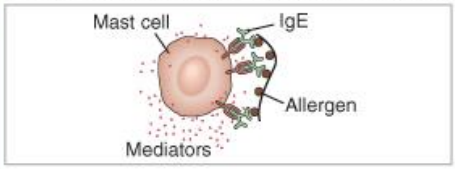
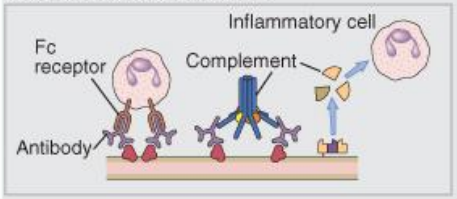
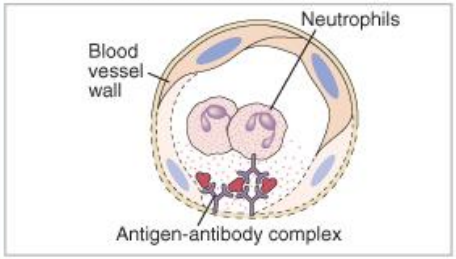
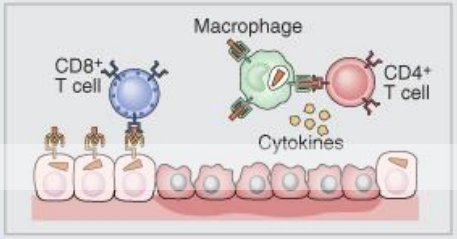
Hypersensitivity diseases

Definition

- **Hypersensitivity** refers to undesirable reactions produced by the normal immune system, including allergies and autoimmunity.

Type of hypersensitivity	Pathologic immune mechanisms	Mechanisms of tissue injury and disease
Immediate hypersensitivity (Type I)	T_H2 cells, IgE antibody, mast cells, eosinophils 	Mast cell–derived mediators (vasoactive amines, lipid mediators, cytokines) Cytokine-mediated inflammation (eosinophils, neutrophils)
Antibody-mediated diseases (Type II)	IgM, IgG antibodies against cell surface or extracellular matrix antigens 	Complement- and Fc receptor–mediated recruitment and activation of leukocytes (neutrophils, macrophages) Opsonization and phagocytosis of cells Abnormalities in cellular function, e.g., hormone receptor signaling
Immune complex–mediated diseases (Type III)	Immune complexes of circulating antigens and IgM or IgG antibodies deposited in vascular basement membrane 	Complement and Fc receptor-mediated recruitment and activation of leukocytes
T cell–mediated diseases (Type IV)	1. $CD4^+$ T cells (delayed-type hypersensitivity) 2. $CD8^+$ CTLs (T cell–mediated cytolysis) 	1. Macrophage activation, cytokine-mediated inflammation 2. Direct target cell lysis, cytokine-mediated inflammation

Type-I Hypersensitivity

Basic terms

- Type-I = Early= IgE-mediated = Atopic = Anaphylactic type of hypersensitivity

- Atopy = genetic predisposition to type-I hypersensitivity diseases. It is a genetic predisposition to react by IgE production to various stimuli.

Frequency of atopic diseases

- 20-30% of general population is estimated to be atopic.
- Prevalence of bronchial asthma:
  - General population 5-6%
  - Children: 10%
- Every year 100 people die in Europe of anapylactic shock due to wasp/bee sting.

Genetic aspects of atopy

- Probability of atopy in a child :
  - Both parents atopics: 80%,
  - One parent atopic: 50%,
  - No parent is atopic: 15%.

- Concordance of asthma in monozygotic twins: only 50-69%

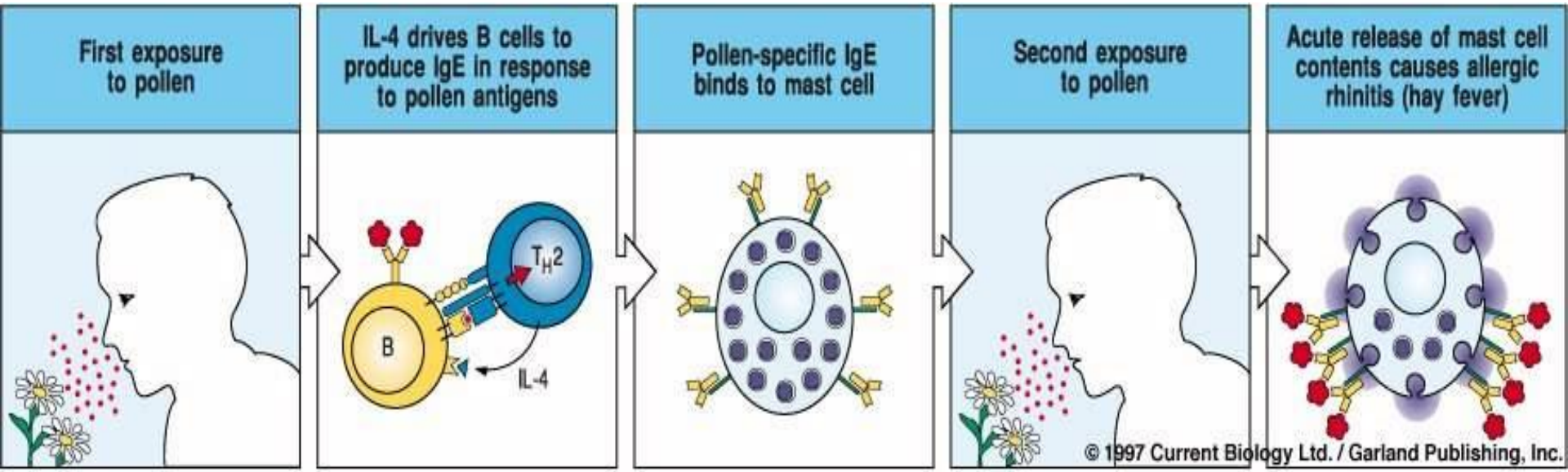
Candidate genes of atopic diseases

- 5q31-33 : cytokines and their receptors: IL-4, IL-5, IL-9, IL-13
- 11q13: high affinity receptor for IgE
- 6p: HLA genes. TNF-α
- 1q, 4q,7q31, 12q14.3-q24.31, 14q11.2-g13, 16p21, 17q, 19q

Common allergens

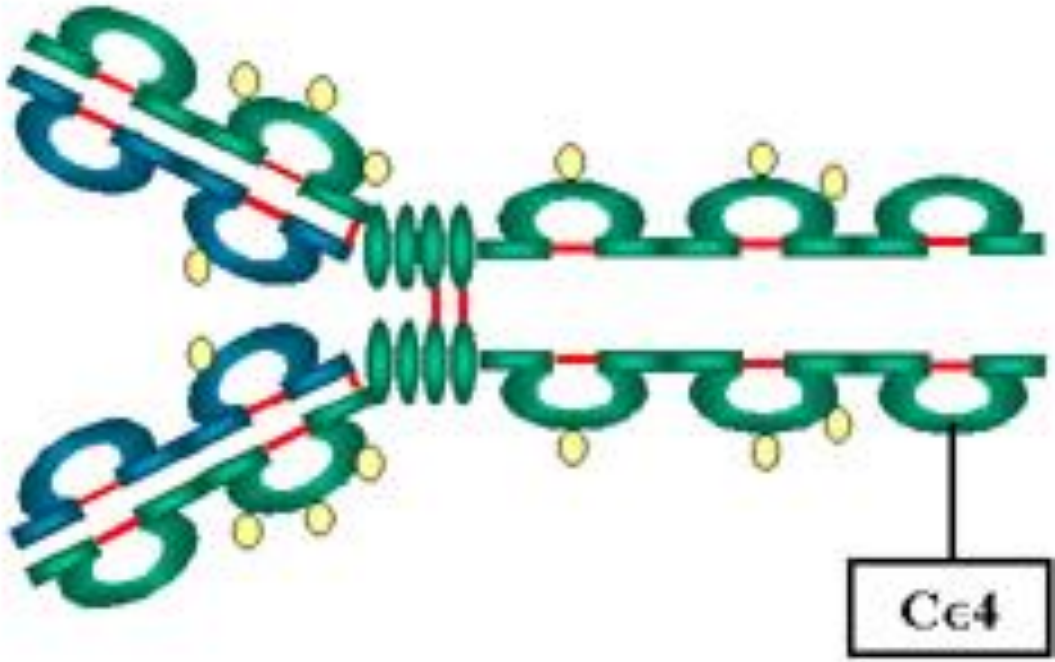
- Pollens (grass, trees)
- House dust mites (*Dermatophagoides pteronyssimus* and *farinae*)
- Foods: nuts, chocolate, shellfish, milk, egg, fruits
- Pets (cat, dog)
- Moulds

Type-I hypersensitivity



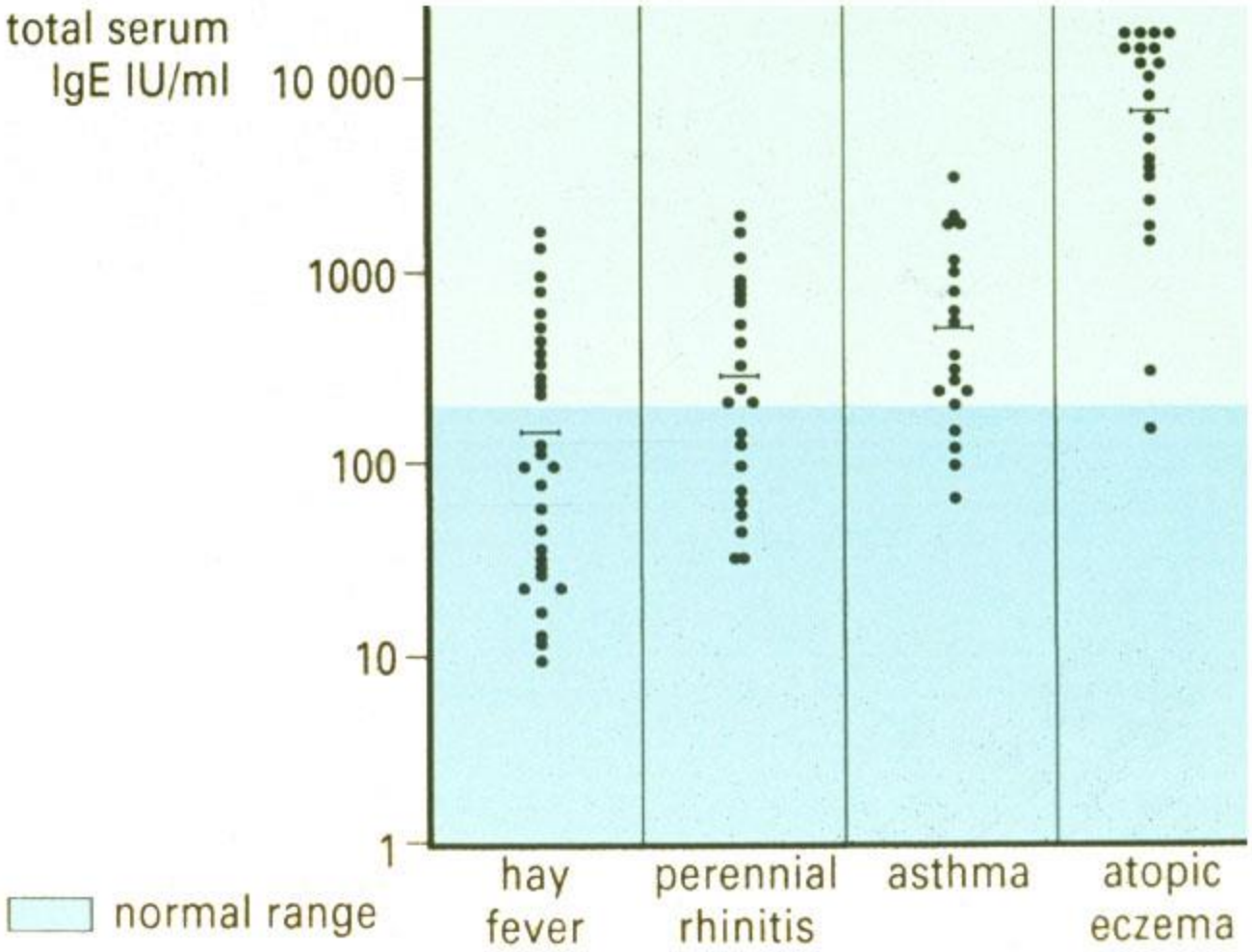
IgE

- Structure
  - Monomer
  - Extra domain (C_{H4})



