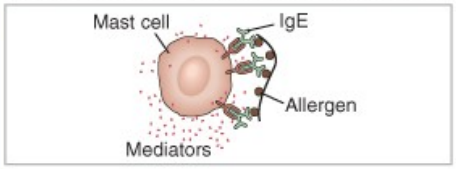
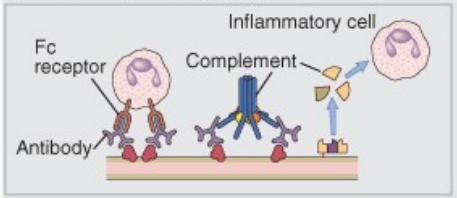
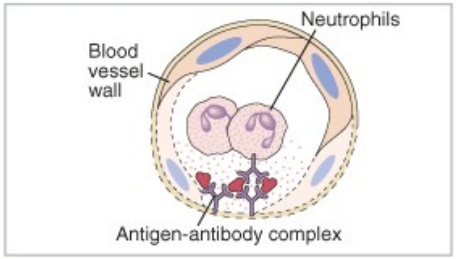
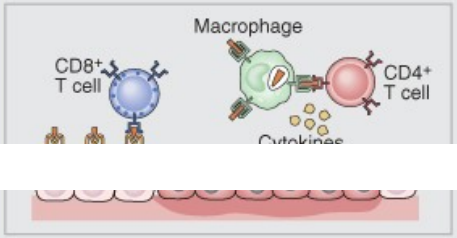
Hypersensitivity diseases

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 patent is atopic: 15%.

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

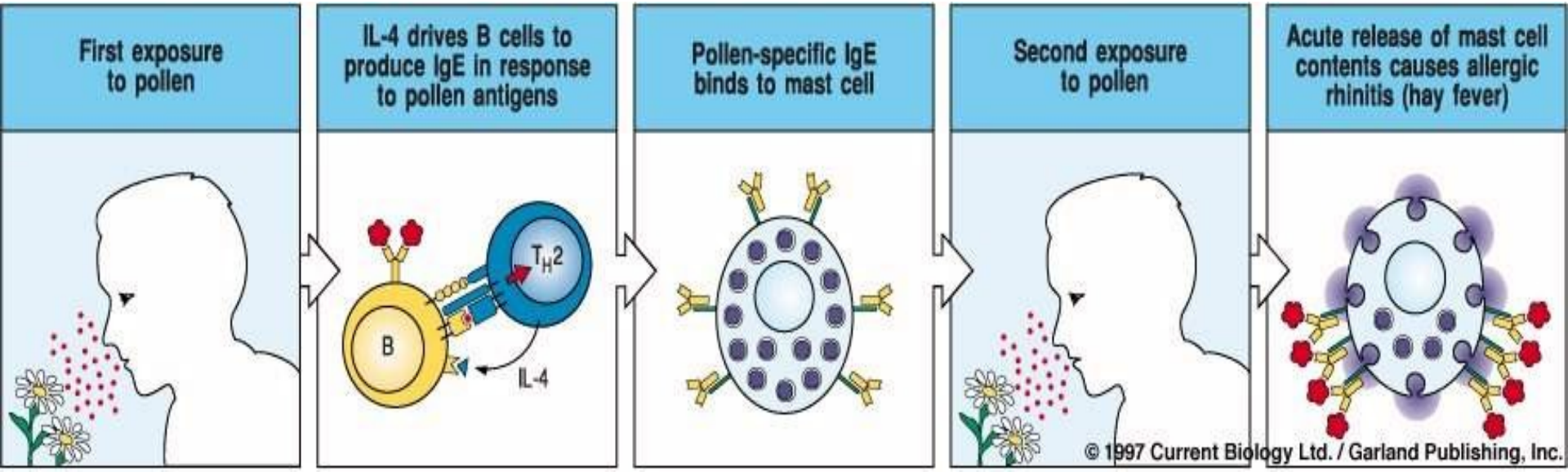
Candidate genes of atopic diseases

- 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

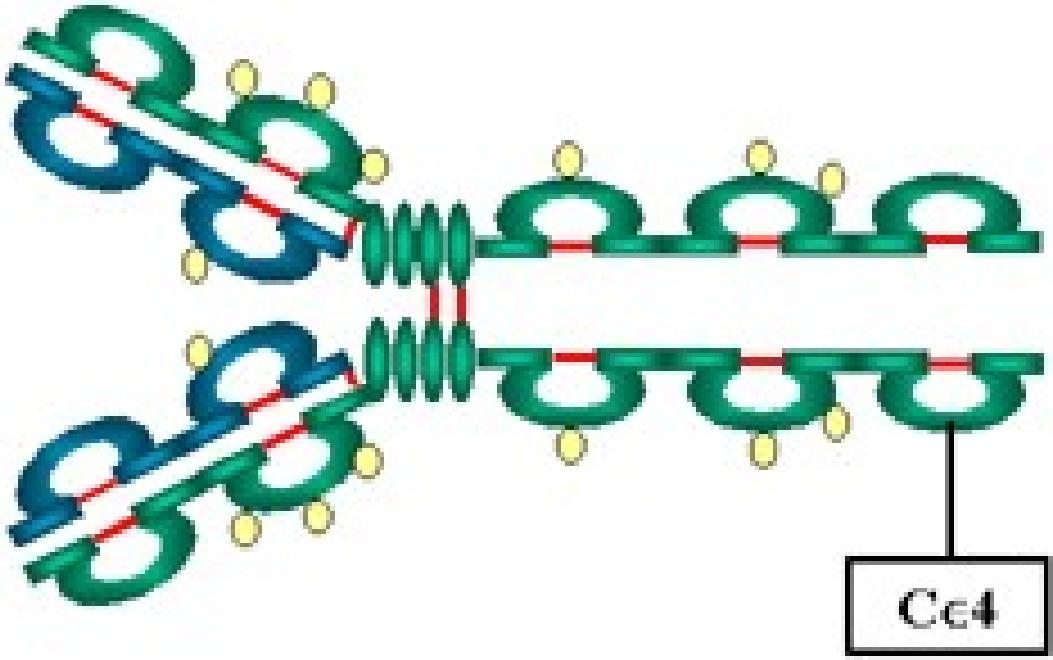
- Pollens (grass, trees)
- House dust mites (*Dermatophagoides pteronyssimus* and *farinae*)
- Foods: nuts, chocolate, shellfish, milk, egg, fruits
- Pets (cat, dog)
- Moulds

