



PÉCSI TUDOMÁNYEGYETEM  
UNIVERSITY OF PÉCS



# Allergic skin reactions

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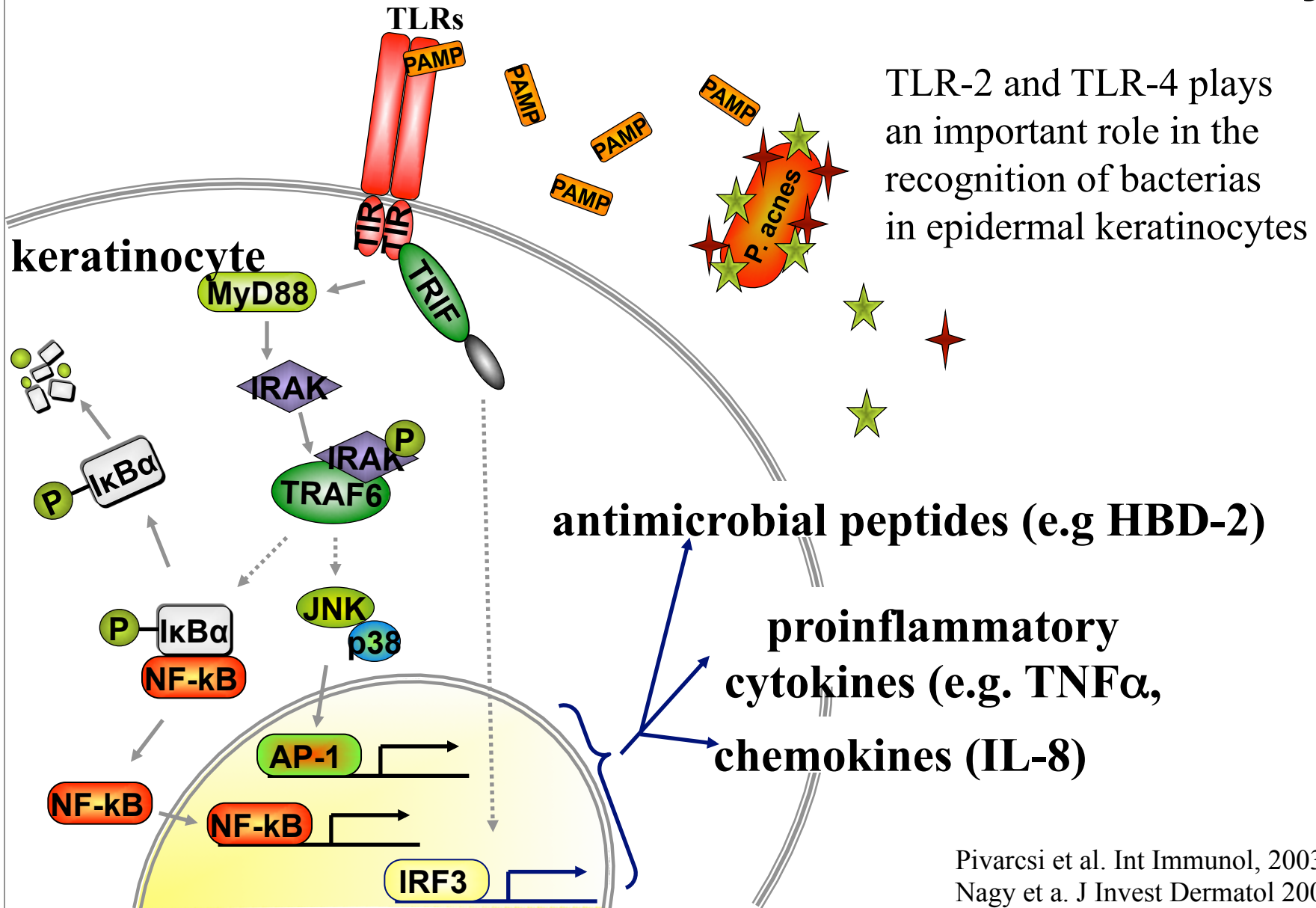
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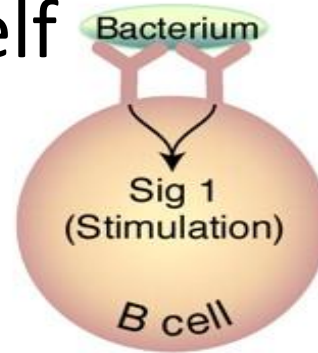
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# Microbes and keratinocytes



# How do we develop an immune reaction against something?

- Recognition of non-self

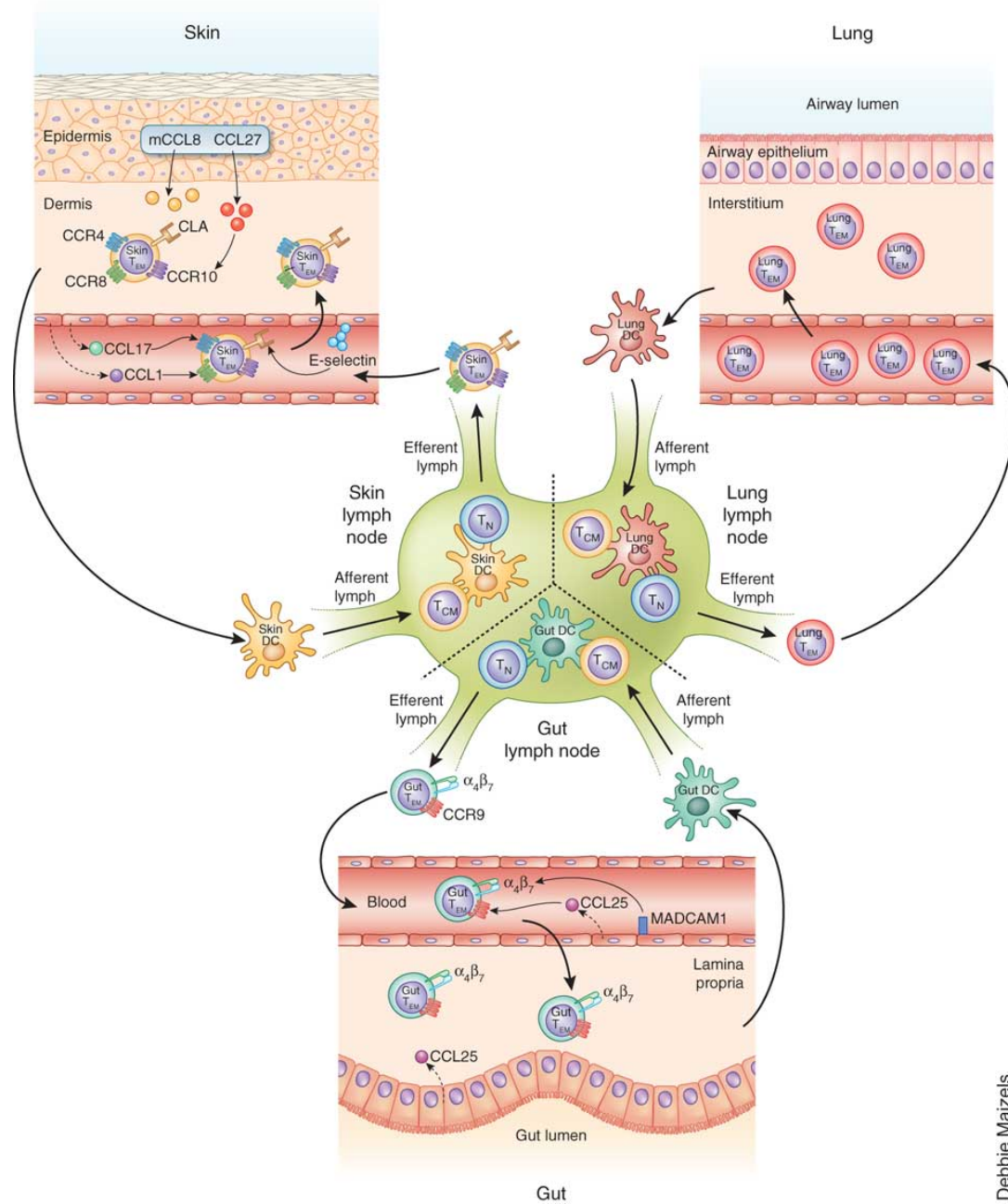


a) 1959, original SNS model said that lymphocytes are activated by recognition of foreign things.

# The 2 steps of adaptive immune reactions

- Induction phase – sensitization
  - Ag is picked up by APC
  - Ag is processed by APC
  - APC moves to lymph node
  - Ag is presented to T or B cells
- Effector phase – elimination of the invader
  - Humoral immunity
  - Cellular immunity

# The immune response is tissue specific



# Allergic reactions



# Allergy

Allergic reactions occur when a person's immune system (over)reacts to normally harmless substances in the environment.



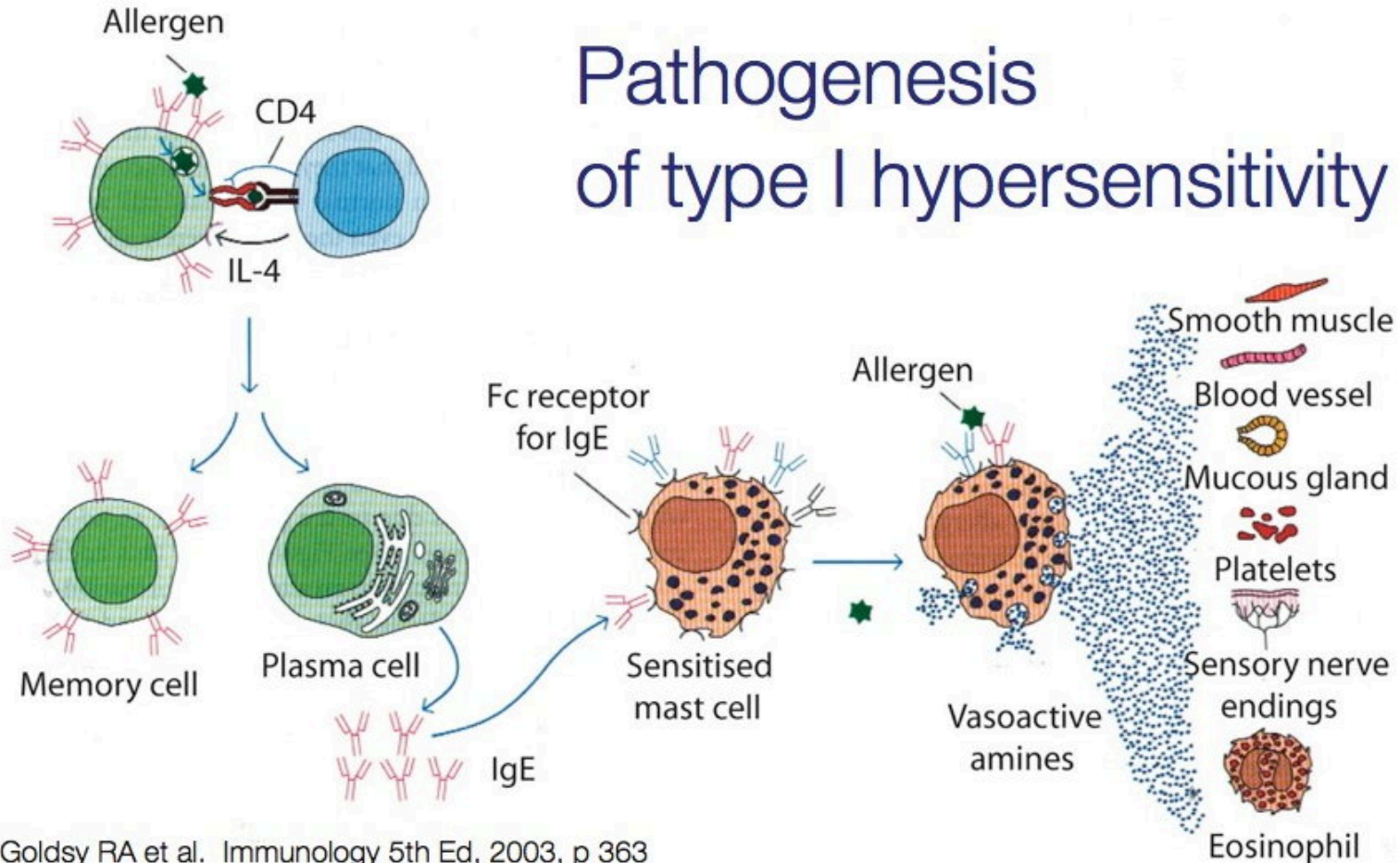
# Coombs-Gell classification\*

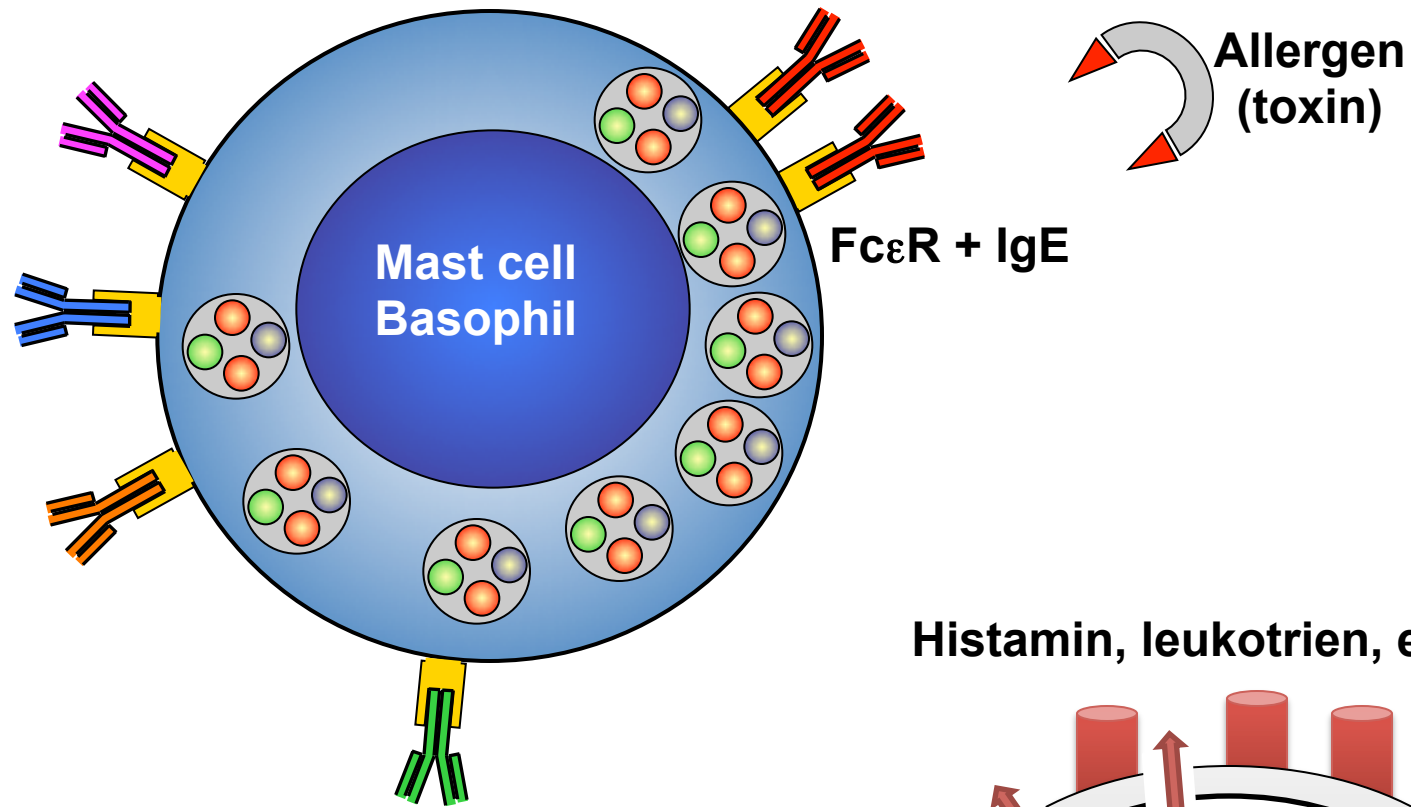
- Coombs's and Gell classification: is it still valid? Toxicology 158:43-49, 2001
- I. anaphylaxis (IgE)
- II. antibody mediated cytotoxicity
- III. immune complex mediated reaction
- IV. delayed type hypersensitivity
  - IV.a  $\gamma$ IFN-monocytes
  - IV.b IL-5 eosinophils
  - IV.c perforin/FasL cytotoxicity
  - IV.d IL-8 PMN

\*Gell PGH, Coombs RRA, eds. Clinical Aspects of Immunology. 1st ed. Oxford, England: Blackwell; 1963.