http://pathmicro.med.sc.edu/mayer/IgStruct2000.htm

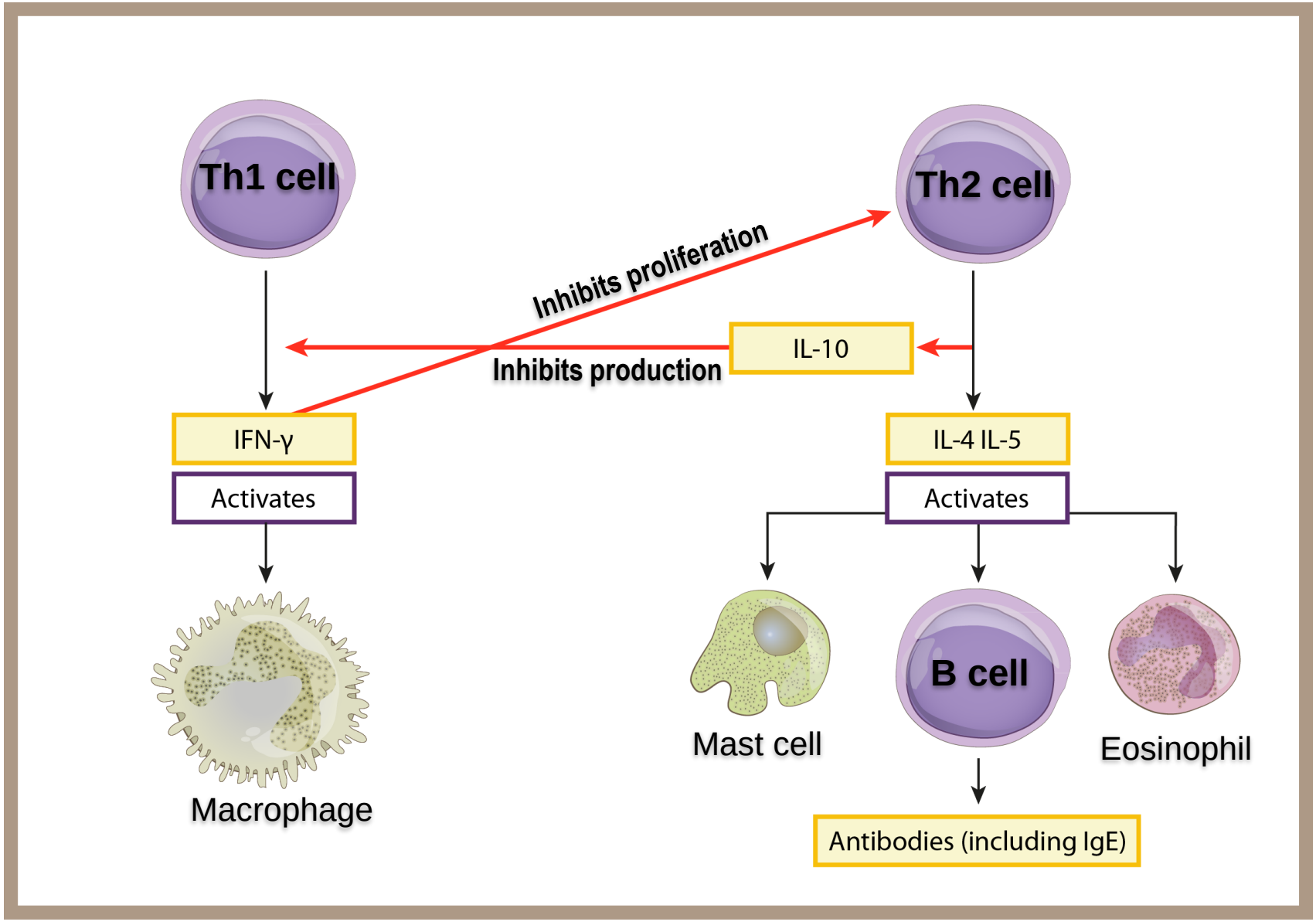
IgE levels and atopic disease



Regulation of IgE production

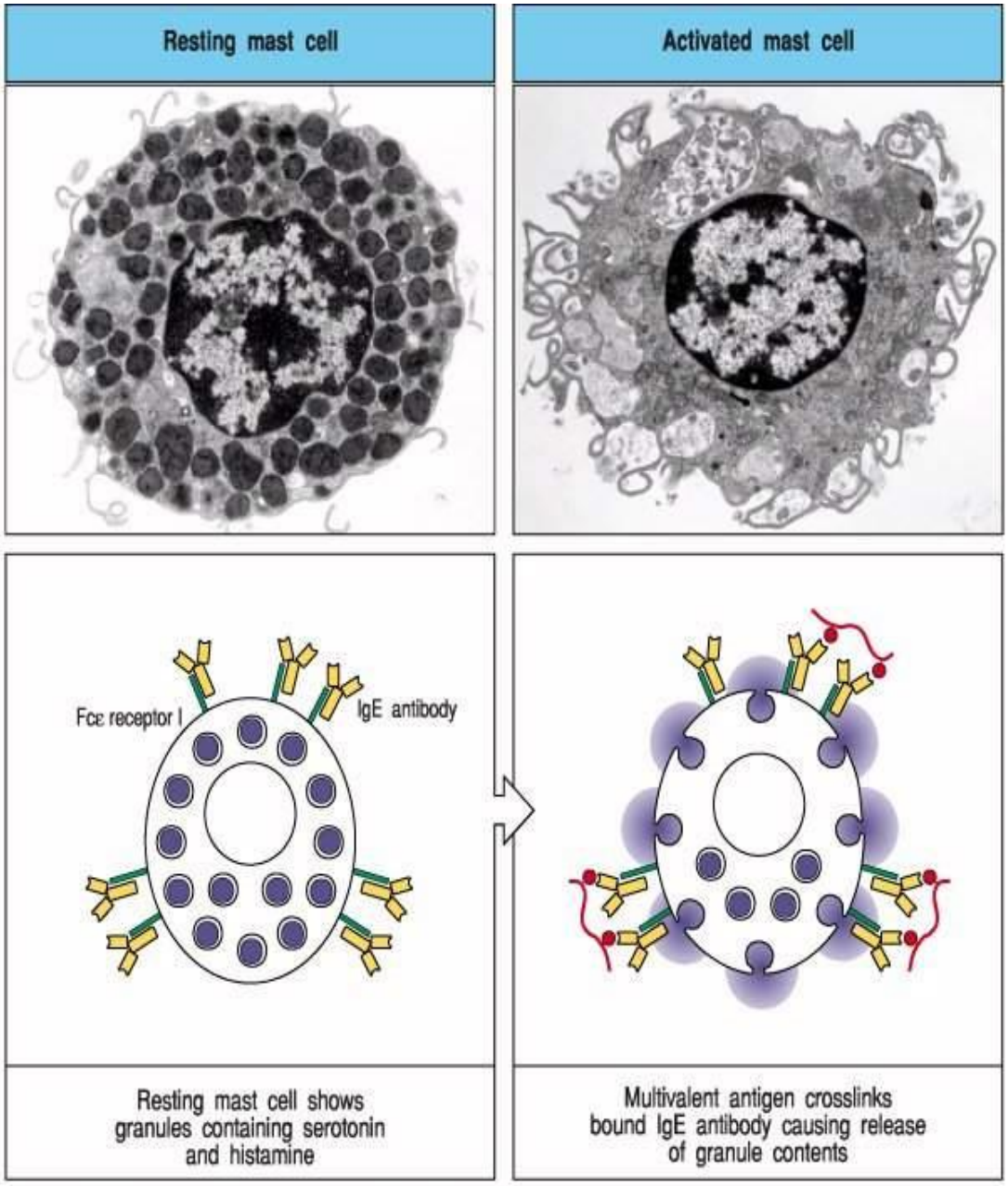
- Positive regulation: IL-4 a IL-13 – products of Th2 cells
- Negative regulation: IFNγ - product of Th1 cells

Functions of Th1 and Th2 cells

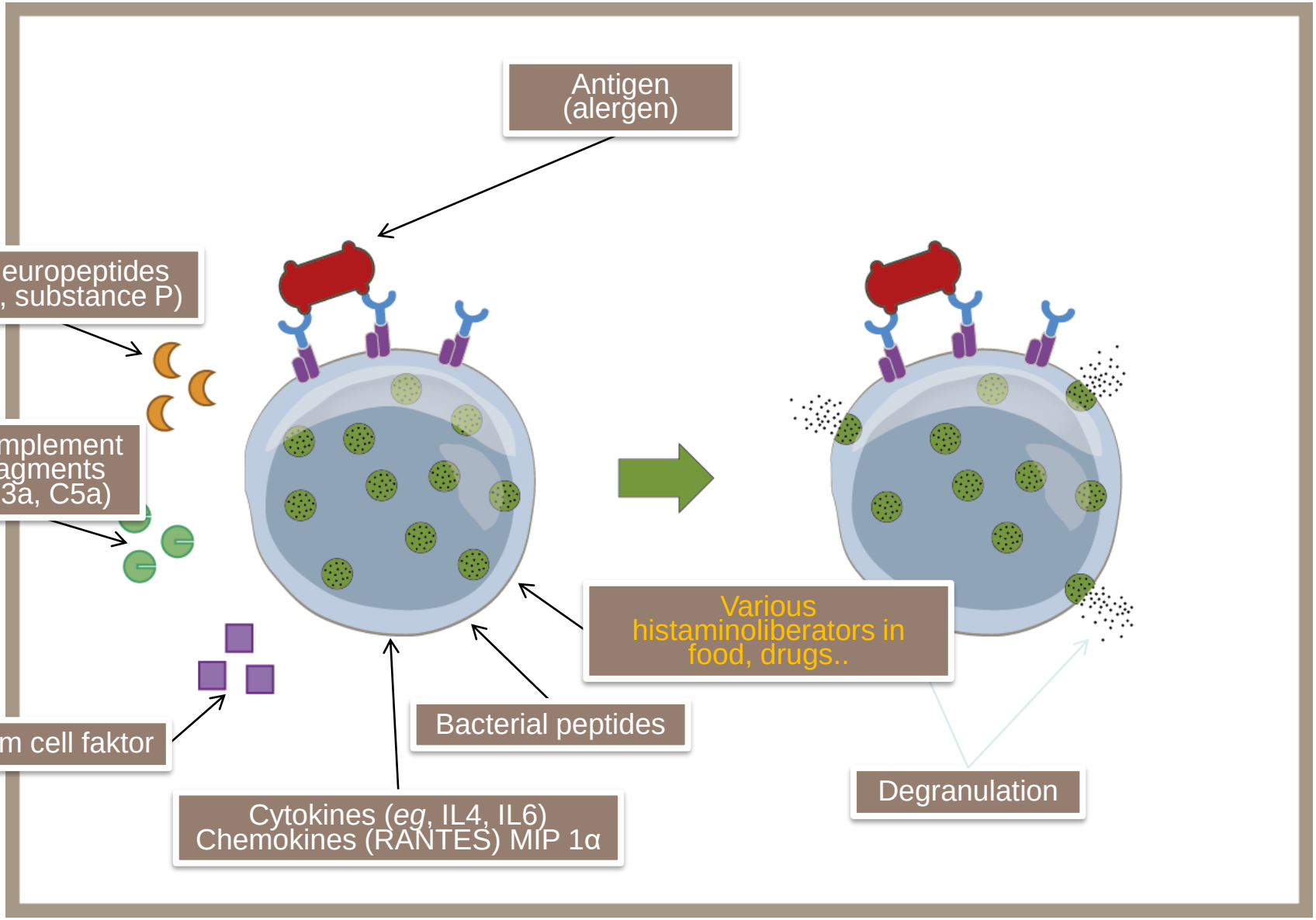


Mast Cell

Mast cells



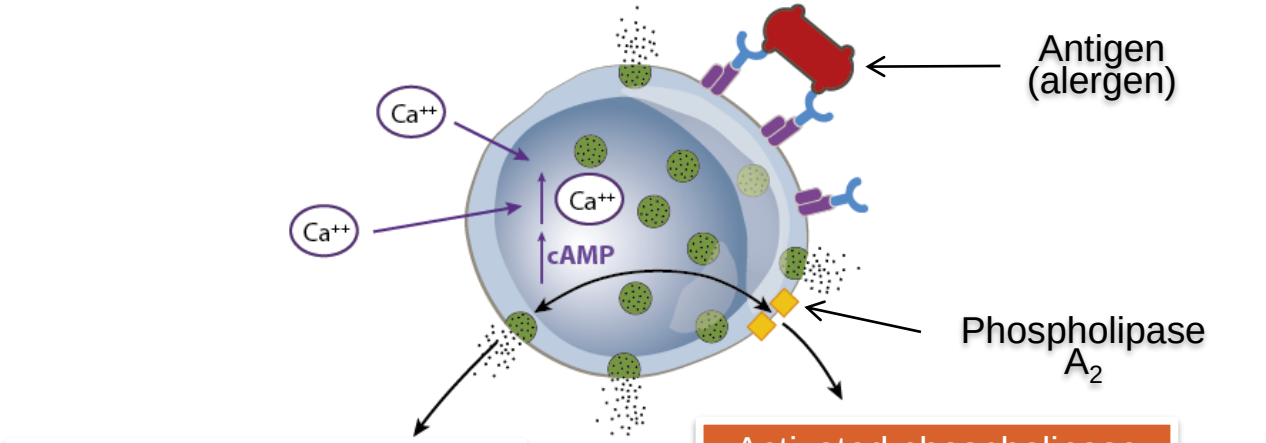
Ways of Activation of Mast Cells



Biological effects of histamin

- H1: Smooth muscle contraction, increased permeability of capillaries, vasodilatation, increased production of nasal and bronchial secretions, chemotaxis of leukocytes
- H2: increase of gastric juice production, increased production of secretions in respiratory tract
- H3: receptors present in CNS