Type-I hypersensitity



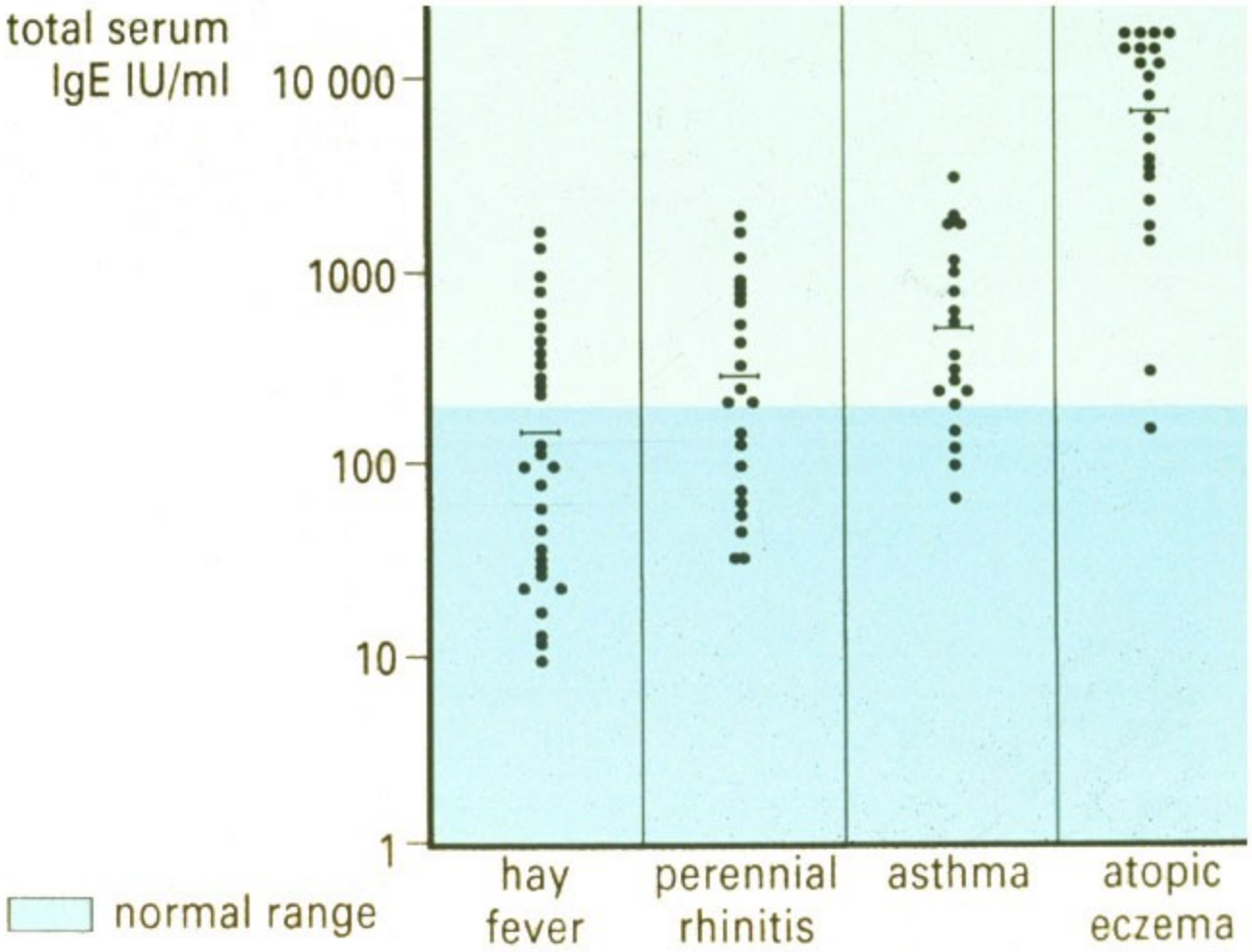
IgE

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



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

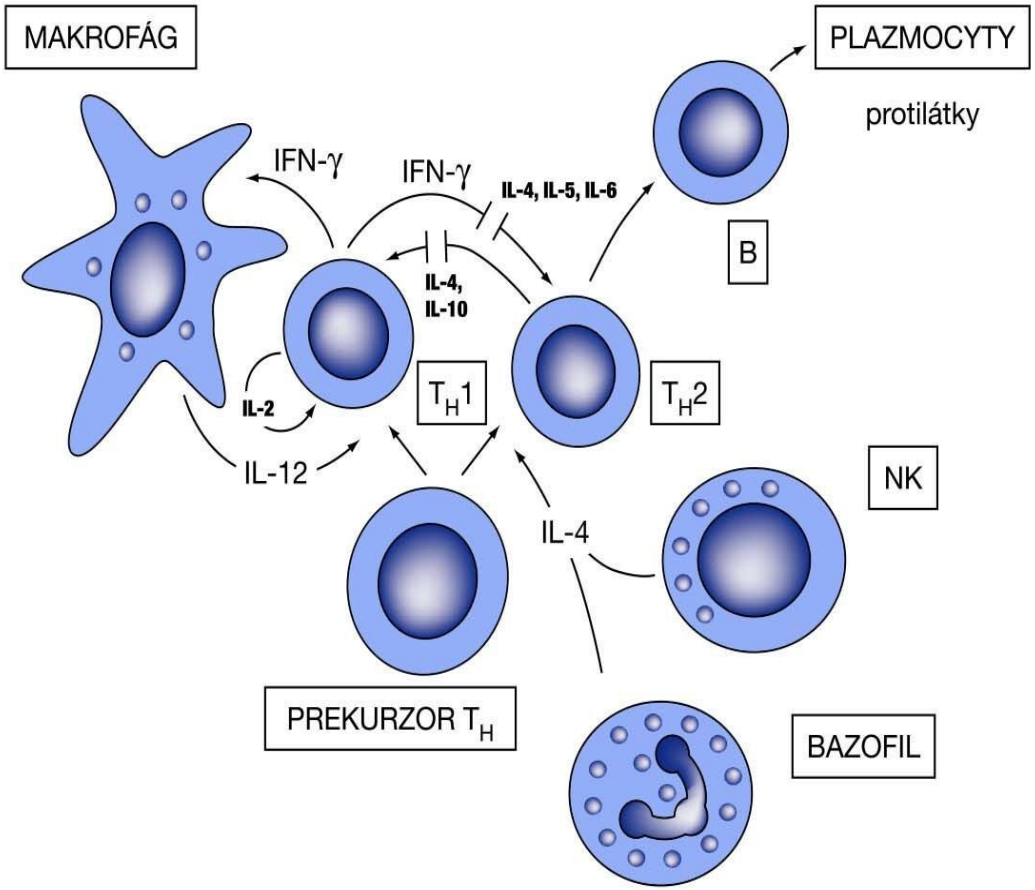
IgE levels and atopic disease



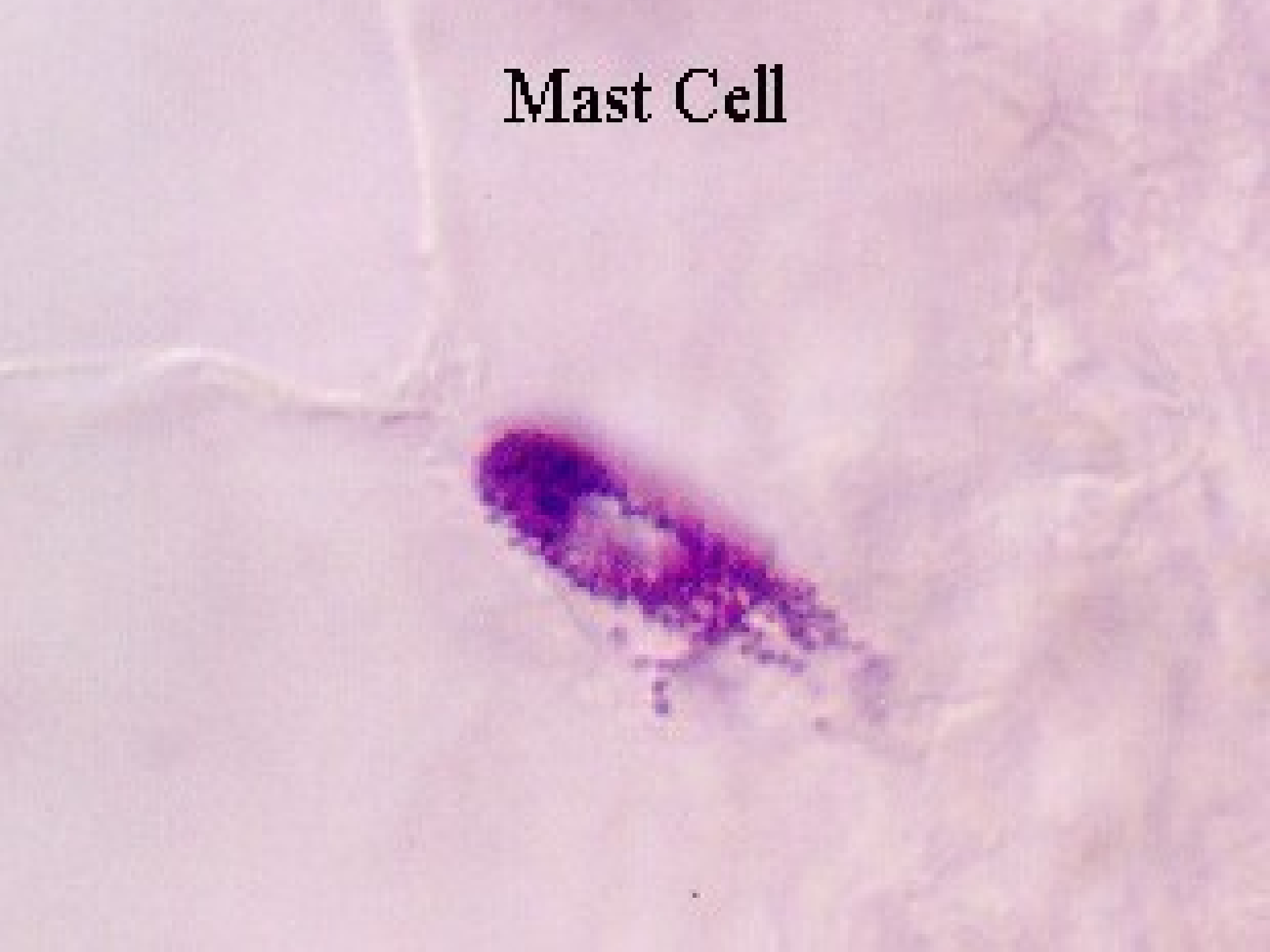
Regulation of IgE production

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

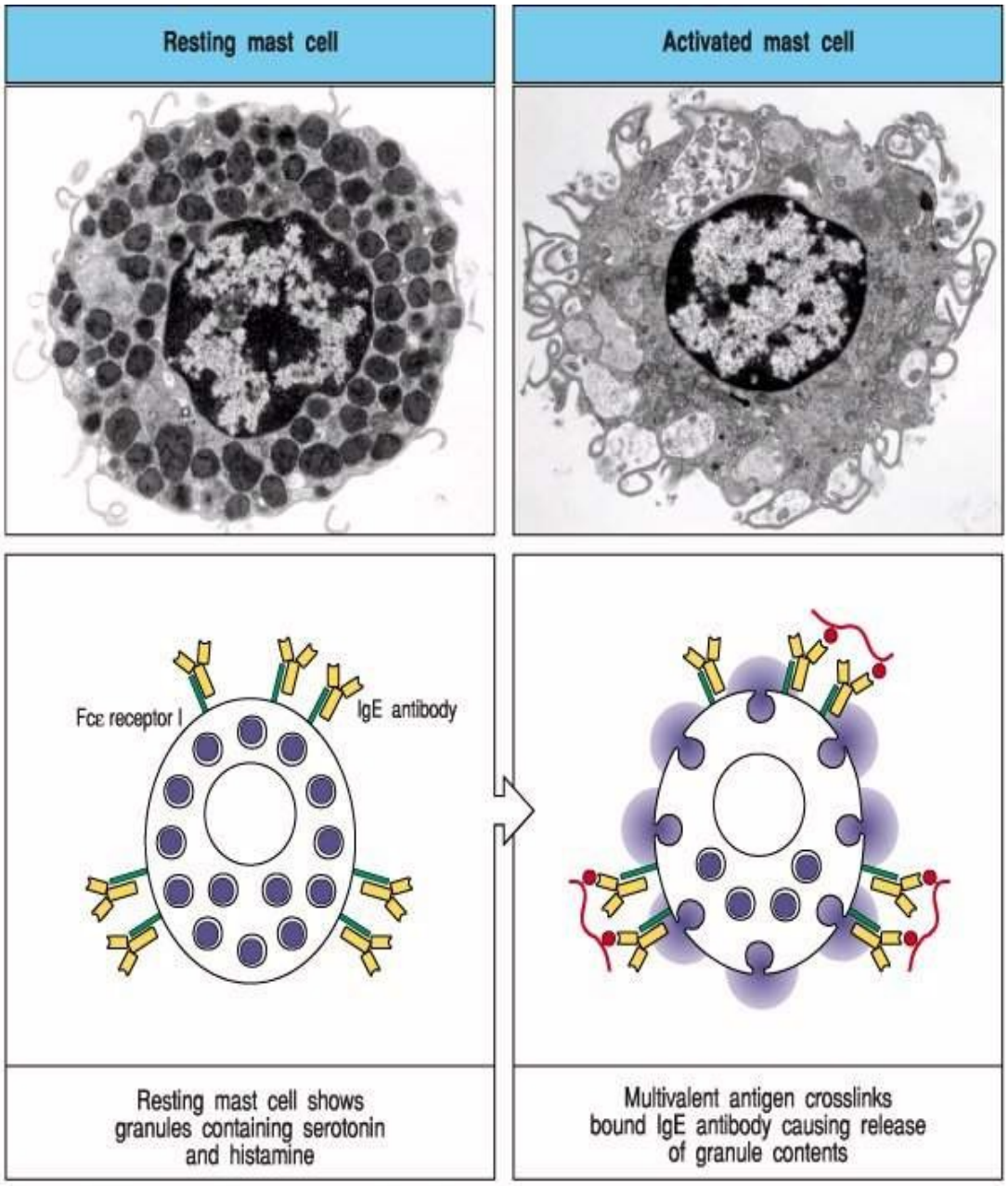
Regulation of production of Th1/Th2 cells