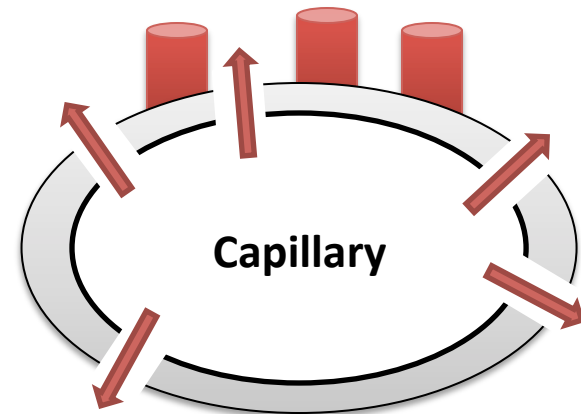
# Type I reaction - anaphylaxis

## Pathogenesis of type I hypersensitivity





**Histamin, leukotrien, etc**



# Urticaria, Quincke- edema



# Acute urticaria





# Mediators of hives and swelling

Mast cells: **histamine**

Prostaglandin D2

Leukotrienes C and D

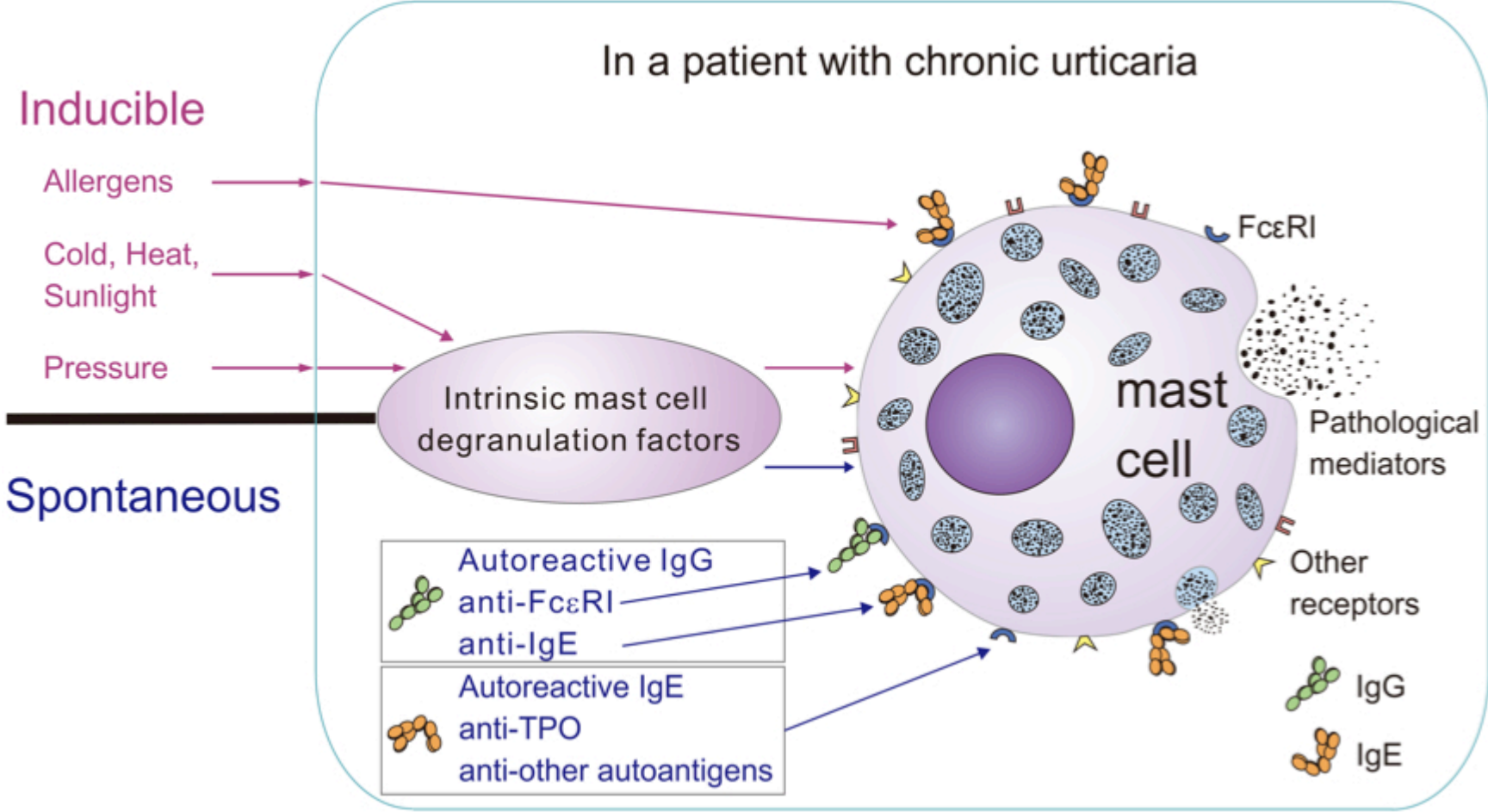
Platelet activating factor

Complement system: **anaphylatoxins, C3a, C4a, C5a,**  
histamine

Hageman factor dependent pathway: **bradykinin**

Mononuclear cells: histamin releasing factors,  
chemokines

# What can lead to mast cell degranulation?





← INDUCIBLE

→ SPONTANEOUS

# ALLERGY

# AUTOALLERGY

Exogenous antigen  
(eg. bee venom)

Endogenous antigen  
(eg. TPO)

IgE against  
exogenous antigen

IgE against  
endogenous antigen

Receptors?

Cold  
Warm  
Mechanical stress  
Light

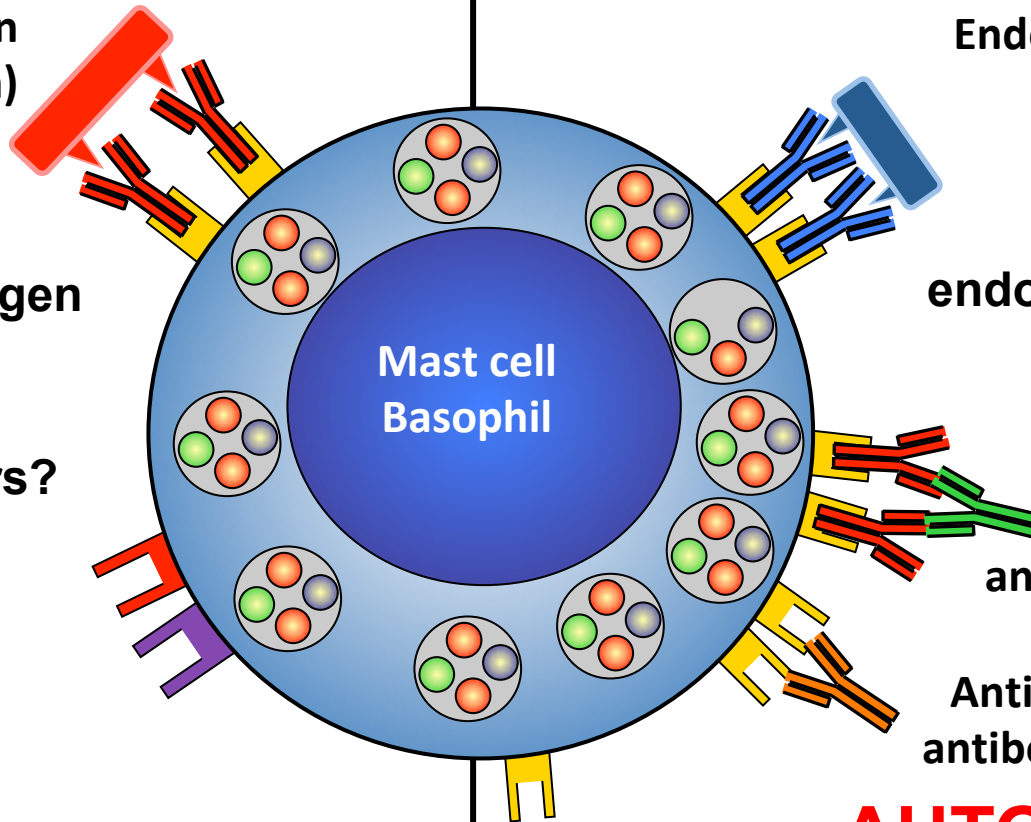
Anti-IgE  
antibody (IgG)

Anti- Fc<sub>ε</sub>RI  
antibody (IgG)