Consequences of Mast Cell Activation



Release of granules

Release of histamine, proteolytic enzymes, heparin, chemotactic factors

Preformed mediators

Activated phospholipase A_2

Arachidonic acid

Cyclo-oxygenase pathway

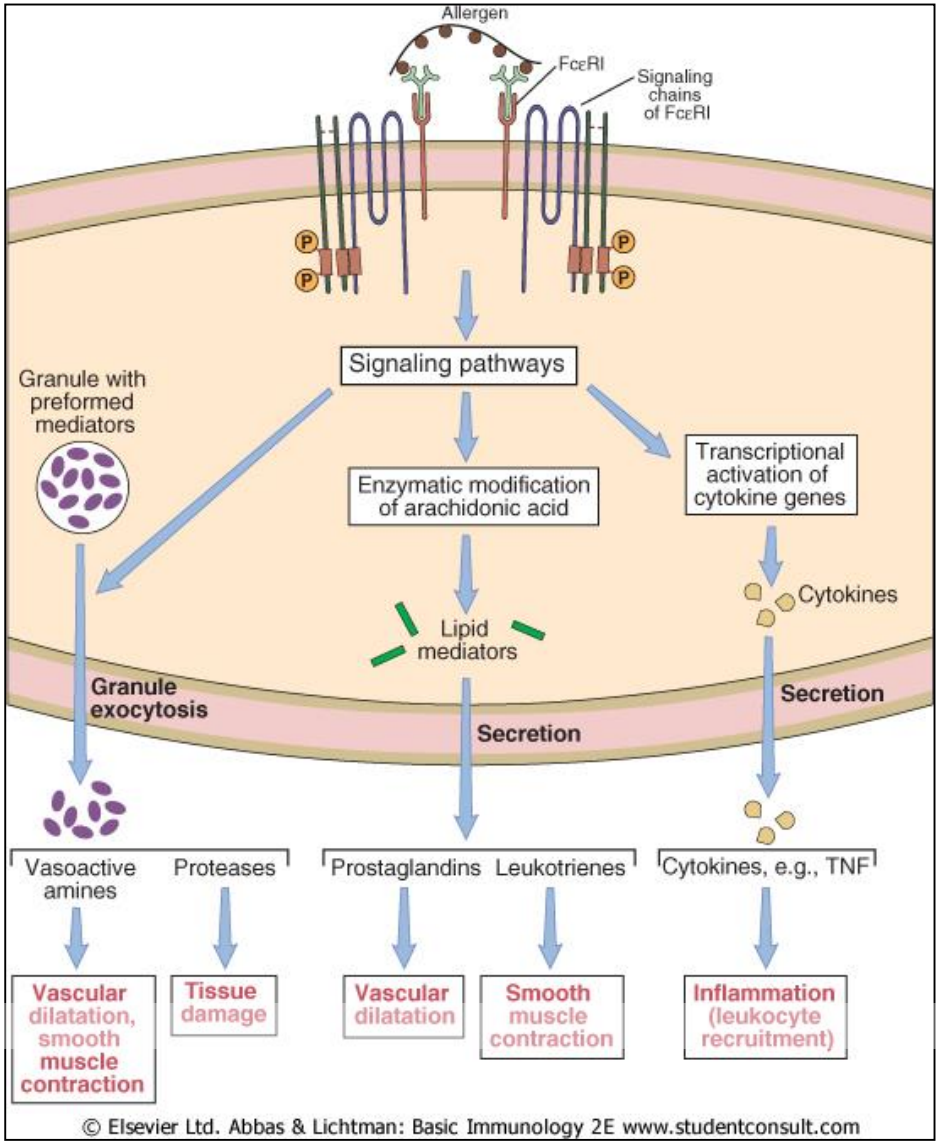
Lypoxygenase pathway

Prostaglandis

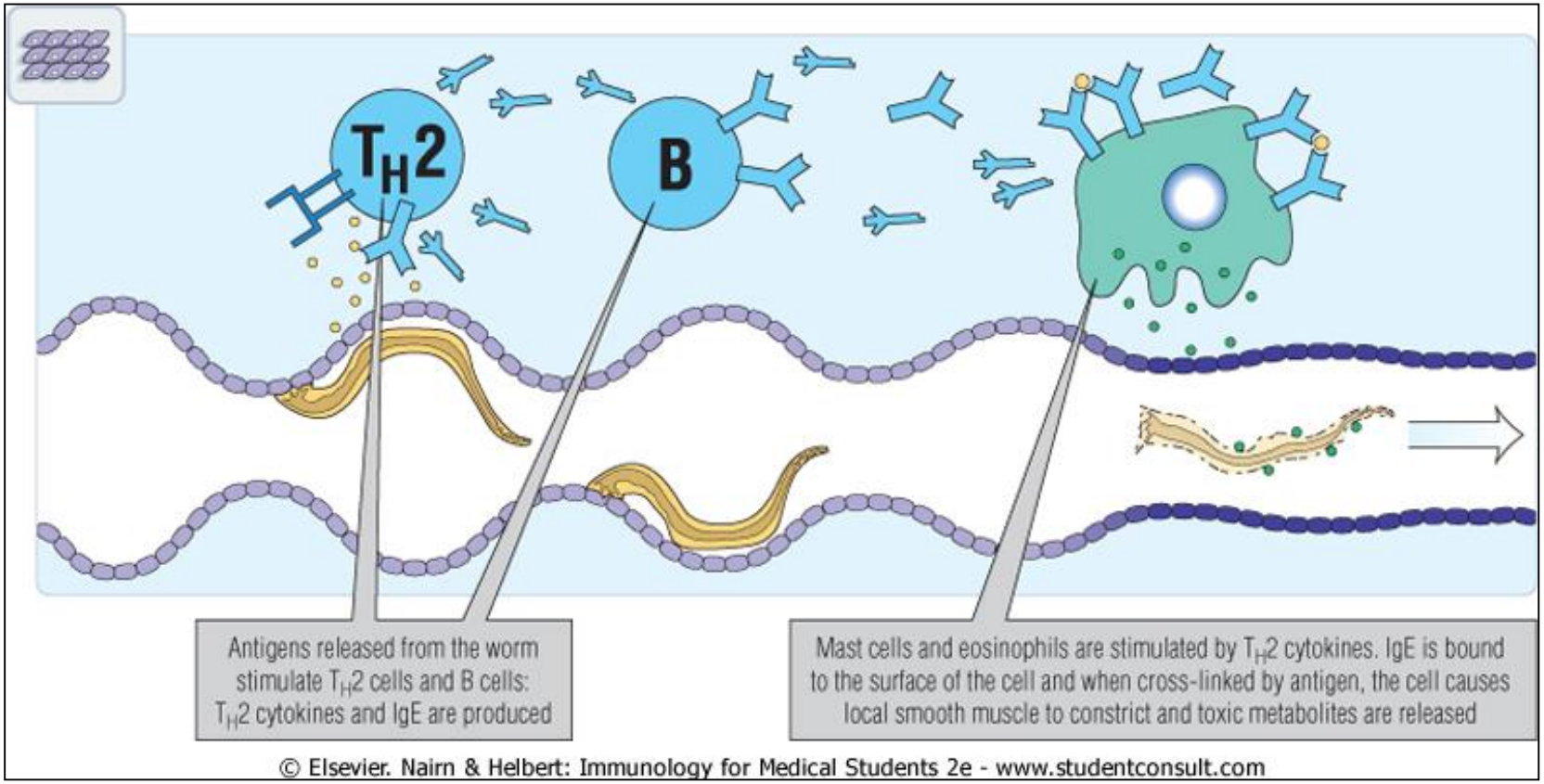
Leukotrienes

Newly-synthesized mediators

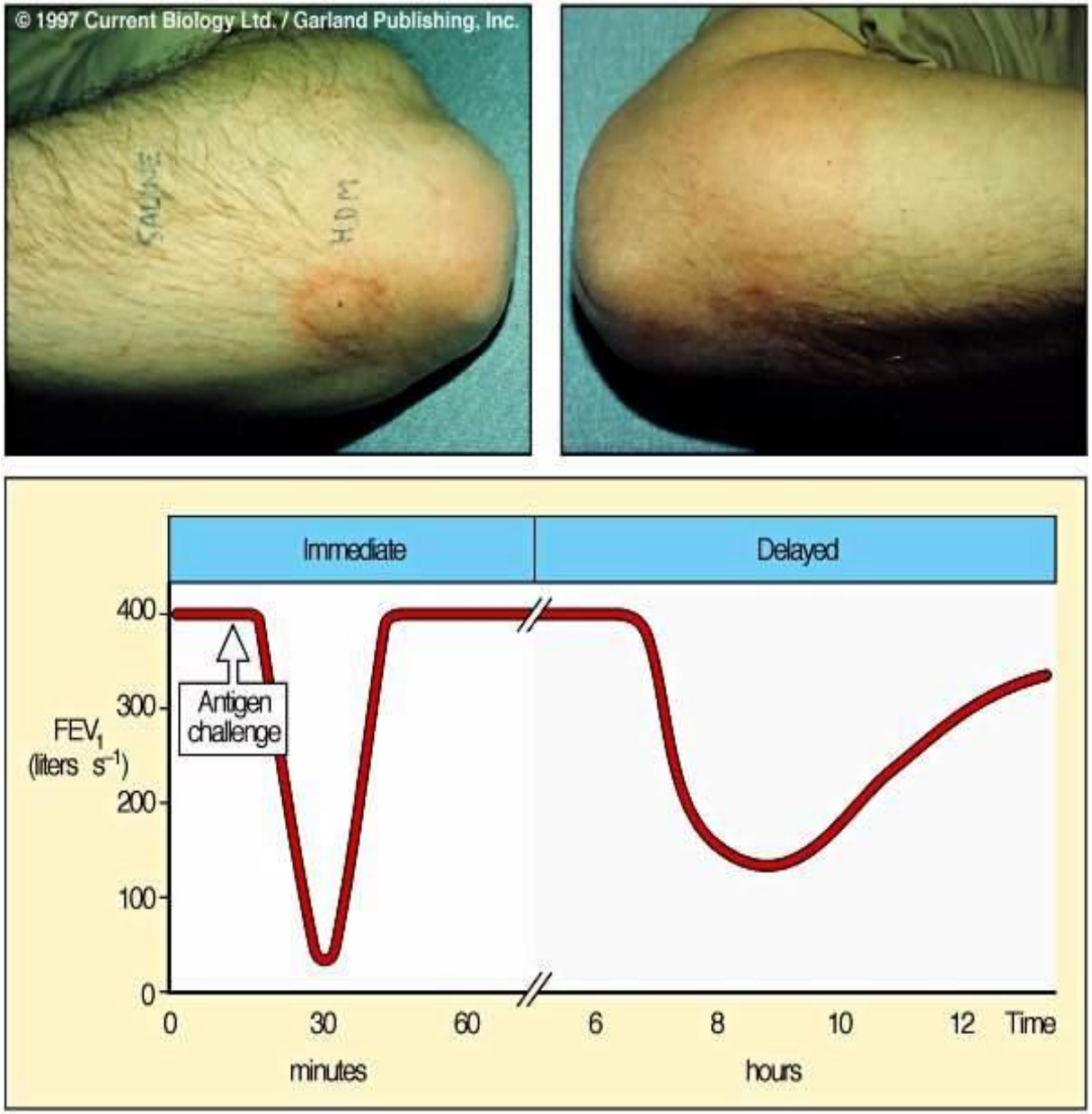
Consequences of activation of mast cells



Physiological role of IgE-Mastocyte-Eosinophil system



Immediate and late phase of allergic reaction

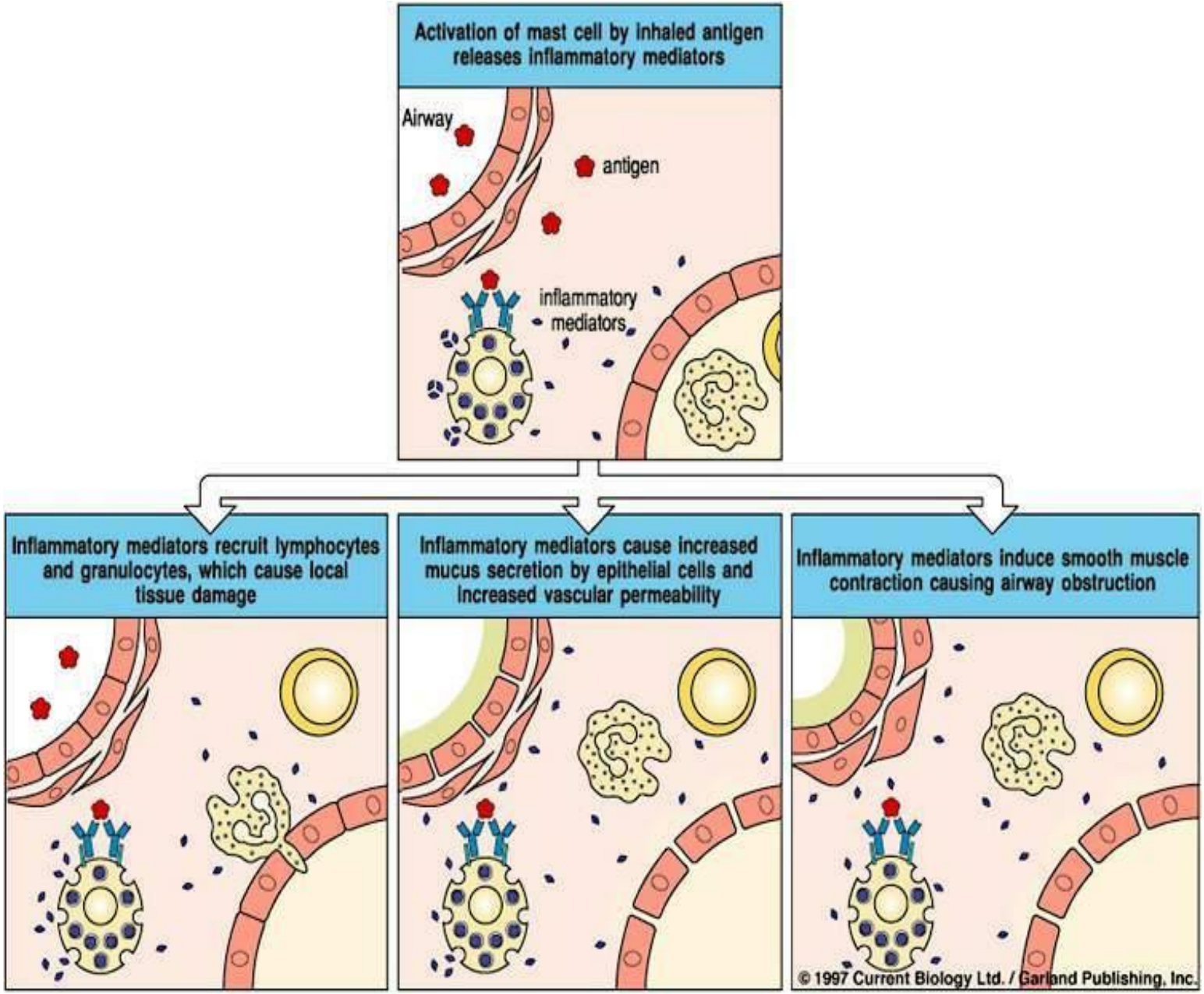


Phases of type-I hypersensitivity reaction

- Immediate phase – clinical symptons evolve in few minutes. Mediated mainly by histamin.

- Late phase – symptoms evolve after hours (6-8). Mediated mainly by leukotriens. Presence of eosinophils plays an important role in allergic inflammation.

Allergic reaction in bronchi

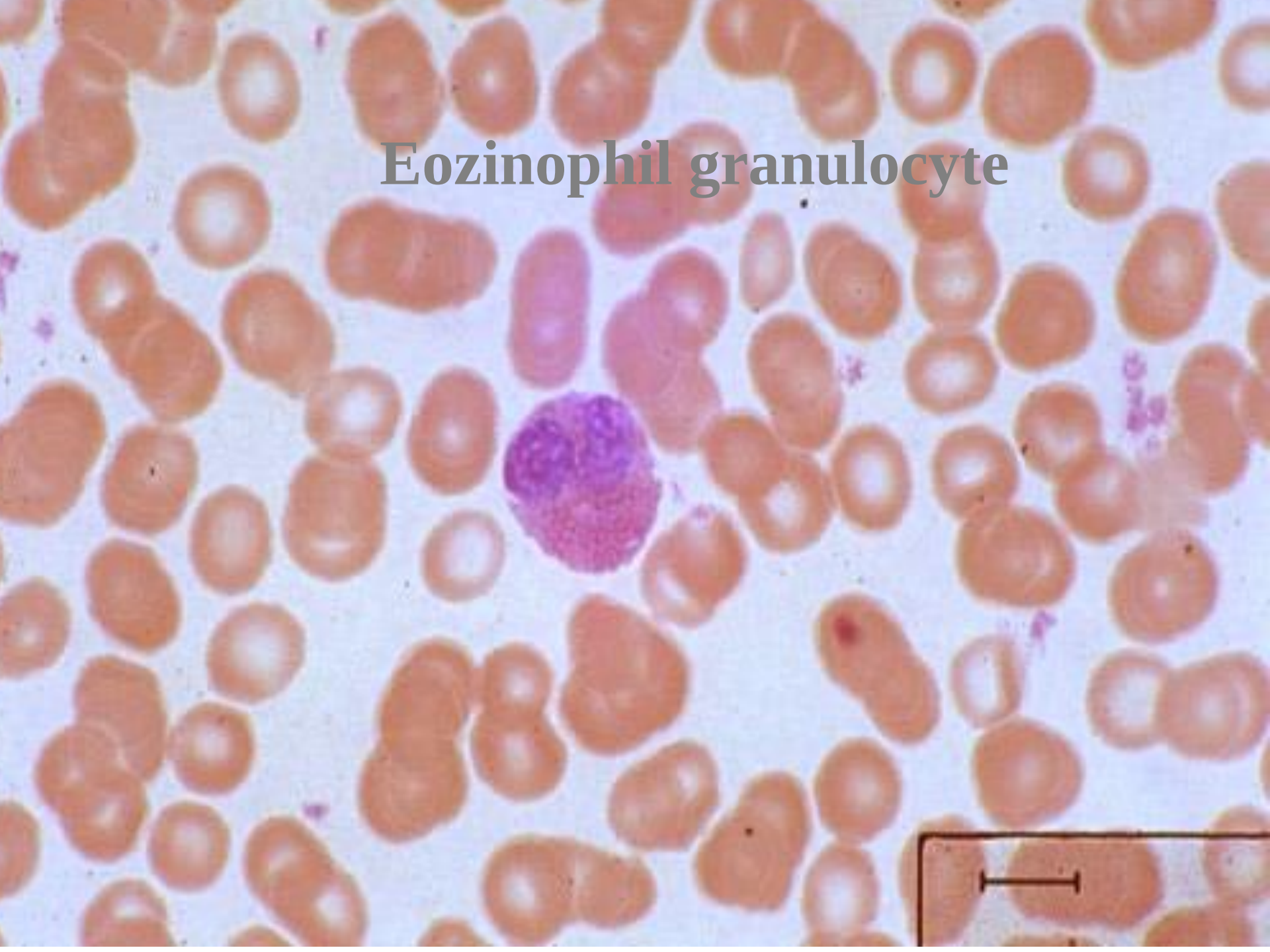


Eosinophil granulocytes

- **Type-I hypersensitivity is usually accompanied by the eosinophilic inflammation.**

