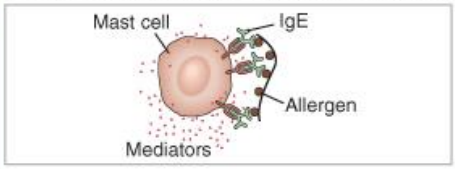
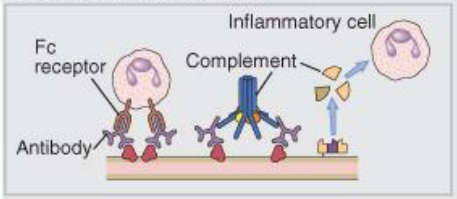
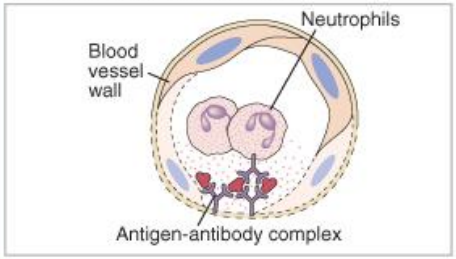
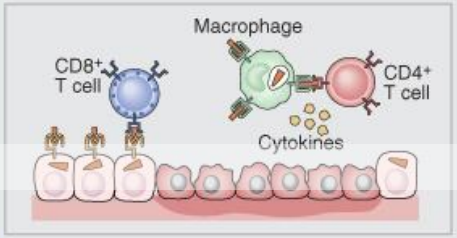
Allergic disorders

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 50-70%

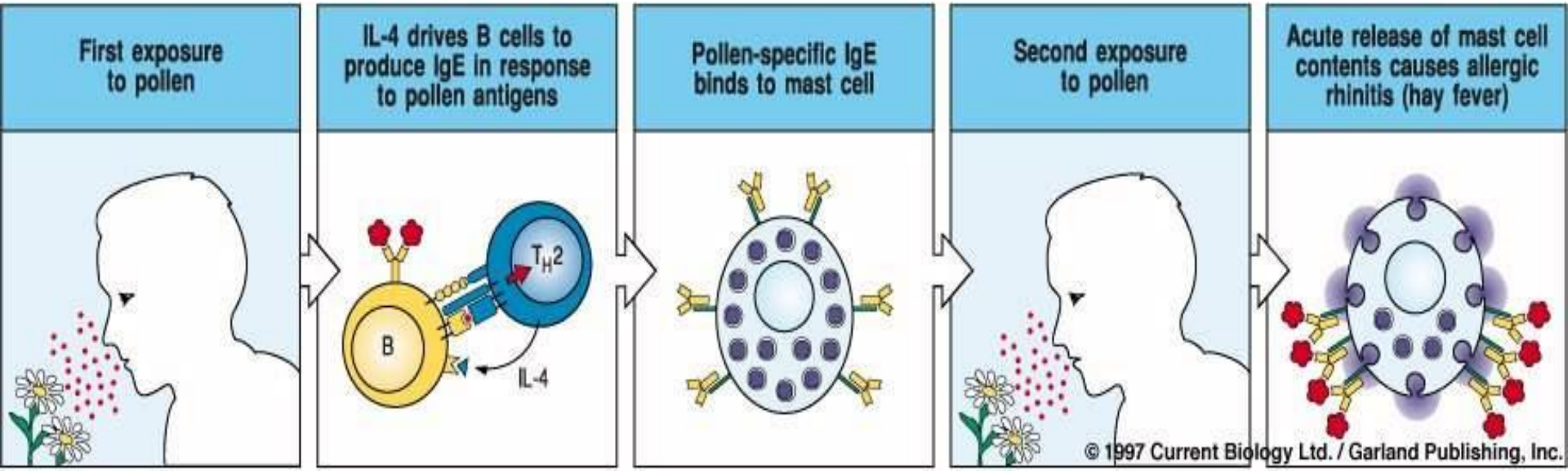
Candidate genes of atopic diseases

- 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 two phases of the disease

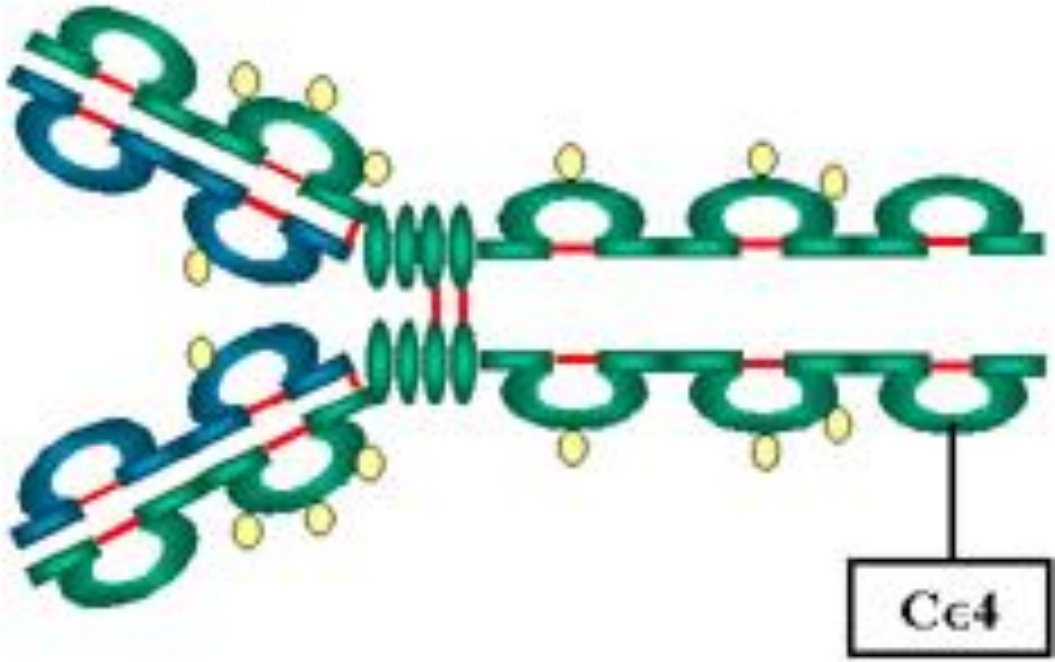


Sensitisation - formation of specific IgE, it binds to mast cells

Clinical manifestaton of allergy

IgE

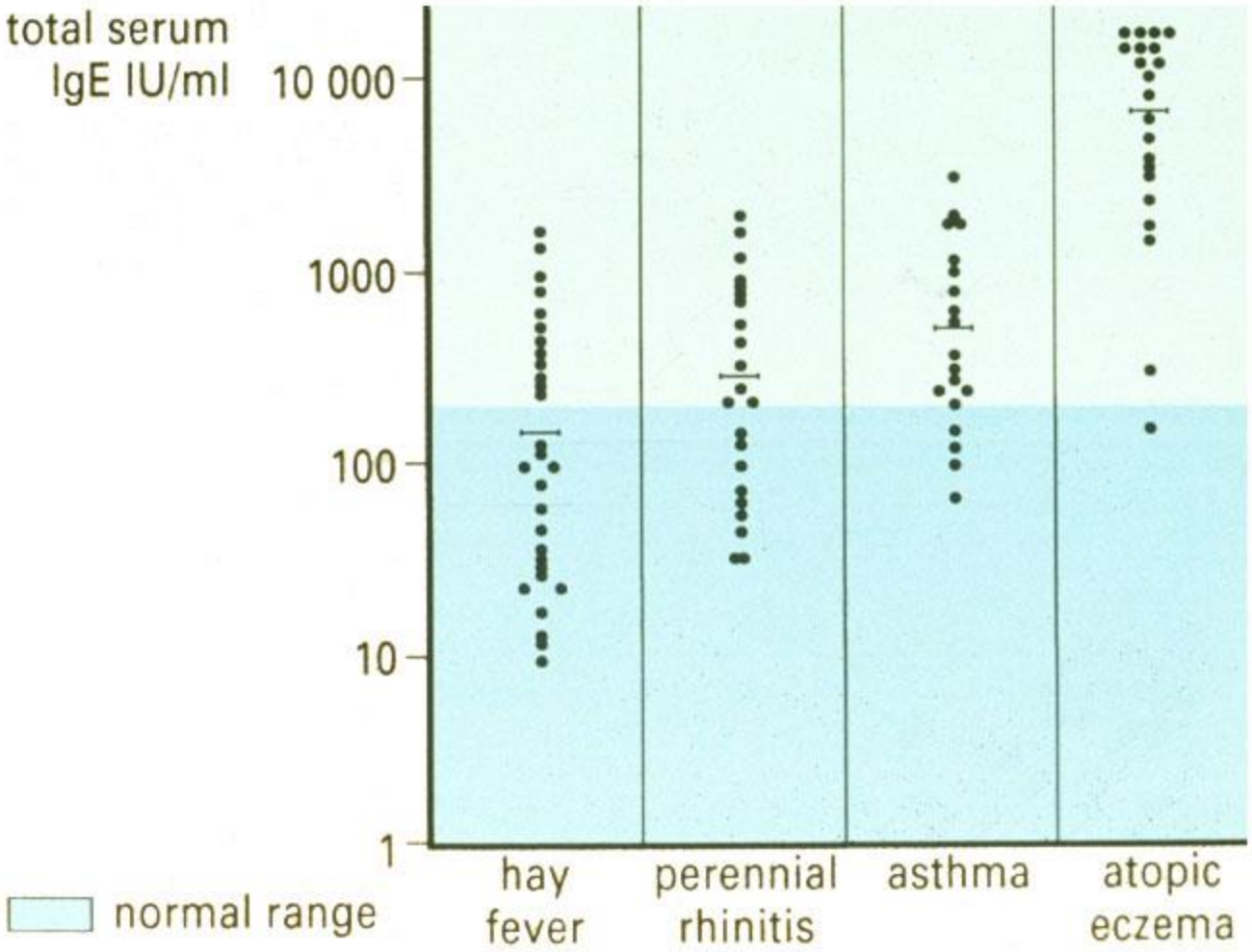
- Structure
  - Monomer
  - Extra domain (C_{H4})



Very low leves in serum (mg/l, normally expressed in IU/ml), short half life in serum (2 days). But long half life if bound to FcεR of mast cells.