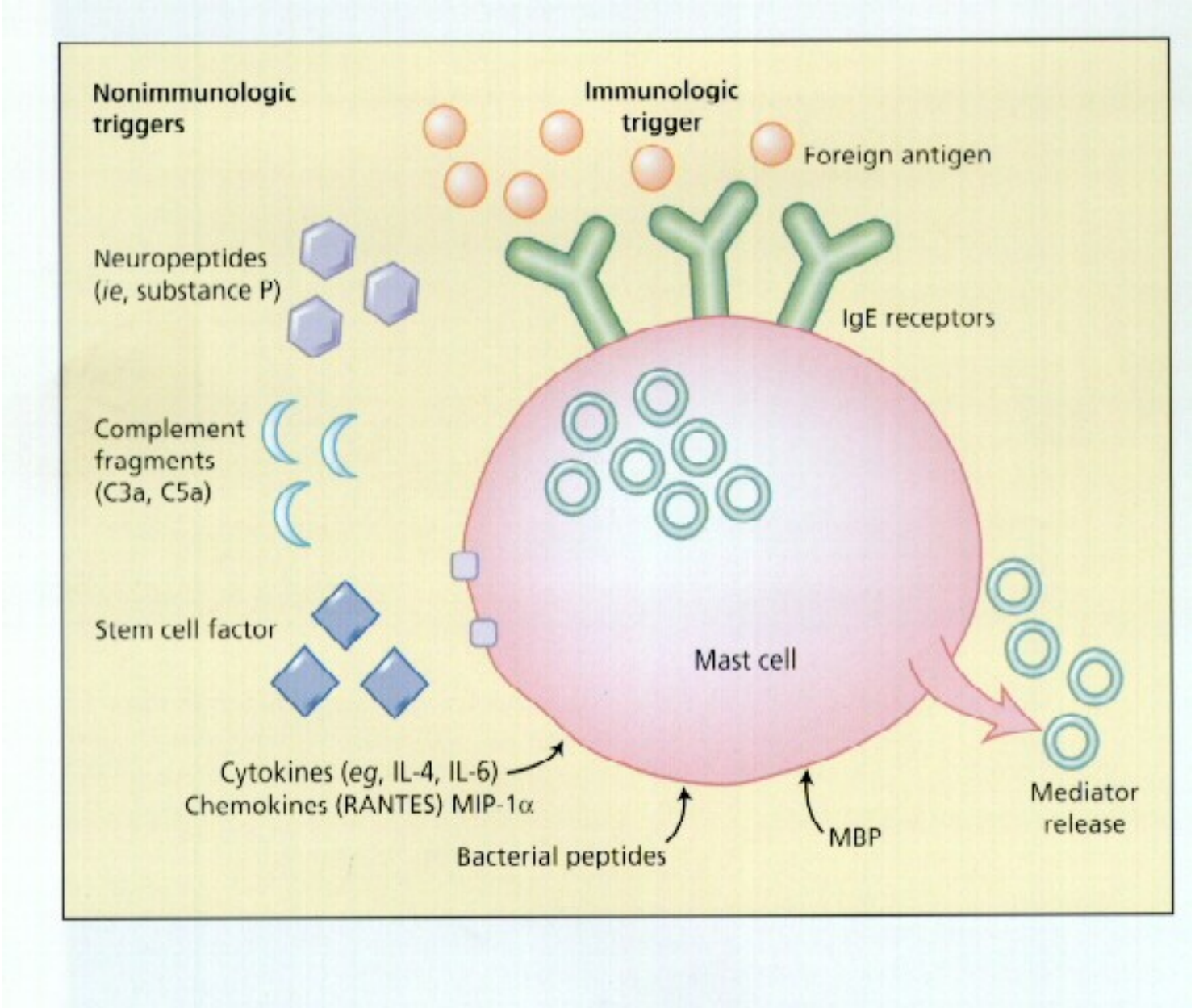
Mast Cell



Mast cells



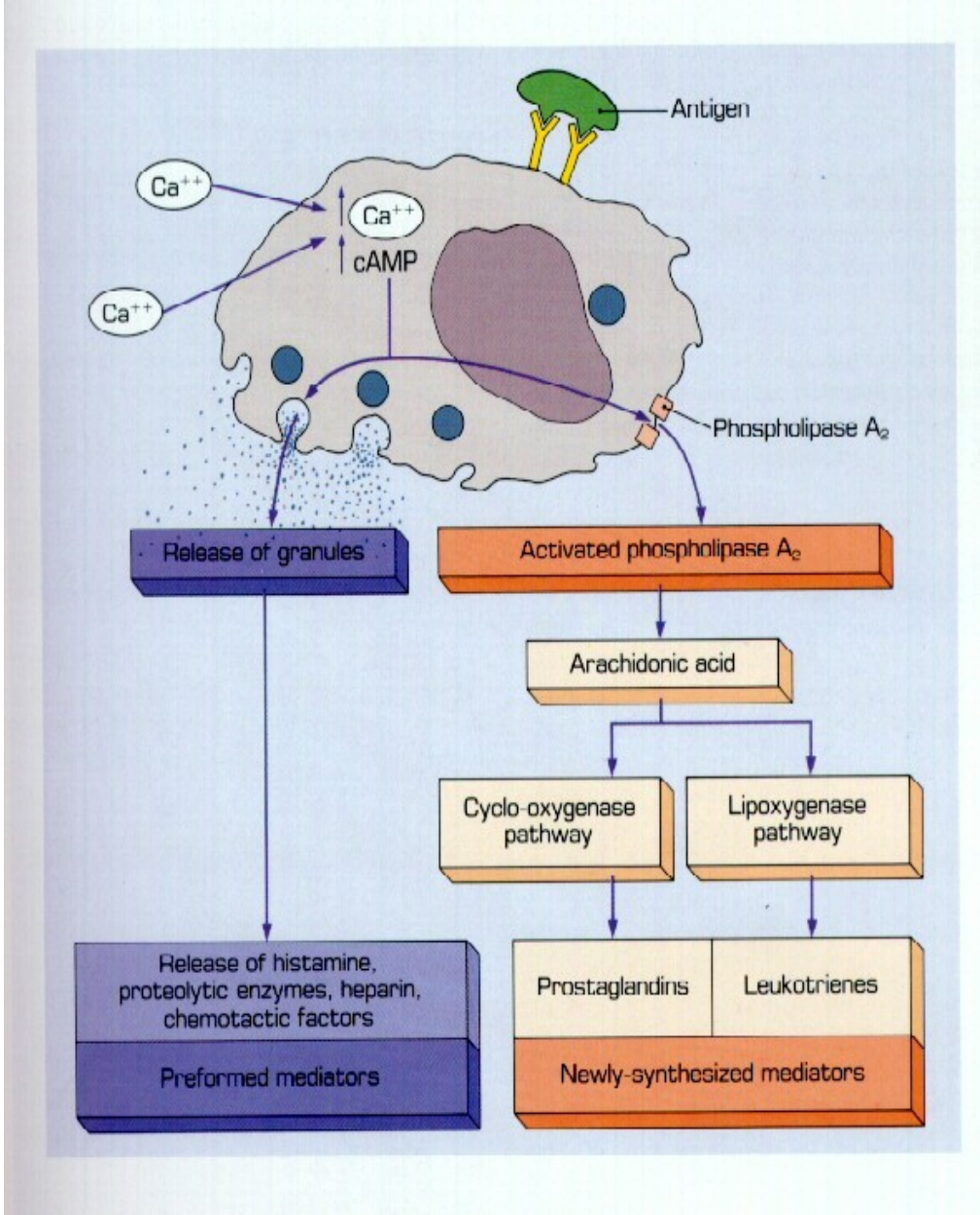
Activation of mast cells



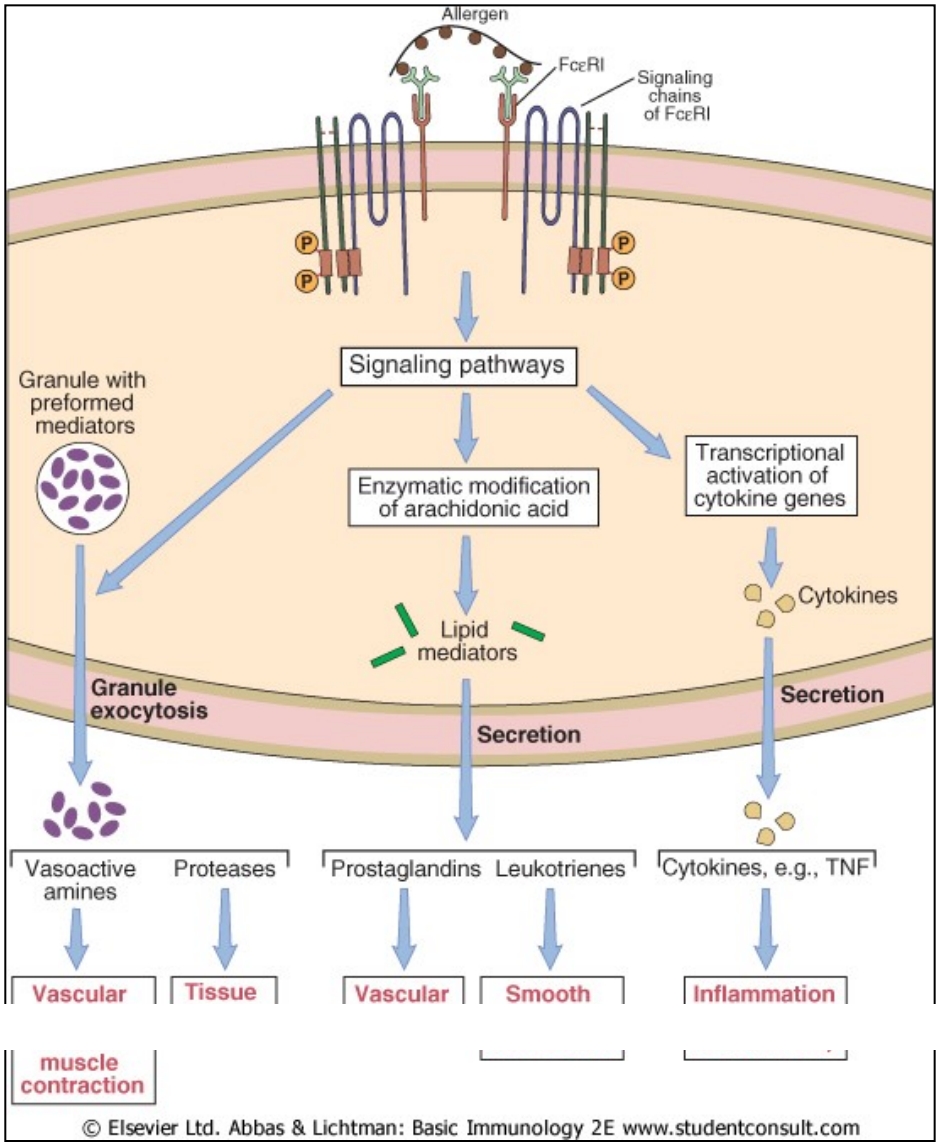
Biological effects of histamin

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

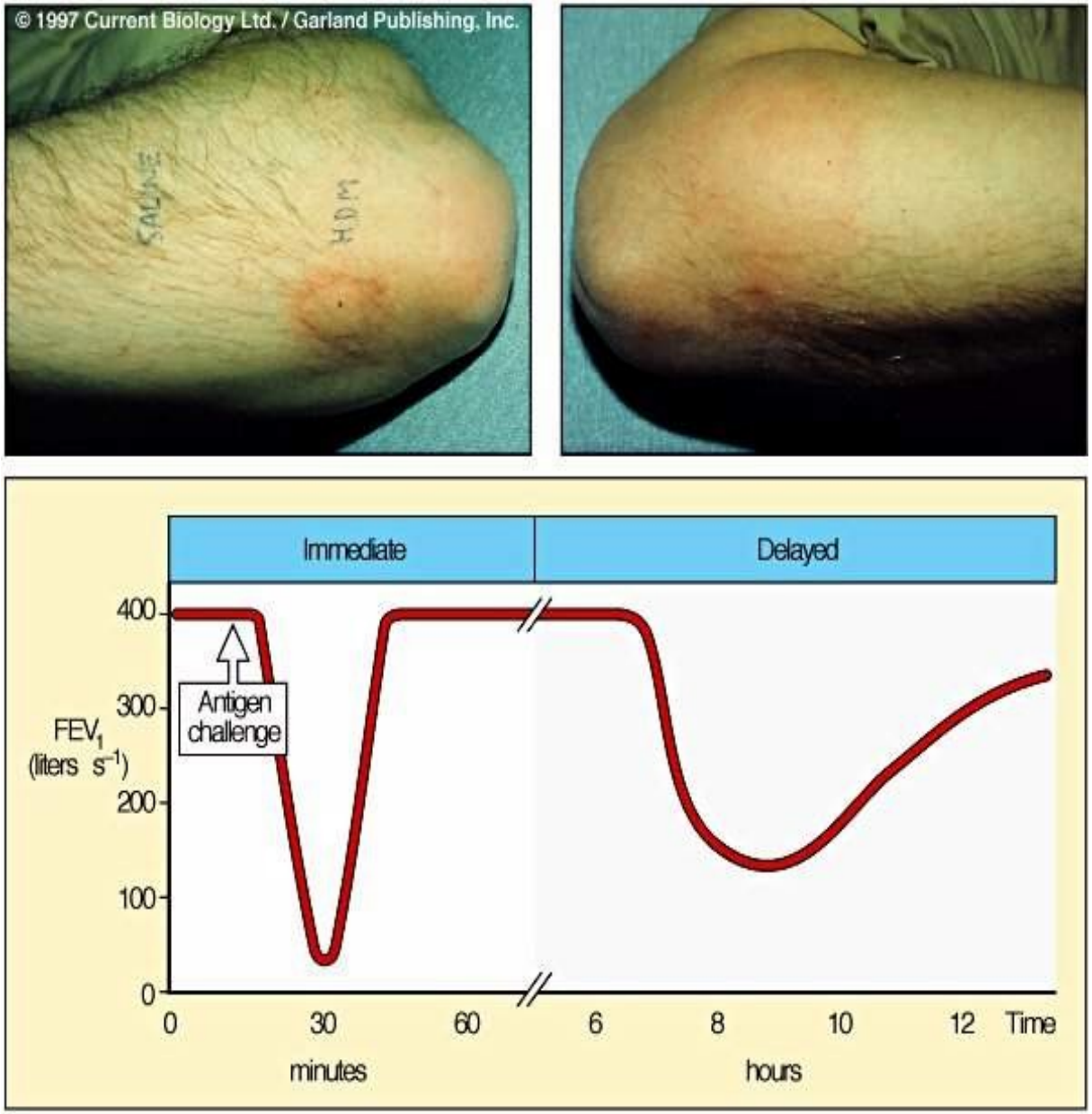
Consequences of activation of mast cells



Consequences of activation of mast cells



Immediate and late phase of allergic reaction

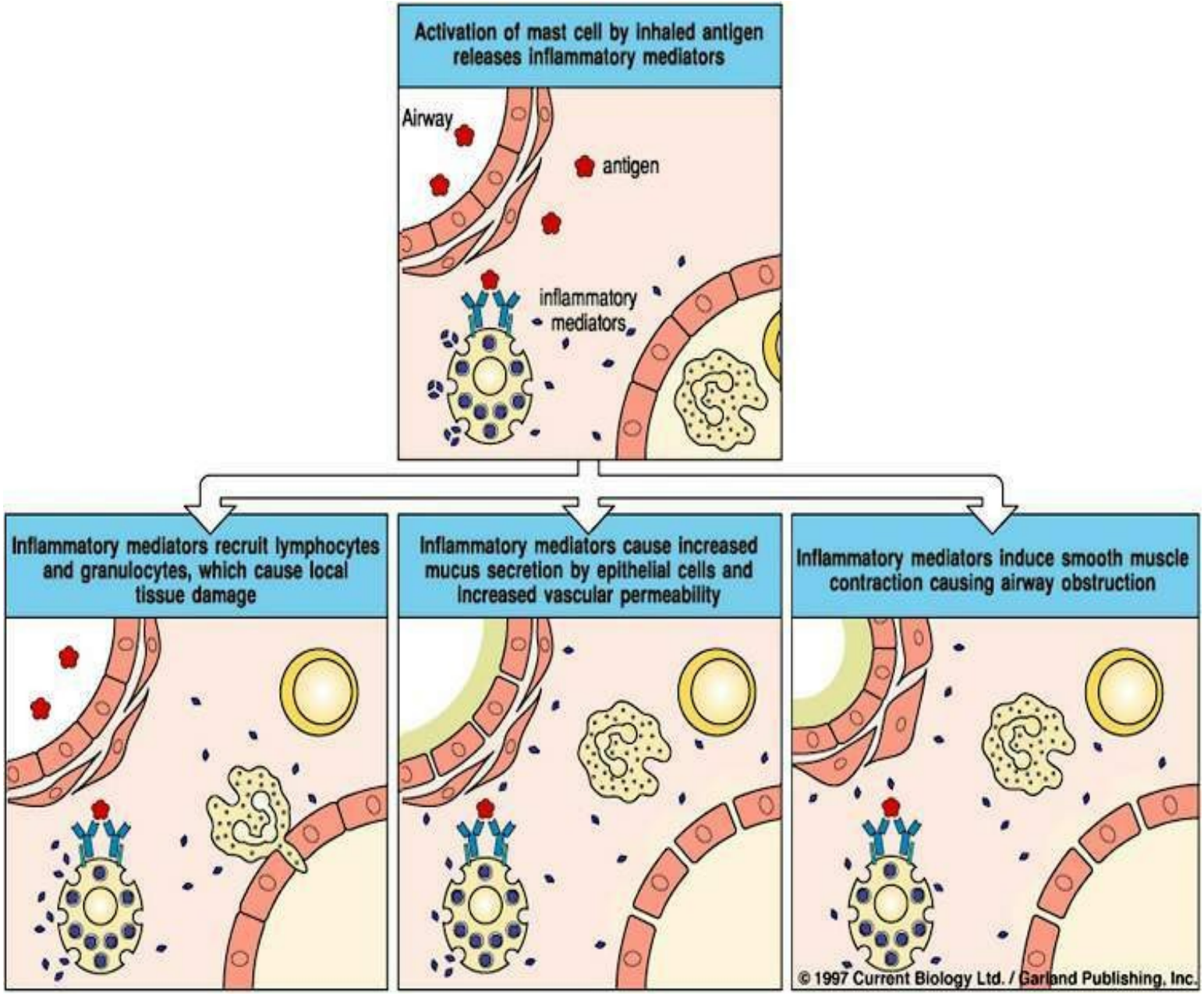


Phases of type-I hypersensitivity reaction

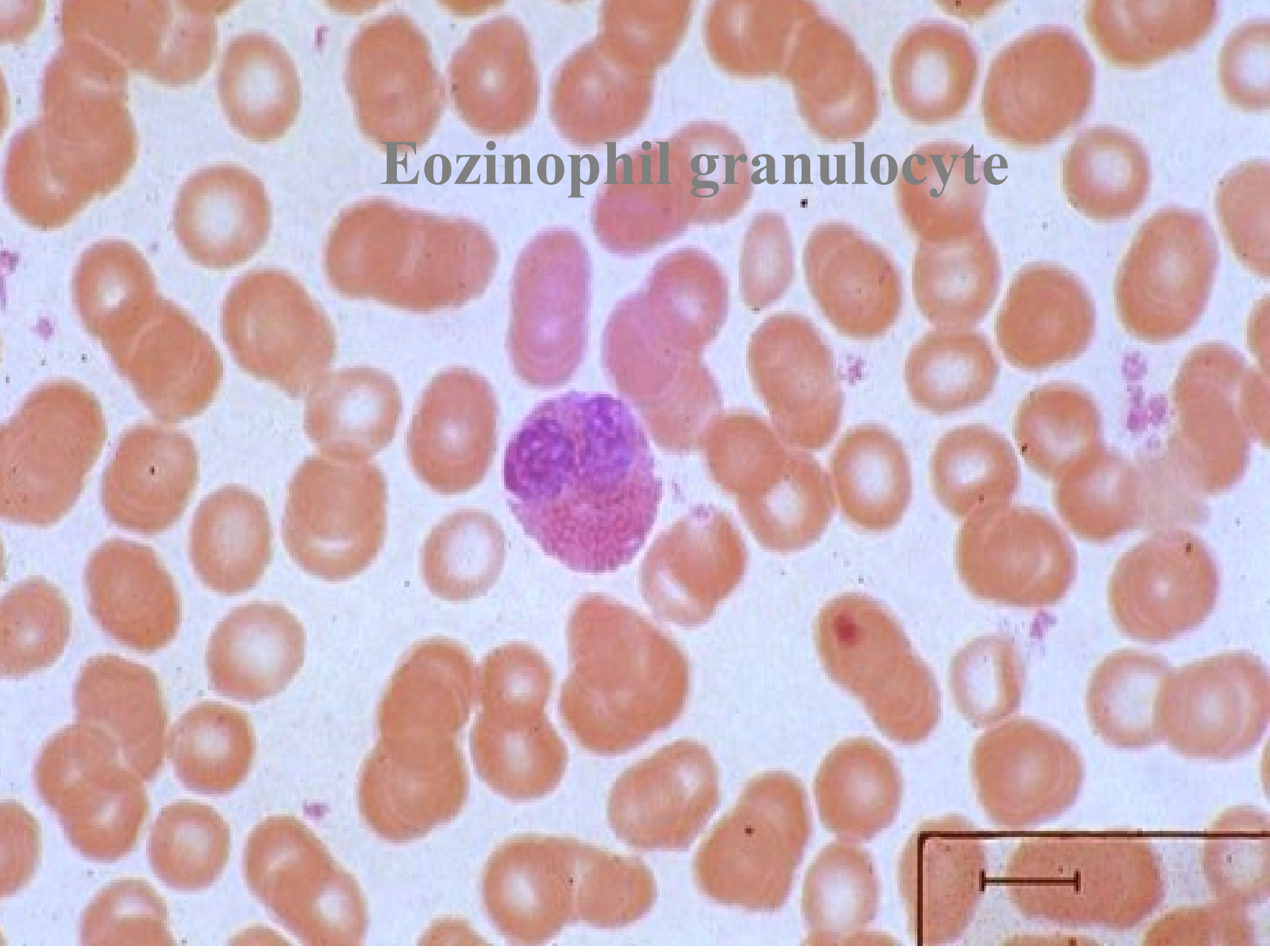
- Immediate phase – clinical symptons evolve in several minutes. Mediated mainly by histamin.

