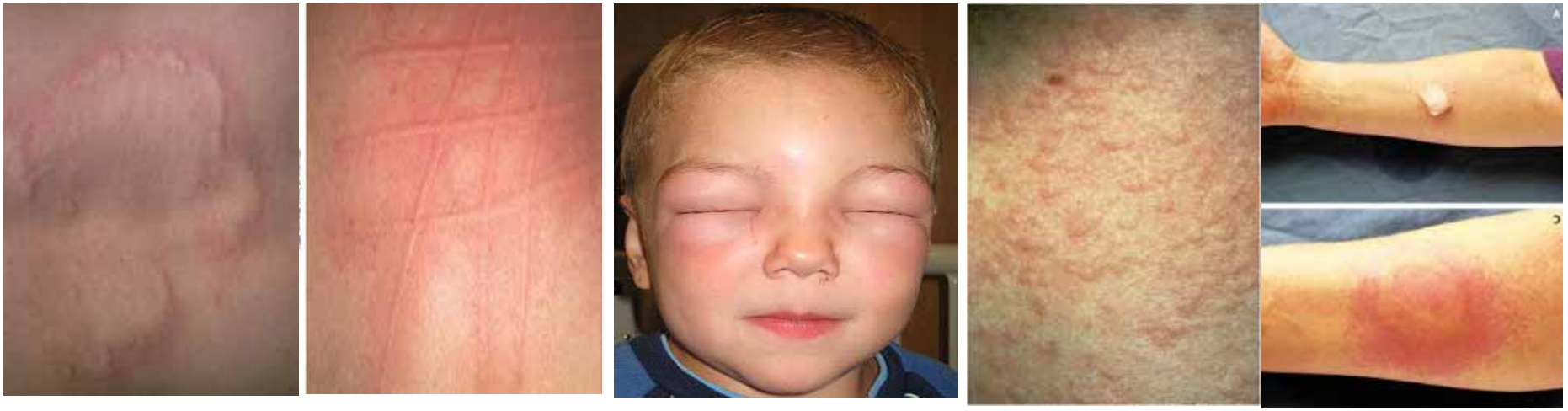


URTICARIA

Kumutnart Chanprapaph MD, MSC
Clinical Instructor
Division of dermatology
Ramathibodi hospital

Objectives

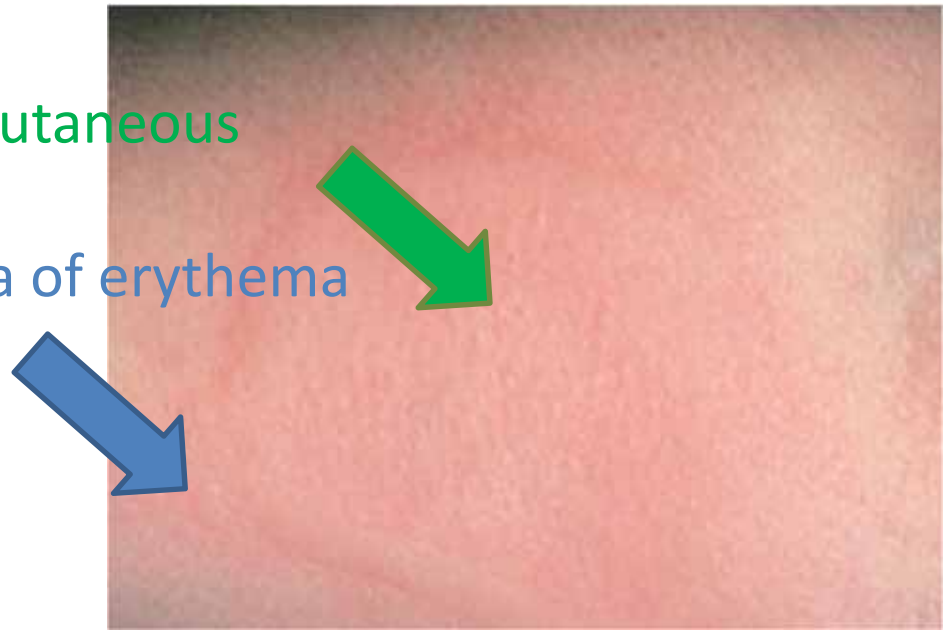
- Give a diagnosis of urticaria
- To recognize the cause of acute, chronic urticaria and angioedma
- The know the provocative challenges for physical urticaria
- Give an appropriate investigatior
- Give proper management