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

IgE levels and atopic disease

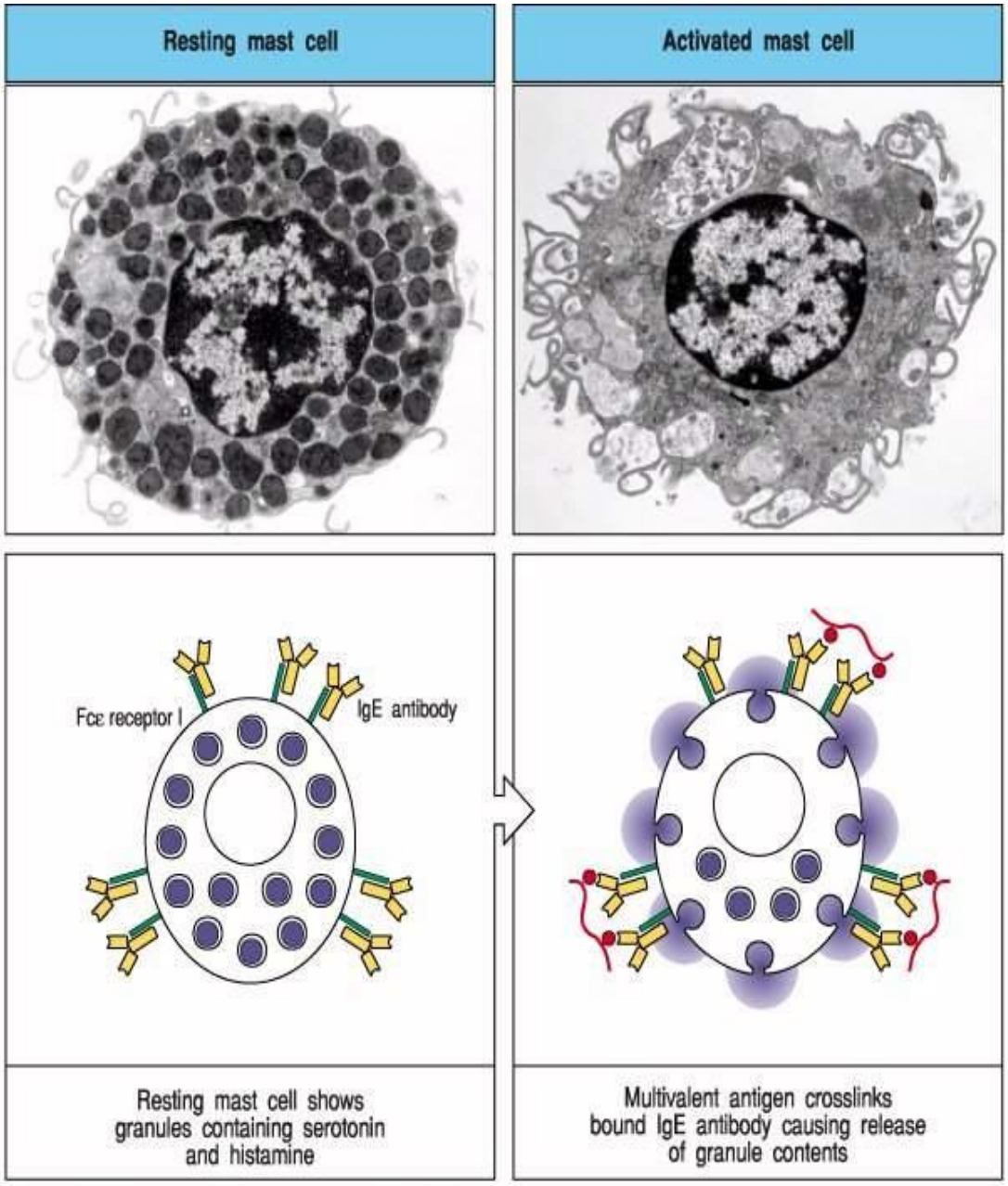


Regulation of IgE production

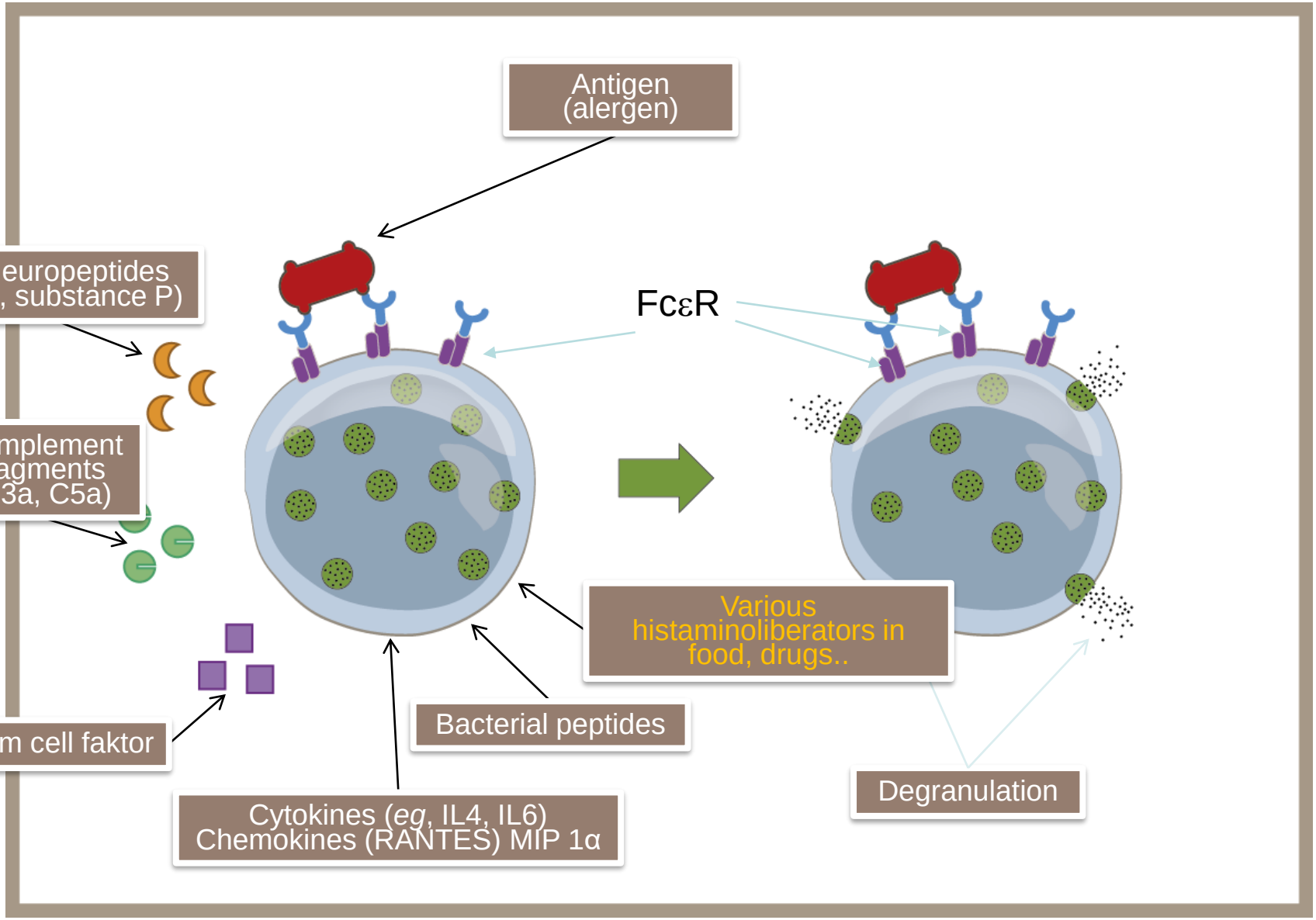
- Positive regulation: IL-4 a IL-13 – products of Th2 cells
- Negative regulation: IFNγ - product of Th1 cells