- **Eosinophils produce several highly toxic mediators: incl. major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil-derived neurotoxin (EDNT), eosinophil peroxidase (EPO) - these proteins are toxic for many cells, including epitelial cells.**

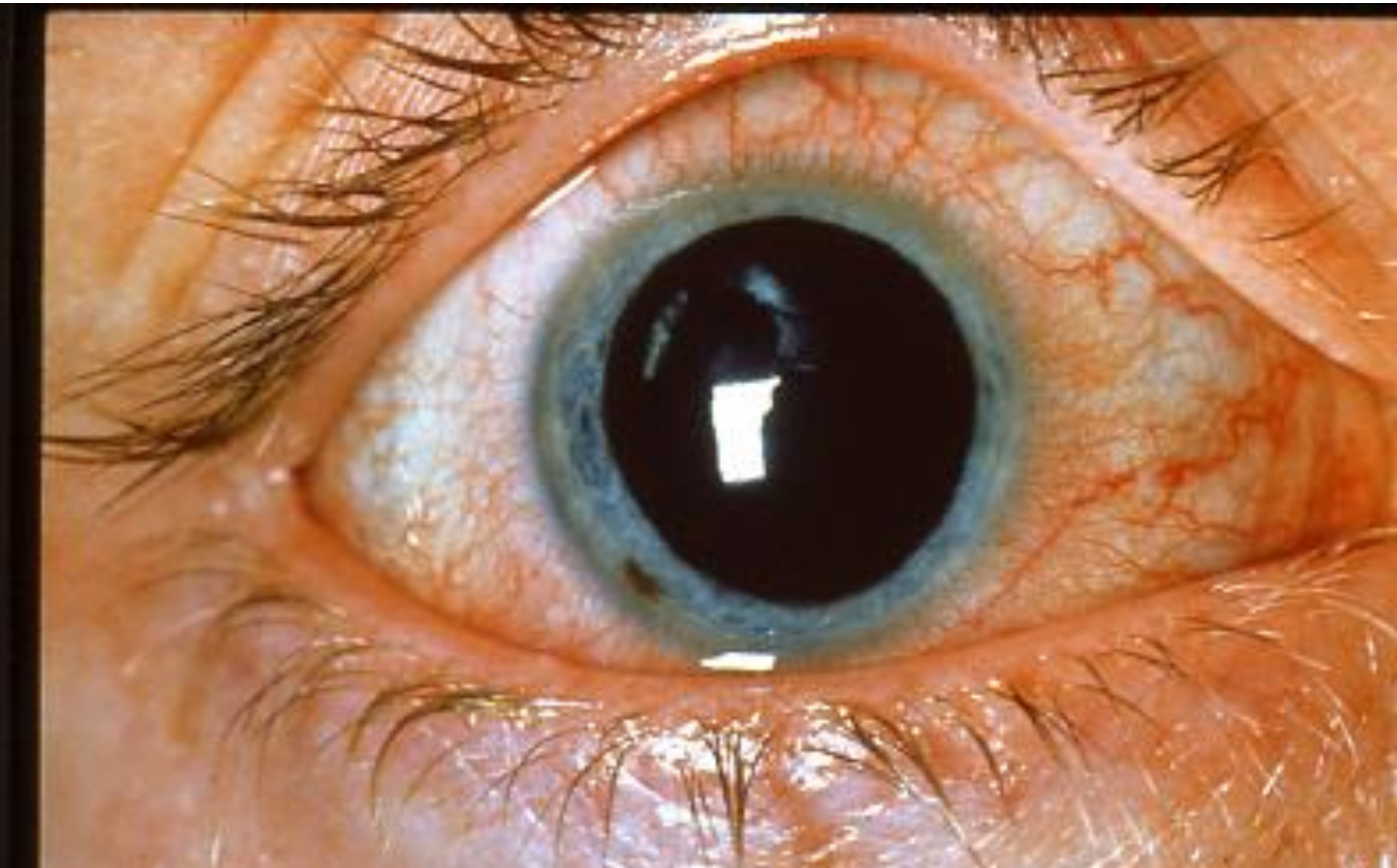
Eozinophil granulocyte



Clinical diseases caused by atopic hypersensitivity

- Allergic conjunctivitis
- Allergic rhinitis
- Bronchial asthma
- Allgergy of gastrointestinal tract
- Urticaria and angioedema
- Atopic eczema
- Anaphylactic shock

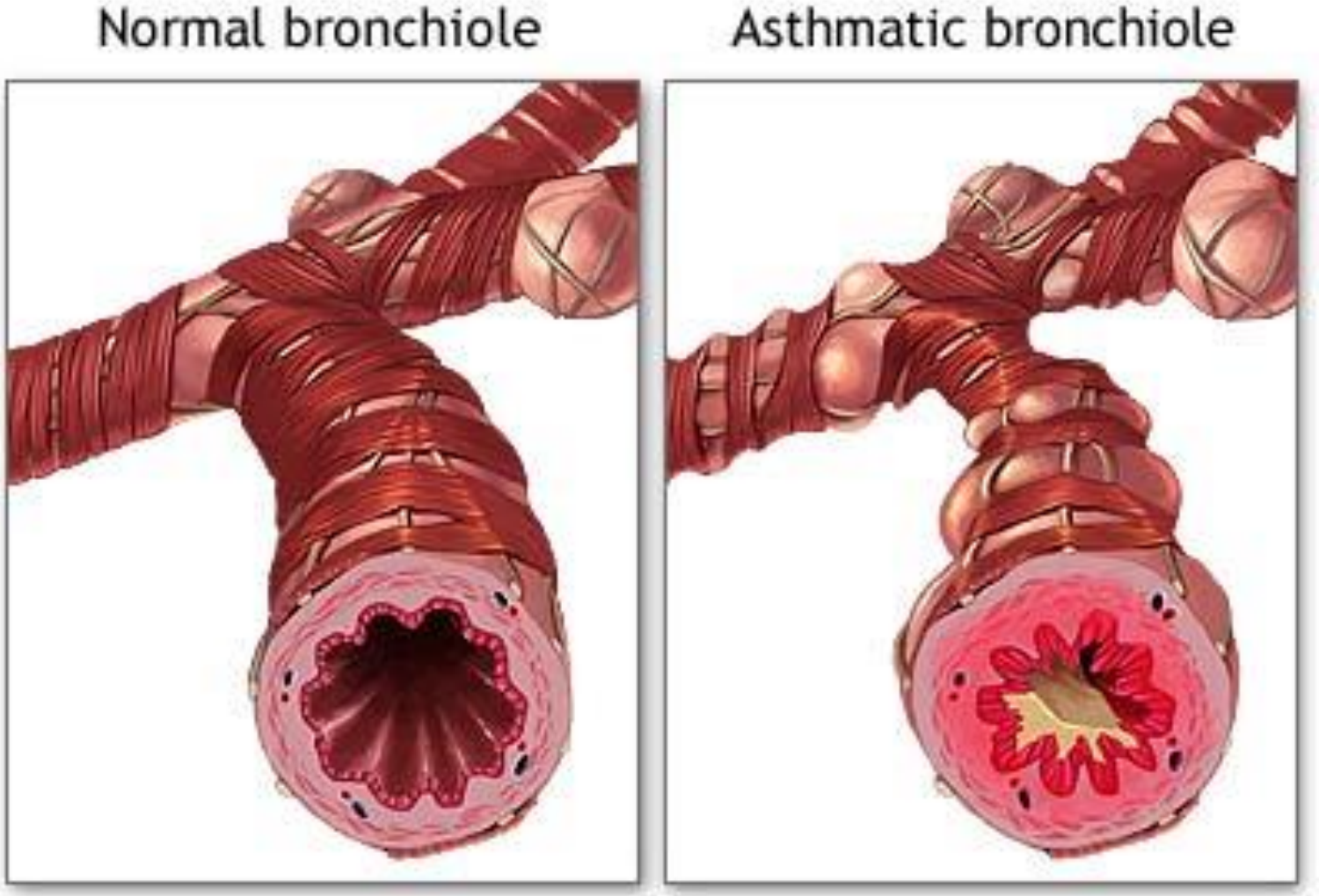
Allergic conjunctivitis



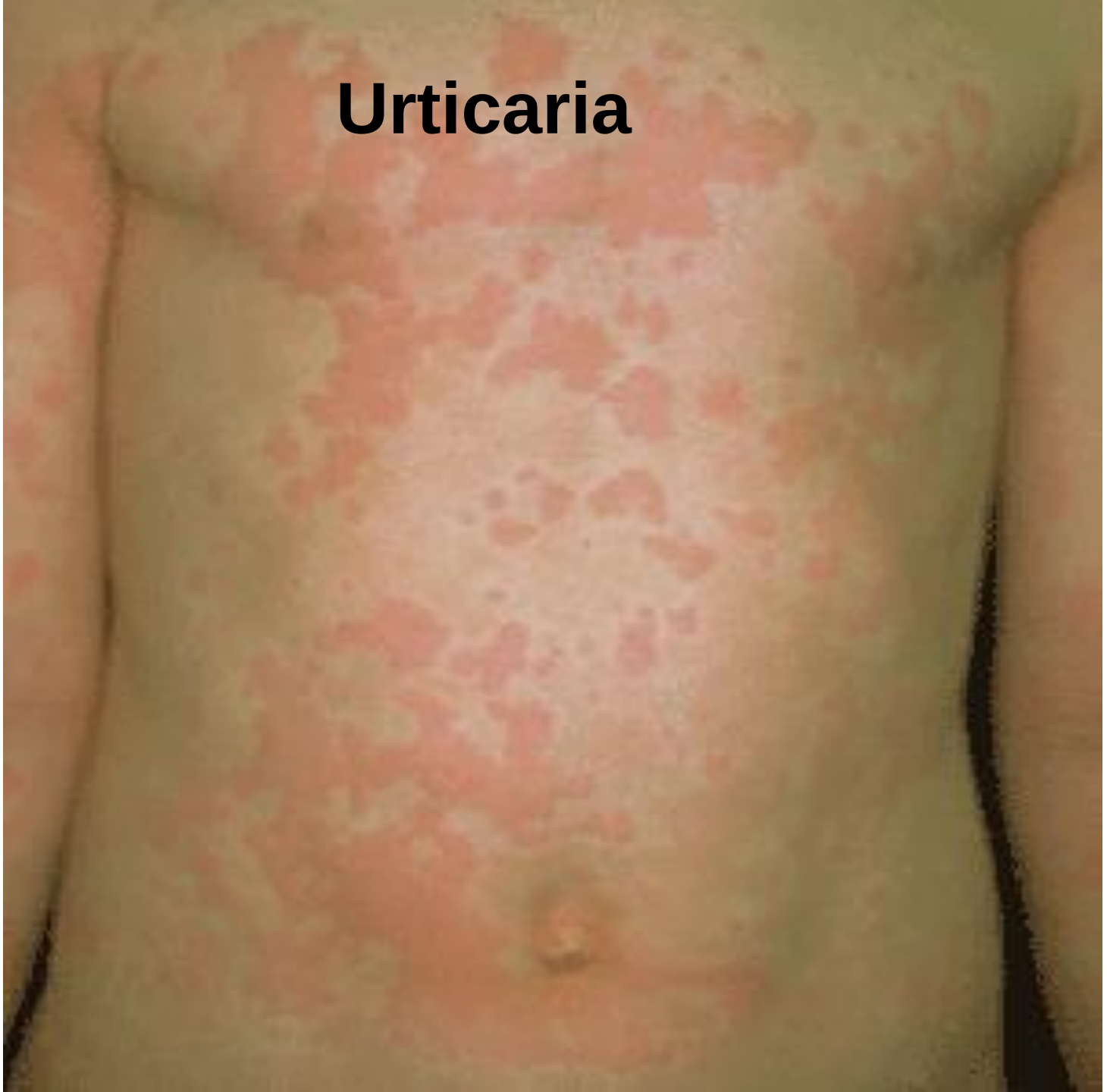
Allergic rhinitis

Bronchial asthma

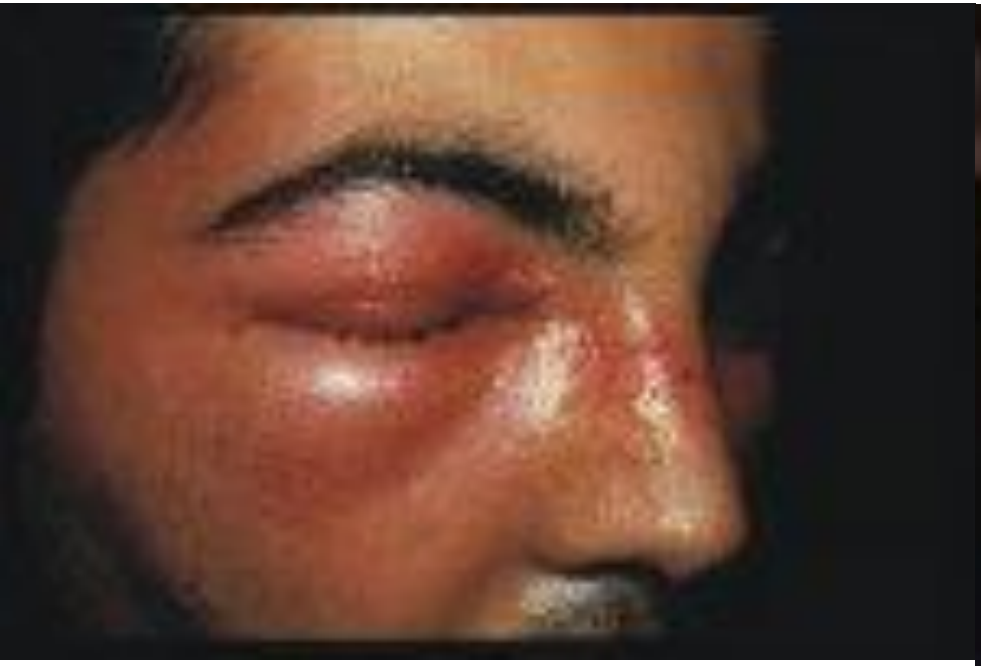
currently defined as chronic eosinophilic inflammation of bronchi