- 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



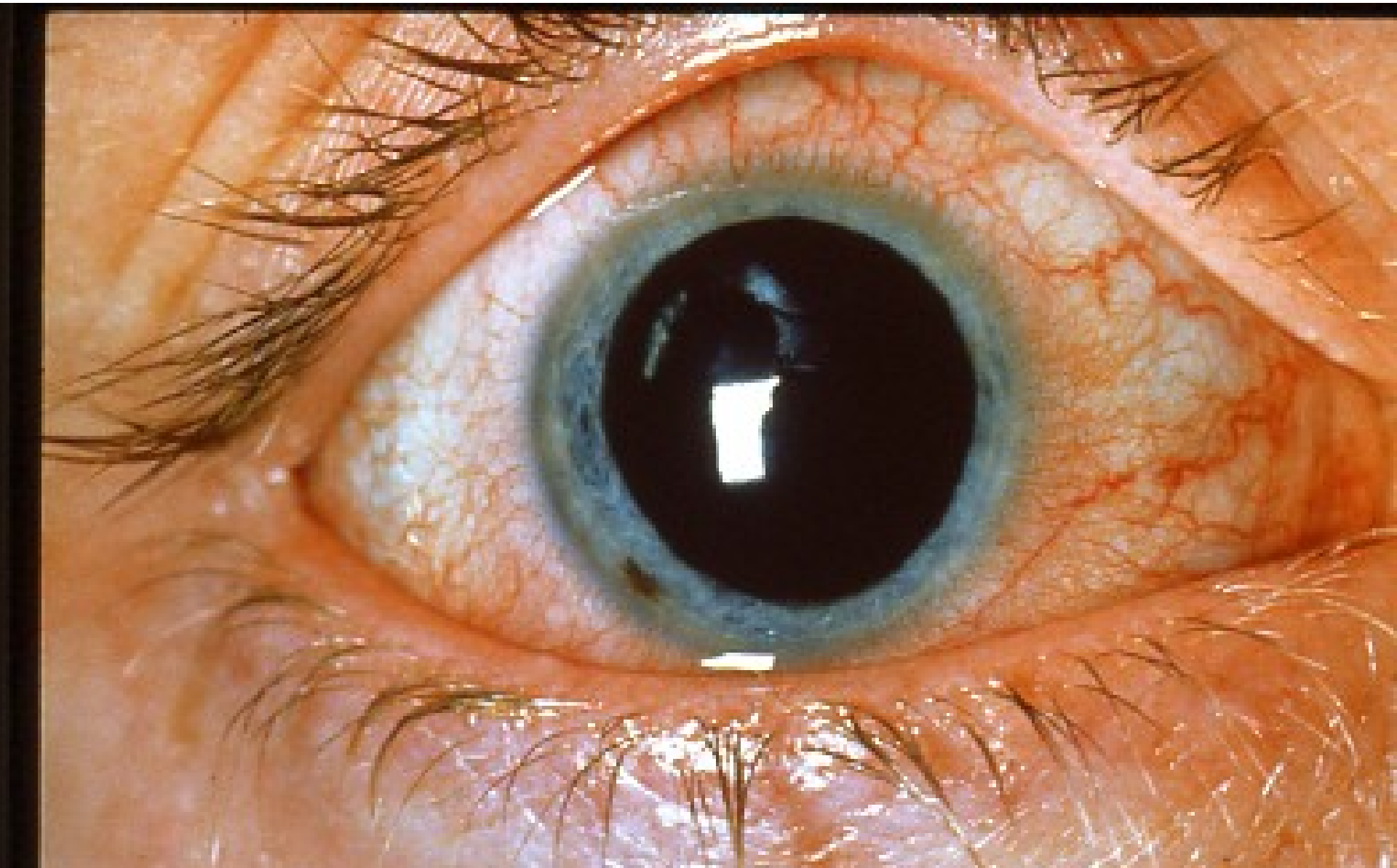
Eozinophil granulocyte



Clinical diseases caused by atopic hypersenitivity

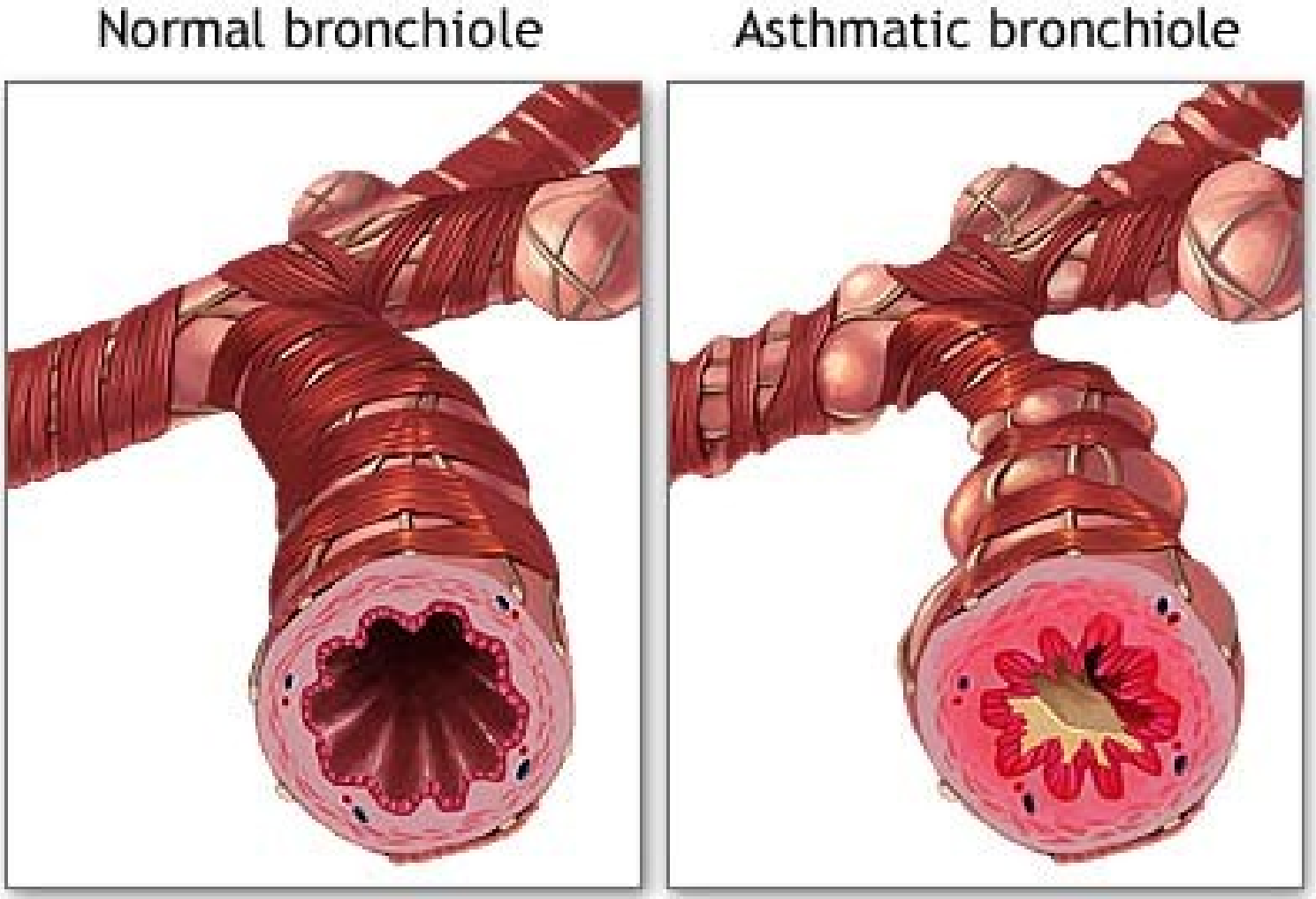
- Allergic conjunctivitis
- Allergic rhinitis
- Bronchial asthma
- Allgergy of gastrointestinal tract
- Urticaria and angioedema
- Atopic eczema
- Anaphylactic shock