Mast Cell

Mast cells



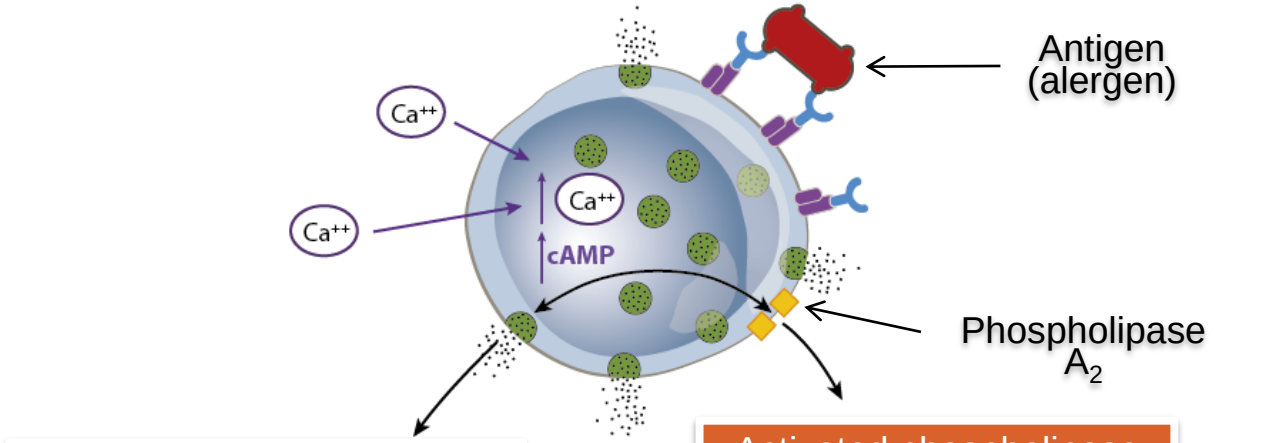
Ways of Activation of Mast Cells



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

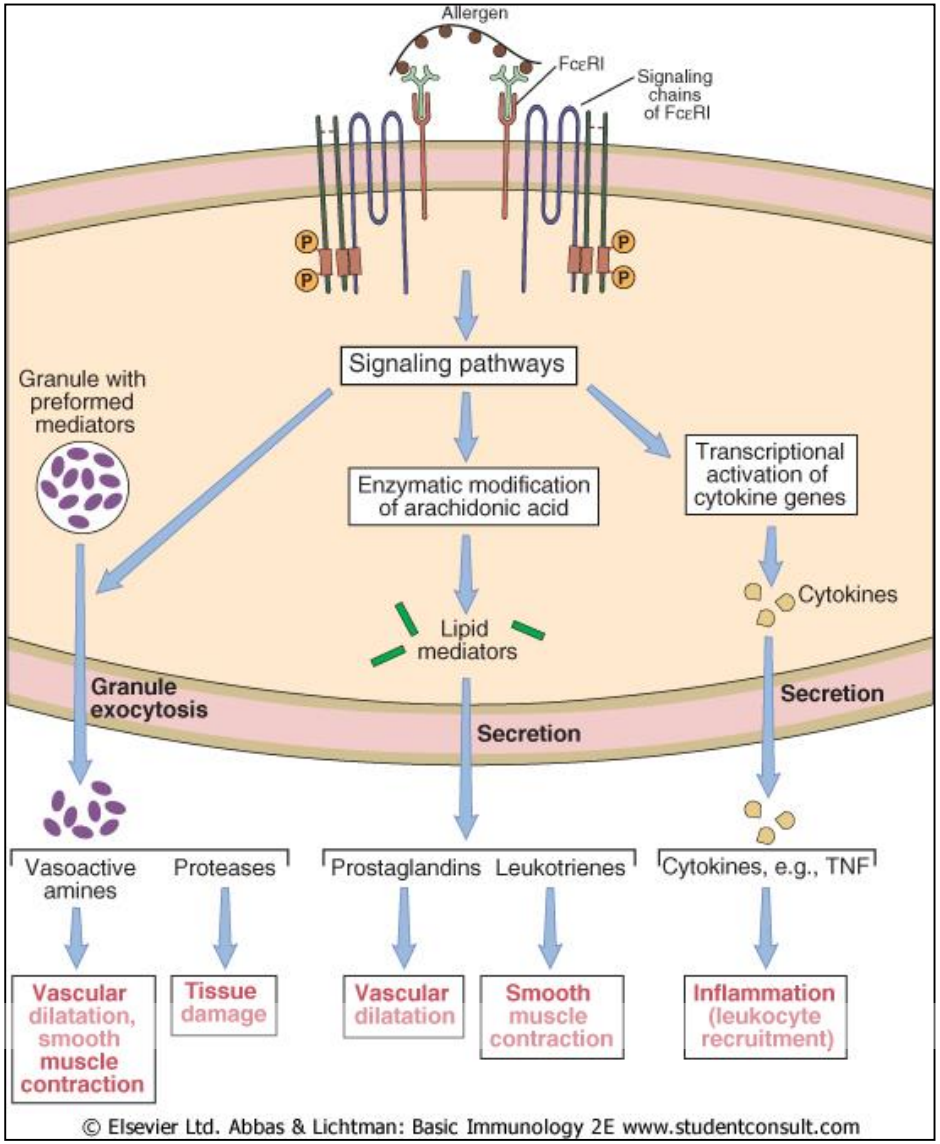
Lypoxygenase pathway

Prostaglandis

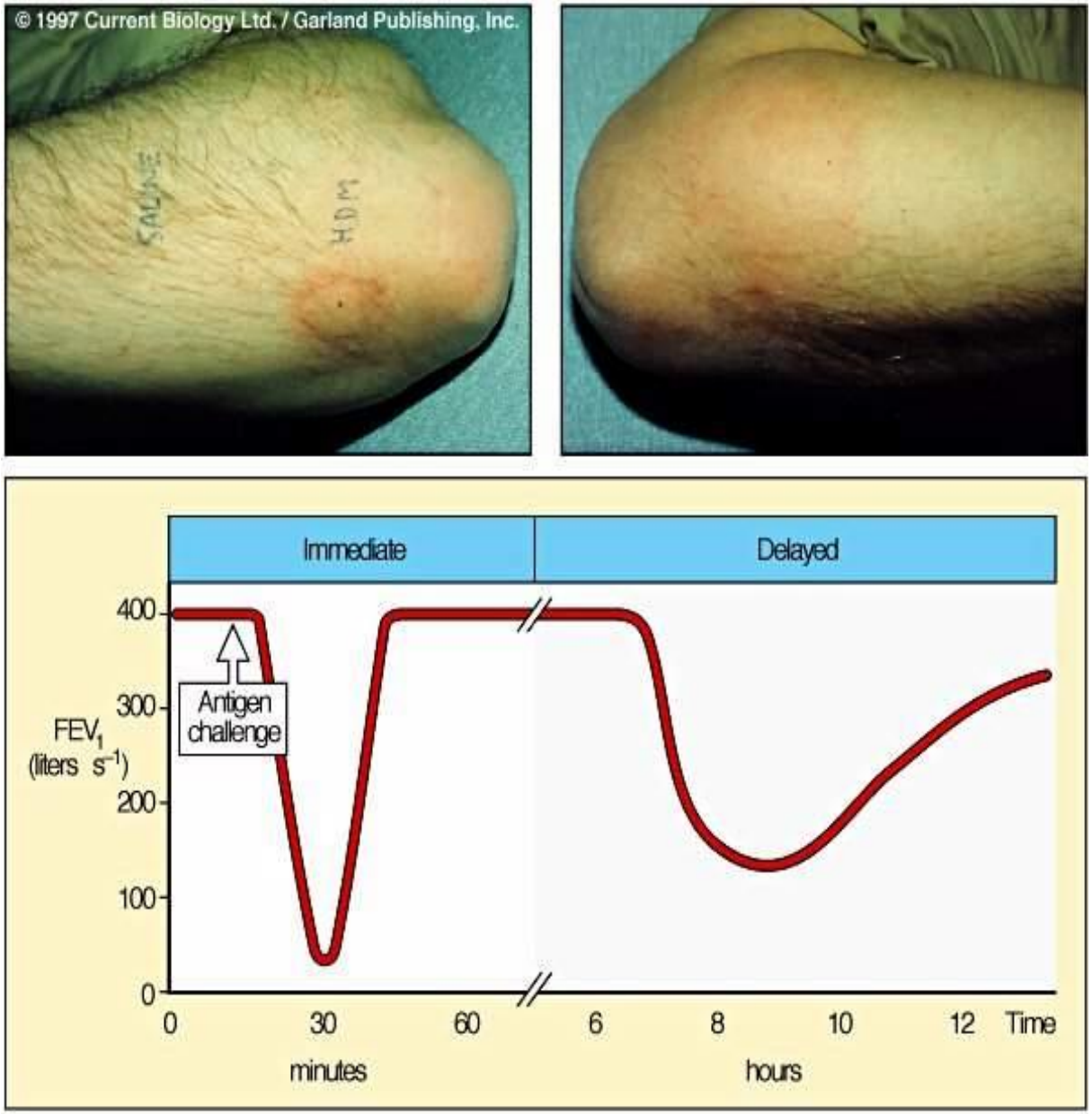
Leukotrienes

Newly-synthesized mediators

Consequences of activation of mast cells



Immediate and late phase of allergic reaction



Phases of type-I hypersensitivity reaction

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