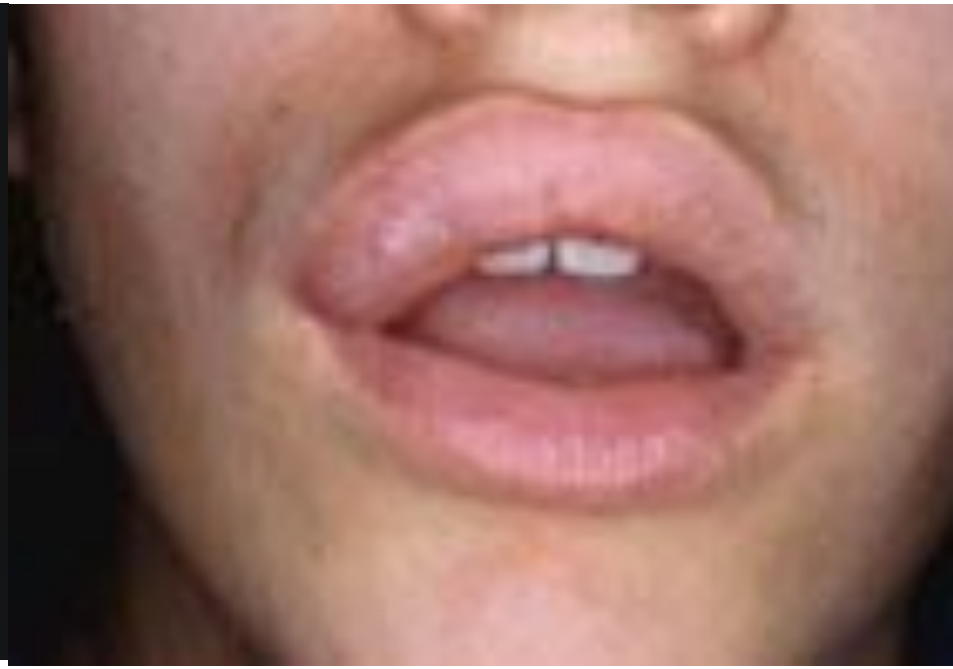


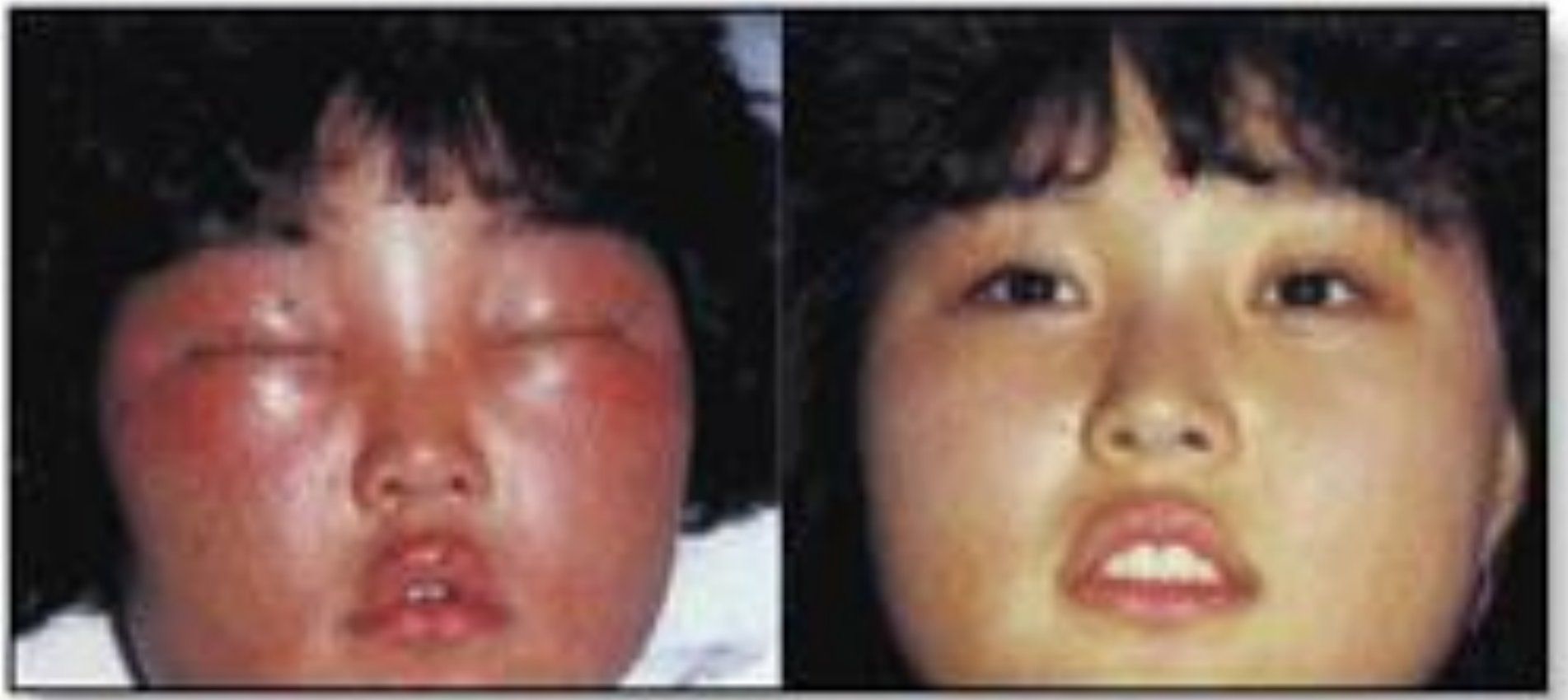
Urticaria



Angioedema



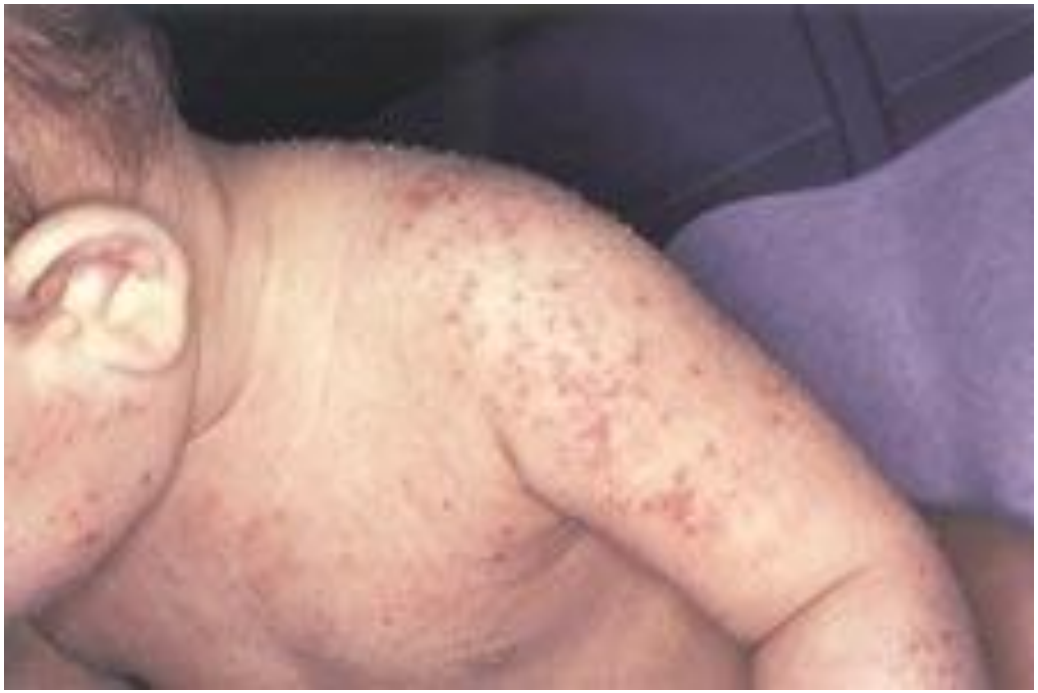


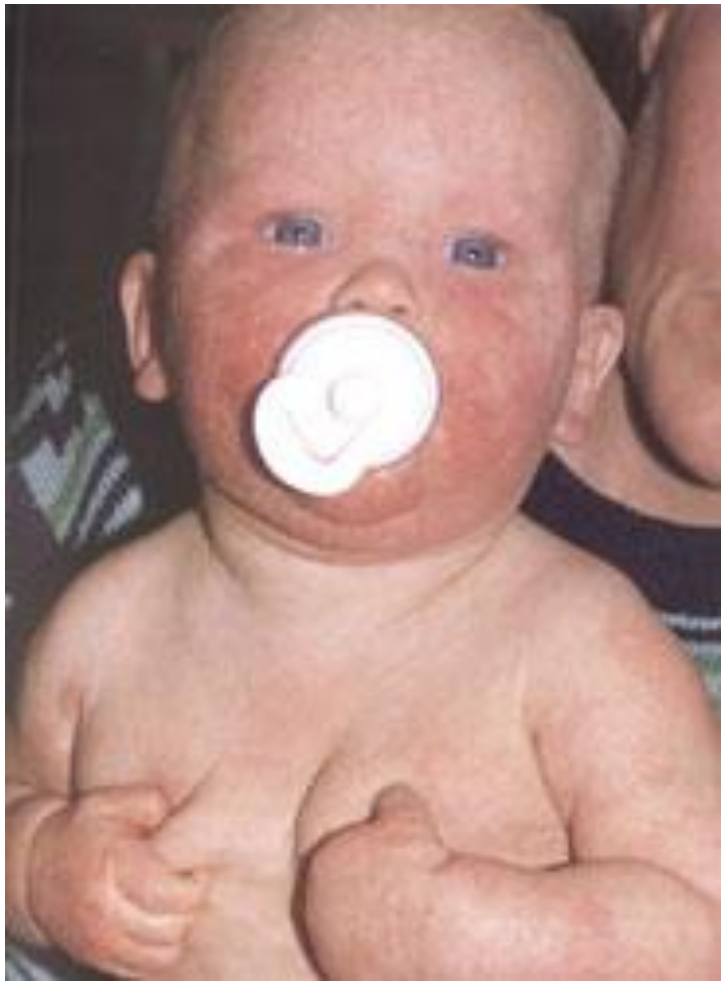


Facial angioedema following allergen exposure (A) and resolution after treatment (B).

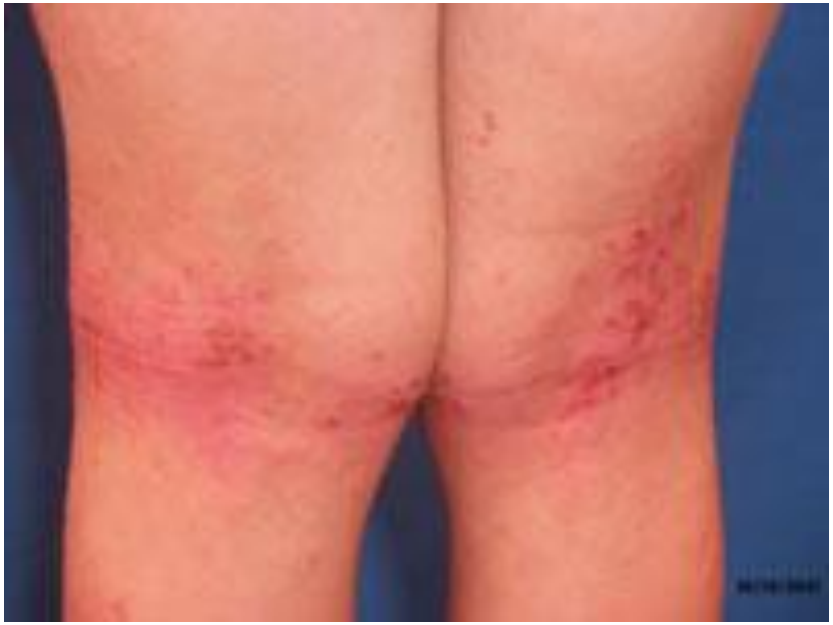
Reprinted from Tharp M, Levine M, Freeman P. Urticaria and angioedema. In: Freeman P, Slavin R (eds). Atlas of Allergies. 2nd ed. London: Mosby-Wolfe; 1996: 250. By permission of the publisher Mosby.