Allergic conjunctivitis

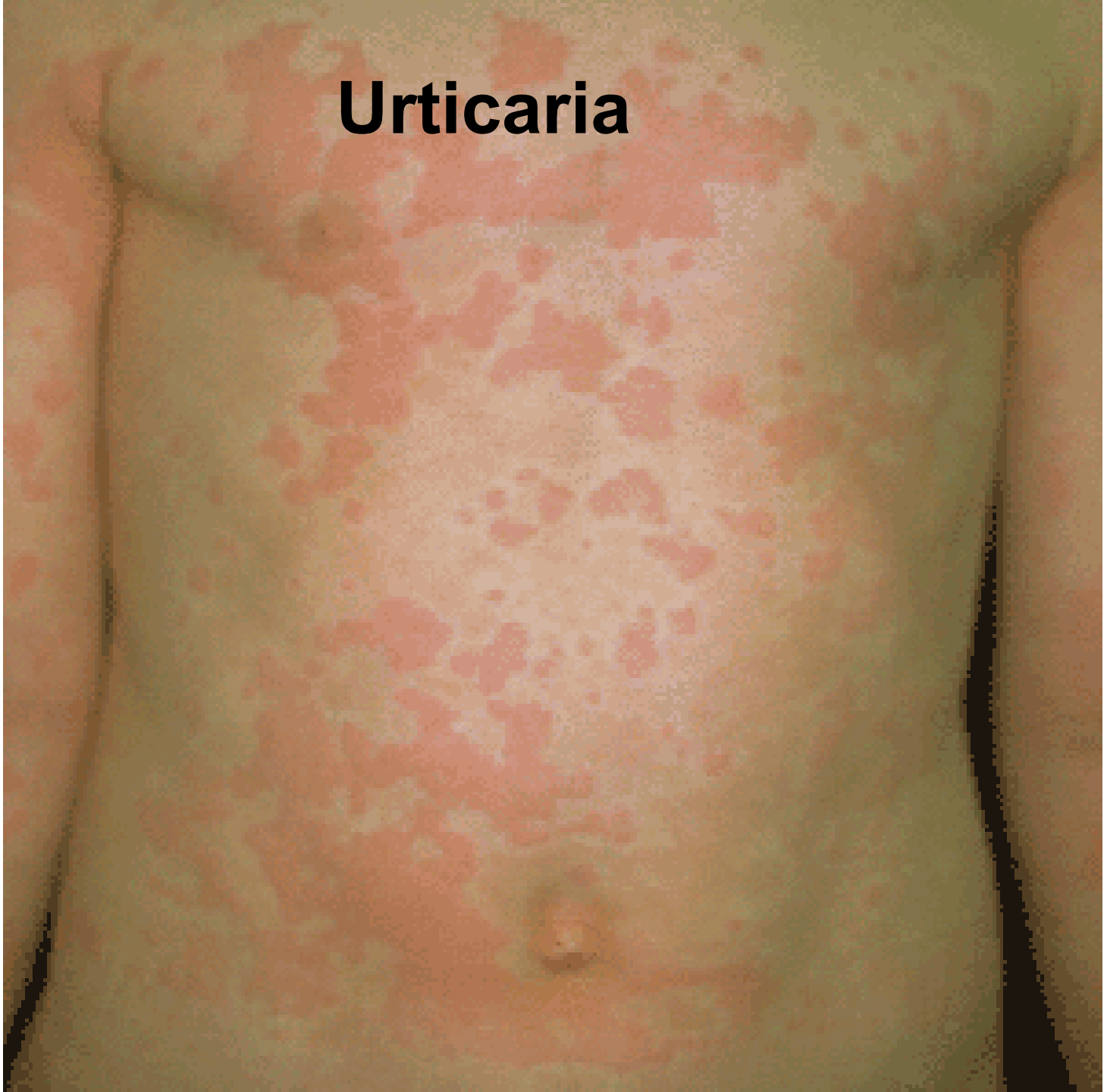


Allergic rhinitis

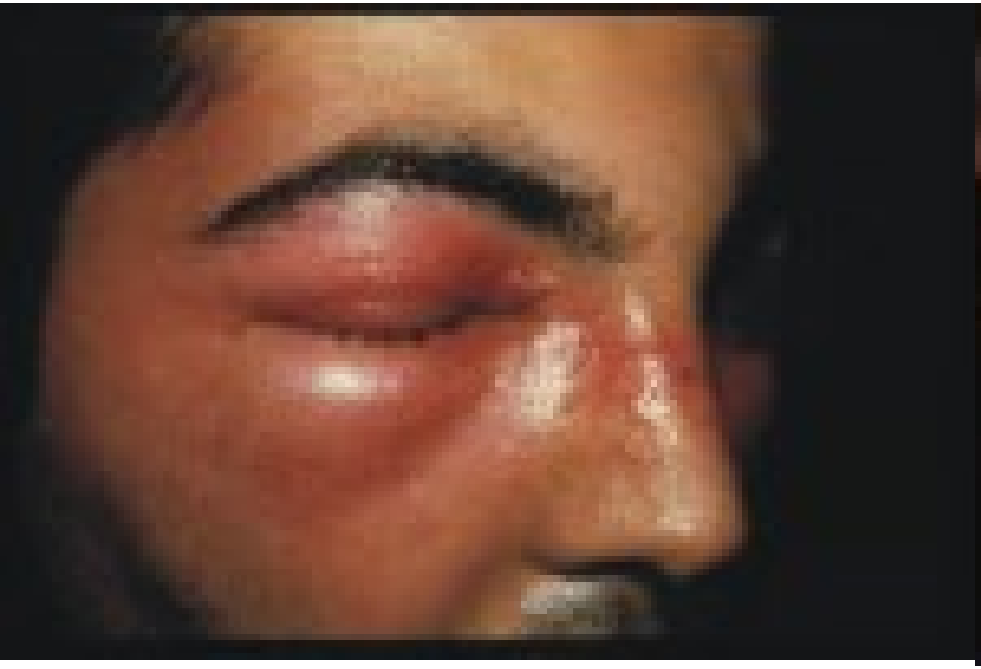
Bronchial asthma

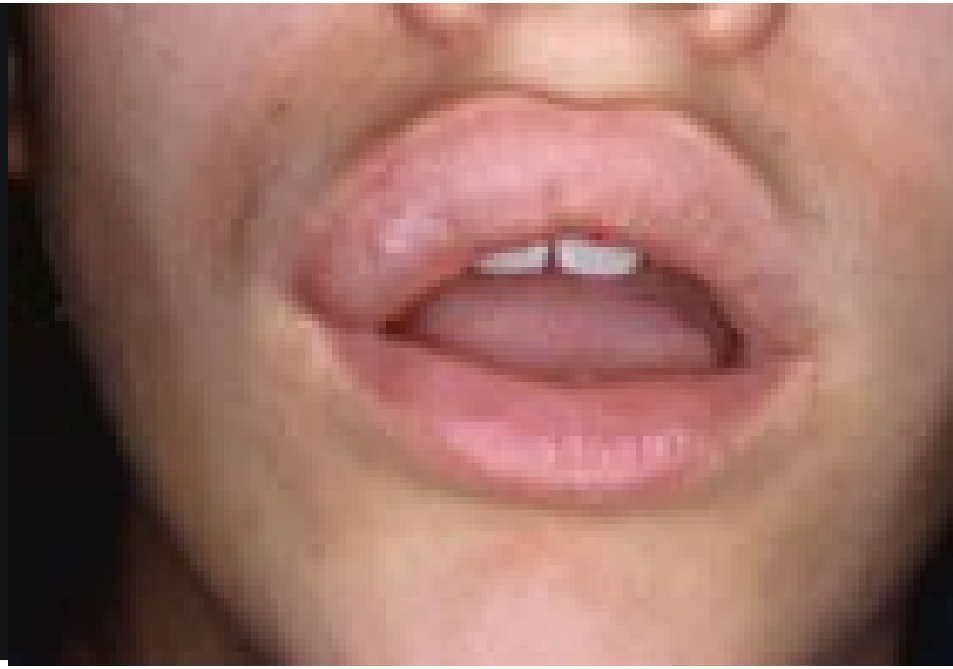


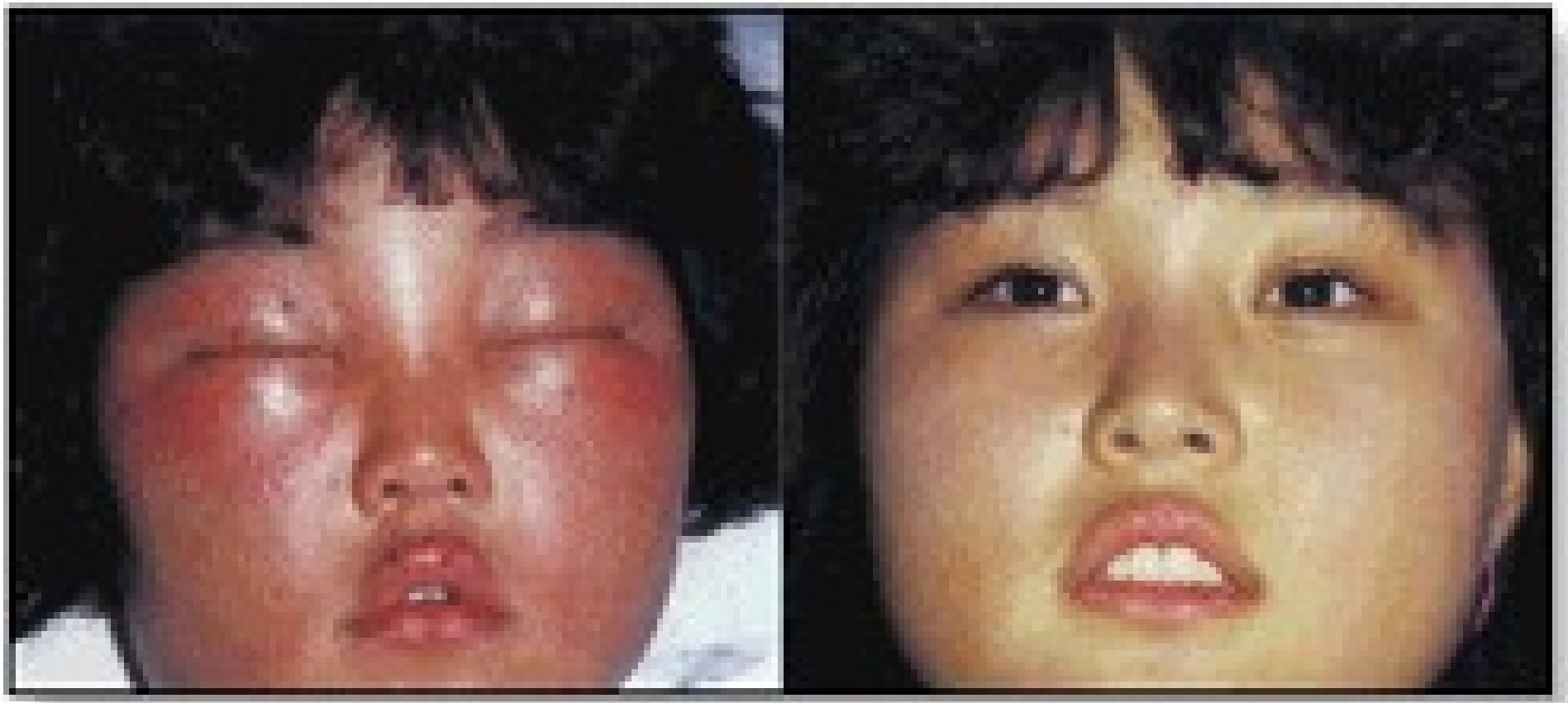
Urticaria



Angioedema



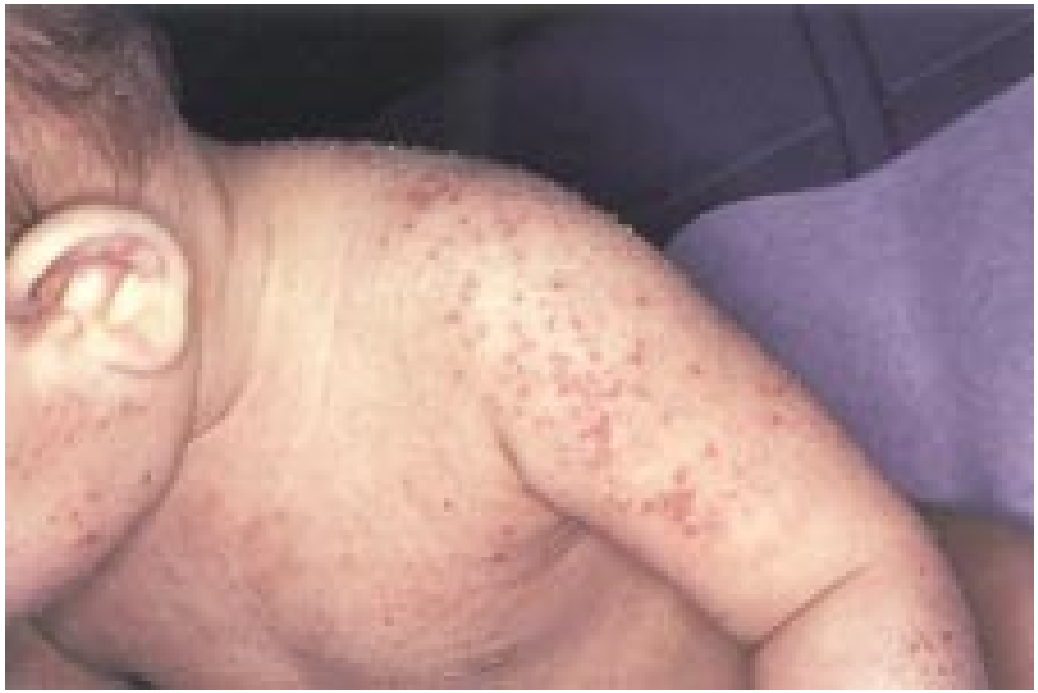


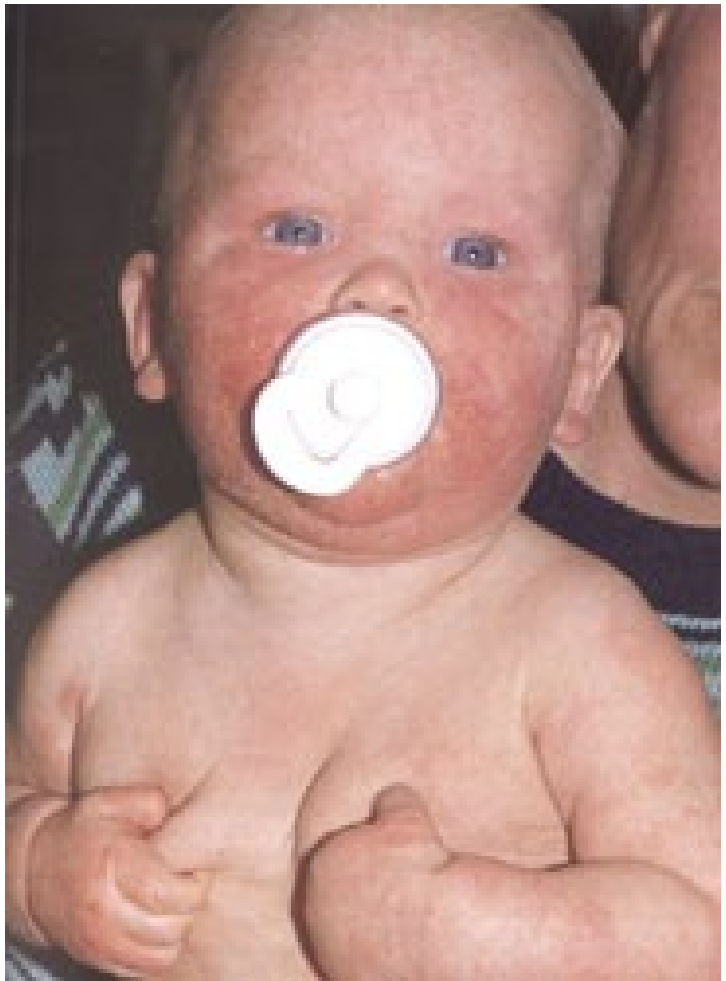


Facial angioedema following allergen exposure (A) and resolution after treatment (B).

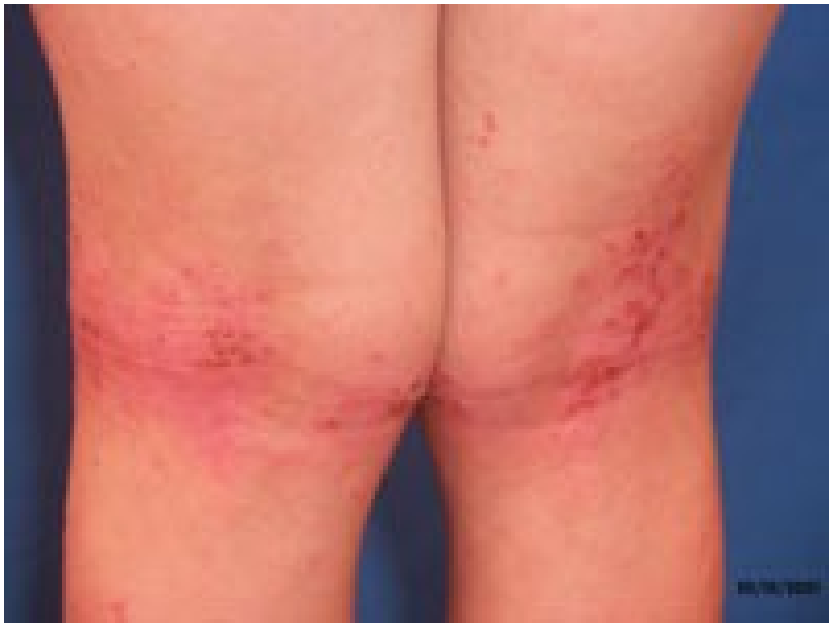
Reprinted from Tharp M, Levine M, Fireman P. Urticaria and angioedema. In: Fireman P, Slavin R (eds). Atlas of Allergies. 2nd ed. London: Mosby-Wolfe; 1996: 250. By permission of the publisher Mosby.