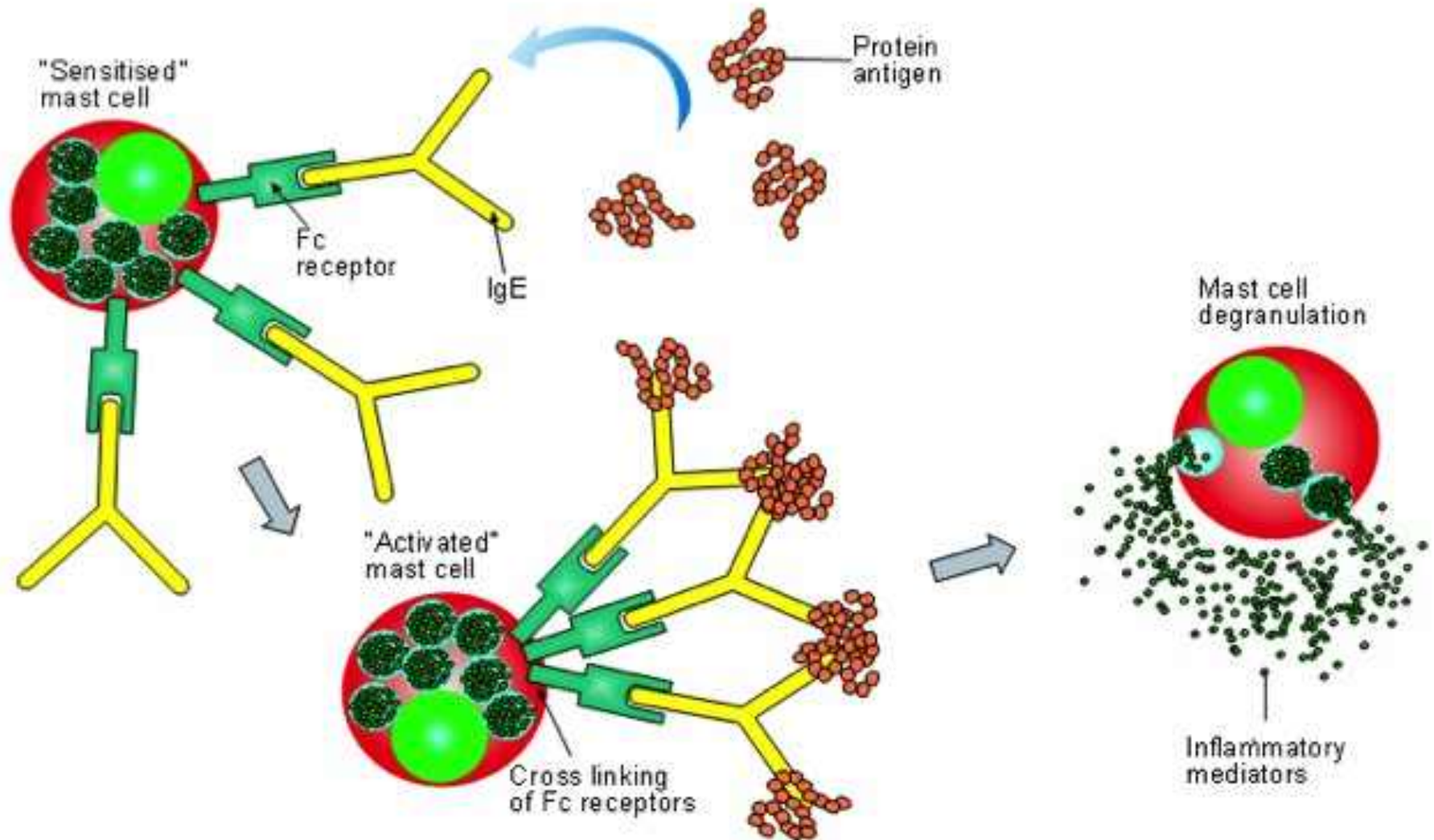
Mast cell  
Basophil

# PHYSICAL

# AUTOIMMUNE



# Type I – IgE mediated hypersensitivity



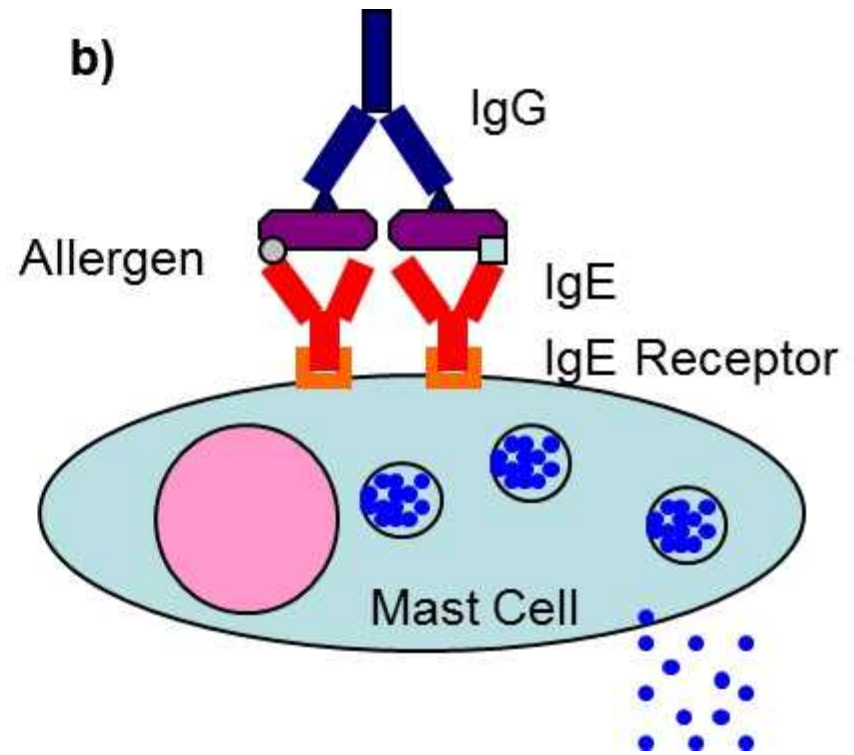
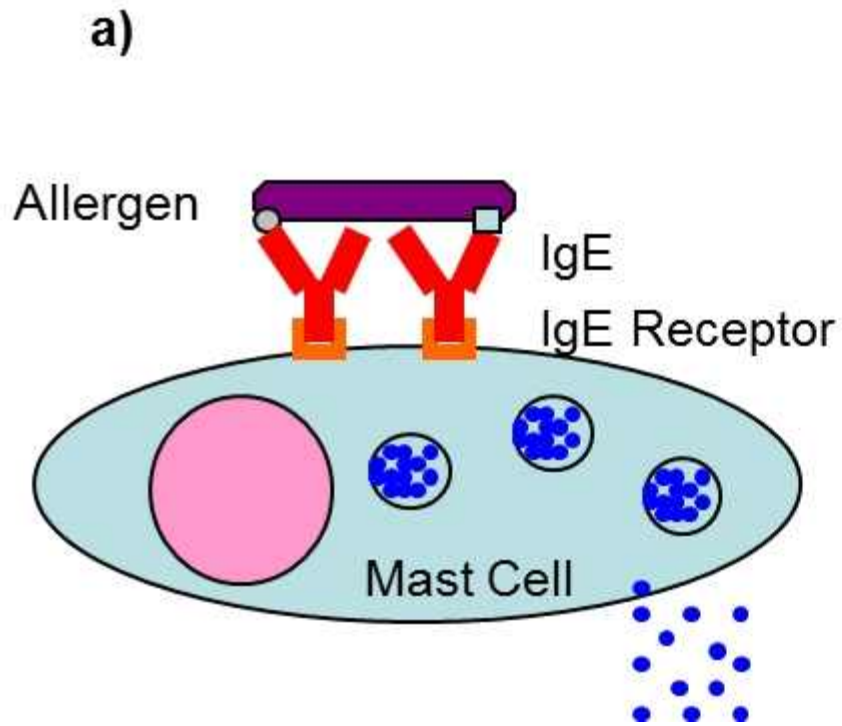
# Common allergens in allergic urticaria



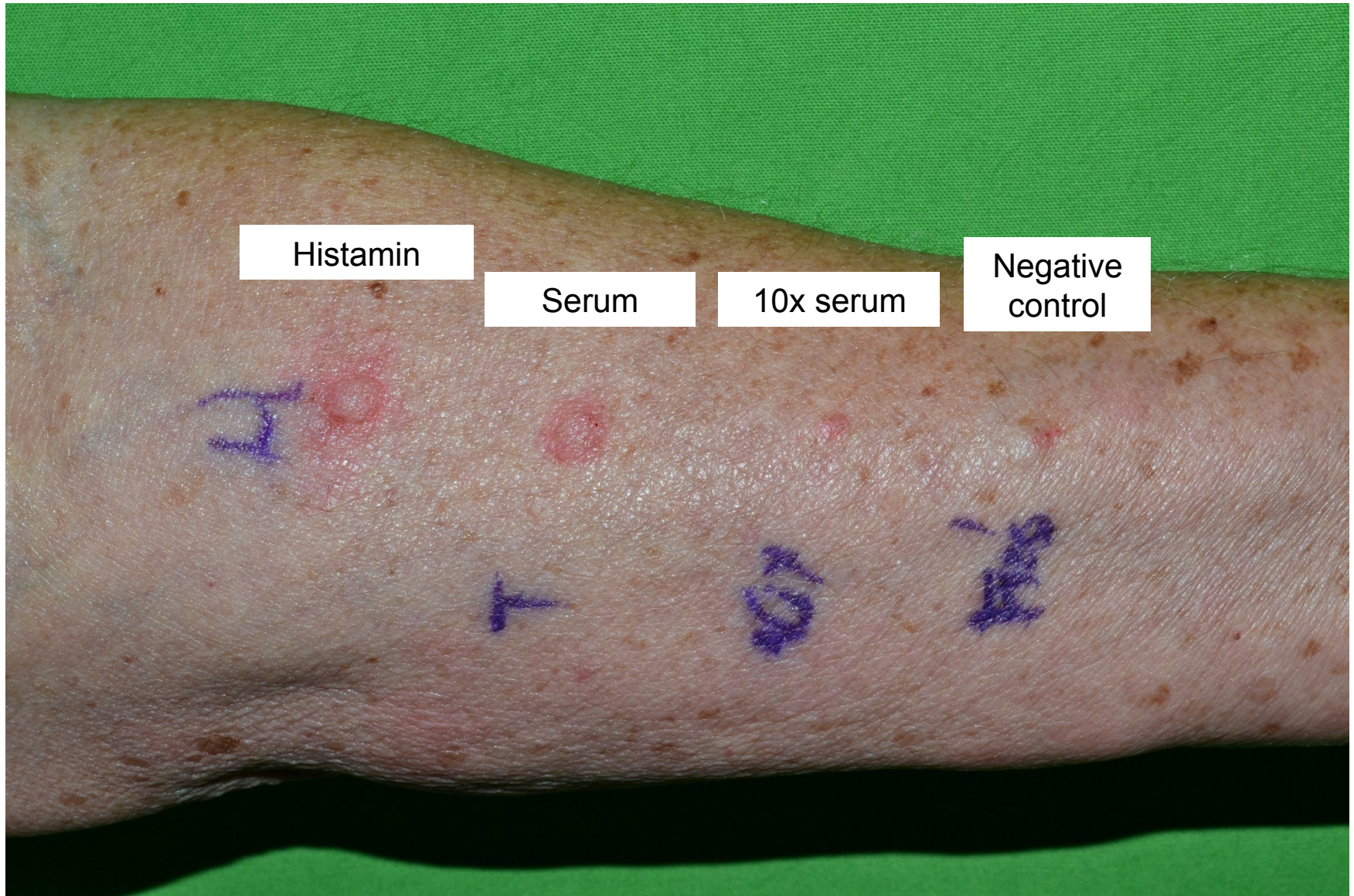
# Clinical symptoms of excessive histamin release

- Urticaria
- Quincke-edema
- Anaphylaxis
- Allergic rhinitis
- Allergic conjunctivitis
  - Diarrhoea
  - Vomitus
- Allergic asthma
- Bronchus constriction

## 2. Autoimmune urticaria



# Autologous serum test




# 3. Pharmacological

- Opioids (Codeine, morphine, pethidine)
- NSAID
- Contrast media

# Aspirin, NSAID intolerance

- ciklooxigenase

• Cox-1  Cox-2

salicylic acid derivates,  
propionic acid derivates

(ibuprofen, ketoprofen)

anilin derivates

(phenacetin, paracetamol)

acetic acid derivates

(indomethacin, diclofenac)

- prostaglandins

- lipoxigenase

- leukotriens



vasoconstriction,  
exudation,  
bronchospasm,  
vasodilatation



## 4. Contact urticaria



## 5. Dermographism – urticaria factitia



I AM THE  
CINNAMON  
PUPPIES  
WIFE  
SMELL ME

YOU TOUCH  
YOUR BELLY TO MY  
IN THE DAY AIR AND'S



pressure  
heart returning  
the feet that

in early days  
soft glow  
goes what  
five  
the

## 5. Cold and heat urticaria

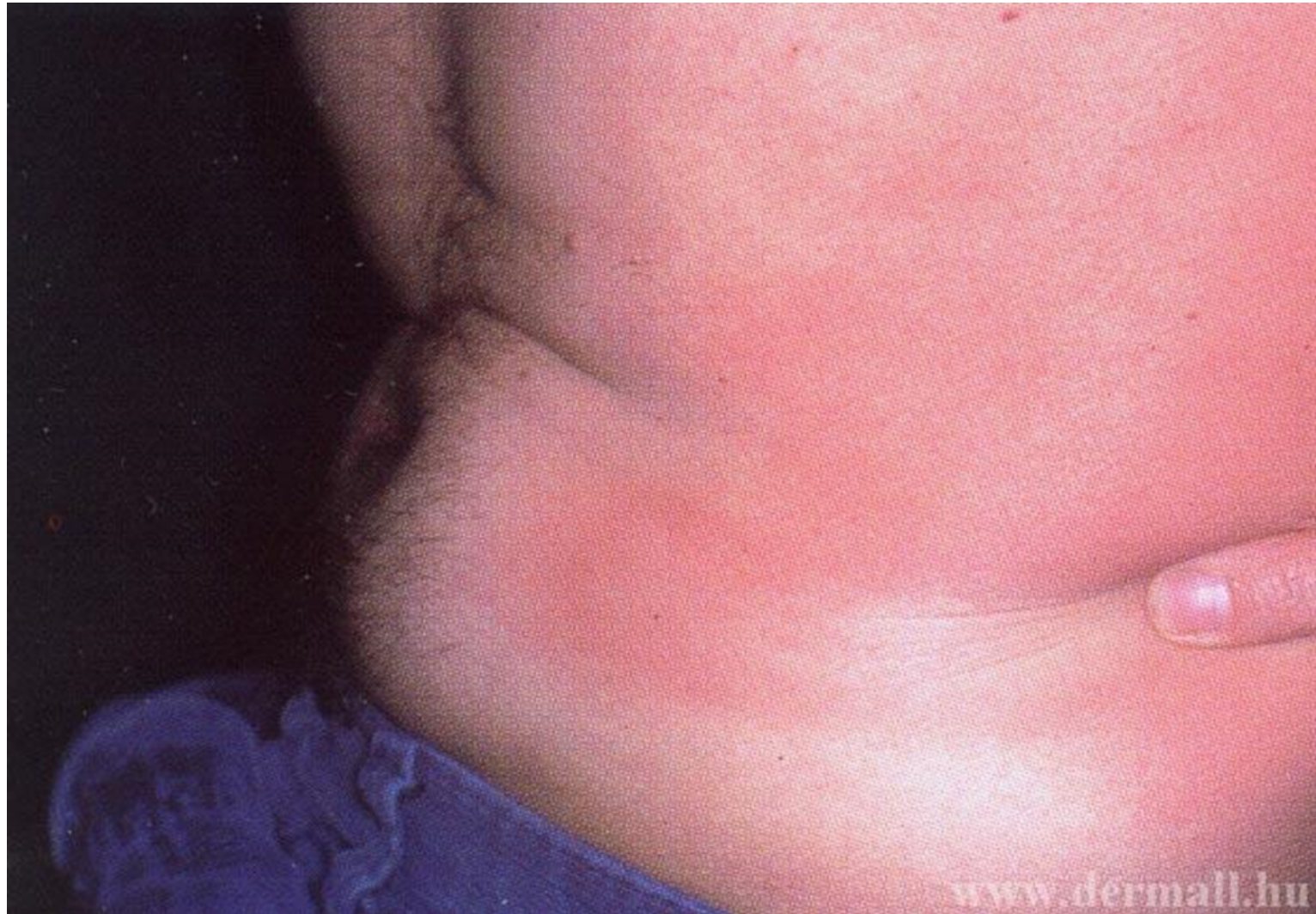


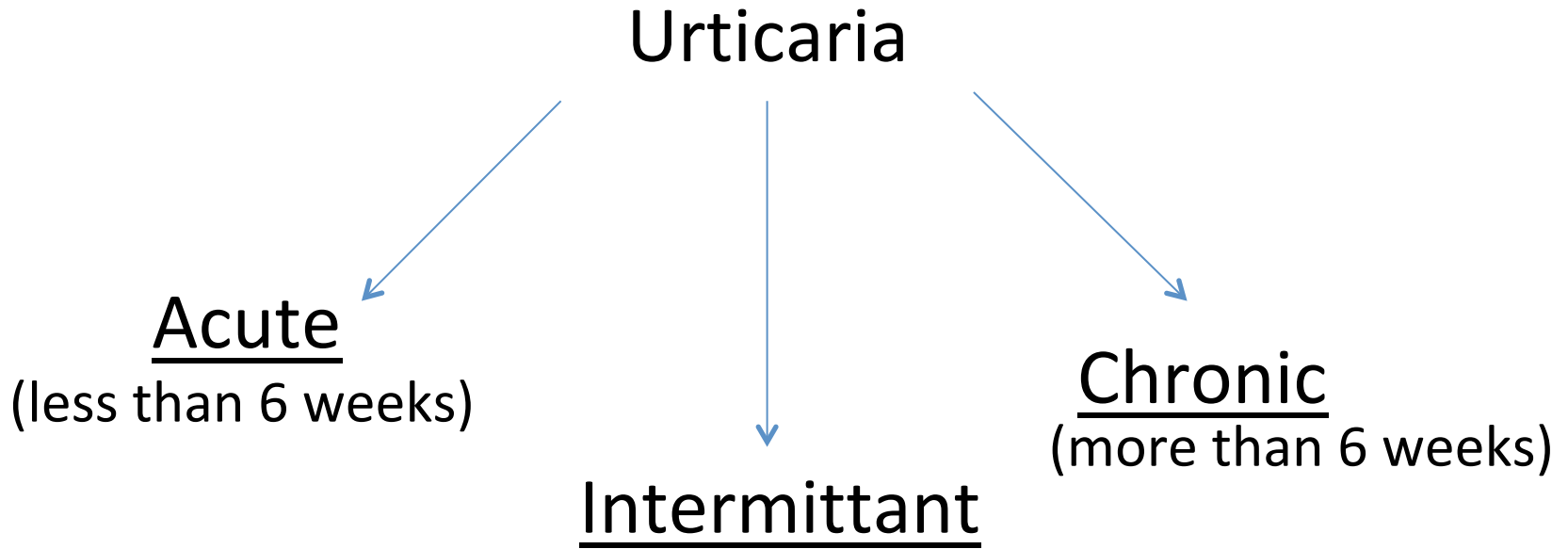
(cryoglobulins, cold agglutinins, cryofibrinogens)