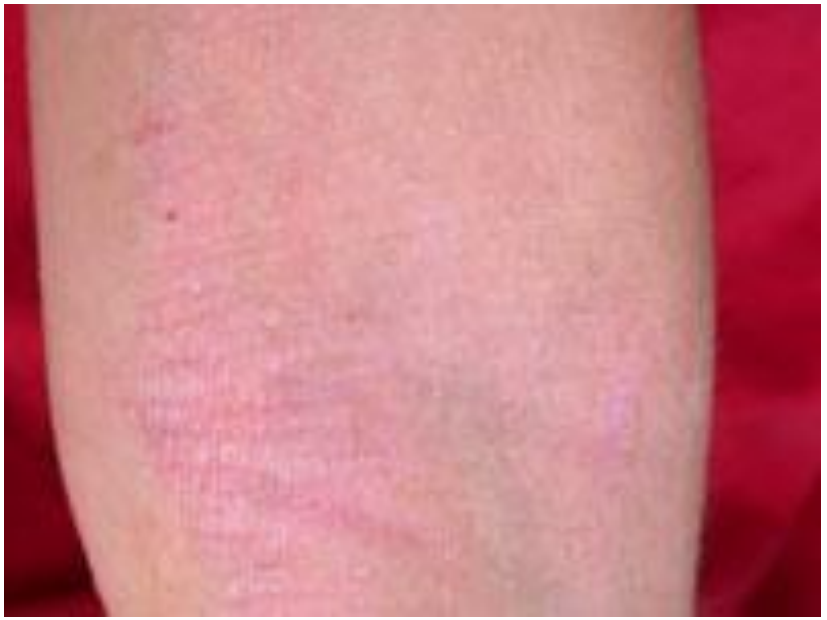
Atopic eczema



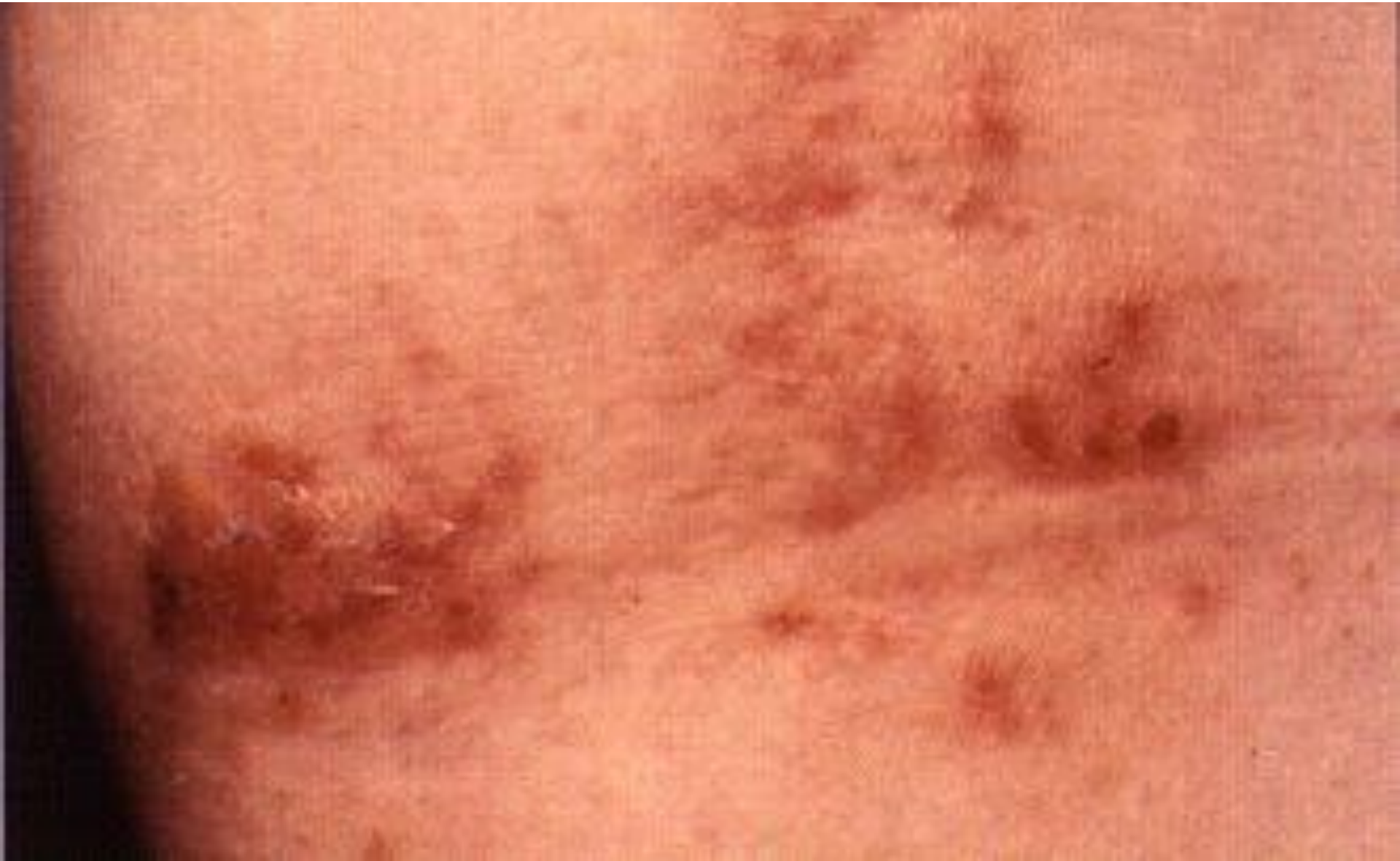


Atopic eczema





Atopic eczema



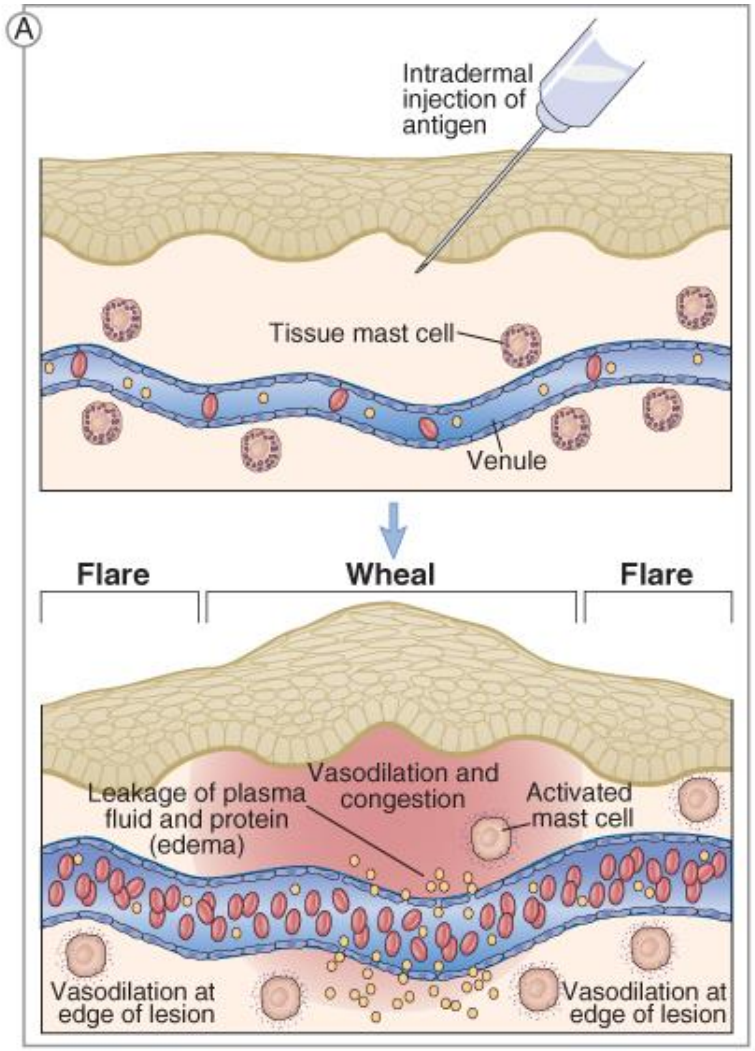
Treatment of allergic diseases

- Allergen avoidance
- Antihistaminics
- Topical or systemic corticosteroids
- Antilekotriens
- Cromons (cromolyn sodium, nedocromil) - stabilise membrane of the mast cells
- In asthma: β-2 agonists, xantins
- Allergen immunotherapy (desensitisation)

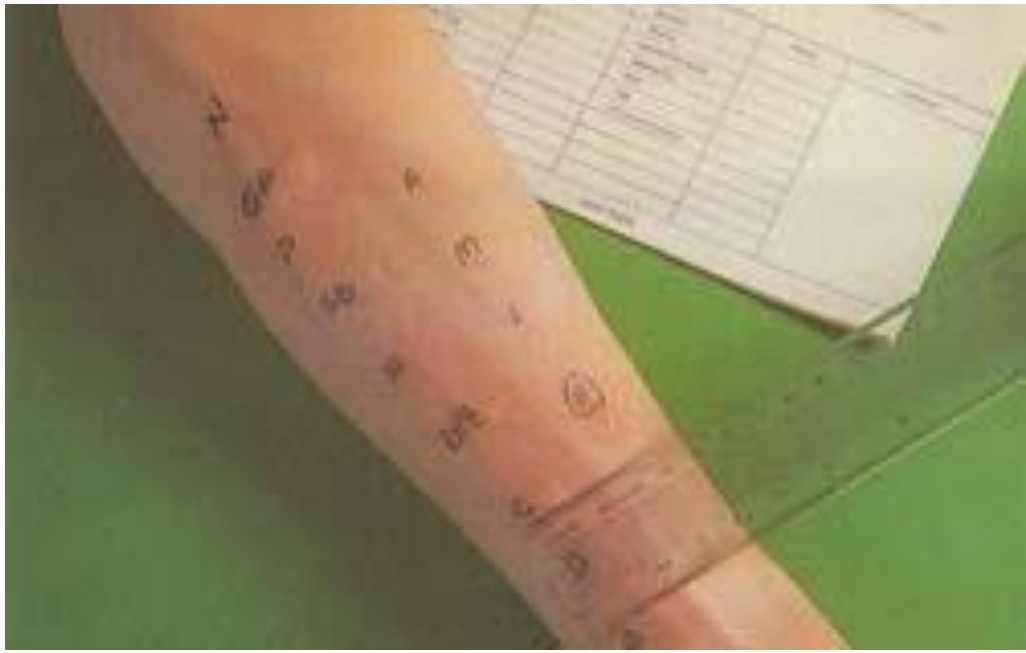
Diagnostic approaches in type-I hypersensitivity

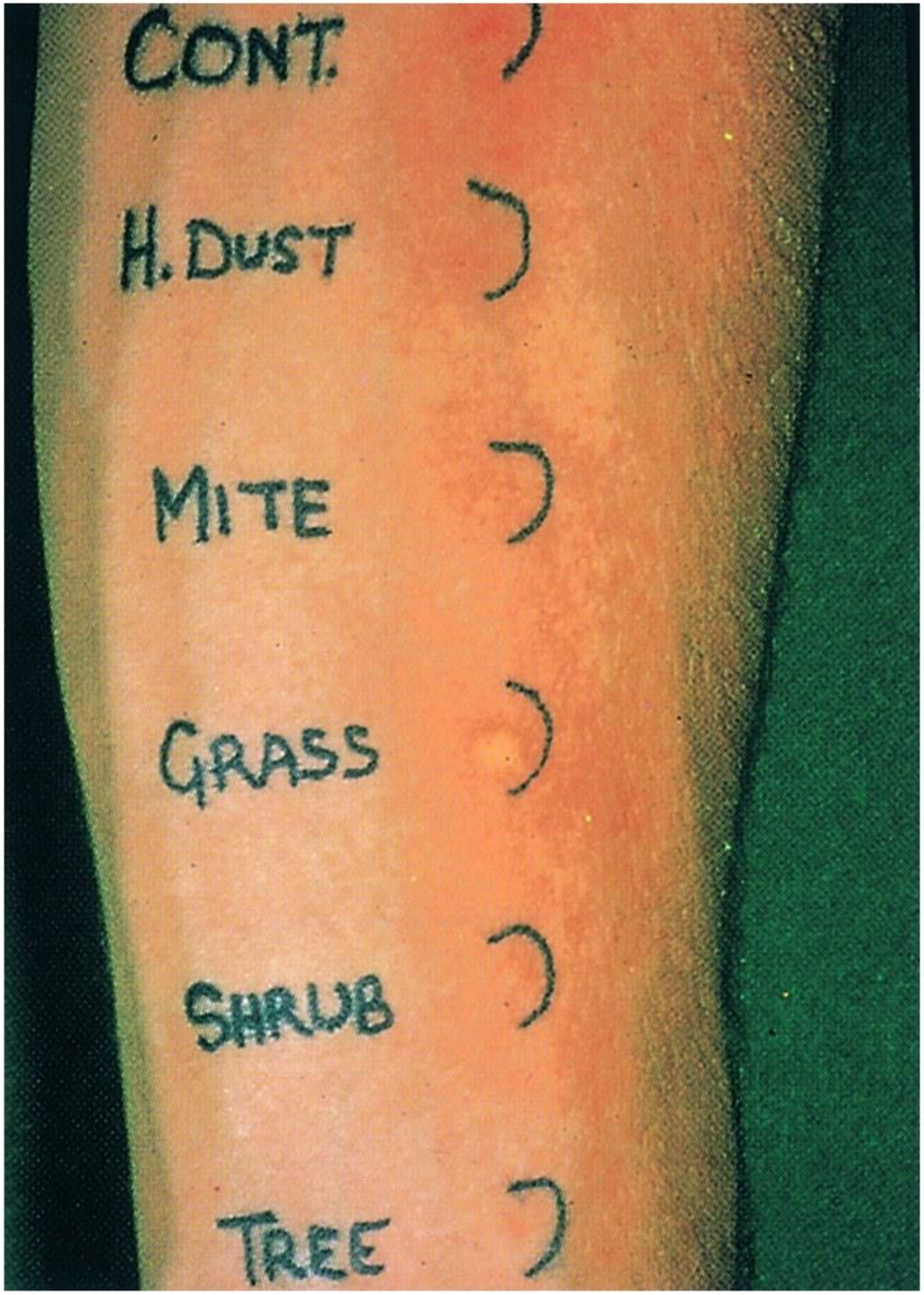
- Past history
- Eosinophilia
- Skin tests
- Laboratory tests for specific IgE
- Provocation and elimination tests

Intradermal allergy test



Skin prick tests




CONT.
H. DUST
MITE
GRASS
SHRUB
TREE

Causes of anaphylactic shock

- Drugs - penicillins, cephalosporins, proteolytic enzymes, local anestetics
- Food - nuts, seafood, chocolate
- Allergen desensitisation, allergen skin tests
- Bee or wasp sting
- X-ray contrast media

Clinical symptoms of anaphylactic shock

- Hypotension (systolic pressure 90 mm Hg or less)
- Tachykardia
- Dyspnea
- Abdominal pain, nausea
- Anxiety
- Urticaria on the skin, sweating, itching
- Contractions of the uterus

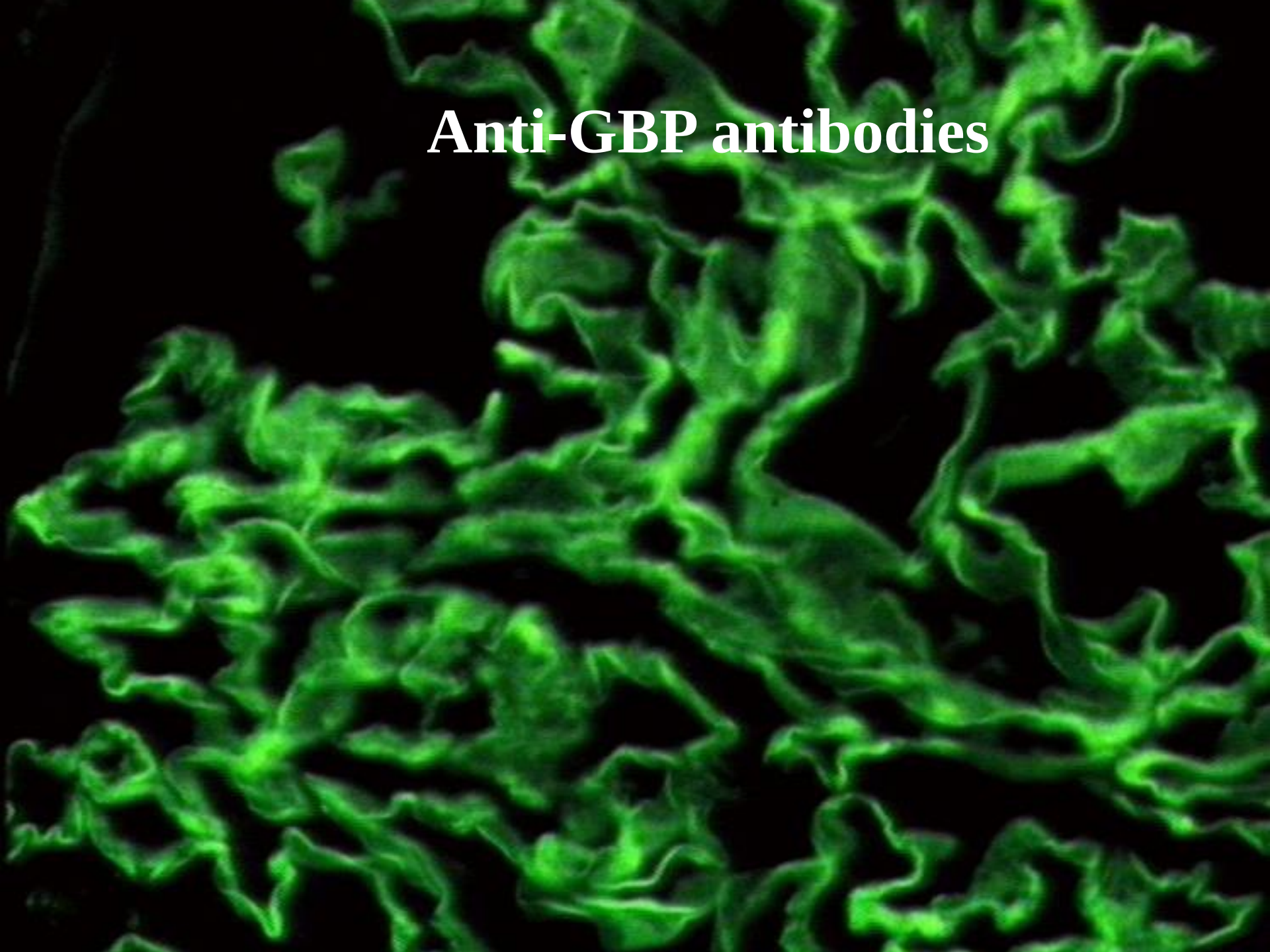
Treatment of anaphylactic shock

- Adrenalin intramusculary or intravenously (in monitored patients)
- Antihistaminics intravenously
- Syntophyllin or inhalation of β-2-mimetics
- Corticosteroids intravenously
- Oxygen
- Vasopressor agents (dopamin or noradrenalin)

Type-II hypersensitivity (cytotoxic)

- Mediated by IgG or IgM.
- Interaction between antigen and antibody leads to cell death, usually mediated by the complement system or phagocytosis.
- The antigen may be autoantigen(so it includes antibody-mediated autoimmune diseases) or may be of external origin (components of microbes, drugs.. which attach to a cell membrane).
- Includes also post-transfusion hemolytic reactions.
- Also interactions between receptors and autoantibodies (leading to receptor activation or blocade are involved in this group of hypersensitivity reactions).