Urticaria

- Wheals and flare reaction: pruritus (itch)

Wheal- localized intracutaneous edema

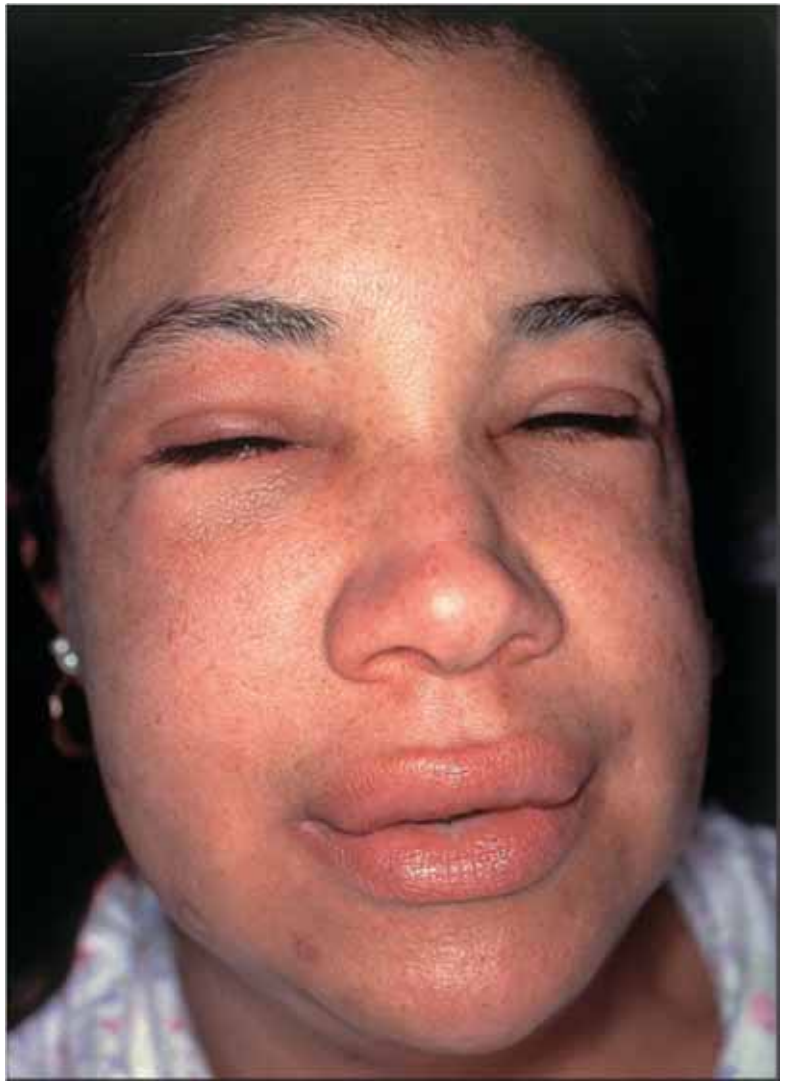
Flare- surrounding area of erythema



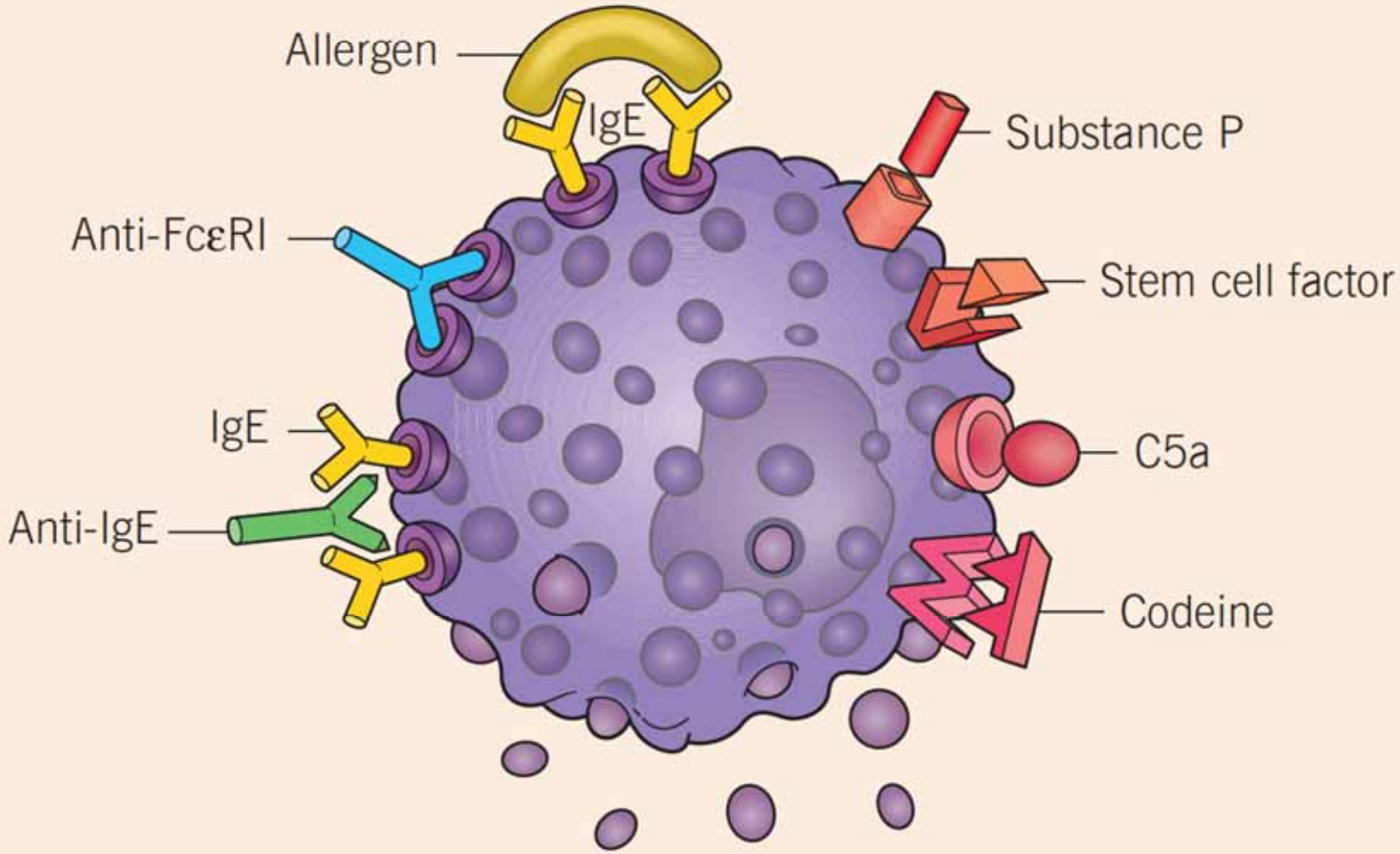
- *AS A RULE: individual* lesions come and go rapidly, within 24 hours
- Leaves no trace

Angioedema

- Deep swelling of the dermis or subcutaneous tissue of the skin or mucosa
- Painful , not well defined
- The lesions often last for 2 to 3 days