## 5. Cold and heat urticaria



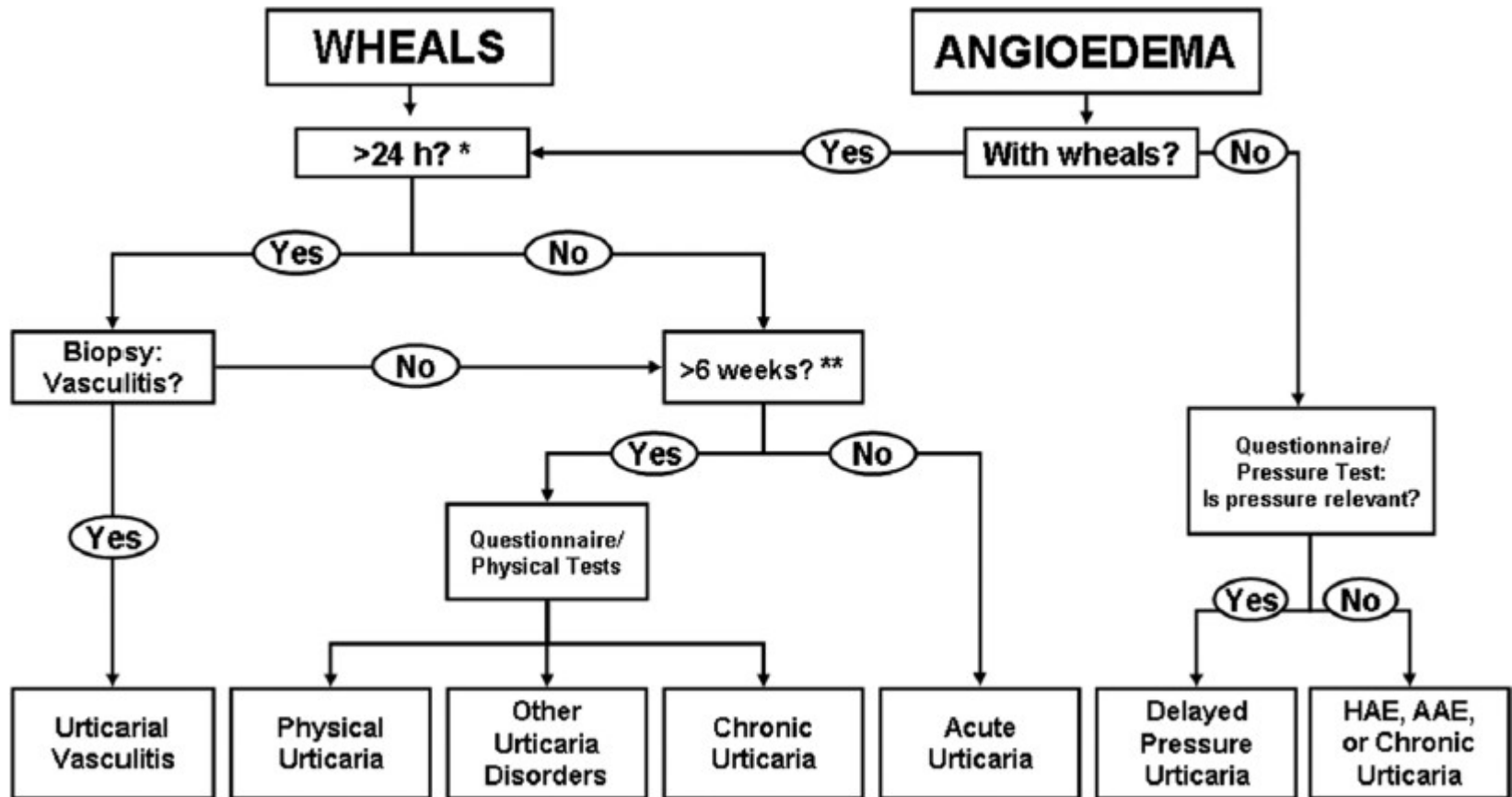
## 5. Solar urticaria





- Individual lesions disappear after 24 hours
  - if not more likely urticaria vasculitis

# Diagnostic algorithm for urticaria





# Bee, wasp venom allergy

- severe anaphylaxis, Quincke edema
- develops in minutes



# Insect bites allergy

Toxic and allergic reactions

Venom contains: vasoactive amines  
enzymatic peptides  
free amino acids

Wasp

Bee

} venom (Prick test)

Specific immunotherapy



# Local reaction to venoms



# Anaphylaxis, shock

- Acute onset (minutes to hours after drug, food, insect bite)
- Lidocain and local anaesthetics!
- Low blood pressure
- Shortness of breath, wheezes, stridor
- Gastrointestinal symptoms (vomiting, diarrhea)

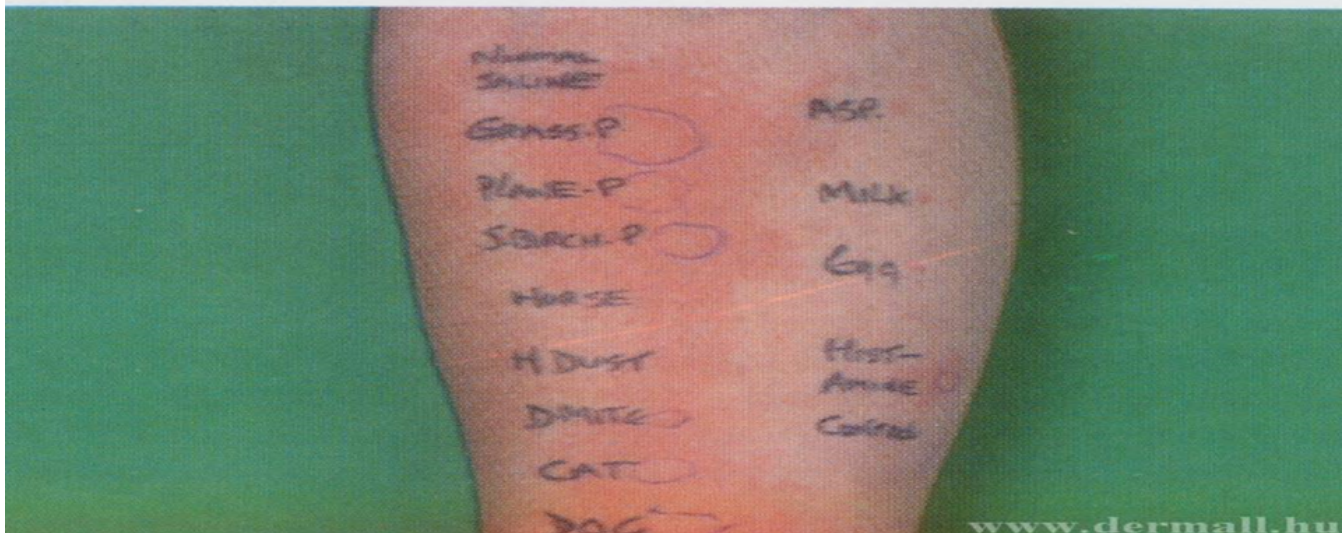
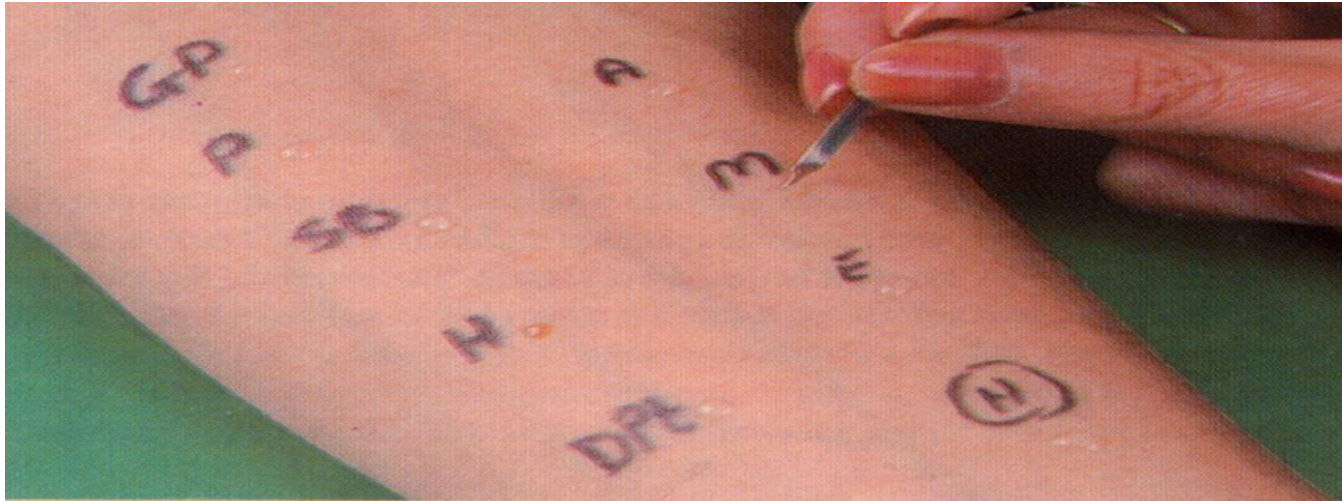
# Epinephrine self injector for patients with severe allergies



# Determination of specific IgE



# Prick-test

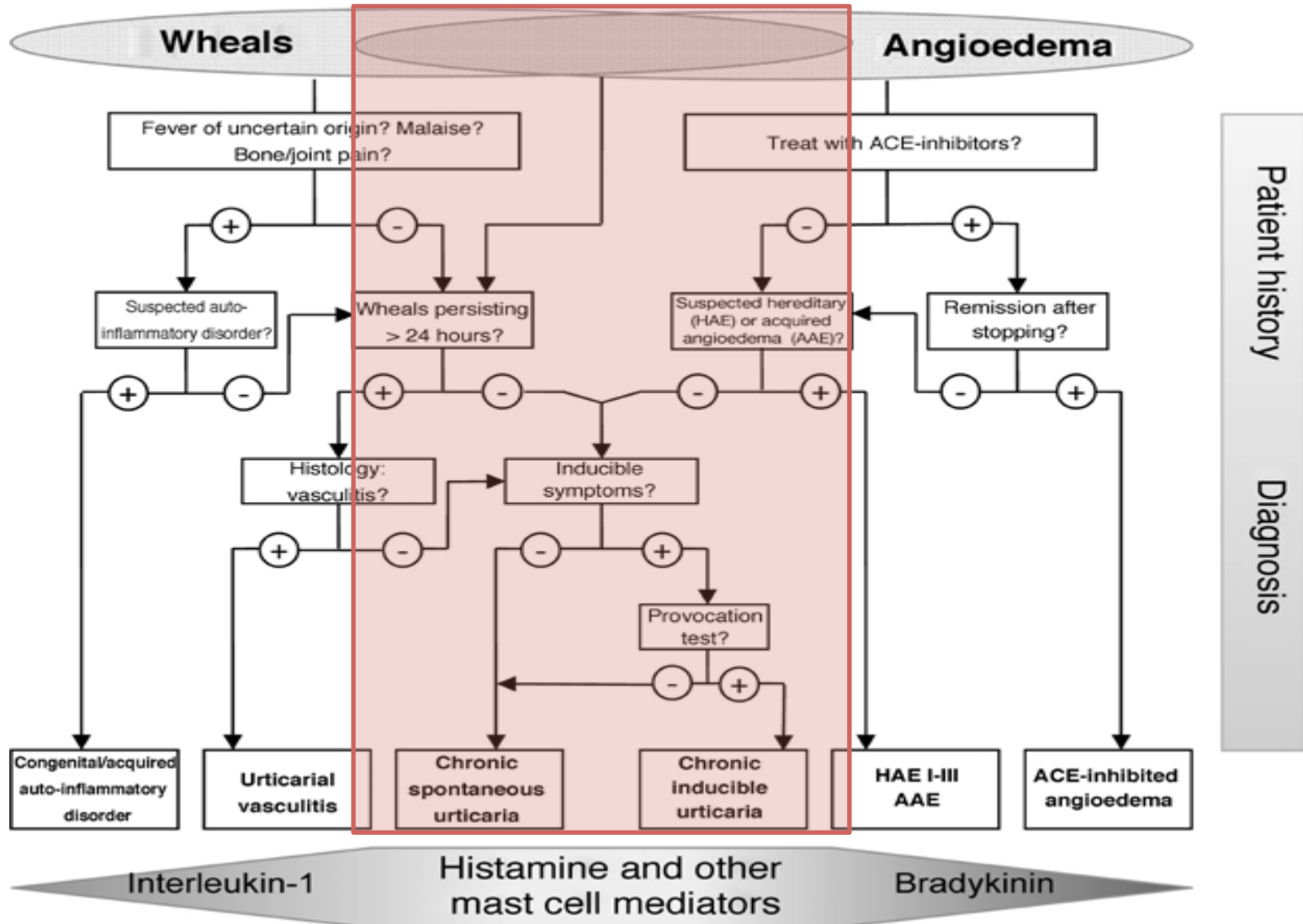


# Diagnosis, investigations

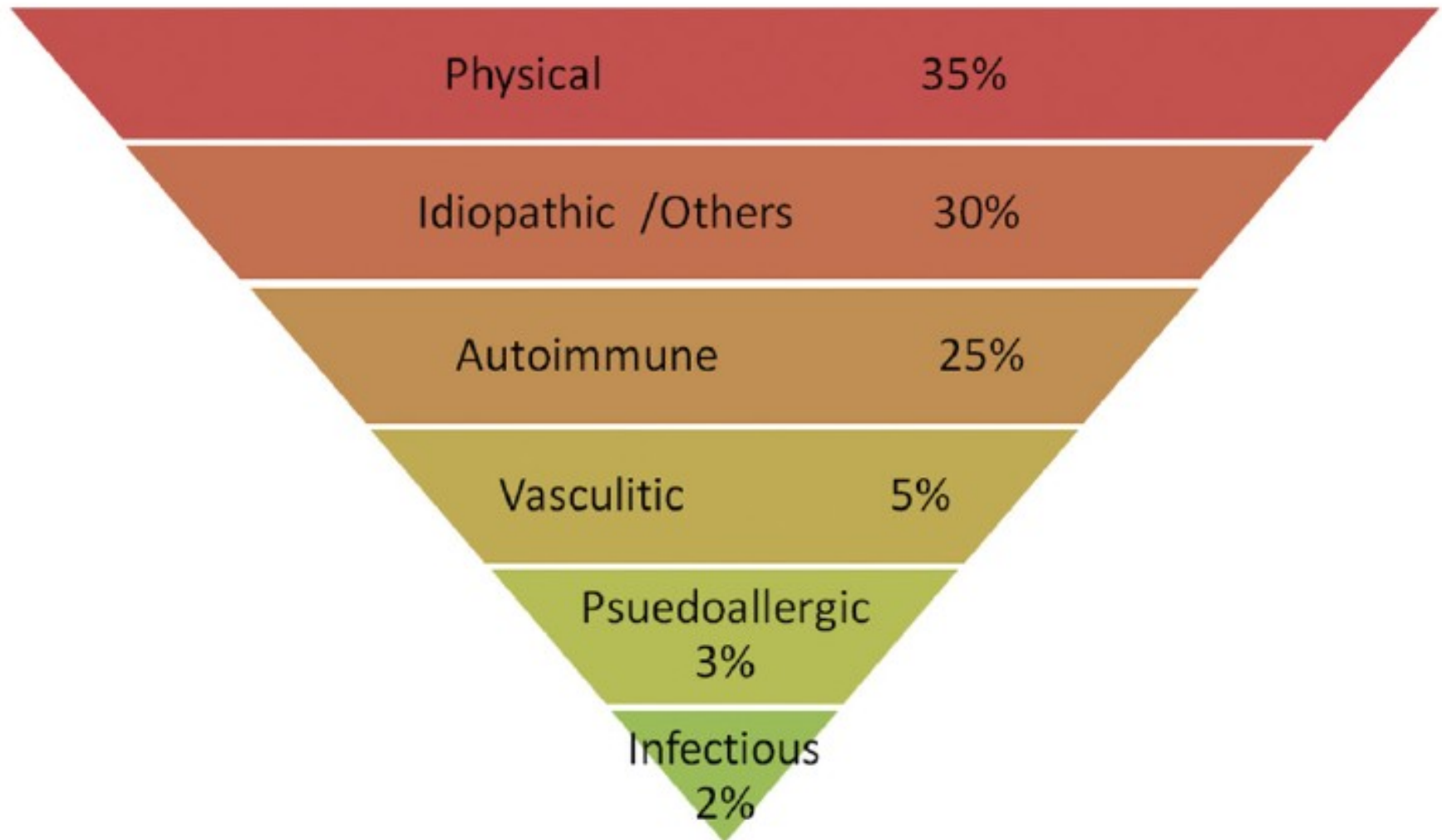
- Acute urticaria – no need for more investigation
- Chronic urticaria – laboratory investigation
  - (CRP, AST, ESR)
  - stool helminth
  - ANA
  - TSH, other thyroid specific antibodies
  - autologous serum test
  - infection: Yersinia, Staphylococcus,  
Streptococcus
  - Helicobacter pylori