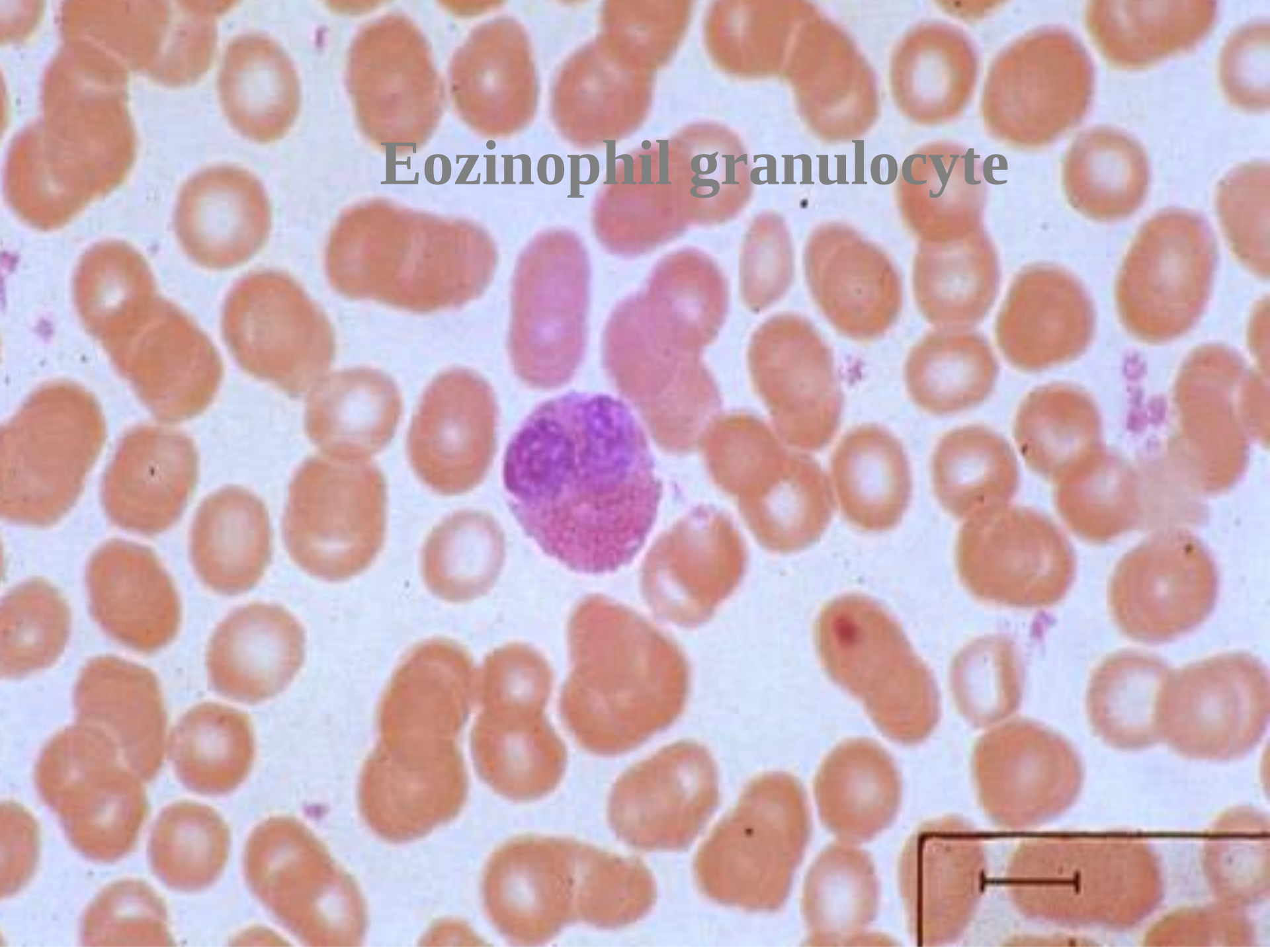
- Late phase – symptoms evolve after hours (6-8). Mediated mainly by leukotriens. Presence of eosinophils plays an important role in allergic inflammation.

Eosinophil granulocytes

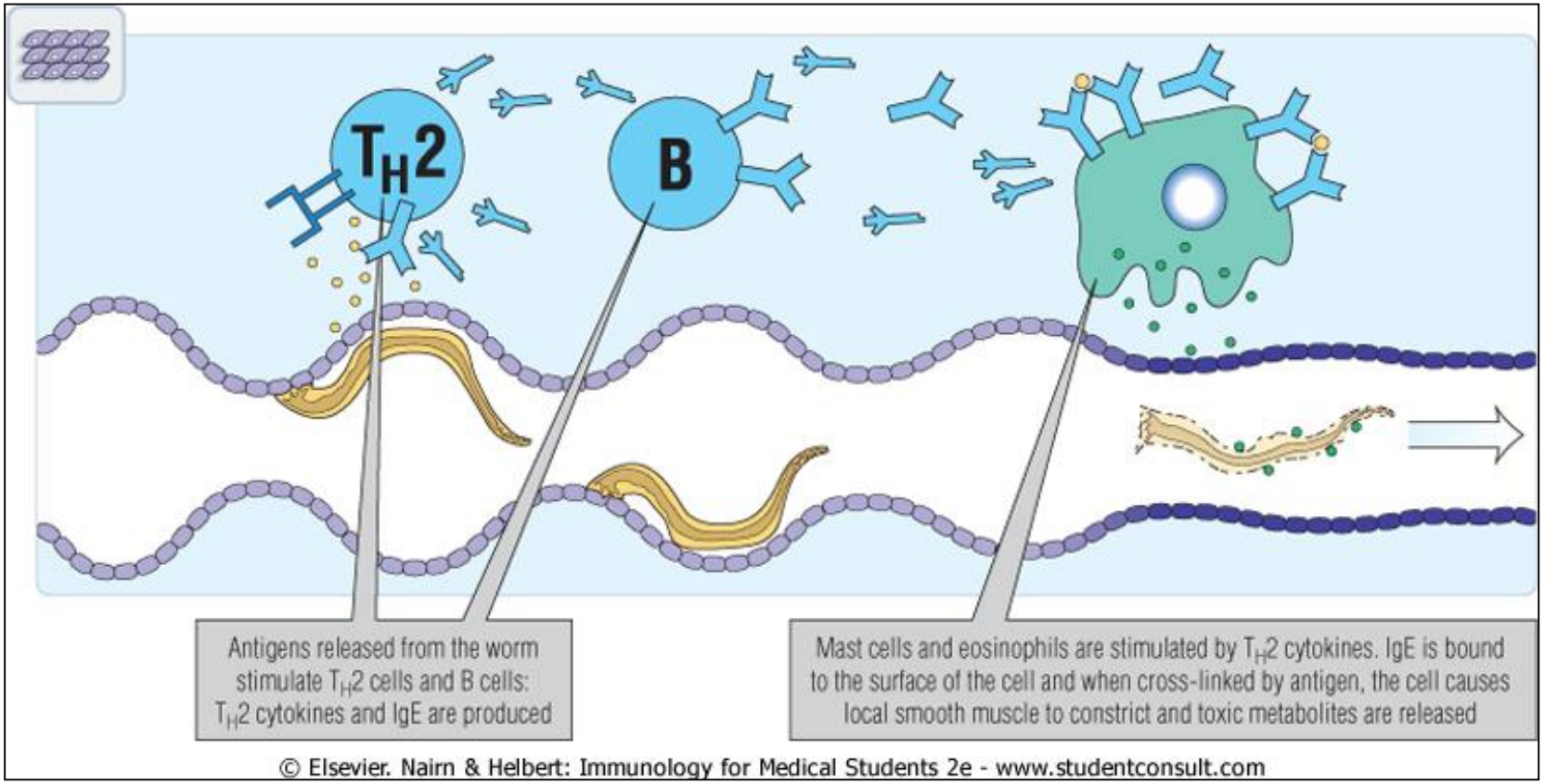
- Type-I hypersensitivity is usually accompanied by the eosinophilic inflammation.

- 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



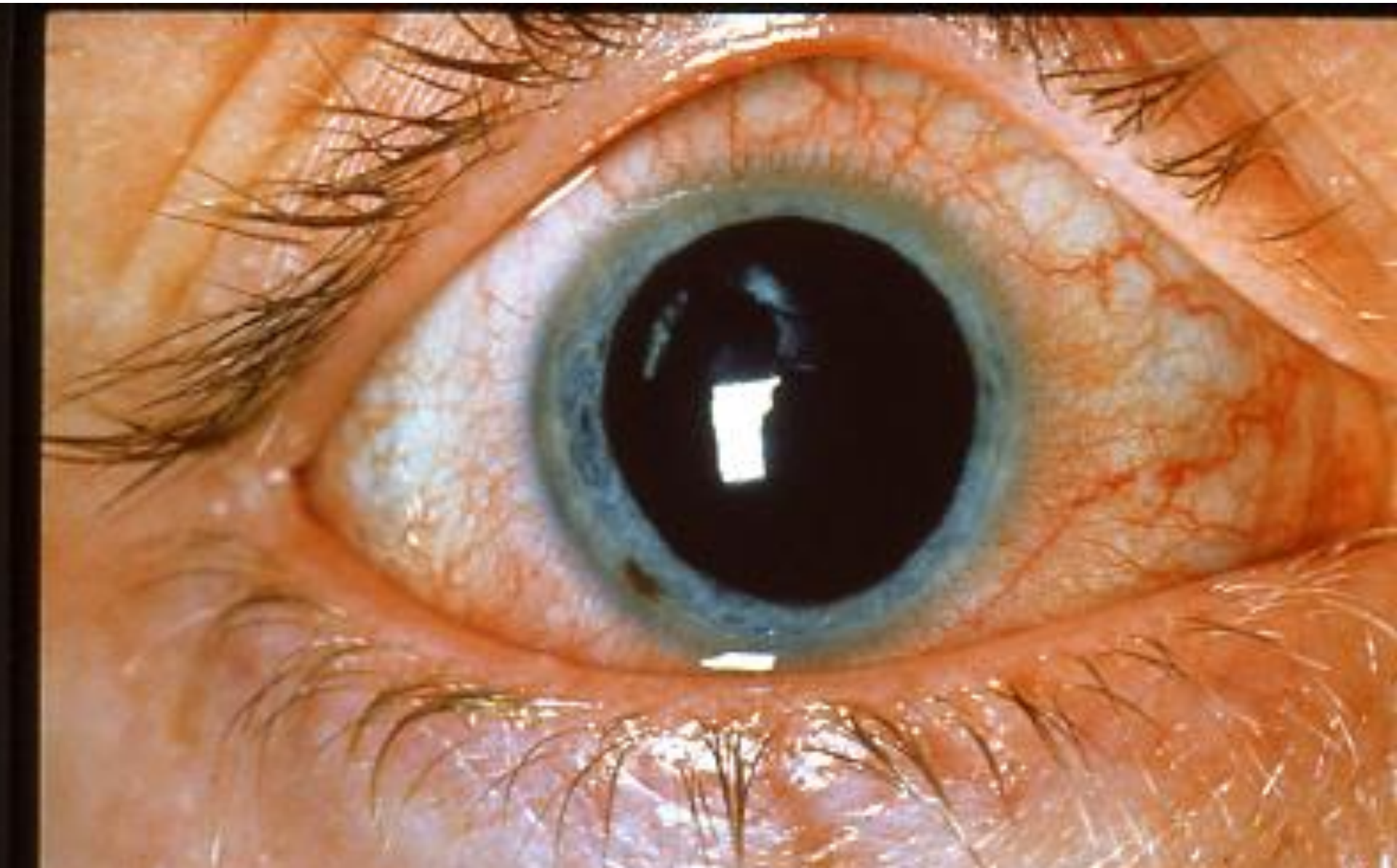
Physiological role of IgE-Mastocyte-Eosinophil system