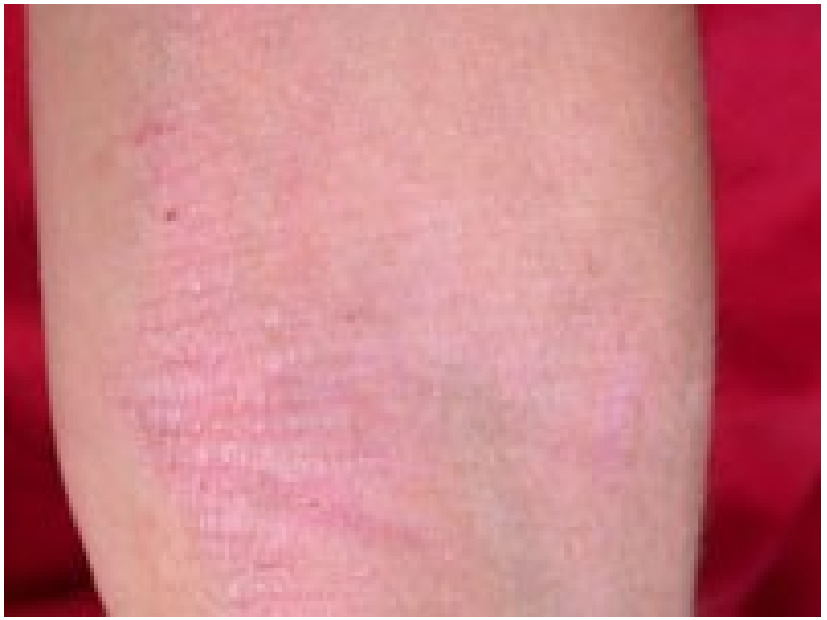
Atopic eczema



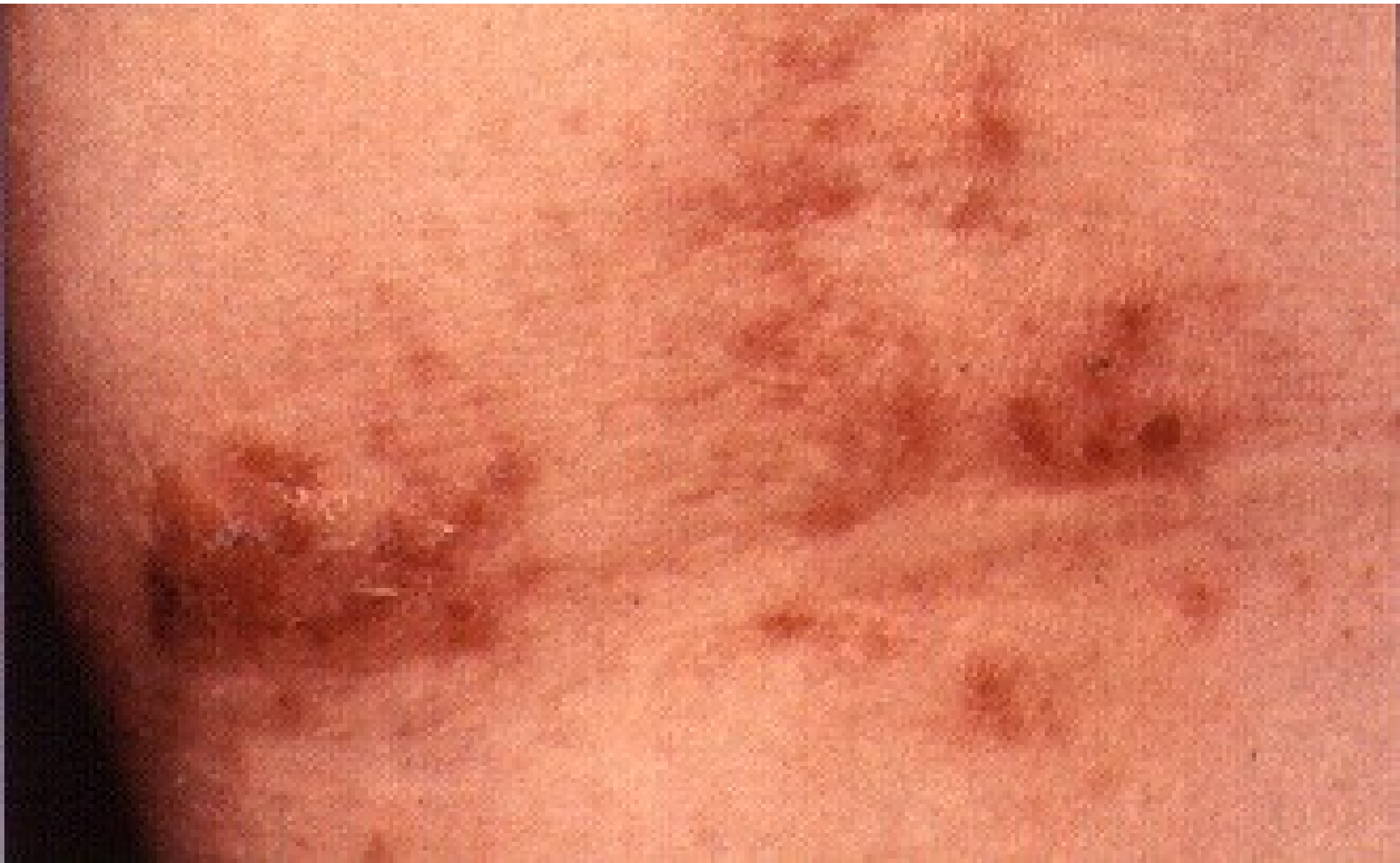


Atopic eczema





Atopic eczema



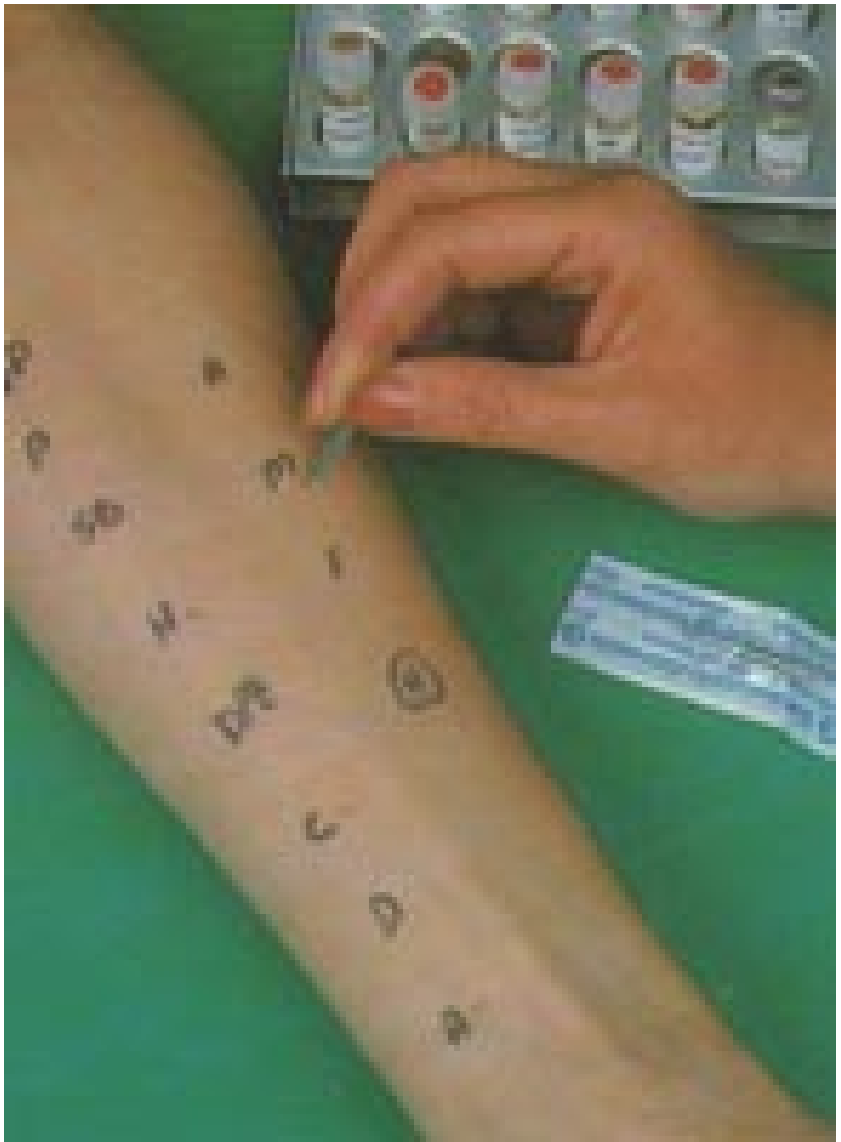
Treatment of allergic diseases

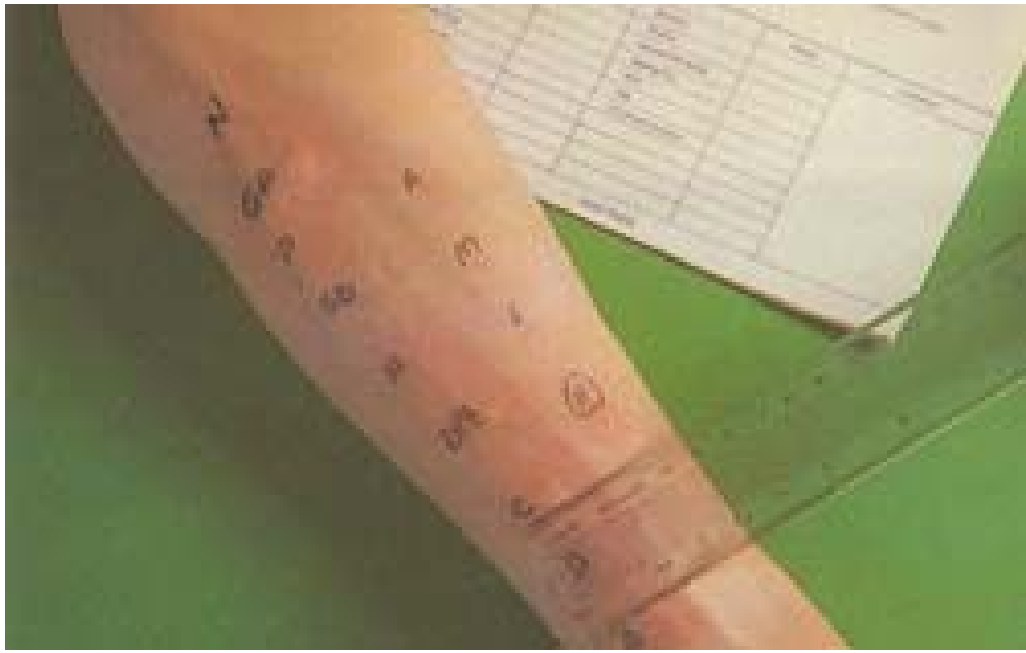
- Allergen avoidance
- Antihistaminics
- Cromons (cromolyn sodium, nedocromil) - stabilise membrane of the mast cells
- Topical or systemic corticosteroids
- Antilekotriens
- In asthma: β-2 agonists, xantins
- Allergen immunotherapy (desensitisation)

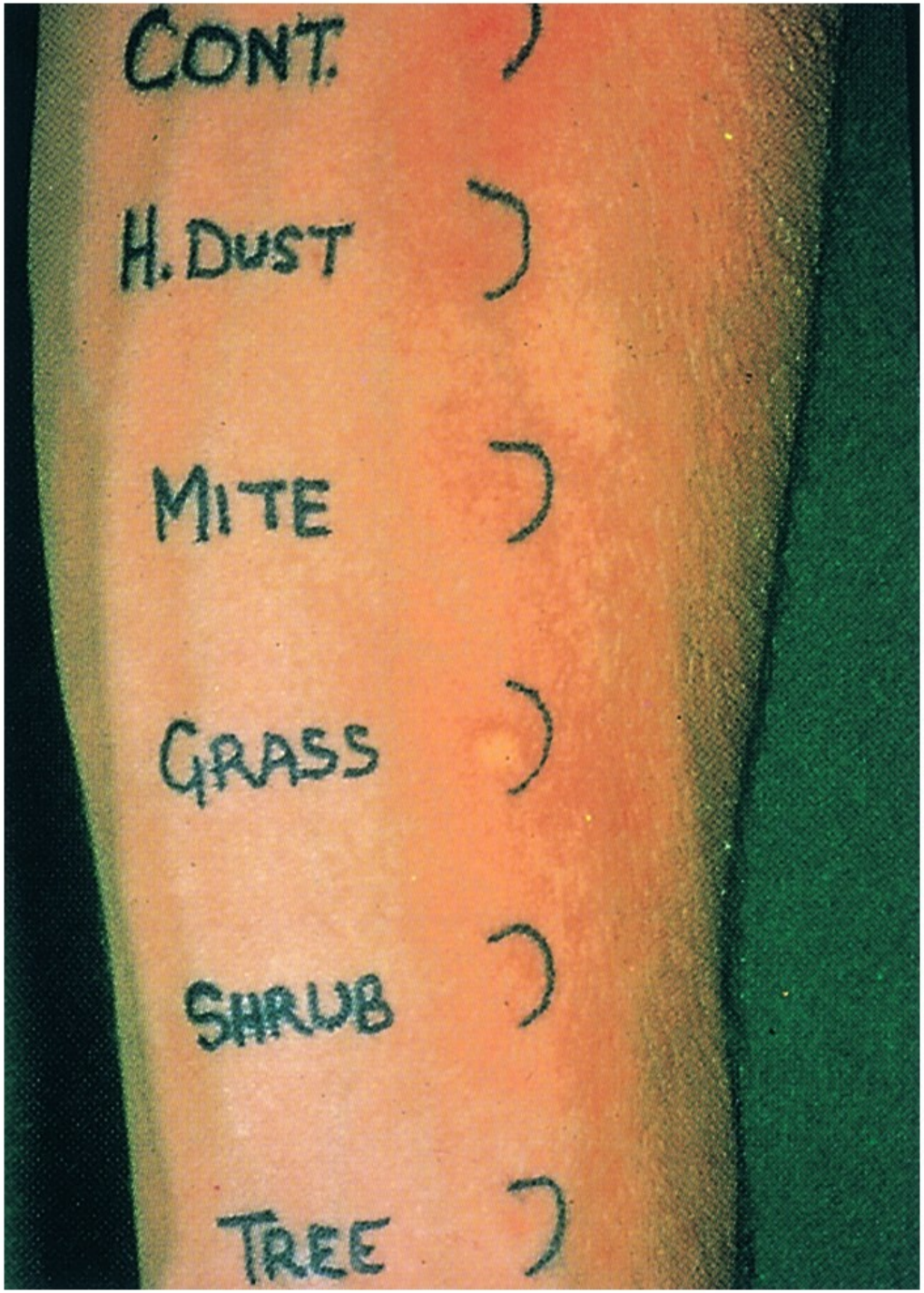
Diagnostic approaches in type-I hypersensitivity