# Diagnostic algorithm for chronic urticaria



# The causes of chronic urticaria



# Oral allergy syndrome

## Pollens

## Foods

**birch**



**potato  
carrot  
apple  
celery**

**tree pollens**



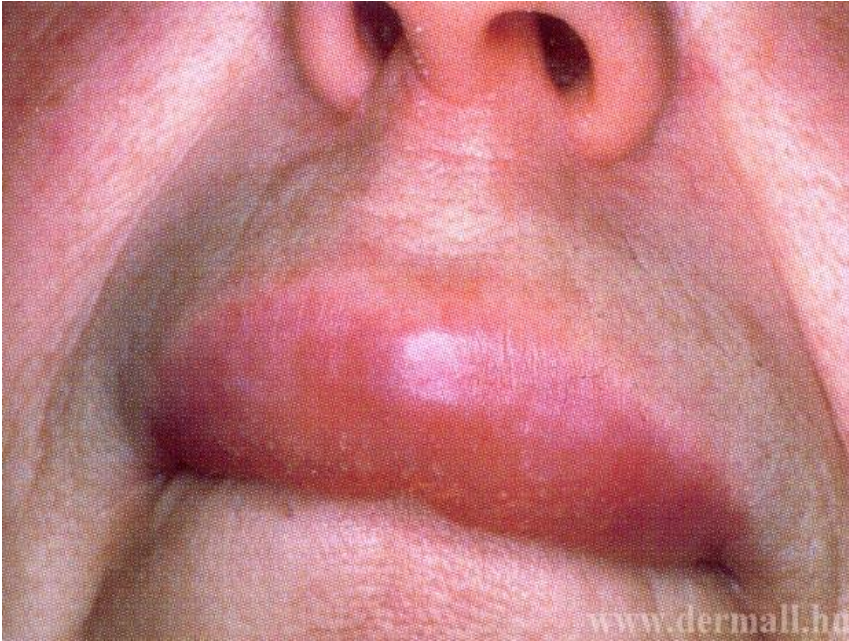
**kiwi  
almond  
curry  
honey**

**mugwort  
weeds  
ragweed**



**parsley  
garlic  
watermelon**

# Oral allergy syndrome



Kiwi sensitivity



Vanilla sensitivity



# Food cross-reactivity

**soy**



**walnut, wheat**

**peanut**



**beans**

**cucumber, tomato**



**carrot**

**propolis**



**vanillin, cinnamon,  
benzoic acid**

**balsam of Peru**

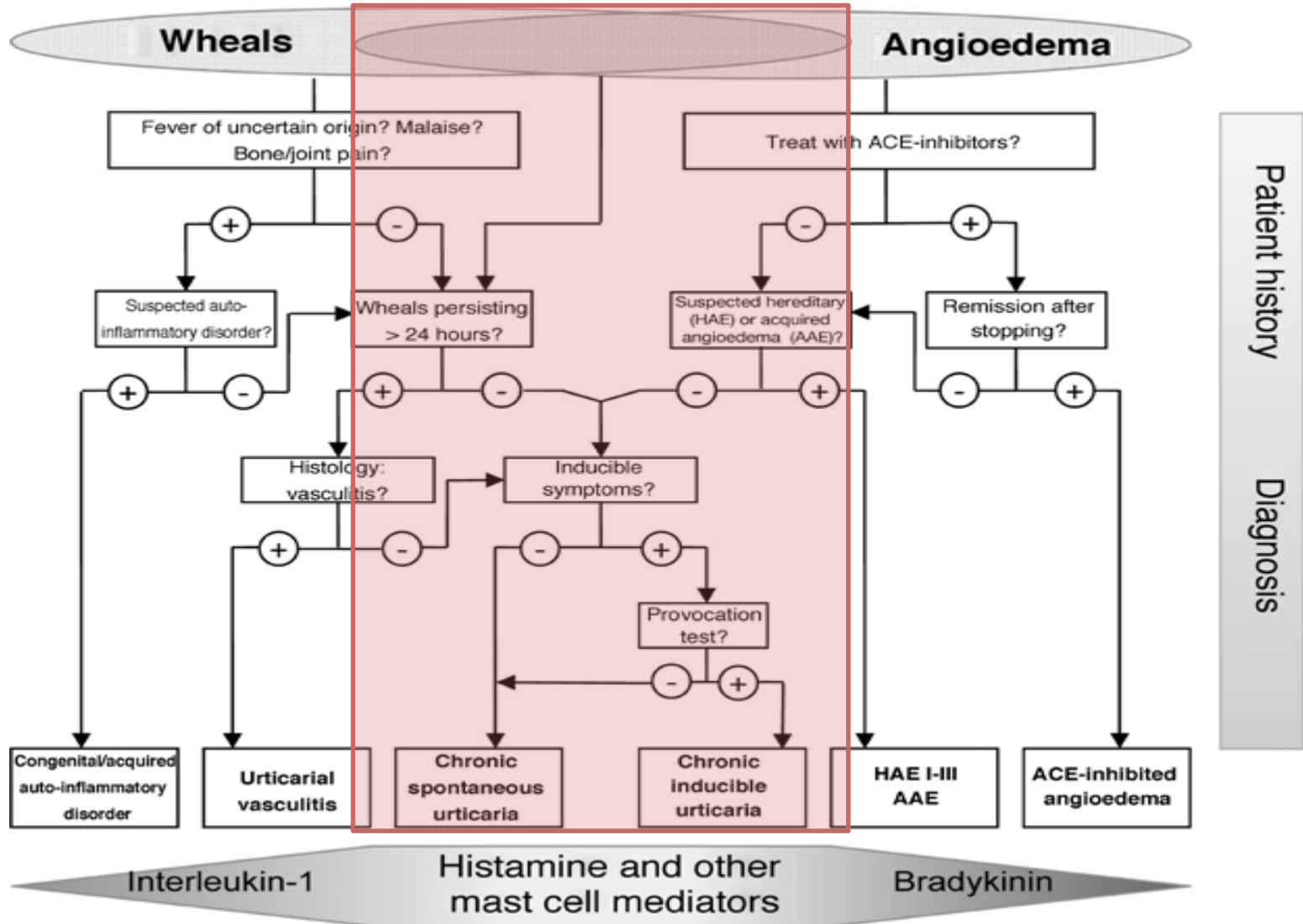


**cosmetics, taste  
enhancers**

# Hereditary angioedema (HANO)

- autosomal dominant inheritance
- recurrent attacks of abdominal pain, massive edema of soft tissues
- absence of C1 esterase inhibitor
- C4 is diminished even without symptoms
- normal even elevated C1INH level: dysfunctional protein
- complement pathway, plasma kinin forming pathway are involved
- Therapy: danazol, stanozolol (androgens induce synthesis of C1 INH and raises C4 level), aminocaproic acid, in acute cases: fresh frozen plasma, C1INH injection (Benedril)

# Diagnostic/therapeutic algorithm for chronic urticaria

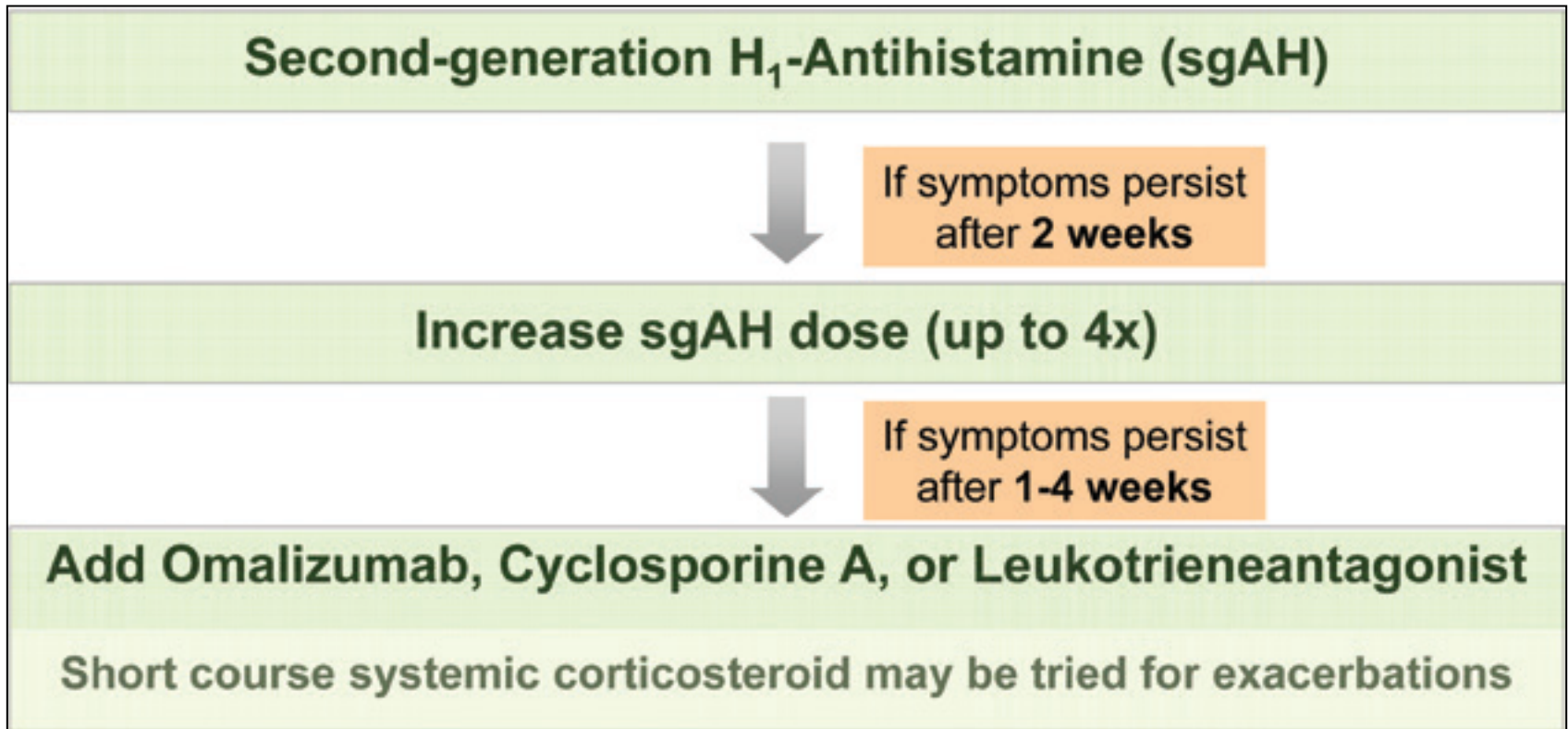




# Therapy I.

- Find and eliminate the cause (the case history is essential)
- Antihistamines: levocetirizine, desloratadine, hydroxyzine
- H1+H2 antihistamines (cimetidine, ranitidine)
- Tranquillizers
- Terbutalin+aminophyllin - cold urticaria
- Cinnarizin+pizotifen - dermographism

# Treatment algorithm for chronic urticaria

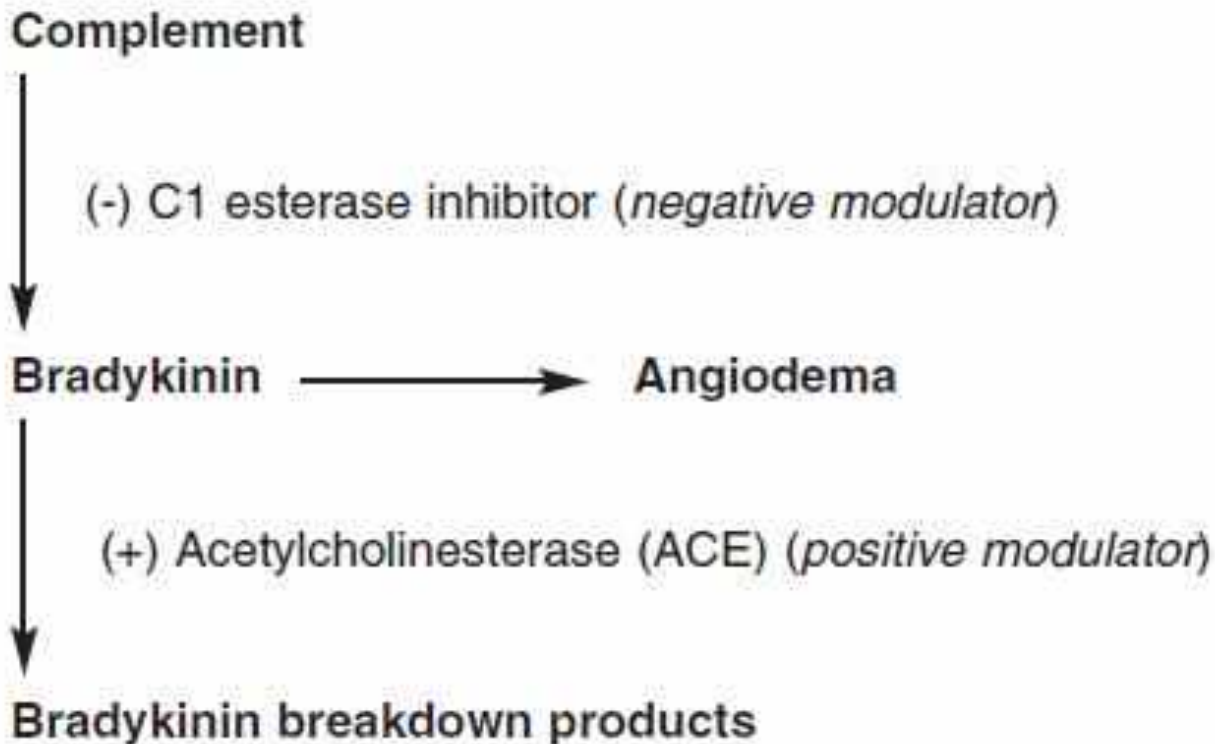


# Therapy II.

- Autoimmune urticaria:
  - high dose antihistamines (4x desloratadine, 4x levocetirizine)
  - steroid
  - cyclosporin
- Urticaria vasculitis:
  - steroid
  - dapsone
- Severe acute urticaria with Quincke edema: epinephrin, steroid, antihistamin if blood pressure is normal or above
- Anaphylaxis: Tonogen!

