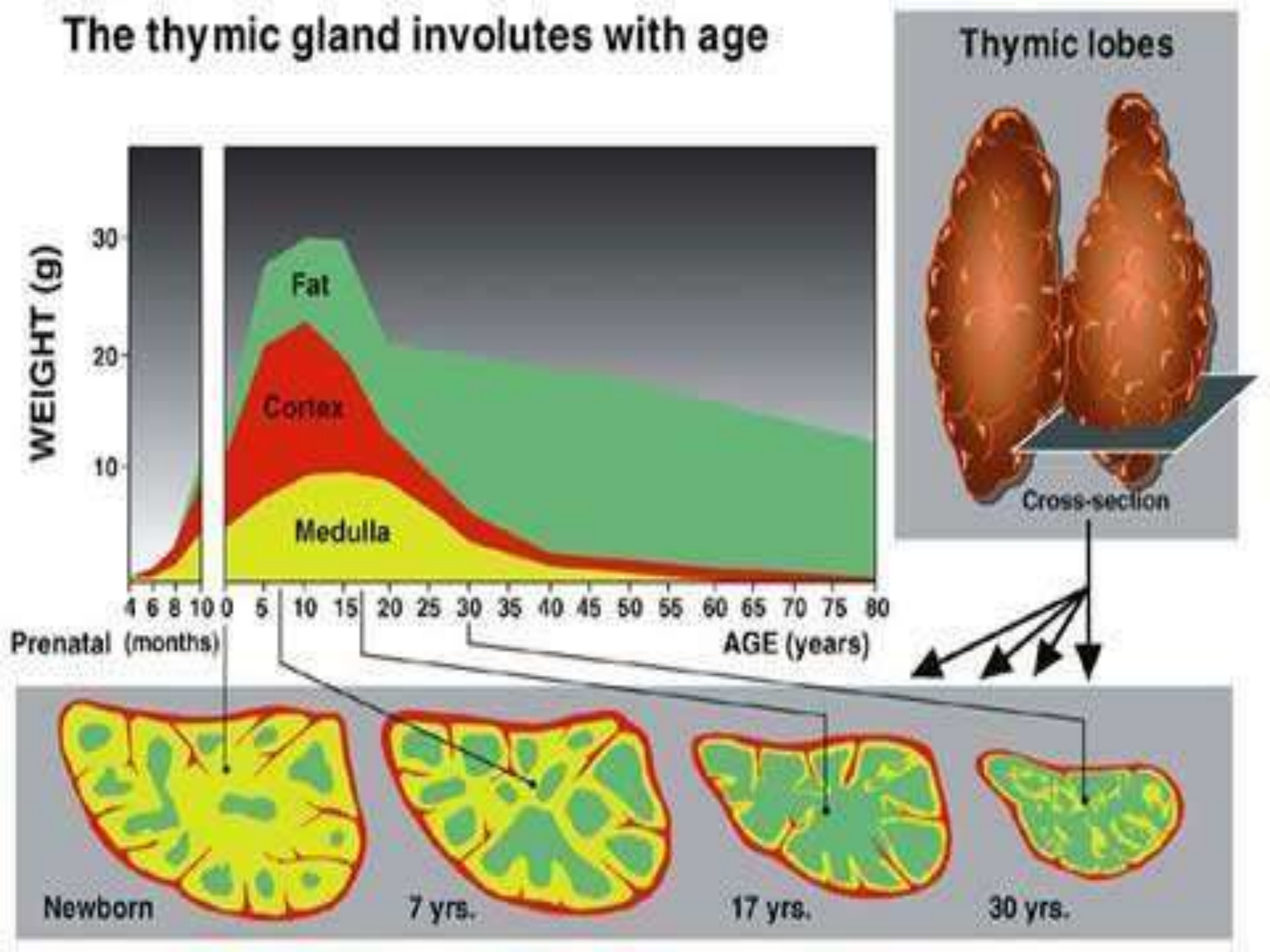
Thymic involution

the shrinking of the thymus with age, resulting in changes in the architecture of the thymus and a decrease in tissue mass.

TCR (T-cell receptors) diversity drops drastically around age 65.

Loss of thymic function and TCR diversity is thought to contribute to weaker immuno-surveillance of the elderly

The thymic gland involutes with age



TREATMENT

One successful therapy is Bone Marrow Transplantation(BMT).

Hormone therapies for innate age-associated dysfunctions,

for example DHEAS supplements (*Dehydroepiandrosterone - DHEA*)are able to enhance superoxide production in neutrophils and can increase NK-cell activity

Gene therapy can treat immunological disorders in old and immunodeficient individuals.
Blocking IL-1 or TNF has been highly successful in patients with rheumatoid arthritis, inflammatory bowel diseases.Agents such as TNF-neutralizing antibodies, soluble TNF receptors, and IL-1 receptor antagonist have been infused into > 10,000 patients.

Conclusions

- Immunosenescent changes particularly affect T cell populations and function
- Immunosenescence affects the response to vaccines
- Vaccine-induced antibody responses wane rapidly in the elderly
- Better vaccine efficacy in the elderly may require

  (i) improved immune responsiveness and

  (ii) changes to vaccine formulation
- Herd immunity applies to the elderly as well as to the young

What can be done to better protect the elderly?

IMMUNIZATION AND VACCINATION

Immunization

- To establish an immunity through primary, secondary and tertiary exposure through a processed specific antigens, by injections or oral

May be natural or artificial

- **Active immunization**
- **Passive immunization**

Active Immunization

A. Natural (any specific infection)

B. Artificial, by injection or oral

1. Living but attenuated organisms

   (small pox,measles, polive etc)

2. Dead and non pathogenic organisms

   (typhoid, whooping cough, dephtheria)

3. Inactivated toxins

   (Tetanus, botulism)

Passive Immunization

A. Natural from mother to baby

B. Transfusion of pre-formed antibodies or T Lymphocytes to a person for temporary protection is called passive immunization

These a/b or T cells are taken from another person or animals and give protection for 2, 3 weeks to 8,10 weeks.

THANK YOU