- Past history
- Eosinophilia
- Skin tests
- Provocation and elimination tests

Skin prick tests






CONT.
H. DUST
MITE
GRASS
SHRUB
TREE

Causes of anaphylactic shock

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

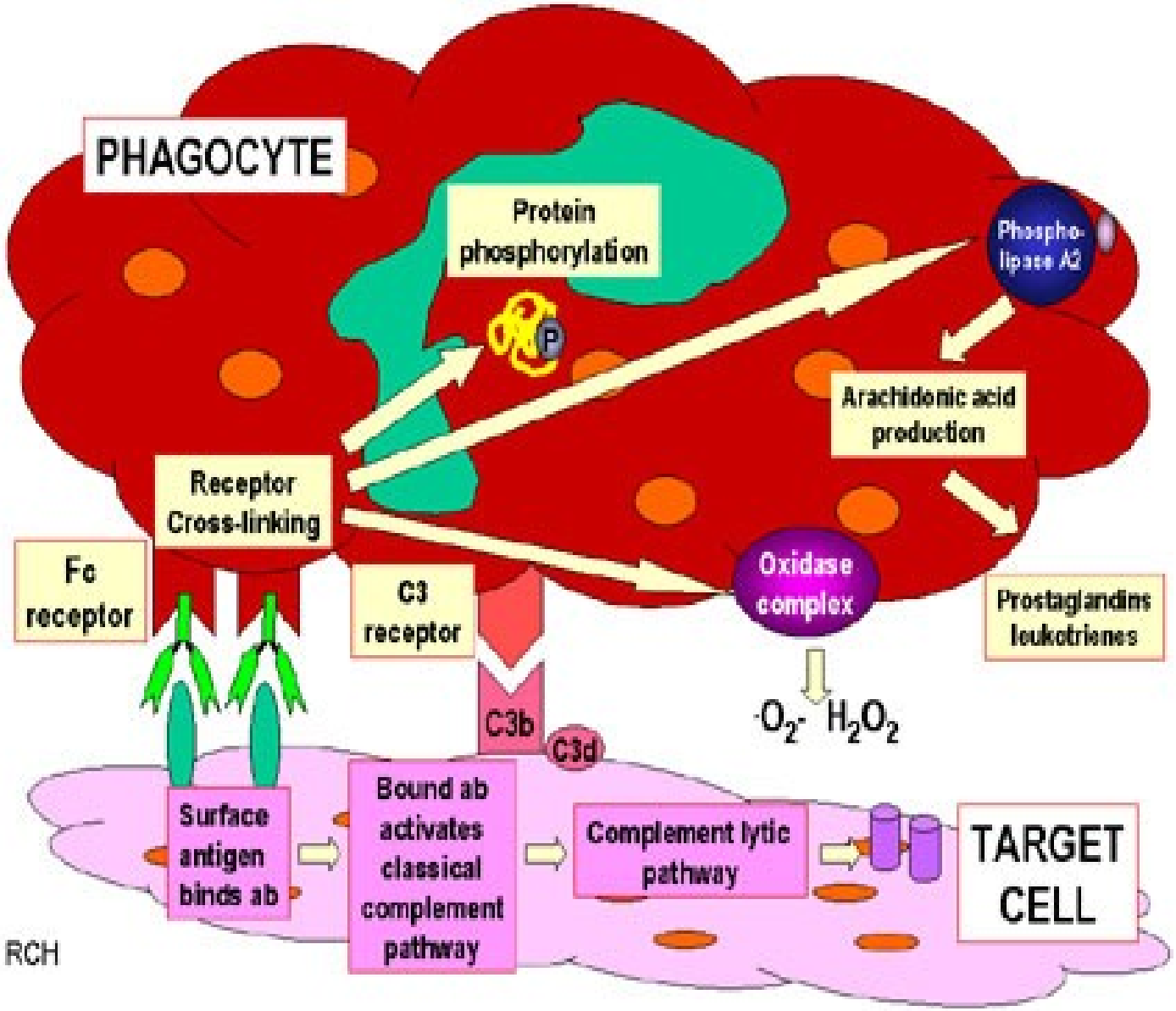
Clinical symptoms of anphylactic shock

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

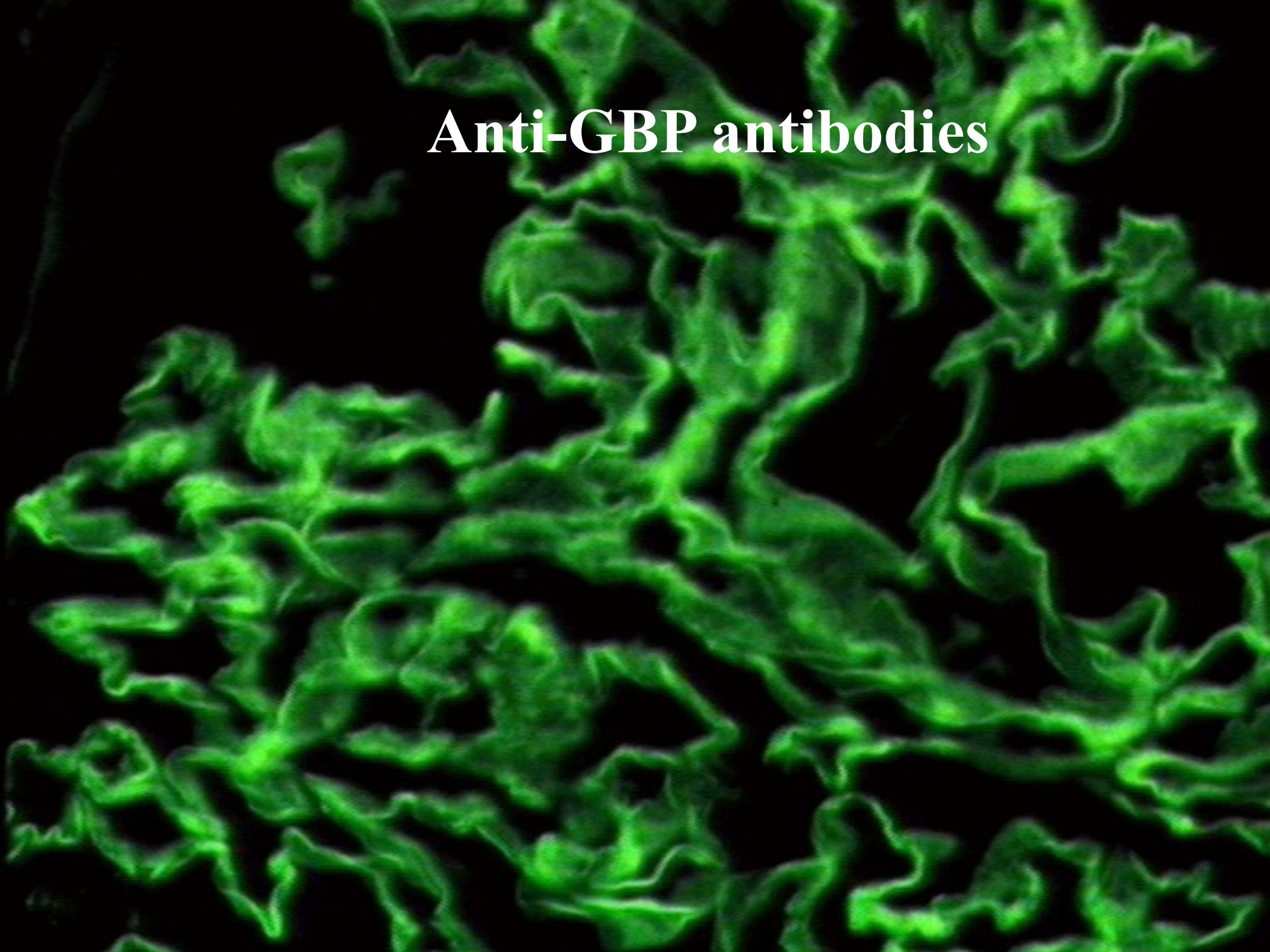
Treatment of anaphylactic shock

- Adrenalin intravenously or intramusculary 10 μg/kg repeatedly
- Antihistaminics intravenously
- Syntophyllin 240 mg intravenously or inhalation of β-2-mimetics
- Corticosteroids (200-500 mg of hydrocortisone) intravenously
- Oxygen
- Vasopressor agents (dopamin or noradrenalin)

Type-II hypersensitivity



Anti-GBP antibodies



Diseased caused by immune complexes deposition

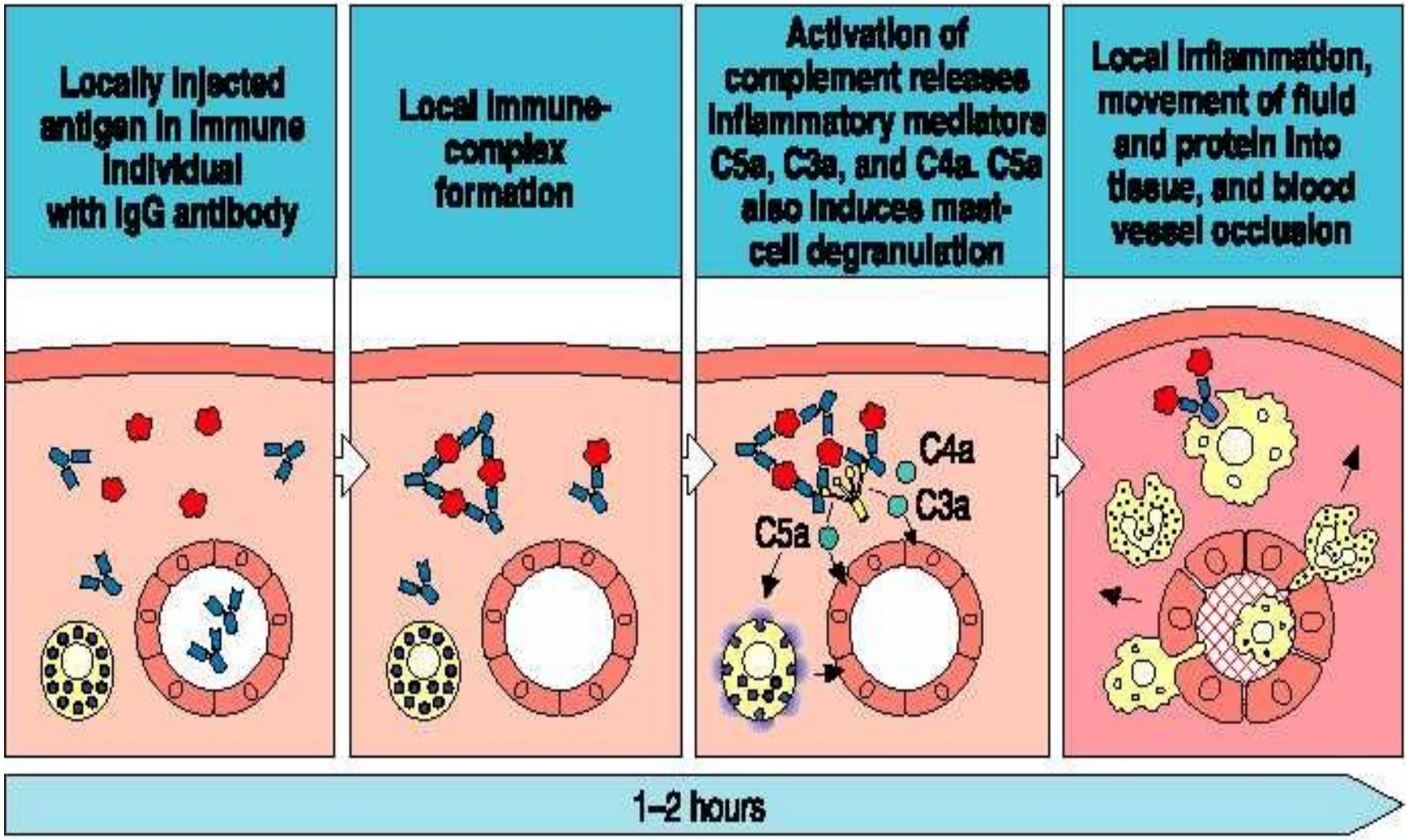
- Caused by a disturbed transport or metabolism of immune complexes.
- They usually deposit in the wall of vessels (causing vasculitis) or glomeruli (causing glomerulonephritis), less frequently in the place of their formation (extrinsic alveolitis).
- The most important laboratory test is the direct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

Immunocomplex diseases (type III immunopathological reaction

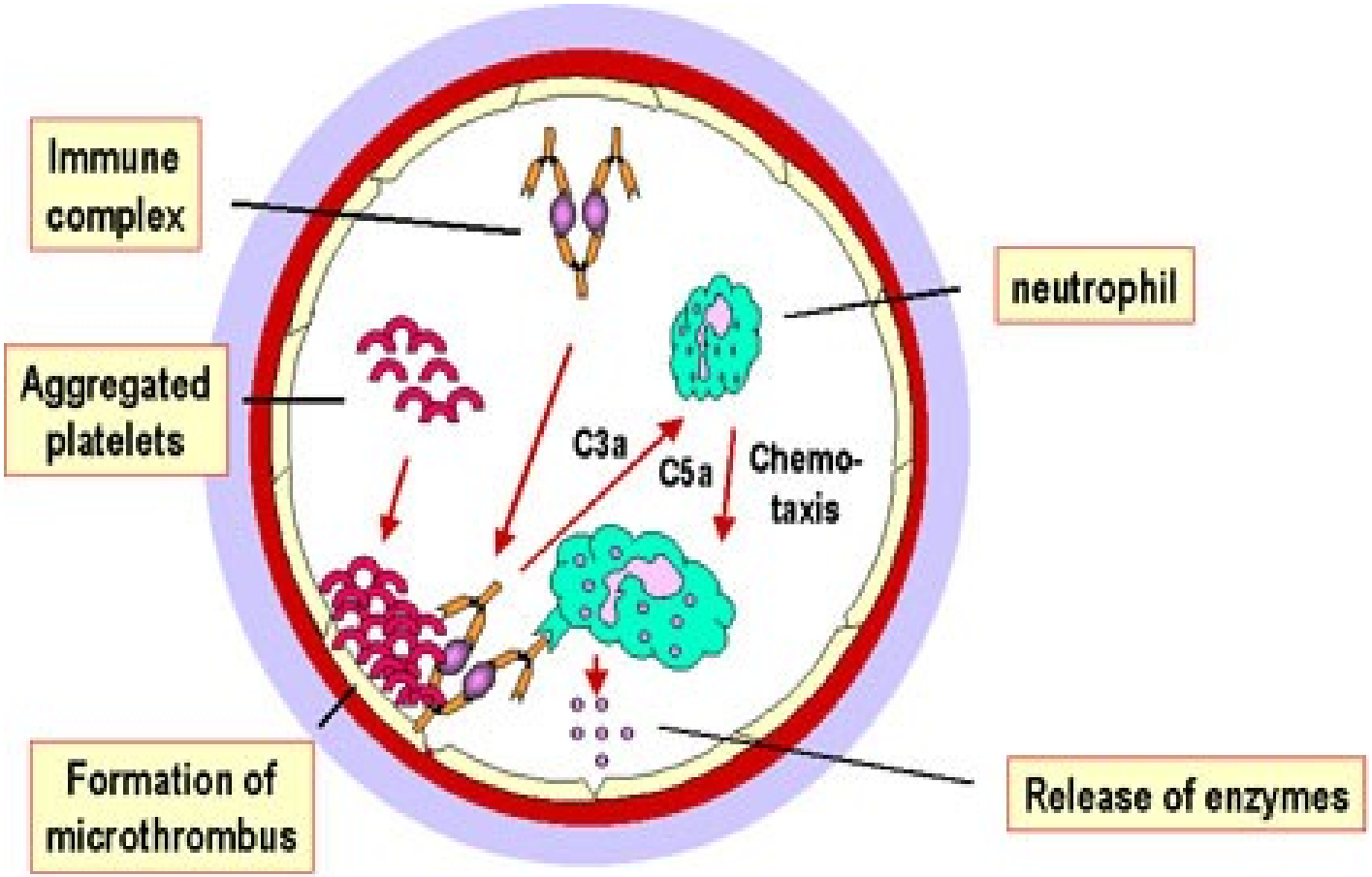
- Caused by deposition of immune complexes in places different from their normal metabolism.
- In case of circulating immune complexes (small, soluble complexes with excess of antigen), they deposit mainly in blood vessels walls and glomeruli leading to vasculitis and/or glomerulonephritis.
- Less frequent 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.