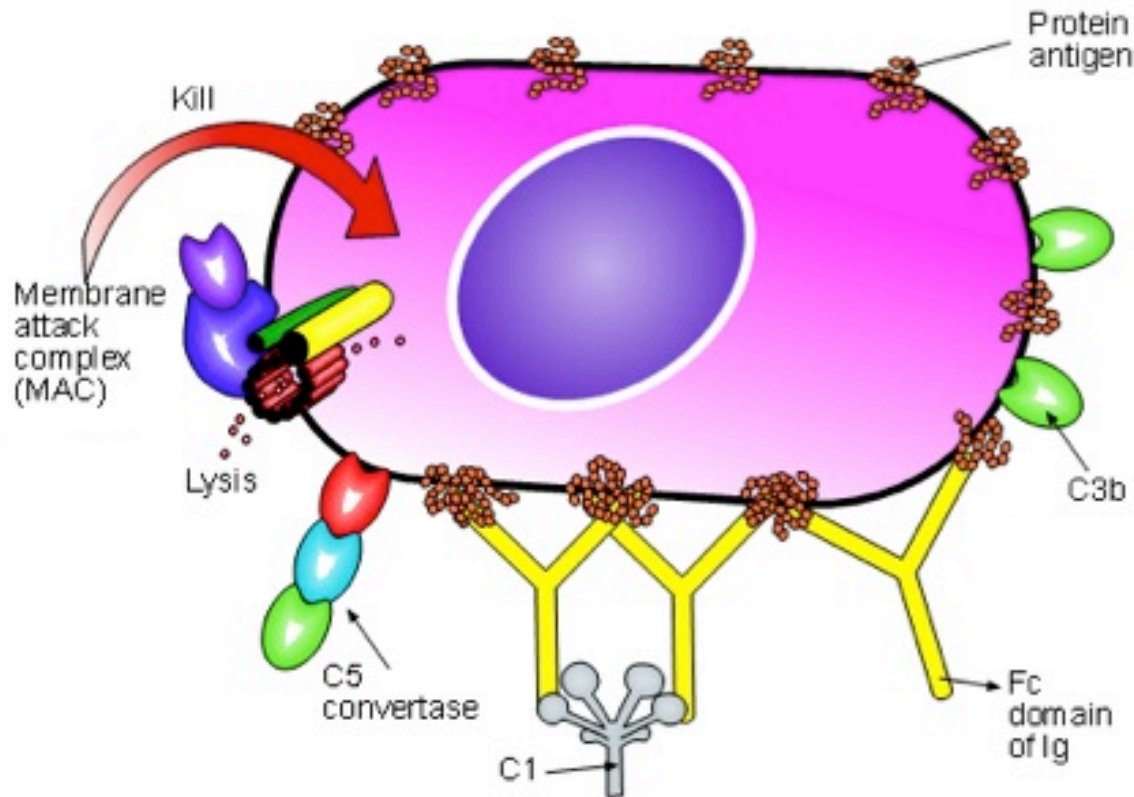
# ACE-inhibitors

- Angiotensin converting enzyme inhibitor –  
bradykinin pathway in the pathogenesis of angioedema





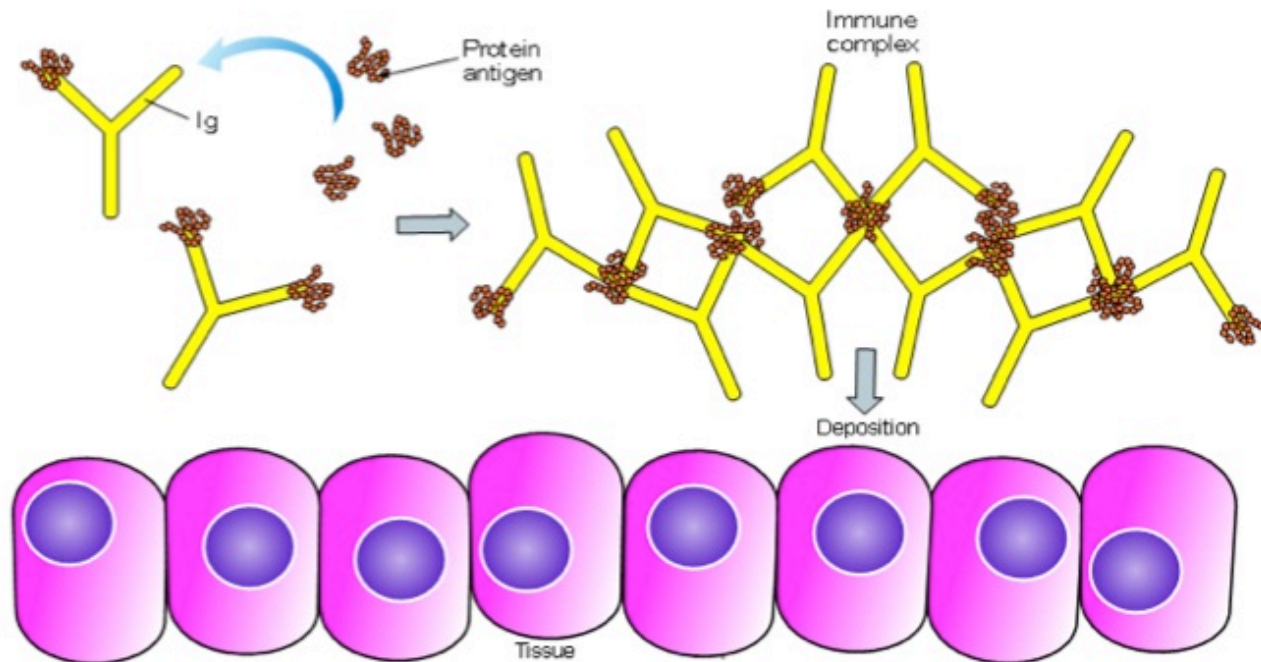
# Type II reaction – antibody dependent cytotoxicity



# Type III reaction – immune complex mediated reaction

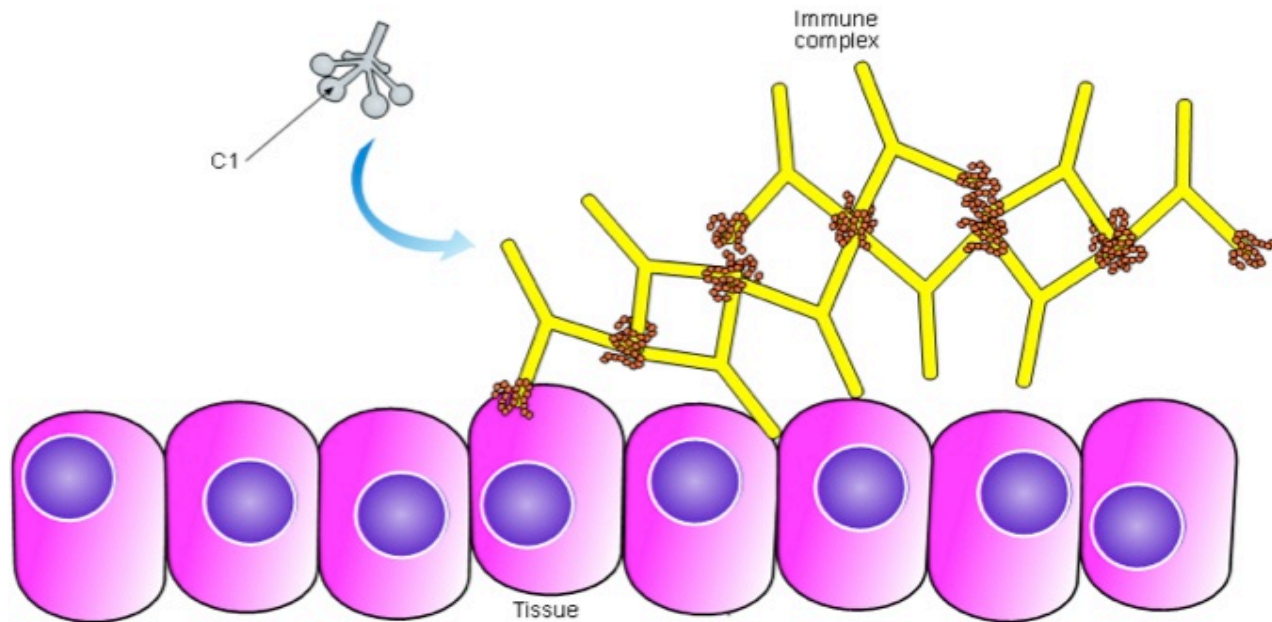
*Type 3 - immune complex hypersensitivity*