Clinical diseases caused by atopic hypersensitivity

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

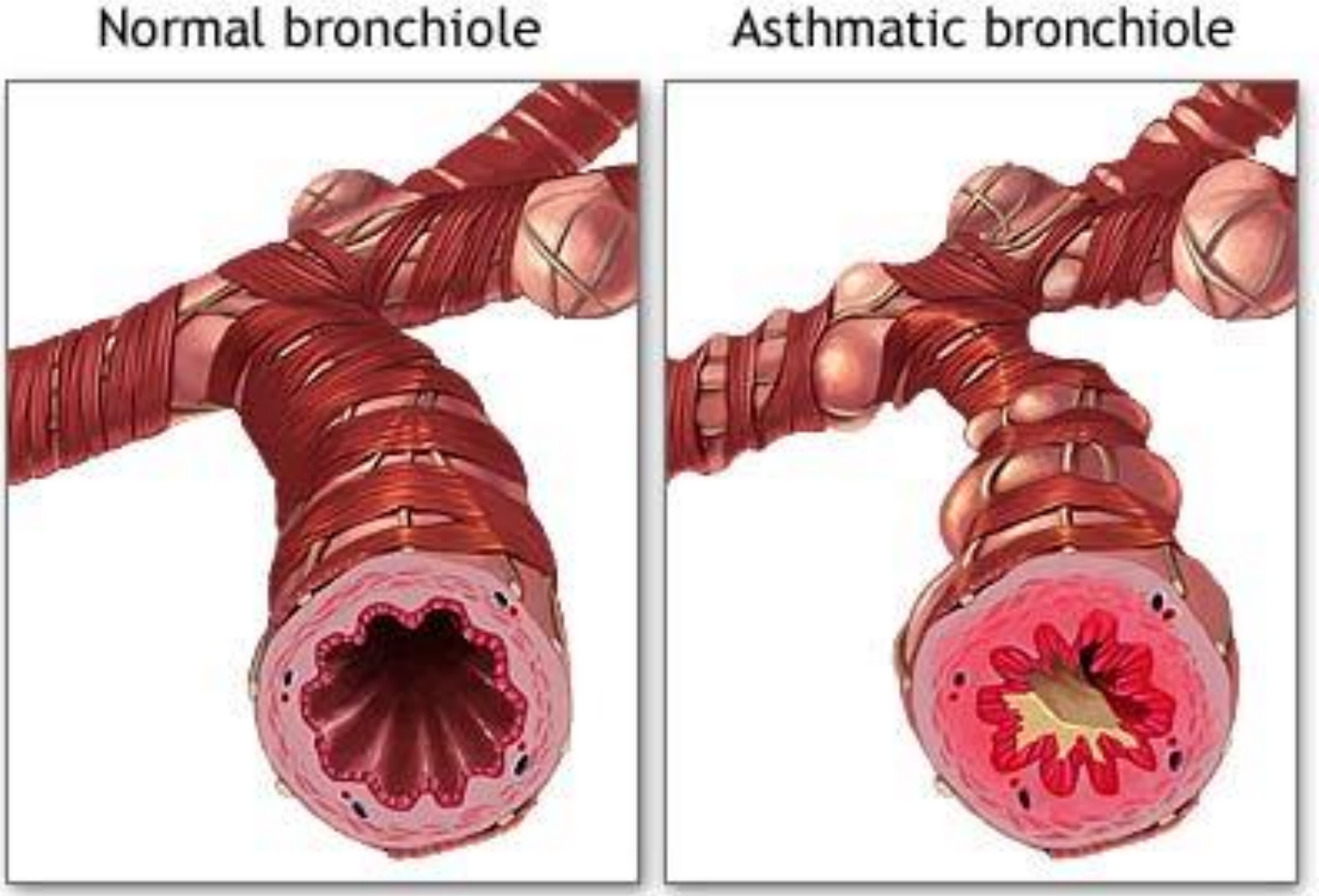
Allergic conjunctivitis



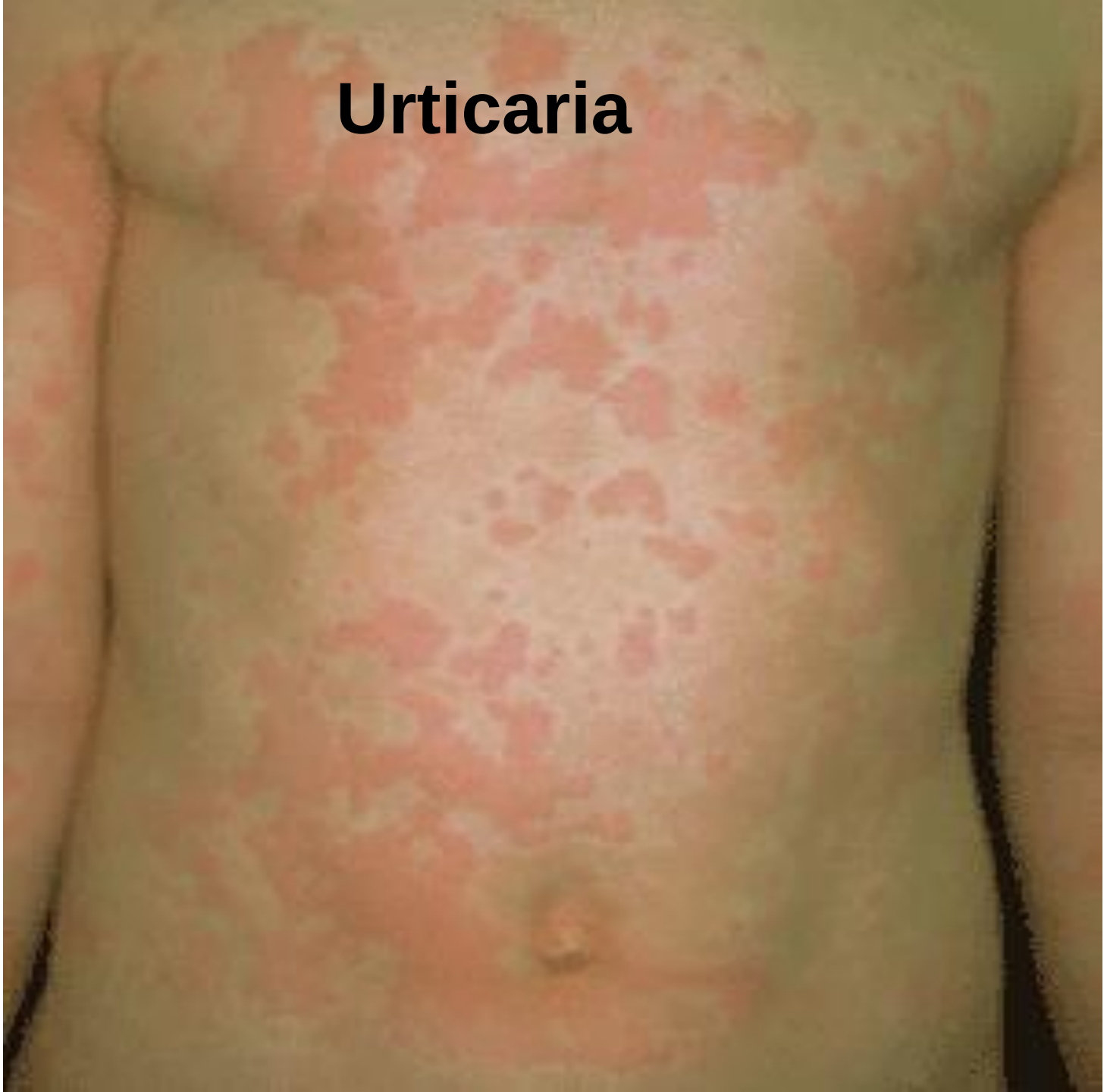
Allergic rhinitis

Bronchial asthma

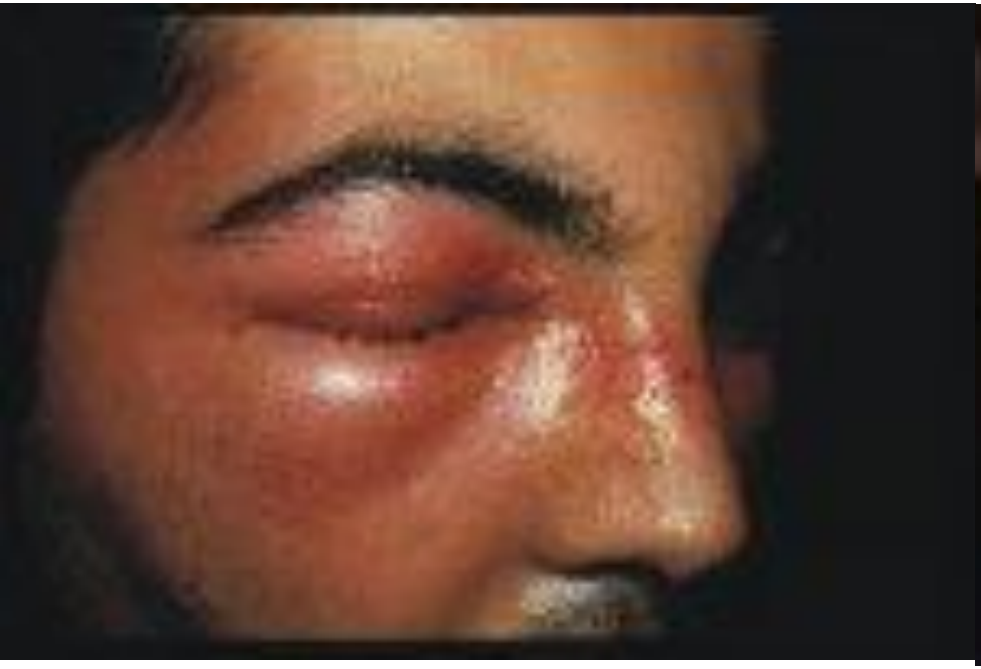
currently defined as chronic eosinophilic inflammation of bronchi