Přecitlivělost III. typu

Figure 10.29



Přecitlivělost III. typu

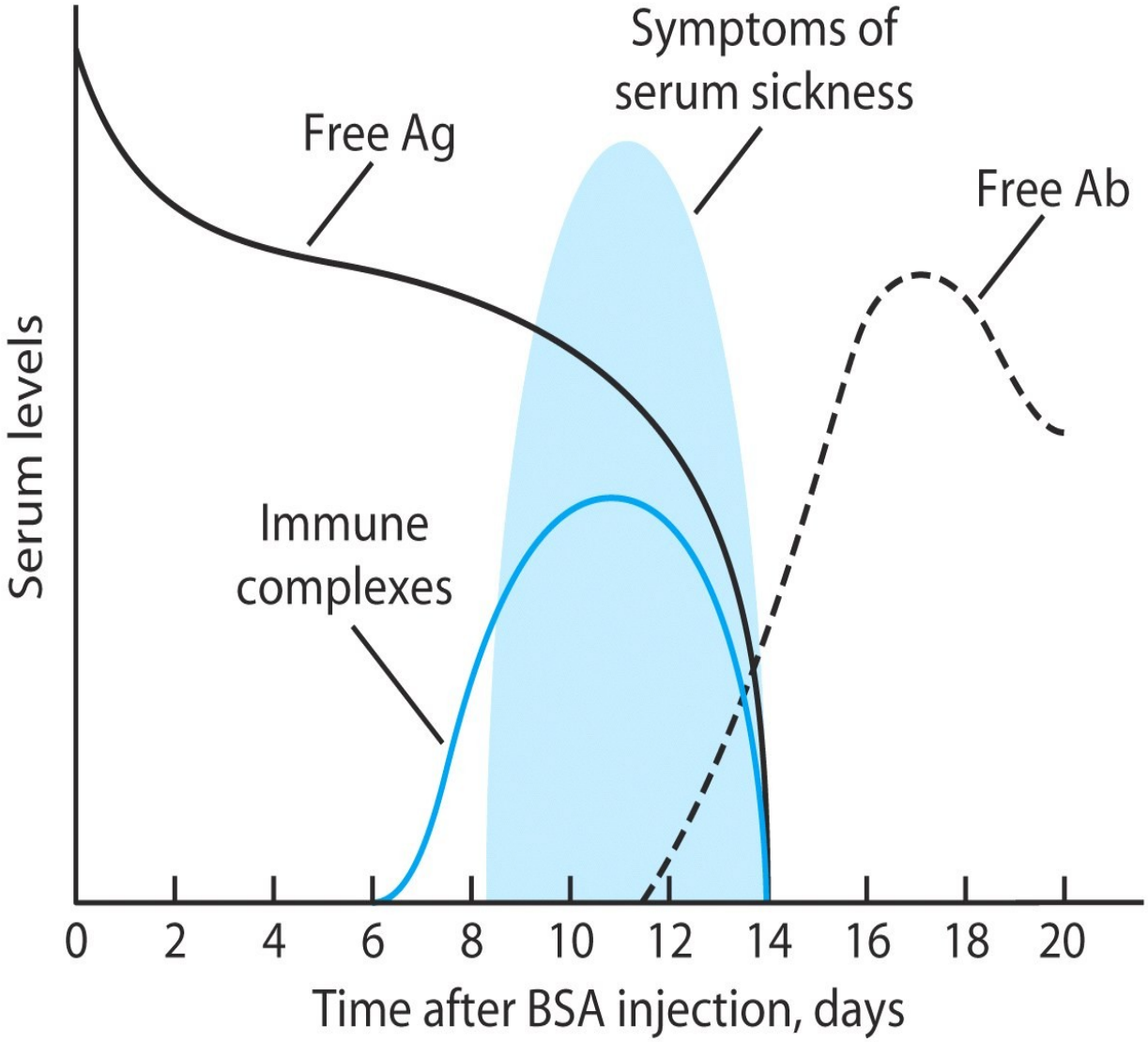


RCH

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 –Type III

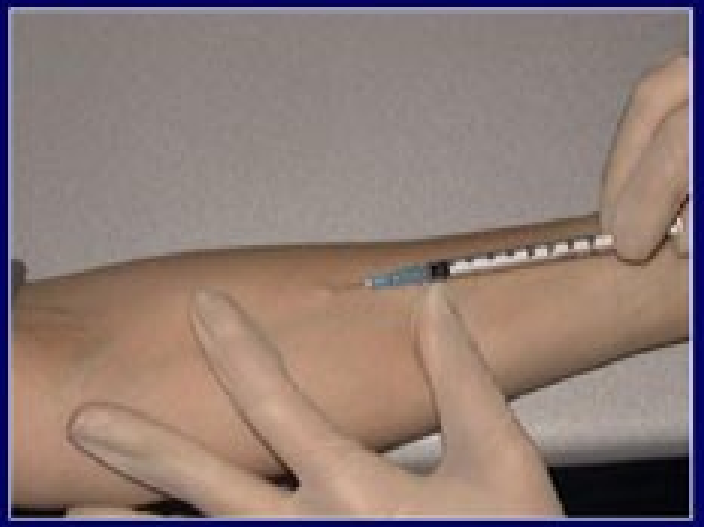


Extrinsic alveolitis

- Caused by deposition if insoluble immune complexes in the lung tissue. The complexes are formed from exogenous antigen and excess if 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).

Administering the Tuberculin Skin Test

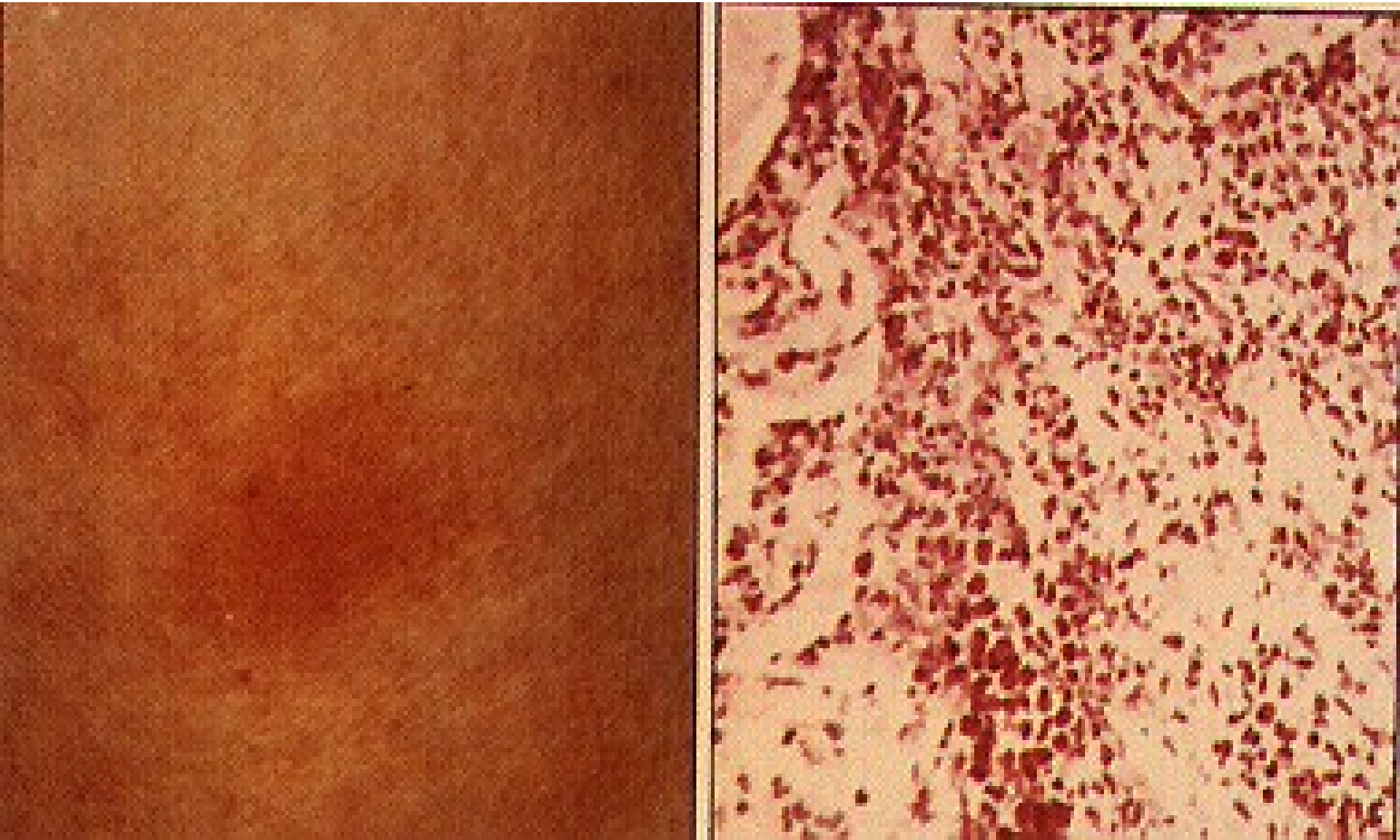
- Inject intradermally 0.1 ml of 5 TU PPD tuberculin
- Produce wheal 6 mm to 10 mm in diameter



- Do not recap, bend, or break needles, or remove needles from syringes
- Follow universal precautions for infection control

CDC

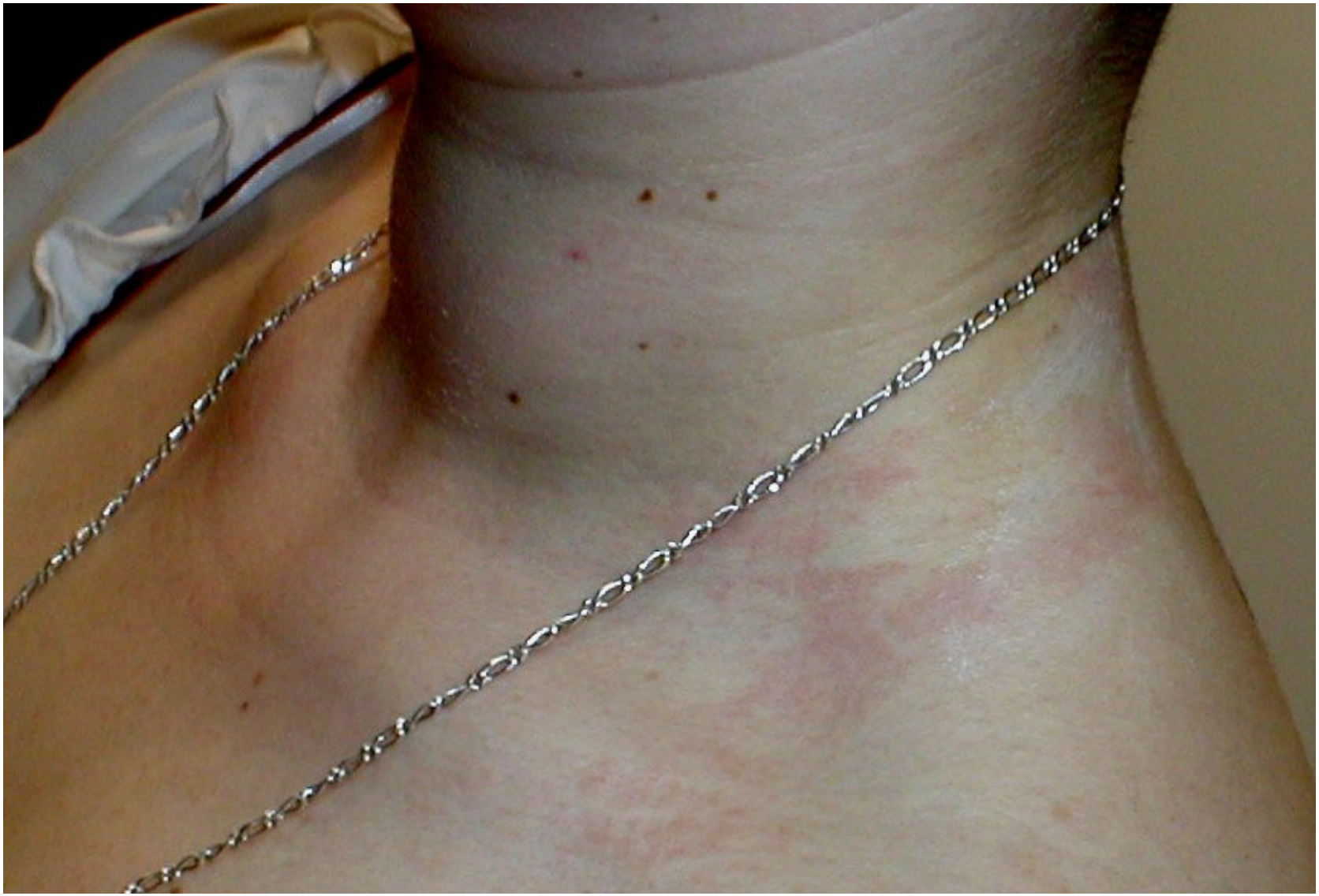
Tuberculin reaction



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



Contact dermatitis