Anti-GBP antibodies



Type-III (immunocomplex) hypersenseitivity

- Caused by inflammation caused by the activation of the immune system by immunocomplexes (usually deposited in inappropitate sites).

- In the case of excess of antibodies, the symptoms appear after several hours anter after exposition to an antigen (approximately 6-8 hour), this type is also called late-type of hypersensitivity.

Examples of antibody- mediated autoimmune diseases (type-II hypersensitivity)

Disease	Target antigen	Mechanisms of disease	Clinicopathologic manifestations
Autoimmune hemolytic anemia	Erythrocyte membrane proteins (Rh blood group antigens, I antigen)	Opsonization and phagocytosis of erythrocytes	Hemolysis, anemia
Autoimmune (idiopathic) thrombocytopenic purpura	Platelet membrane proteins (gpIIb:IIIa integrin)	Opsonization and phagocytosis of platelets	Bleeding
Pemphigus vulgaris	Proteins in intercellular junctions of epidermal cells (epidermal cadherin)	Antibody-mediated activation of proteases, disruption of intercellular adhesions	Skin vesicles (bullae)
Goodpasture's syndrome	Noncollagenous protein in basement membranes of kidney glomeruli and lung alveoli	Complement- and Fc receptor–mediated inflammation	Nephritis, lung hemorrhages
Acute rheumatic fever	Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen	Inflammation, macrophage activation	Myocarditis, arthritis
Myasthenia gravis	Acetylcholine receptor	Antibody inhibits acetycholine binding, down-modulates receptors	Muscle weakness, paralysis
Graves' disease (hyperthyroidism)	Thyroid-stimulating hormone (TSH) receptor	Antibody-mediated stimulation of TSH receptors	Hyperthyroidism
Pernicious anemia	Intrinsic factor of gastric parietal cells	Neutralization of intrinsic factor, decreased absorption of vitamin B_{12}	Abnormal erythropoiesis, anemia

Diseased caused by immune complexes deposition

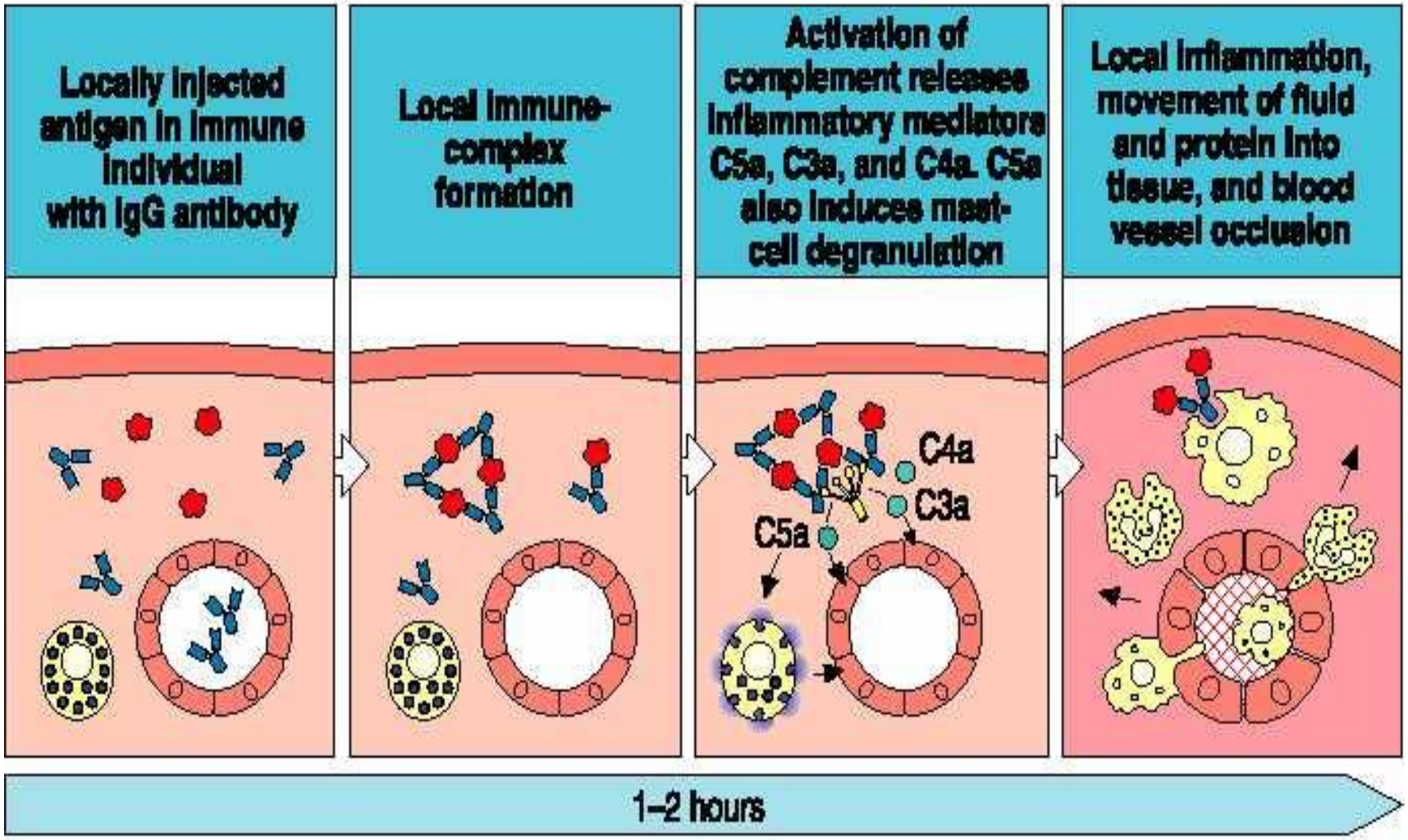
- Caused by a disturbed transport or metabolism of immune complexes.
- They usually deposit in the wall of vessels (causing vasculitis) or glomeruli (causing glomerulonephritis), less frequently in the place of their formation (extrinsic alveolitis).
- The most important laboratory test is the direct immunofluorescence to detect the IgG part of the complexes.

Immunocomplex diseases (type III immunopathological reaction

- Caused by deposition of immune complexes in places different from their normal metabolism.
- In case of circulating immune complexes (small, soluble complexes with excess of antigen), they deposit mainly in blood vessels walls and glomeruli leading to vasculitis and/or glomerulonephritis.
- Less frequent is the situation when immune complexes deposit in the place of their formation (large complexes with excess of antibodies). They deposit in the place of their formation.
- By activation of the complement system and phagocytioc cells they induce local inflammation.

Type III hypersensitivity

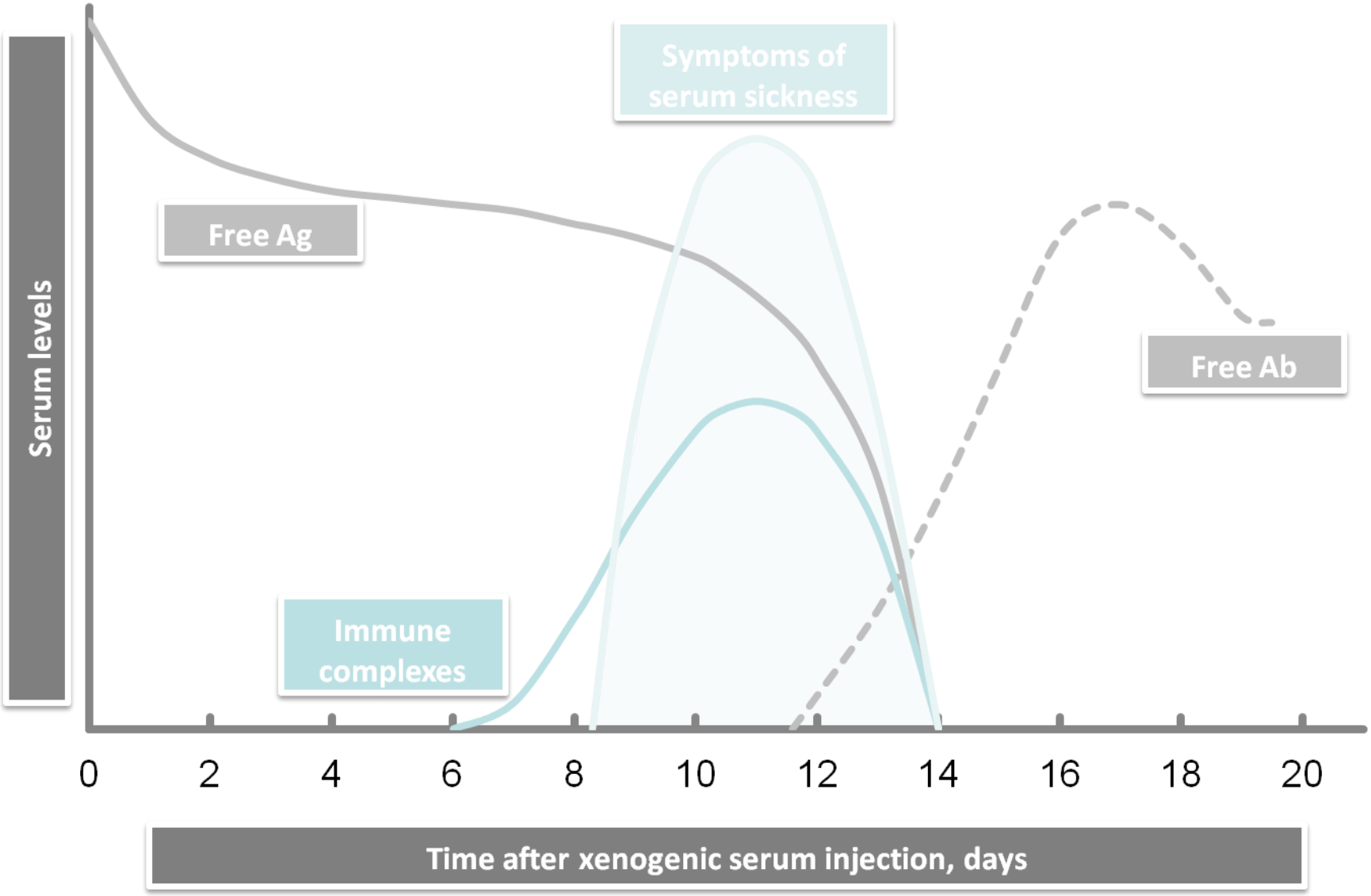
Figure 10.29



Serum sickness

- Manifests 8-12 days after the uses of xenogenic serum.
- Urticaria, fever, arthralgia, lymphadenopathy
- Albuminuria
- Deposits of immunocomplexes in vessels.
- Self-limiting disease, in case of need steroids or antihistaminics can be used.

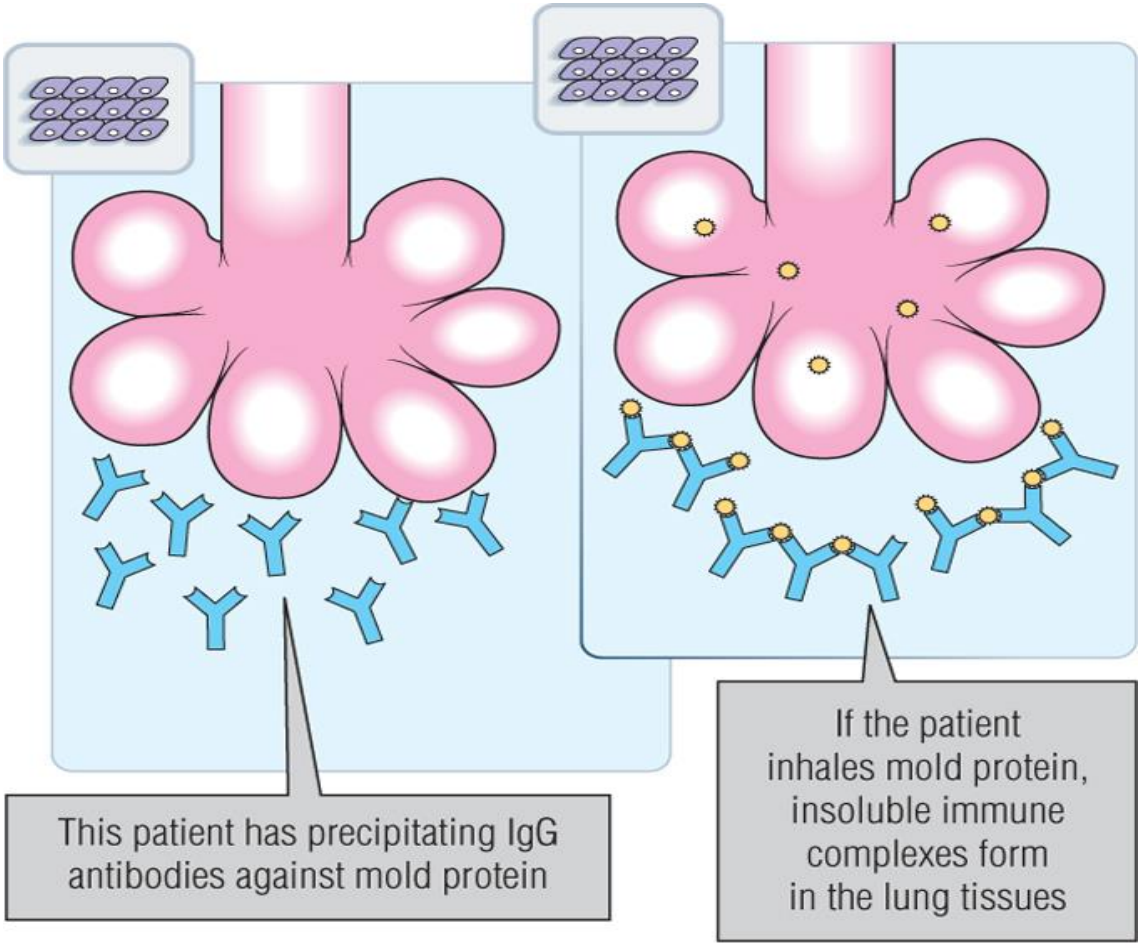
Serum Sickness



Extrinsic alveolitis

- Caused by deposition if insoluble immune complexes in the lung tissue. The complexes are formed from exogenous antigen and excess of antibodies of IgG class.
- 6-8 hours after exposition the patient suffers from dry cough, dyspnea, increased body temperature, lymphadenopathy.
- Repeated expositions lead to lung fibrosis..
- Most frequently caused by bird antigens (pigeons – pigeon breeder´s disease, parrots), thermophil actinomycetes (farmers´s lungs disease).