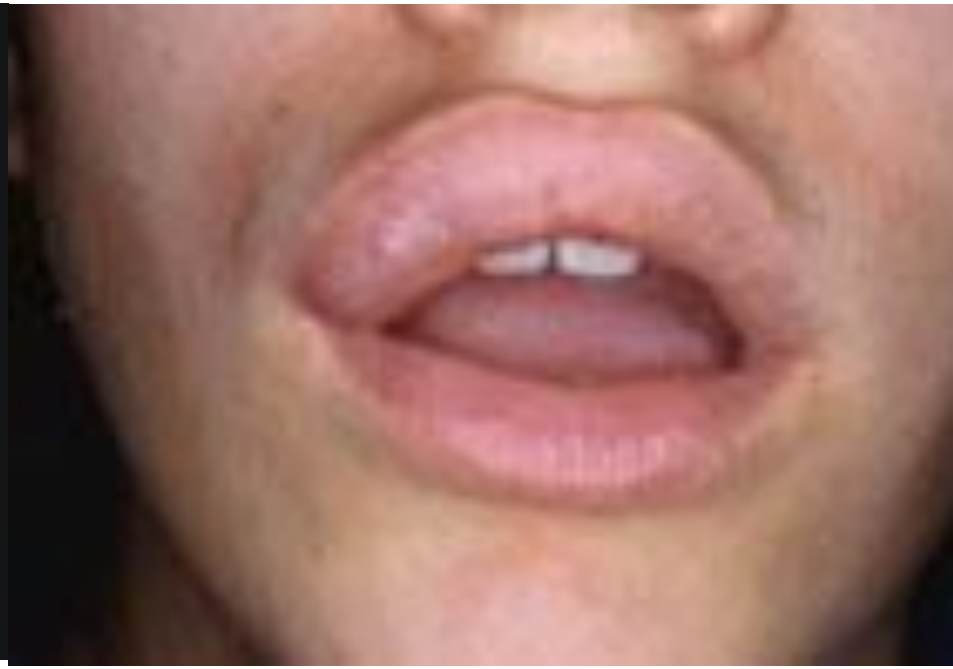


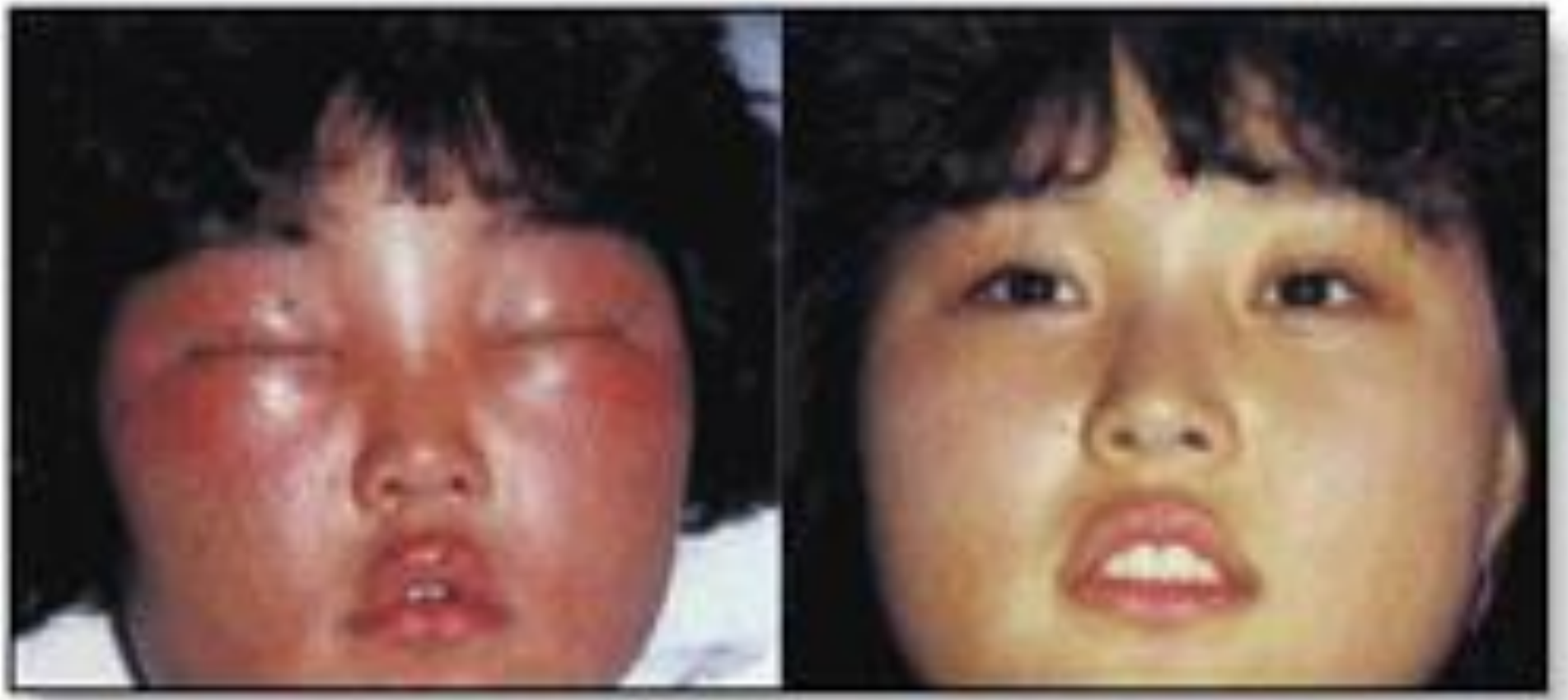
Urticaria



Angioedema



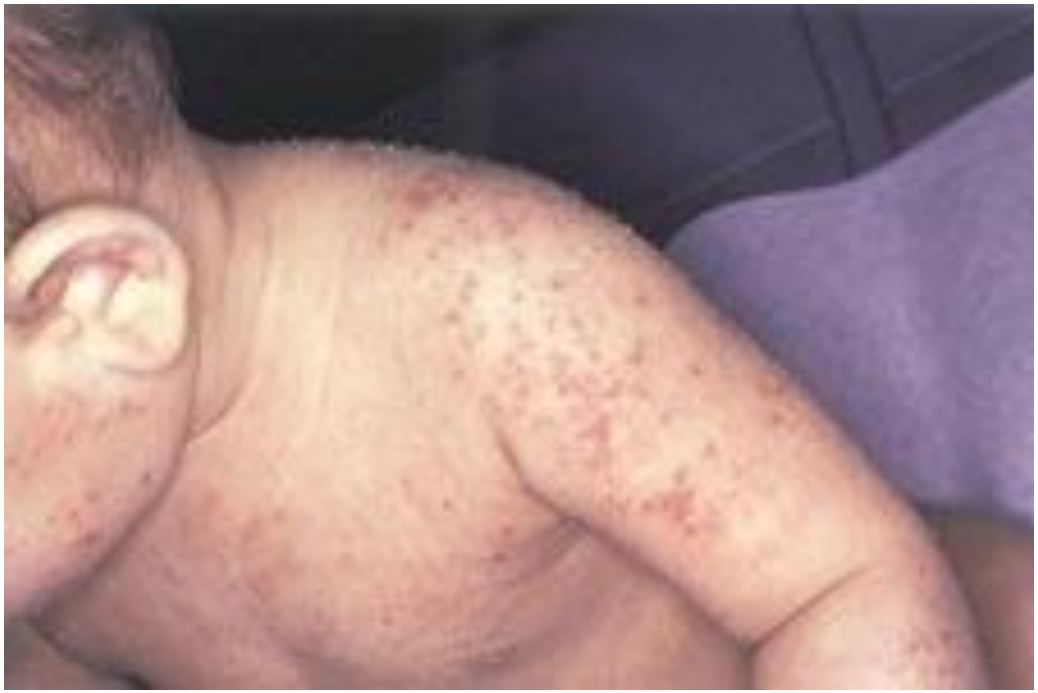


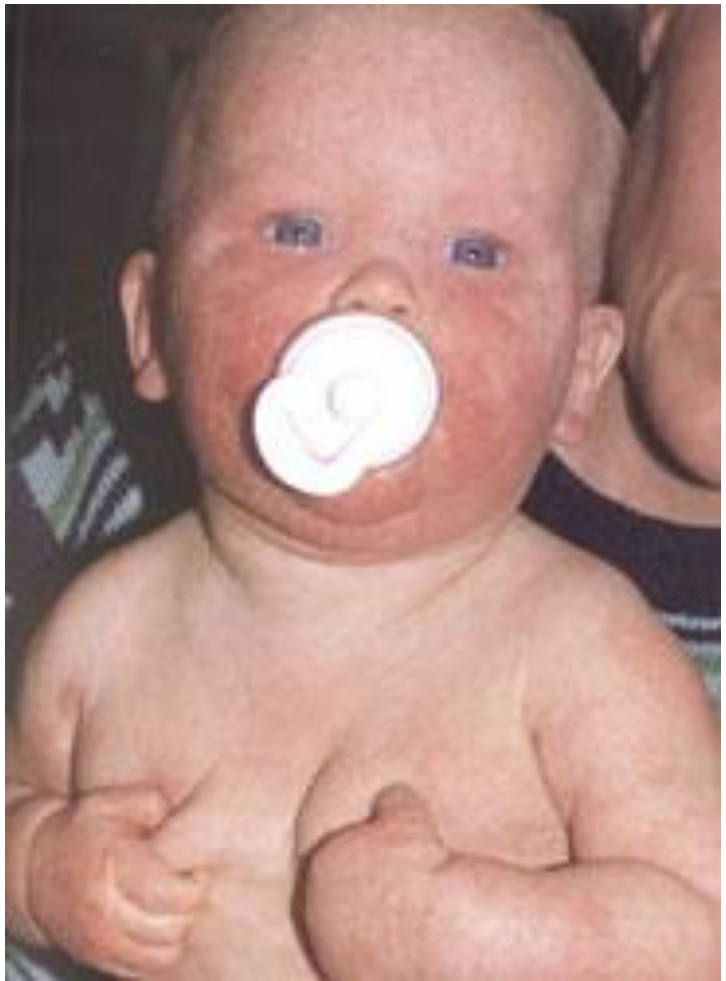


Facial angioedema following allergen exposure (A) and resolution after treatment (B).

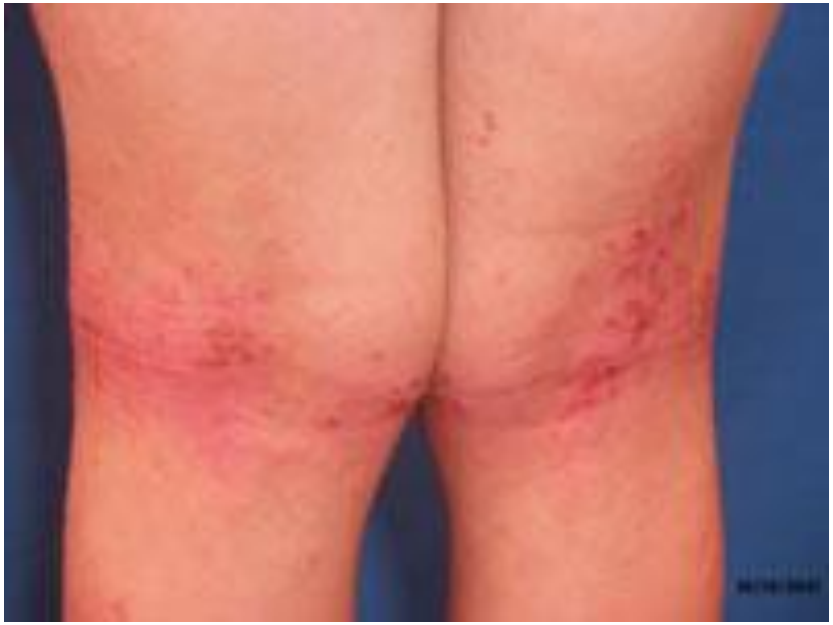
Reprinted from Tharp M, Levine M, Freeman P. Urticaria and angioedema. In: Freeman P, Slavin R (eds). Atlas of Allergies. 2nd ed. London: Mosby-Wolfe; 1996: 250. By permission of the publisher Mosby.