MAST CELL DEGRANULATING STIMULI

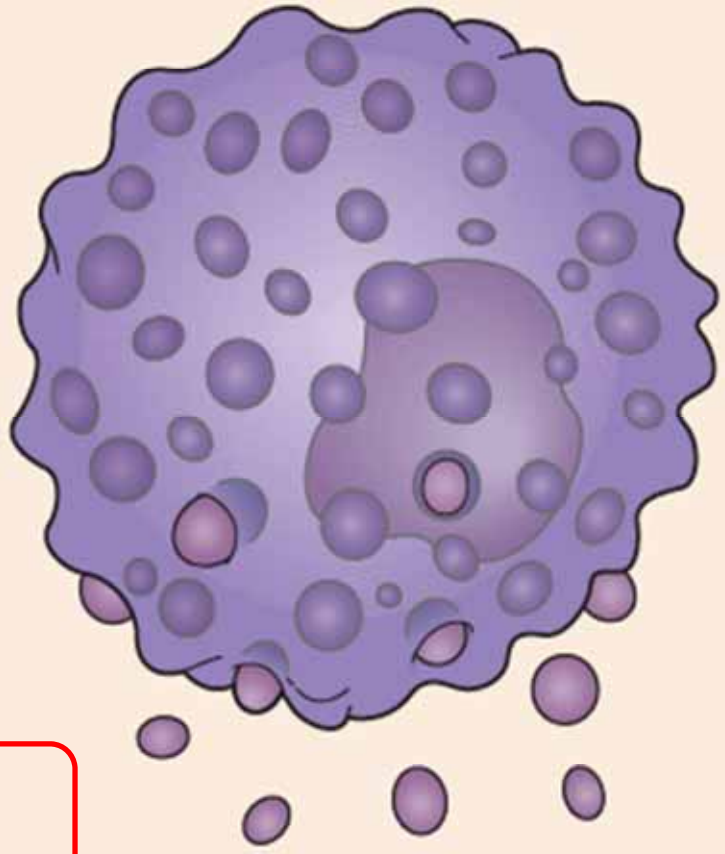


Cutaneous mast cell

Release histamine in response to

- compound 48/80
- C5a
- morphine
- codeine
- substance P (SP)
- vasoactive intestinal peptide (VIP)
- somatostatin