Figure 3a



# Type III reaction – immune complex mediated reaction

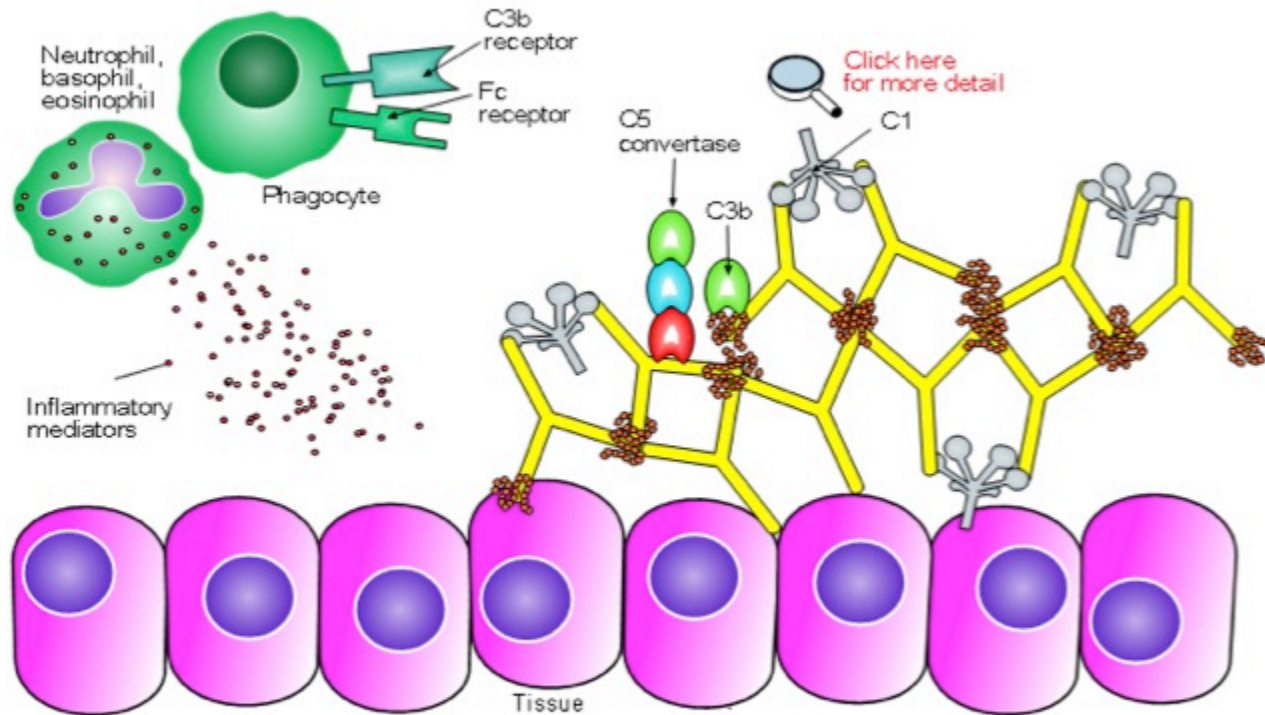
Figure 3b





# Type III reaction – immune complex mediated reaction

Figure 3c



# Arthus reaction

- Late type (3-8 hours)
- Serum sickness
  - Arthralgia
  - Vasculitis

# Immune-complex vasculitis



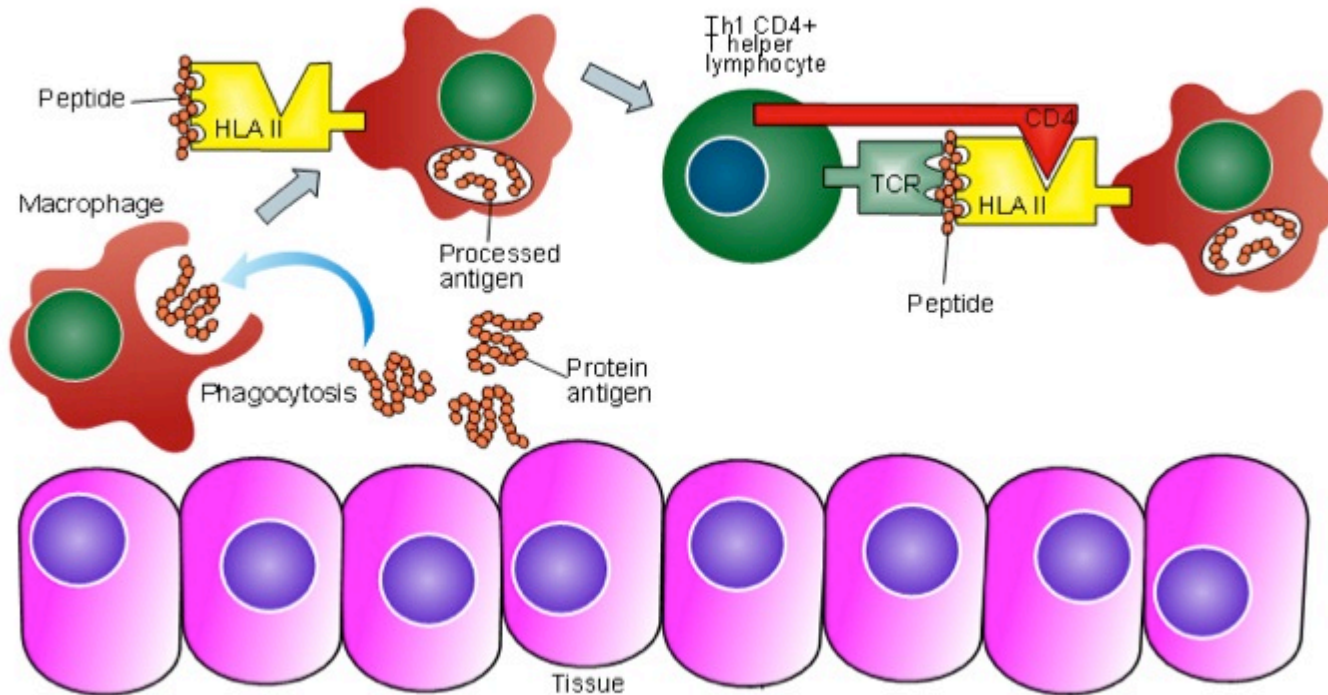
palpable purpura

# Palpable purpura



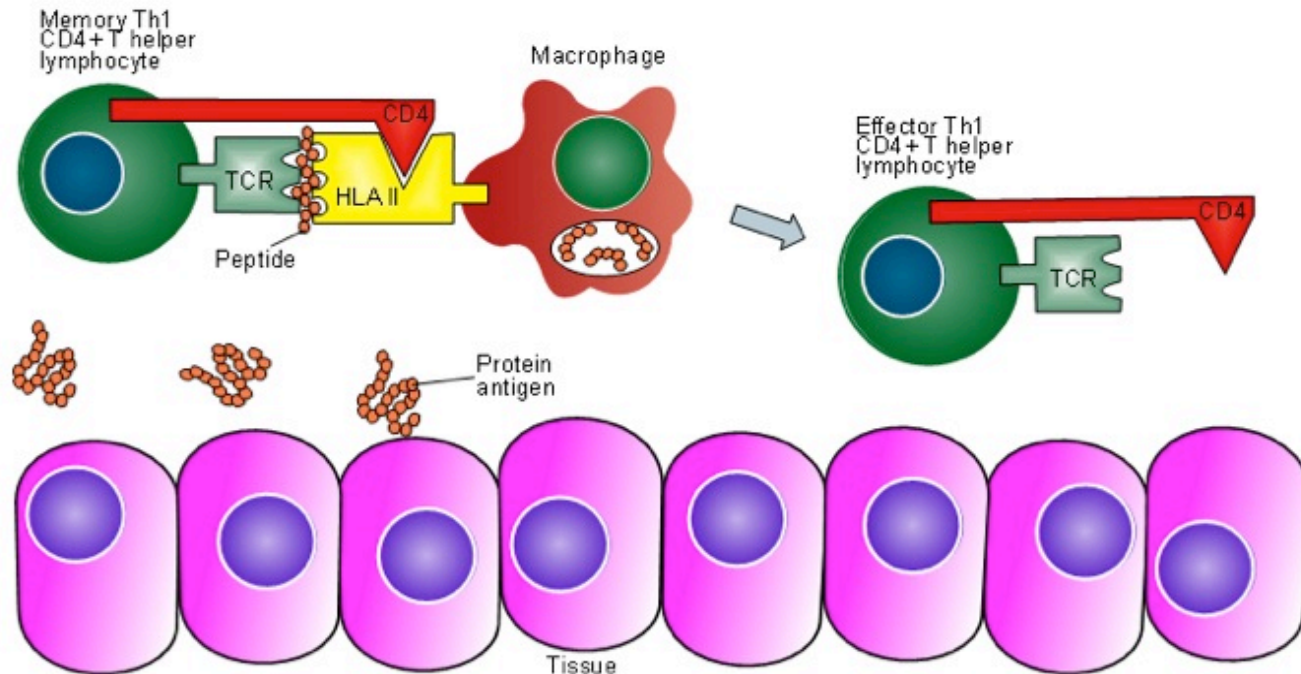
# Type IV reaction – delayed type hypersensitivity

Figure 4a: Primary exposure



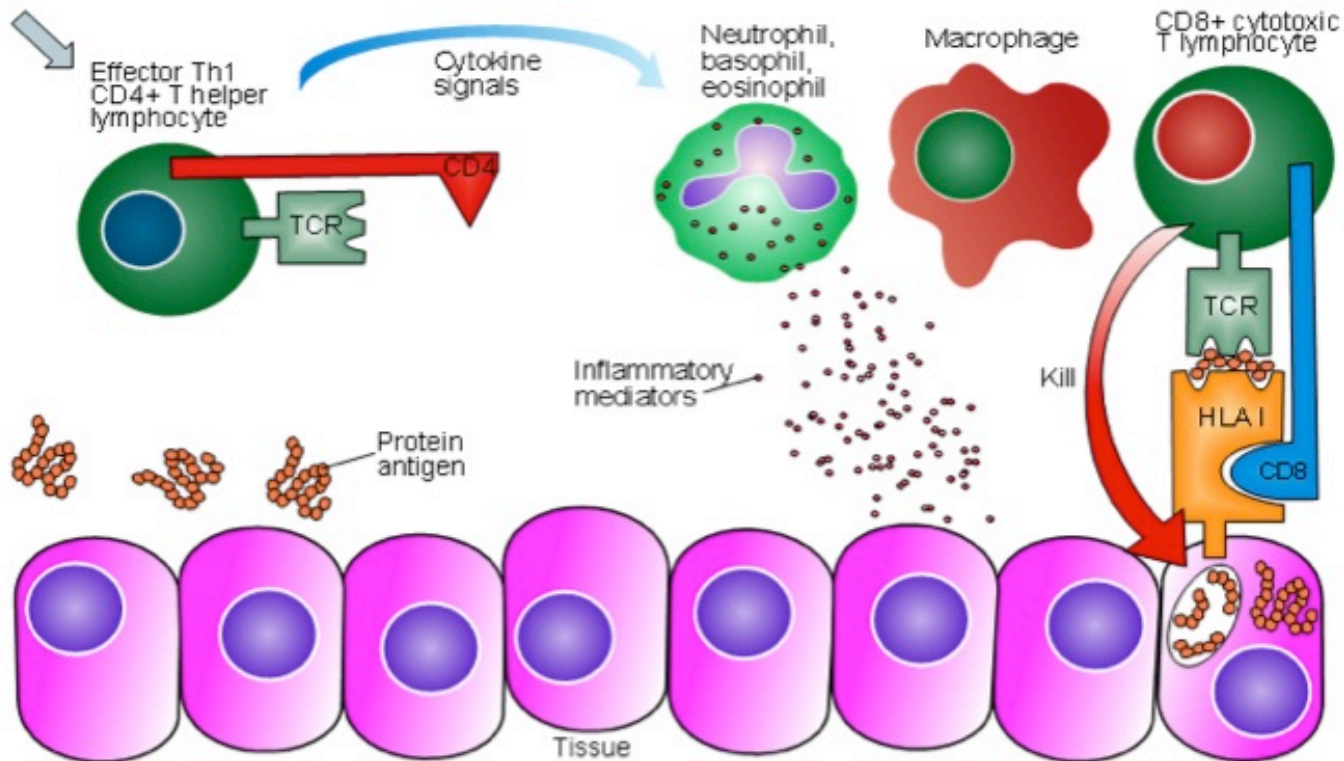
# Type IV reaction – delayed type hypersensitivity

*Figure 4b: Re-exposure*



# Type IV reaction – delayed type hypersensitivity

Figure 4c



# Allergic contact dermatitis





# Allergic contact dermatitis



# Allergic contact dermatitis



# Allergic contact dermatitis



# Type IVb reaction – Th2/IL-5 eosinophils DRESS syndrome



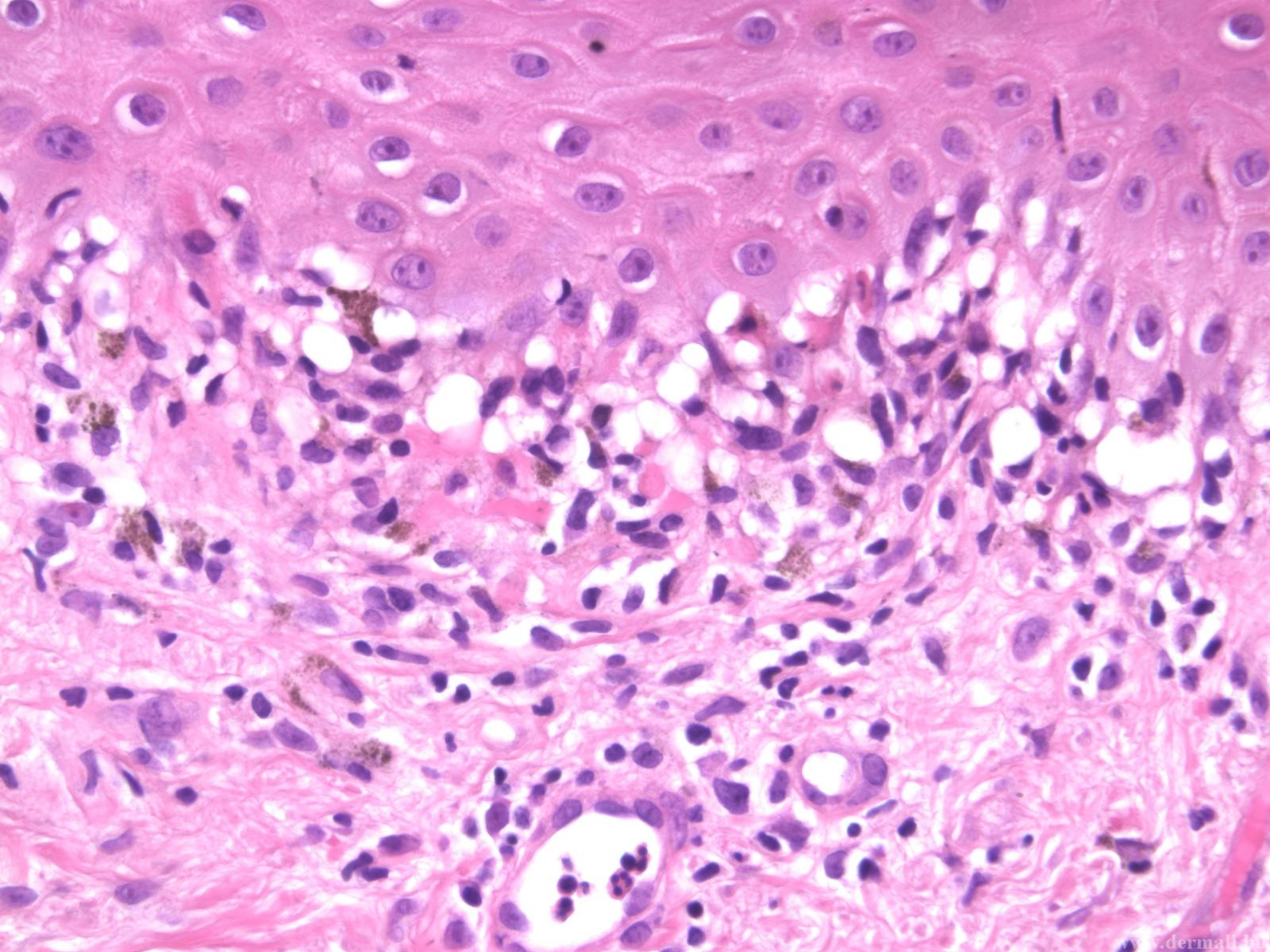
Drug hypersensitivity syndrome with eosinophilia/DRESS  
(drug reaction/rash with eosinophilia and systemic symptoms)-IV.  
b (Th2/IL5/eosinophils)

### (Anticonvulsant Drug Hypersensitivity/ADH)

Drug Induced Delayed Multiorgan Hypersensitivity Syndrome  
(DIDMOHS)

- carbamazepine 2-6 weeks (2-86 days)
- lamotrigine Generalized erythema
- phenytoin Liver function abnormalities
- phenobarbital Fever
- sodium valproate Eosinophilia
- felbamate Epicutaneous patch test can help