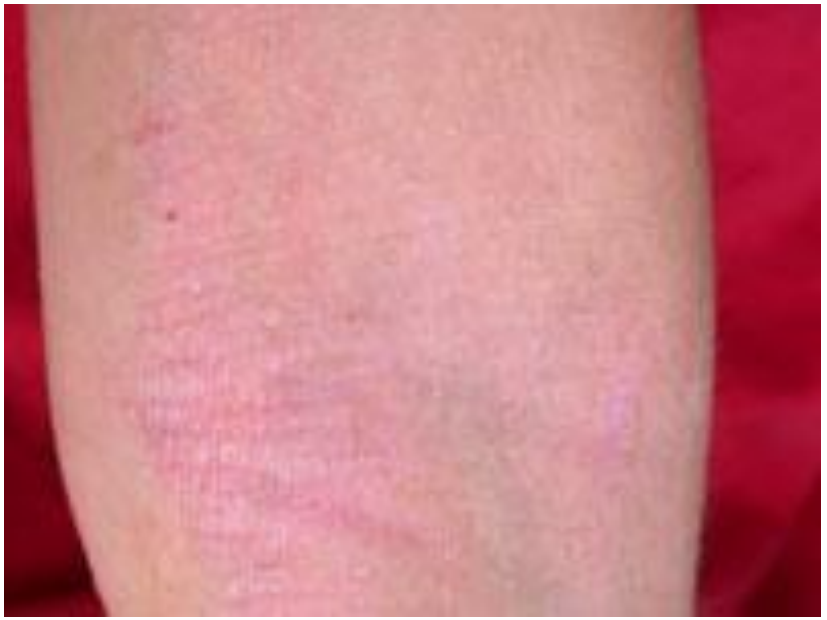
Atopic eczema



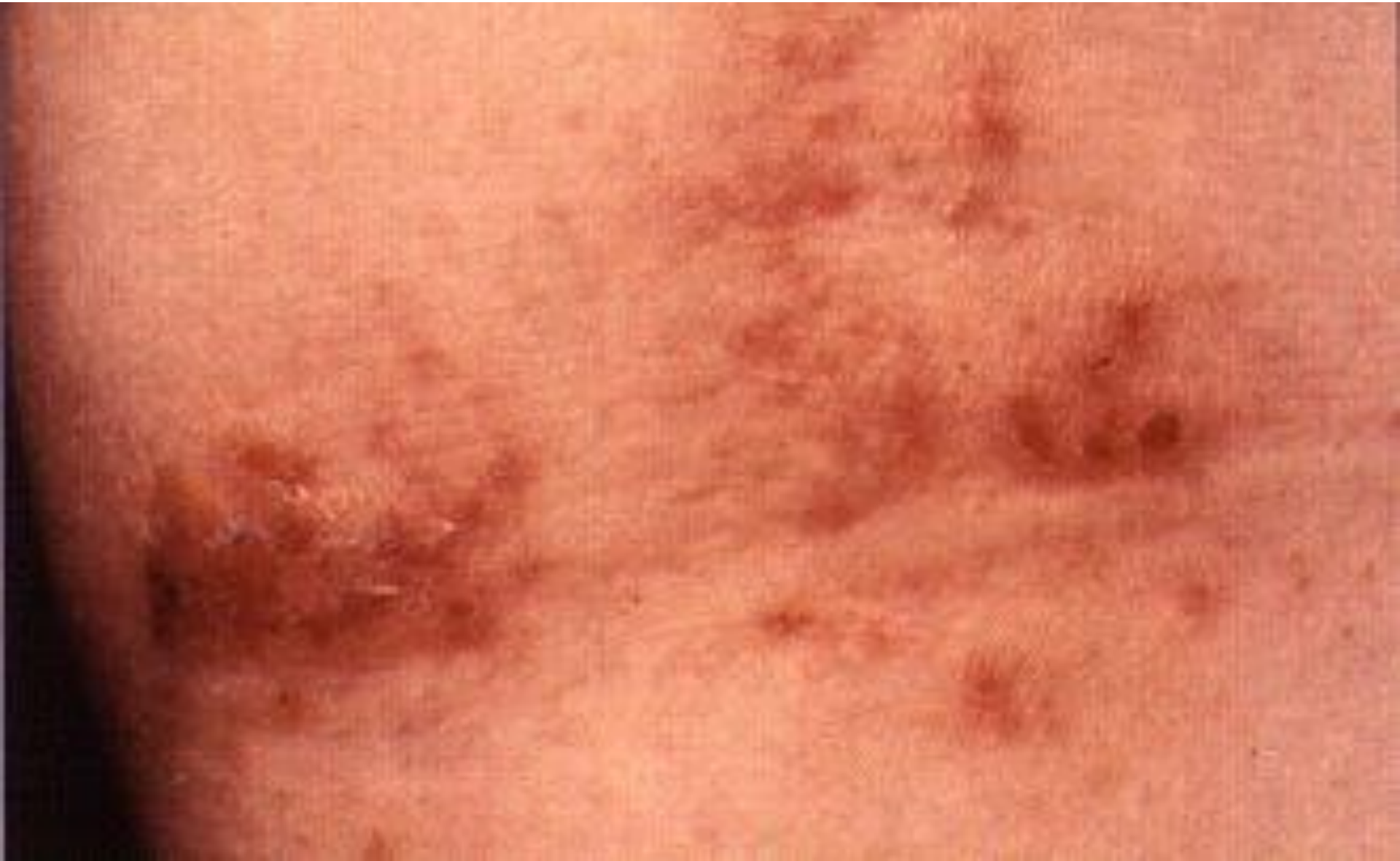


Atopic eczema





Atopic eczema



Treatment of allergic diseases

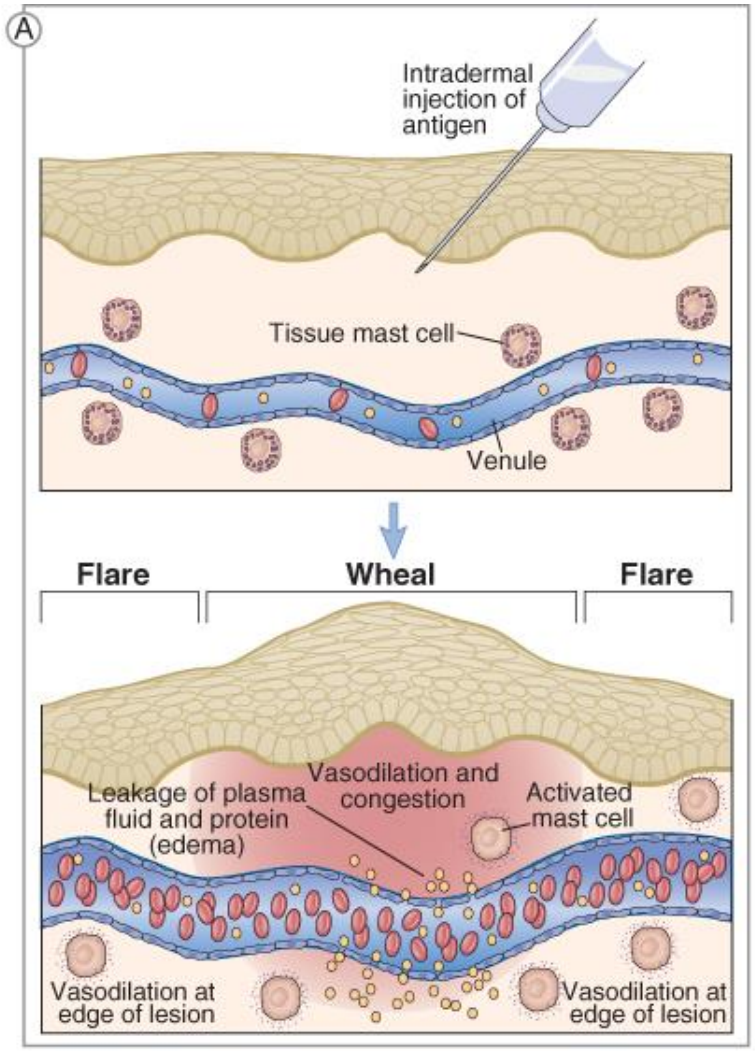
- Allergen avoidance
- Antihistaminics
- Topical or systemic corticosteroids
- Antilekotriens
- Cromons (cromolyn sodium, nedocromil) - stabilise membrane of the mast cells
- In asthma: β-2 agonists, xantins
- Allergen immunotherapy (desensitisation)

Diagnostic approaches in type-I hypersensitivity

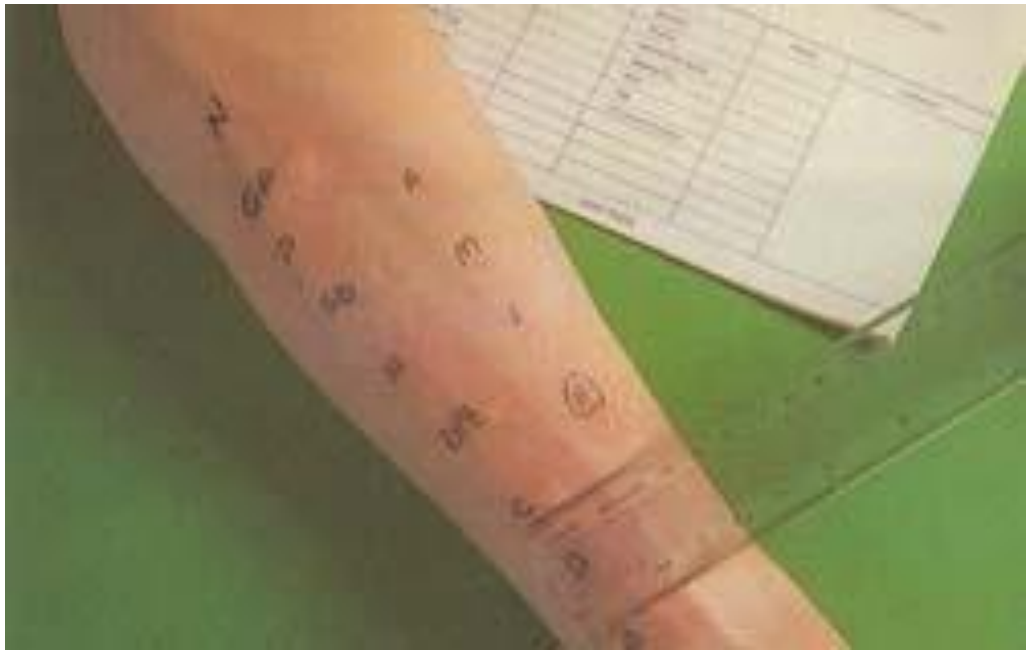
- Done by any doctor:
- Past history
- Eosinophilia

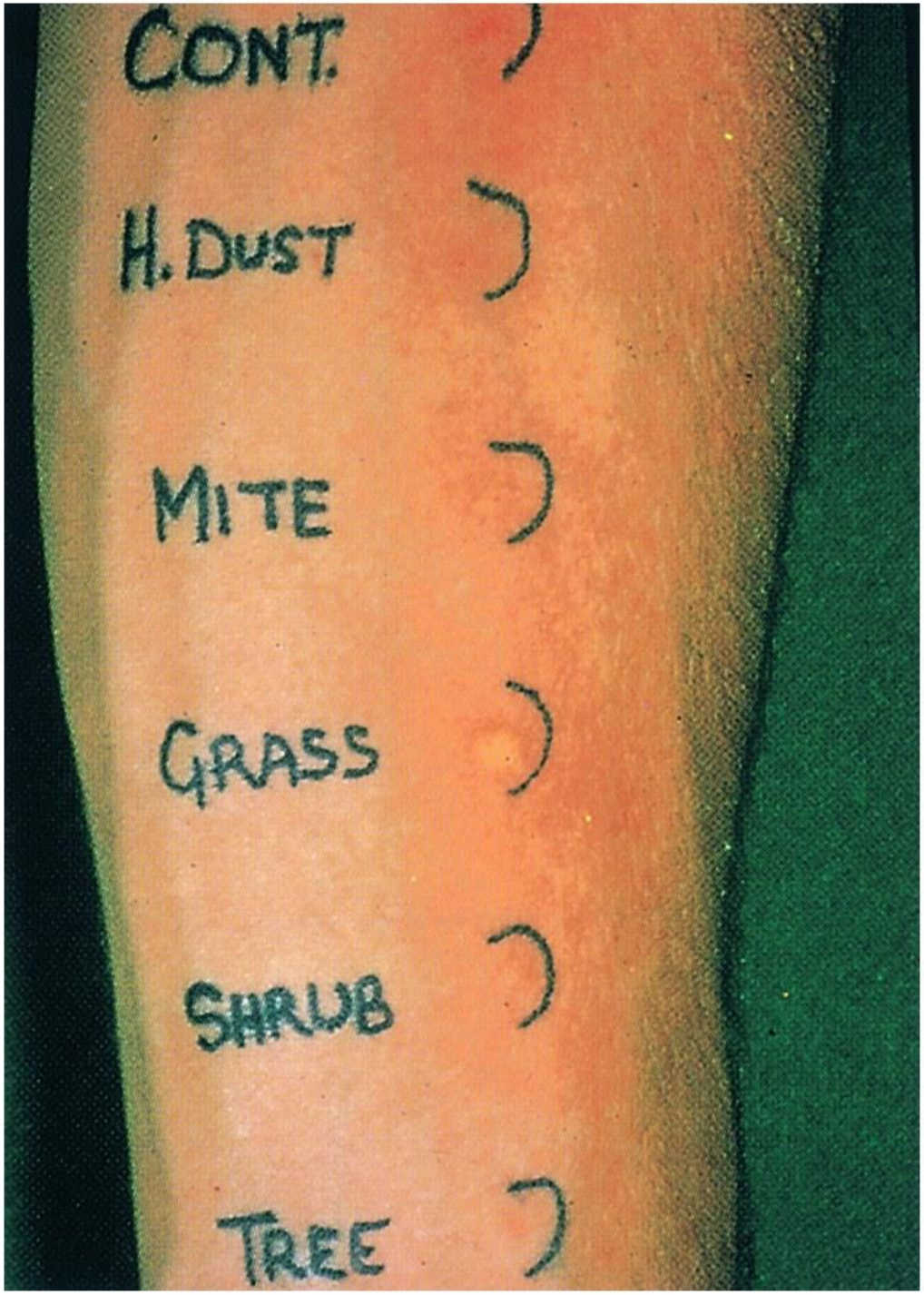
- Done by specialists, usully by allergists
- Skin tests
- Laboratory tests for specific IgE
- Provocation and elimination tests

Intradermal allergy test



Skin prick tests




CONT.
H. DUST
MITE
GRASS
SHRUB
TREE

Skin prick test

- Water solution of the antigen is dropped on the skin (usually forearm).
- Using a lancet, a prick (in the place of the drop) into the epidermis is made – it transfers the allergen into the epidermis.
- The allergen triggers local IgE mediated allergic reaction.
- The results are read after 15 minutes.
- Positive reaction is a red weal (usually more than 4 mm in diameter).

Anaphyctic shock

- A severe and sometimes life-threatening immune system reaction to an allergen (or other stimuli).
- Systemic effect of released histamin plays a crucial pathogenic role.
- Gemeralized vasodilation and increased capillary permeability leads to hypotension and compensatory tachycardia.
- Other organ (skin, respiratory, GIT tract..) symptoms are frequently present. If these symptoms are present without circulation collapse we speak about **anaphylactic reaction**.

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)