MEDIATORS RELEASED BY DERMAL MAST CELL DEGRANULATION



Release of pre-formed mediators

Proteases
e.g. tryptase

Heparin

Histamine

Most important

Cytokines
e.g. IL-3,-4,-5,-6,-8,-13
GM-CSF; TNF-α

Synthesis of newly-formed mediators

Prostaglandin D_2

Most important

Leukotrienes C_4, D_4, E_4

Platelet-activating factor

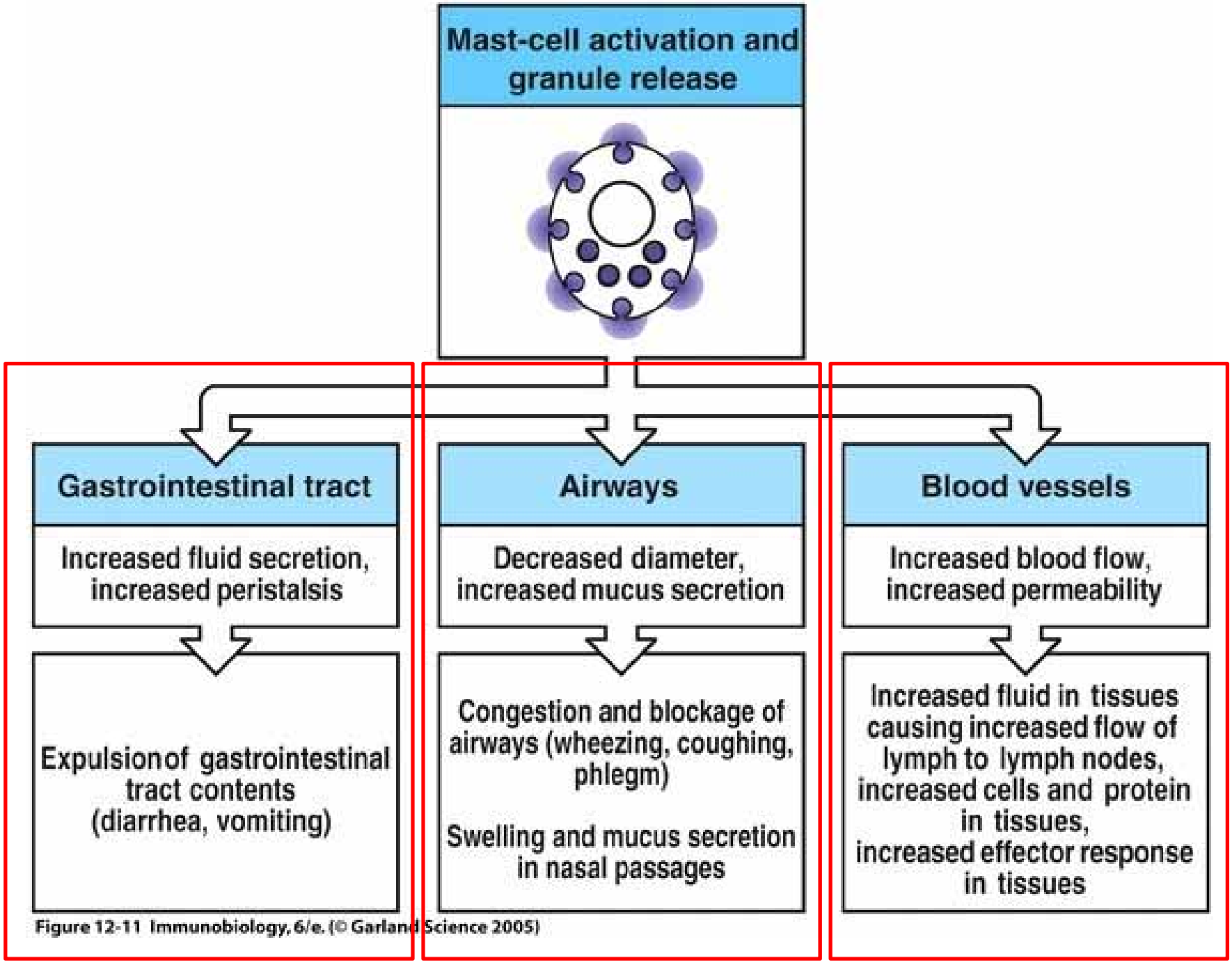


Figure 12-11 Immunobiology, 6/e. (© Garland Science 2005)

Vascular permeability in skin

- H1 histamine receptors- 85%
- H2 histamine receptors- 15%

Urticaria

Ordinary urticaria

- Acute uticaria (<6wk)
- Chronic urticaria (>6wk)

Urticarial lesion

- Cutaneous disease
- Systemic disease