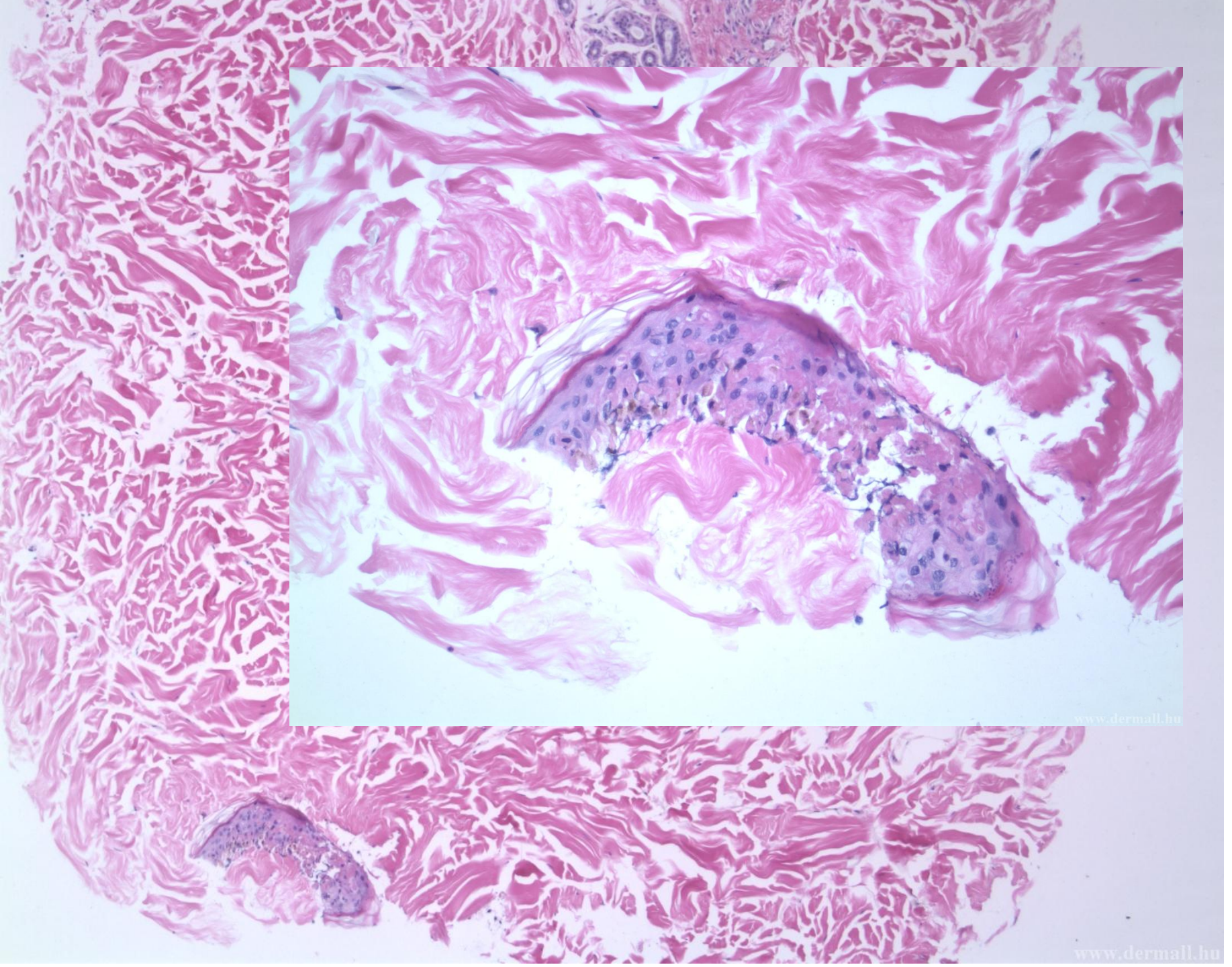




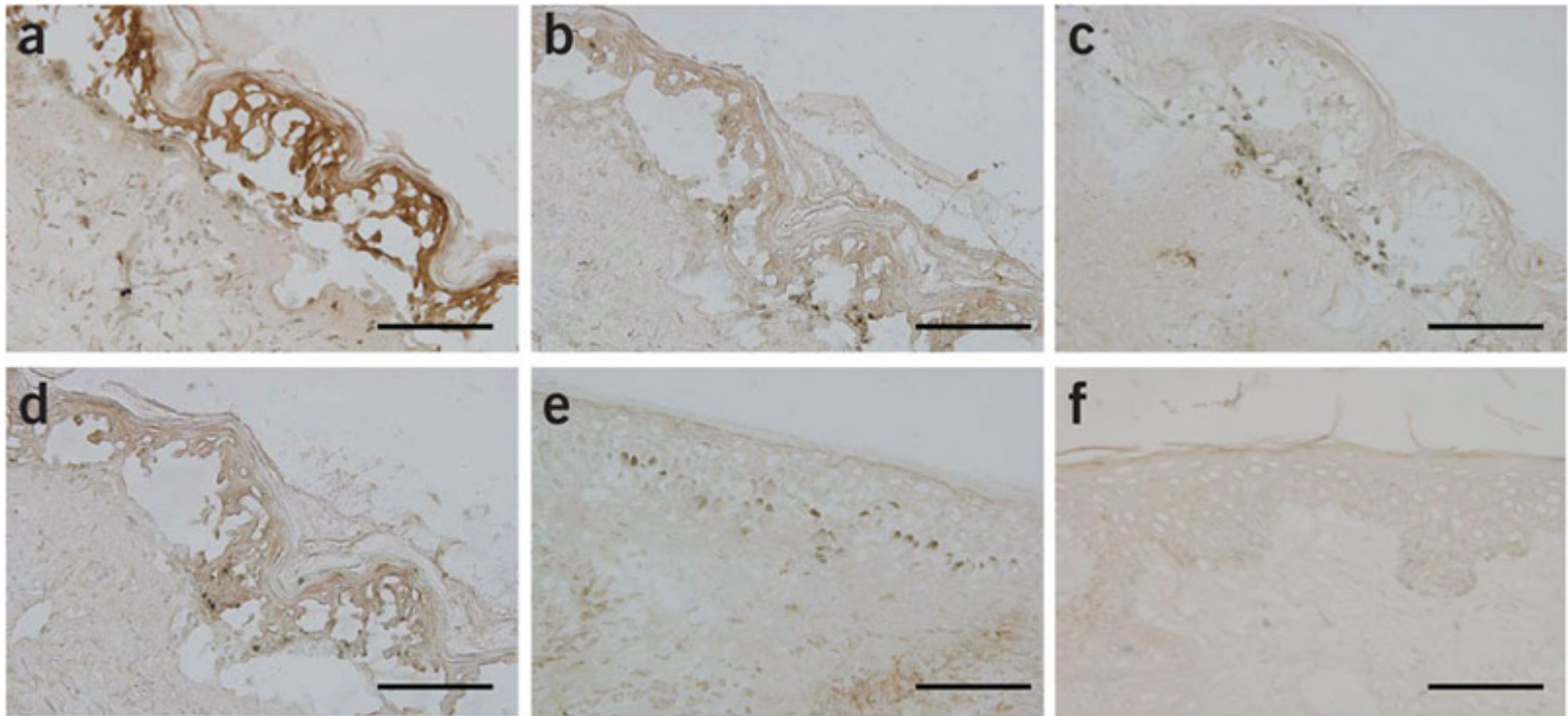
# Type IVc reaction – CD8+ FasL/perforine/ granzyme B cytotoxicity







# Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis



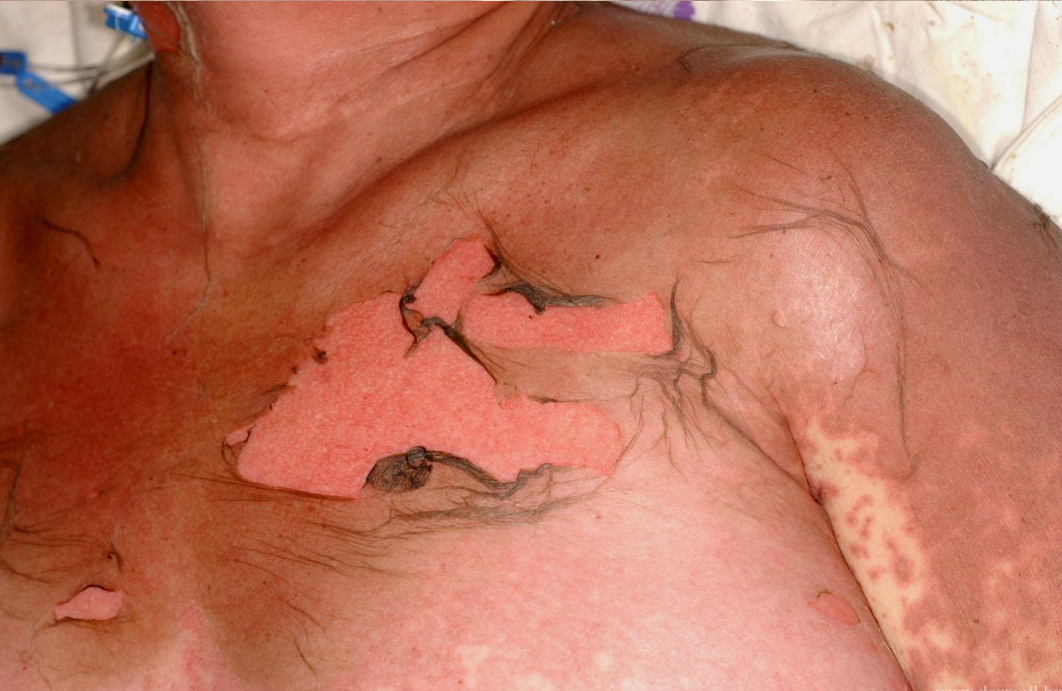
granulysin (a), granzyme B (b), perforin (c) and FasL (d)



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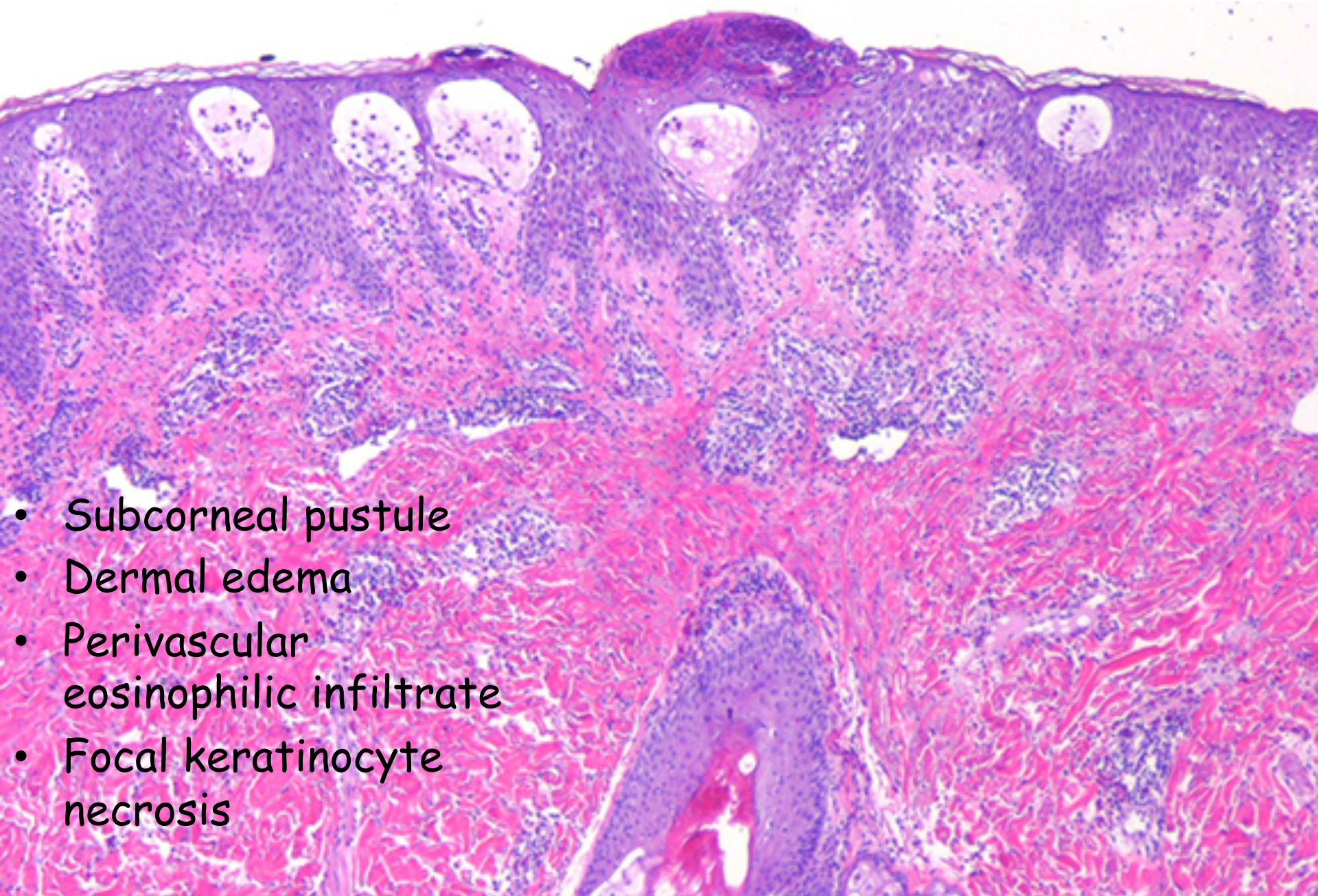
**BSA 70%**  
**SCORTEN 5**

# Type IVd reaction – IL8/GM-CSF/neutrophils

## Acute generalized exanthematous pustulosis (AGEP)

- **Symptoms:**
  - sterile pustule on erythematous base
  - Fever, leukocytosis eosinophilia
  - Acute onset, spontaneous remission after discontinuation of drug
- **Drugs:**  
terbinafine, metronidazole, carbamazepine, olanzapine,
- **Therapy**
- **Avoid drug**
  - 0,5 - 1 mg/kg prednisolone p.o.
  - antihistamine





- Subcorneal pustule
- Dermal edema
- Perivascular eosinophilic infiltrate
- Focal keratinocyte necrosis





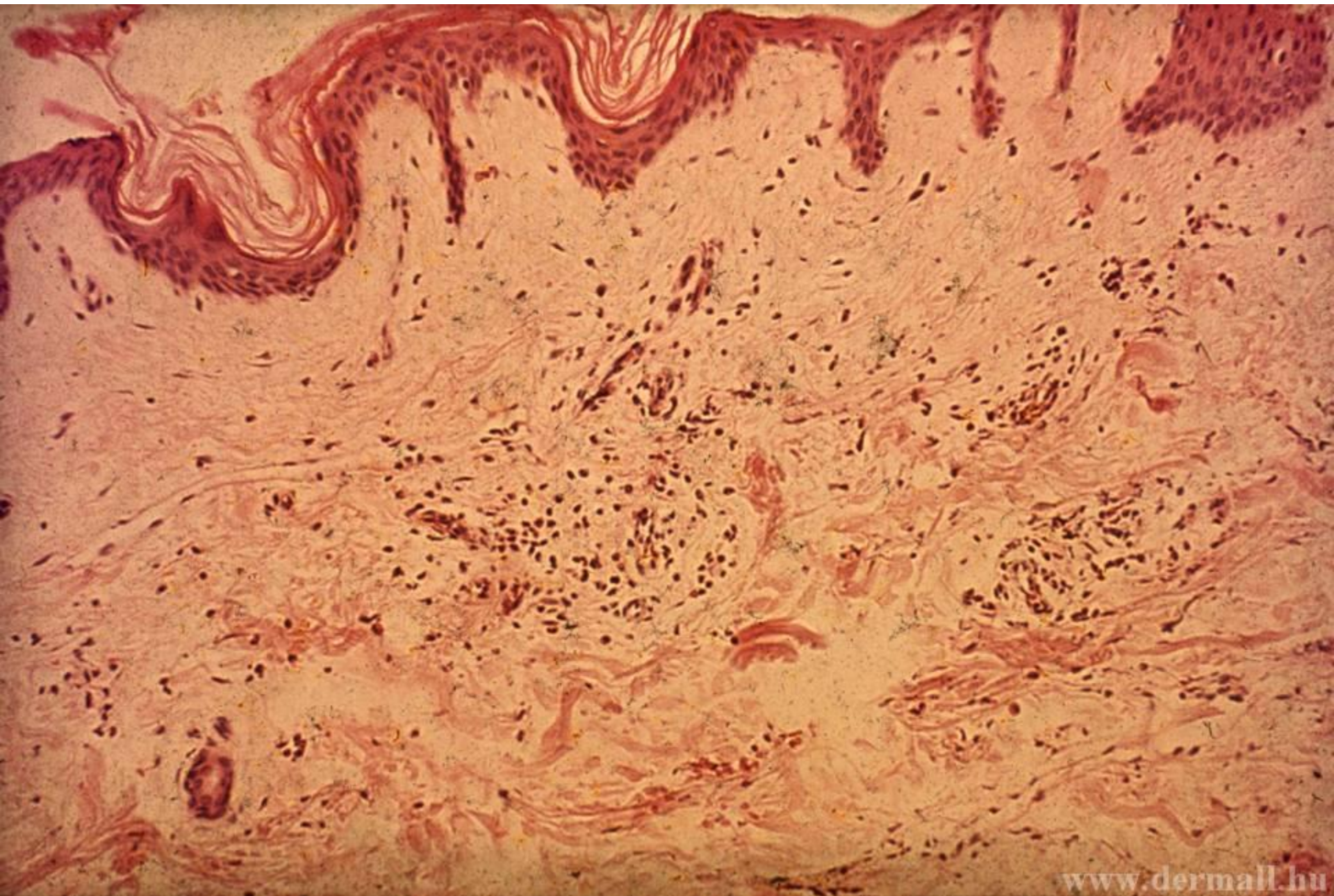
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# Diagnostic tests

- Type I reaction
  - In vivo: Prick test
  - In vitro: Specific IgE
- Type II reaction
  - Direct/indirect immunofluorescence
  - ELISA
- Type III reaction ???
- Type IV reaction
  - In vivo: epicutaneous (patch) test
  - In vitro: Lymphocyte transformation test

# Prick-test: type I hypersensitivity reactions



# Epicutaneous test: type IV hypersensitivity reactions



**+?: mild erythema**

**+: erythema, edema,  
infiltration**

**++: papule, vesicle**

**+++: papule, vesicle, bulla,  
erosion, ulcer**

**(crescendo)**

**IR: irritative reaction**

**(decrescendo)**

# Standard allergens – epicutaneous test



European and  
Hungarian standards

Dental materials

Steroids

Fragrance-cosmetics

Fotoallergens

Hair-care products

Atopy patch test

48-72 hours/7-10 days foto-patch: at 24 hours  $5 \text{ J/cm}^2$  UVA

# Steroid contact dermatitis



## **High allergic potential:**

**budenosid (Apulein)**

**tixocortol pivalat**

**prednicarbat**

## **Low allergic potential:**

**hydrocortison acetat (Laticort)**

**momethason fuorat (Elocom)**

**bethametason dipropionat**

**Soós és mtsai. Bőr. Vener. Szmlé.  
2004. 80:203-208**