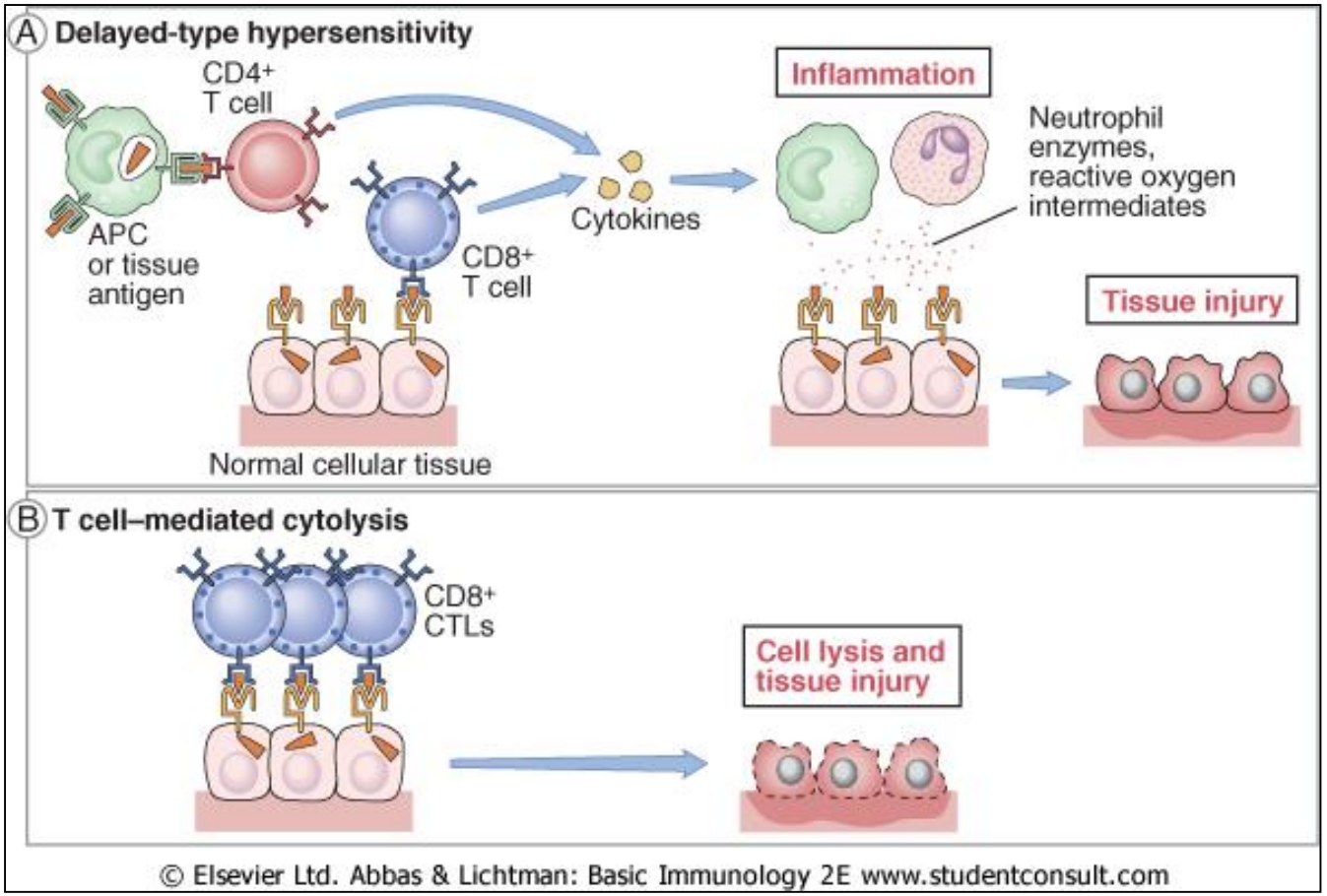
Patogenesis of extrinsic alveolitis



Type-IV hypersensitivity

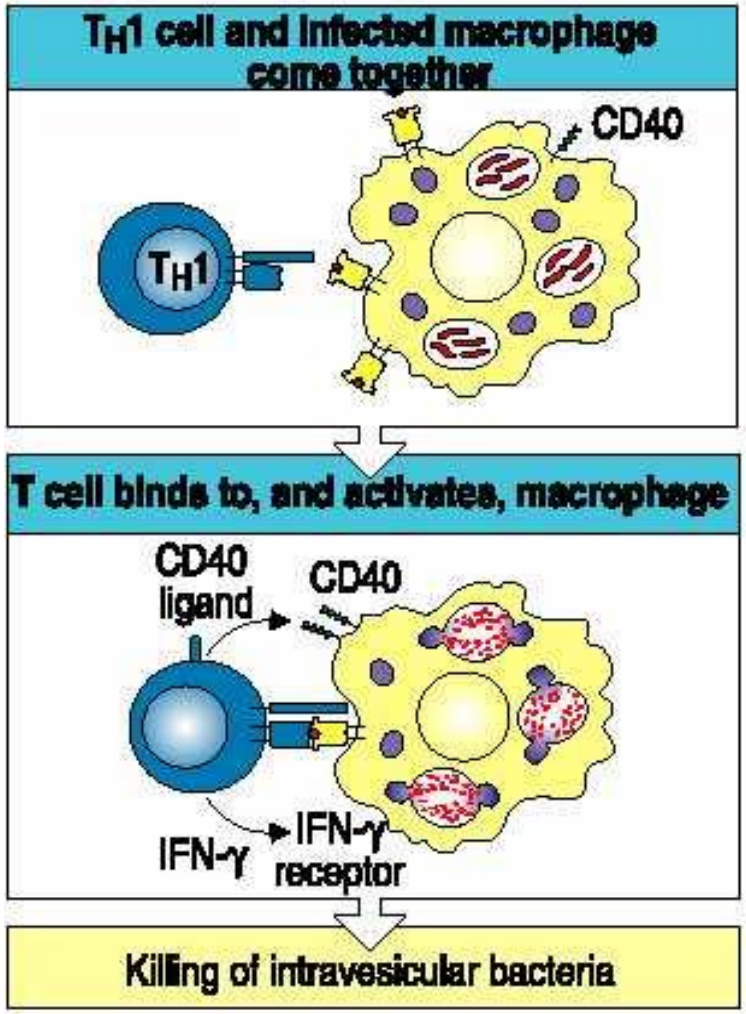
- Mediated by T-lymphocytes, predominantly Th1 lymphocytes which consequently activate macrophages – also called cellular hypersensitivity
- This reaction develops 1-2 days after exposure – delayed type of hypersensitivity.
- Also autoimmunity caused by Tc lymphocytes is included into this group of immunopathological diseases.

Mechanisms of T-cell mediated tissue injury (type-IV hypersensitivity)

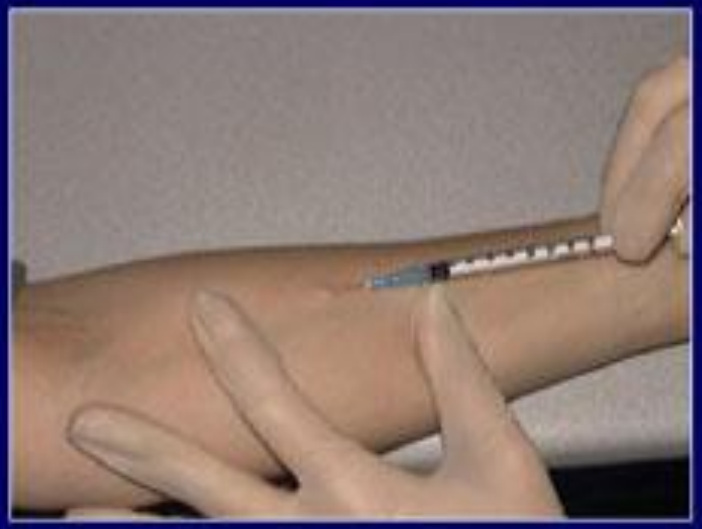


Function of Th1 cells

Figure 6.27



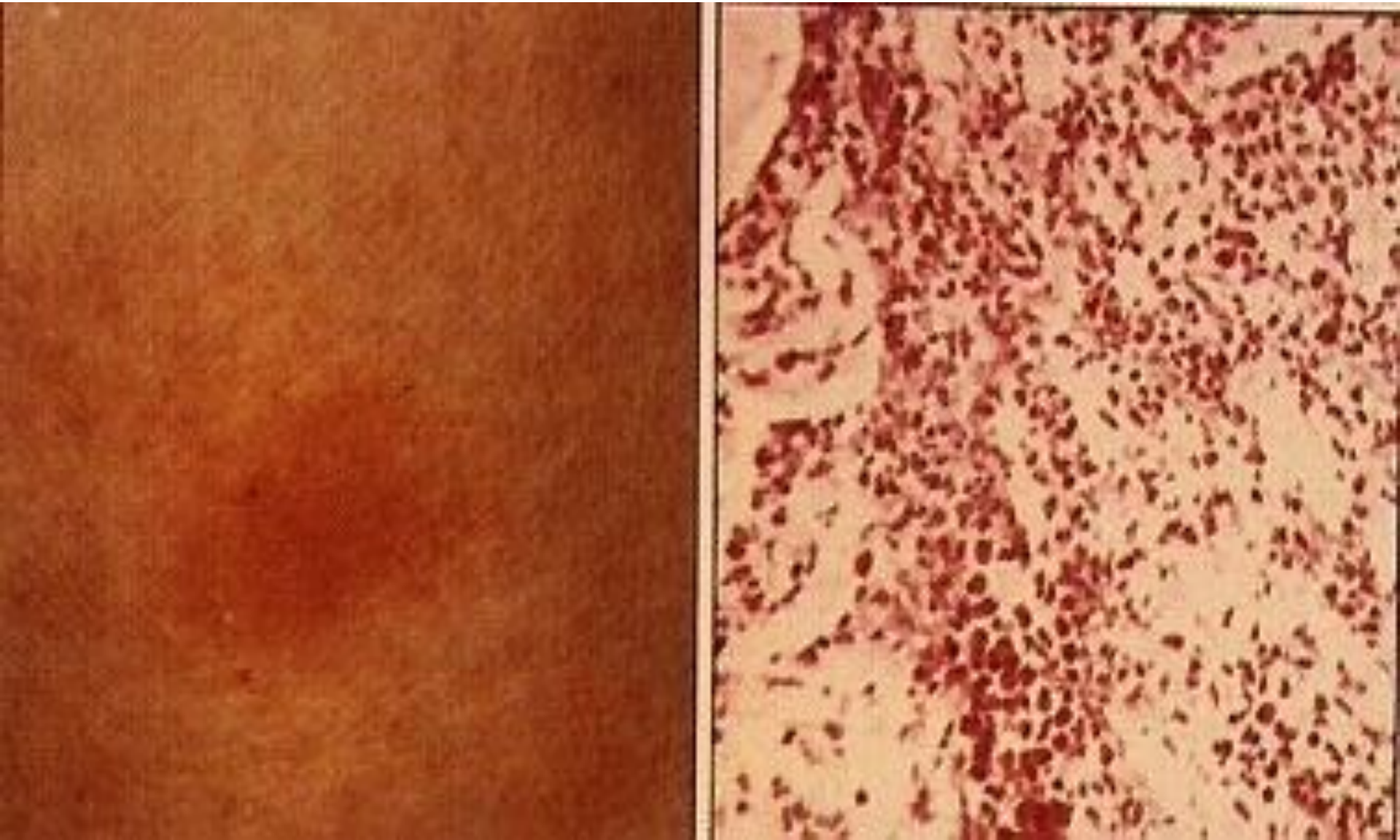
Administering the Tuberculin Skin Test



- Inject intradermally 0.1 ml of 5 TU PPD tuberculin
- Produce wheal 6 mm to 10 mm in diameter
- Do not recap, bend, or break needles, or remove needles from syringes
- Follow universal precautions for infection control

CDC

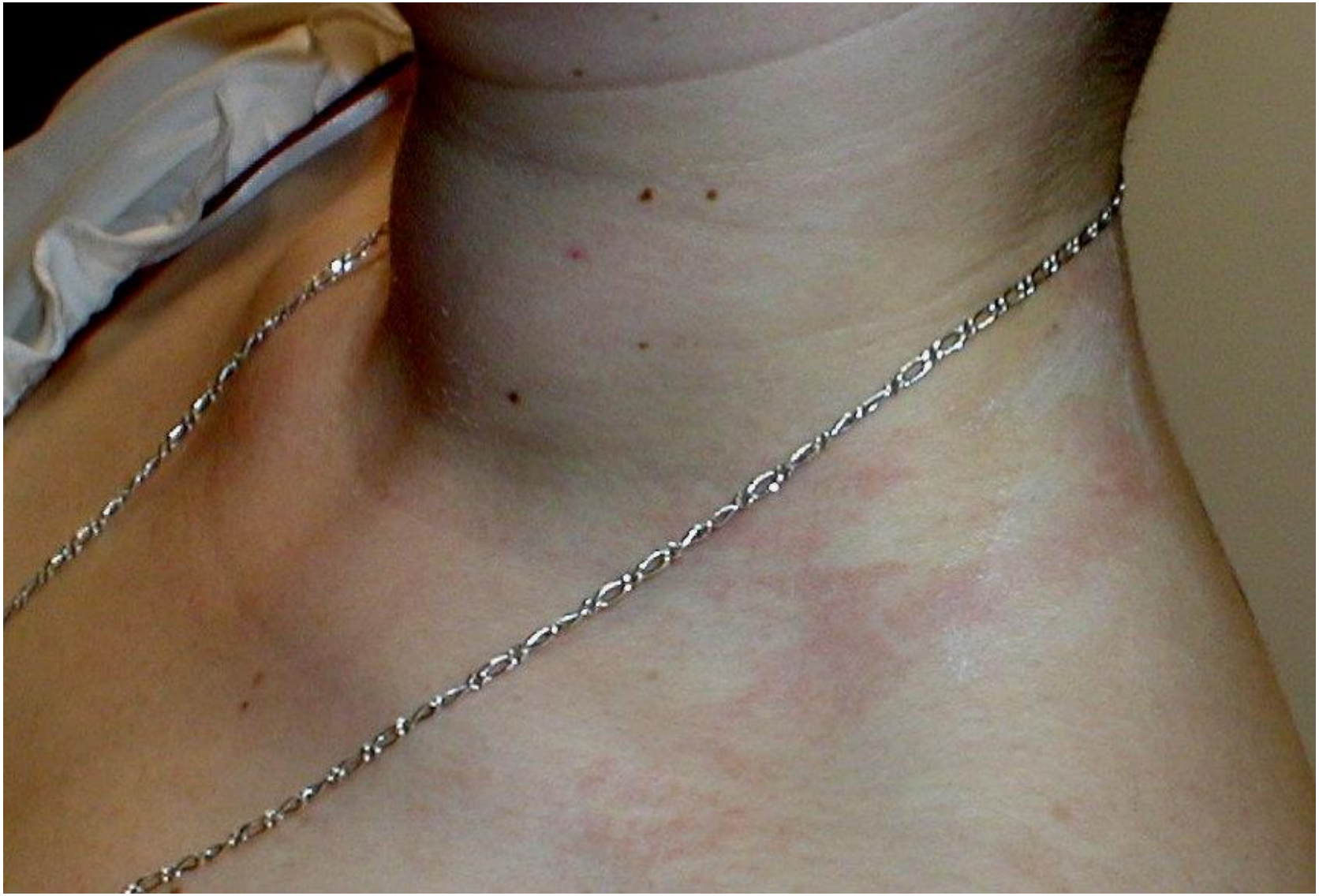
Tuberculin reaction



Examples of diseases where type-IV hypersensitivity plays a key role

- Contact exzema
- Cavitation in tuberculosis
- Sarcoidosis
- Several types of vasculitis
- Autoimmune diseases where T-lymphocytes play a major role (multiple sclerosis)

Contact dermatitis due to nickel hypersensitivity



Allergy Capital: *Contact dermatitis*. Australian Allergy, Asthma and Immunology Information.
http://www.allergycapital.com.au/allergycapital/Contact_dermatitis.html

Contact dermatitis