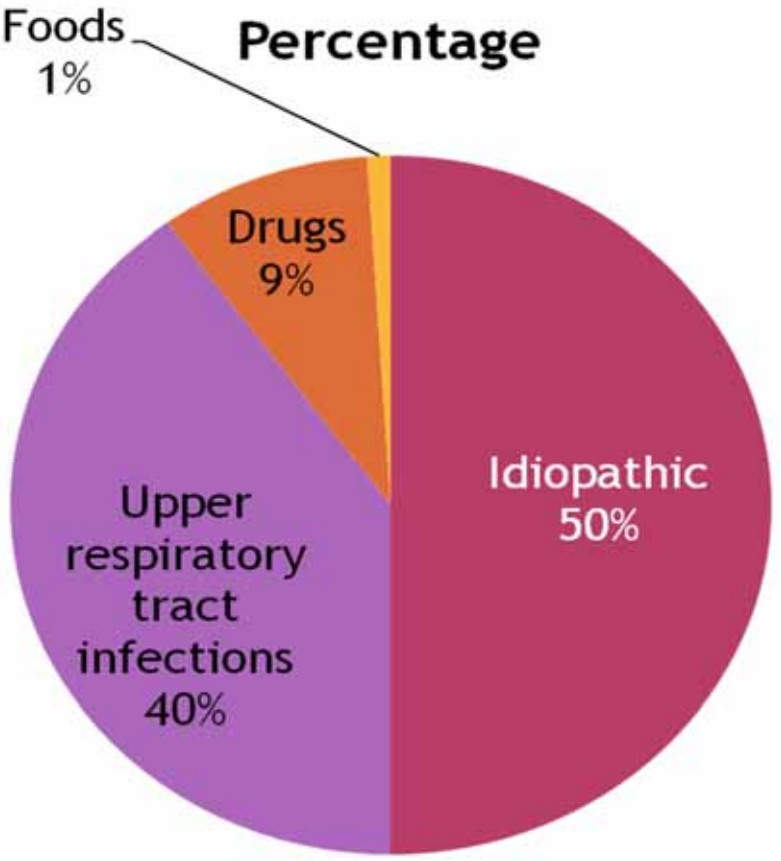
Main features distinguishing common urticaria from other urticarial lesions

Common urticaria	Other urticarial lesions
Typical wheals: • Erythematous, edematous lesions • Transient < 24-36 hrs • Asymmetrical distribution • Complete resolution No other primary lesions Pruritic +/- angioedema	Atypical wheals: • Infiltrated plaques • Persistent>24-36 hrs • Symmetrical distribution • Resolution with sighs eg hypo/hyperpigmentation, scarring No other primary lesions Pruritic Not associated with angioedema

Acute urticaria

- Wheal and flare of less than 6 weeks duration
- Children- infections and food
- Adults- medications

Causes of acute urticaria



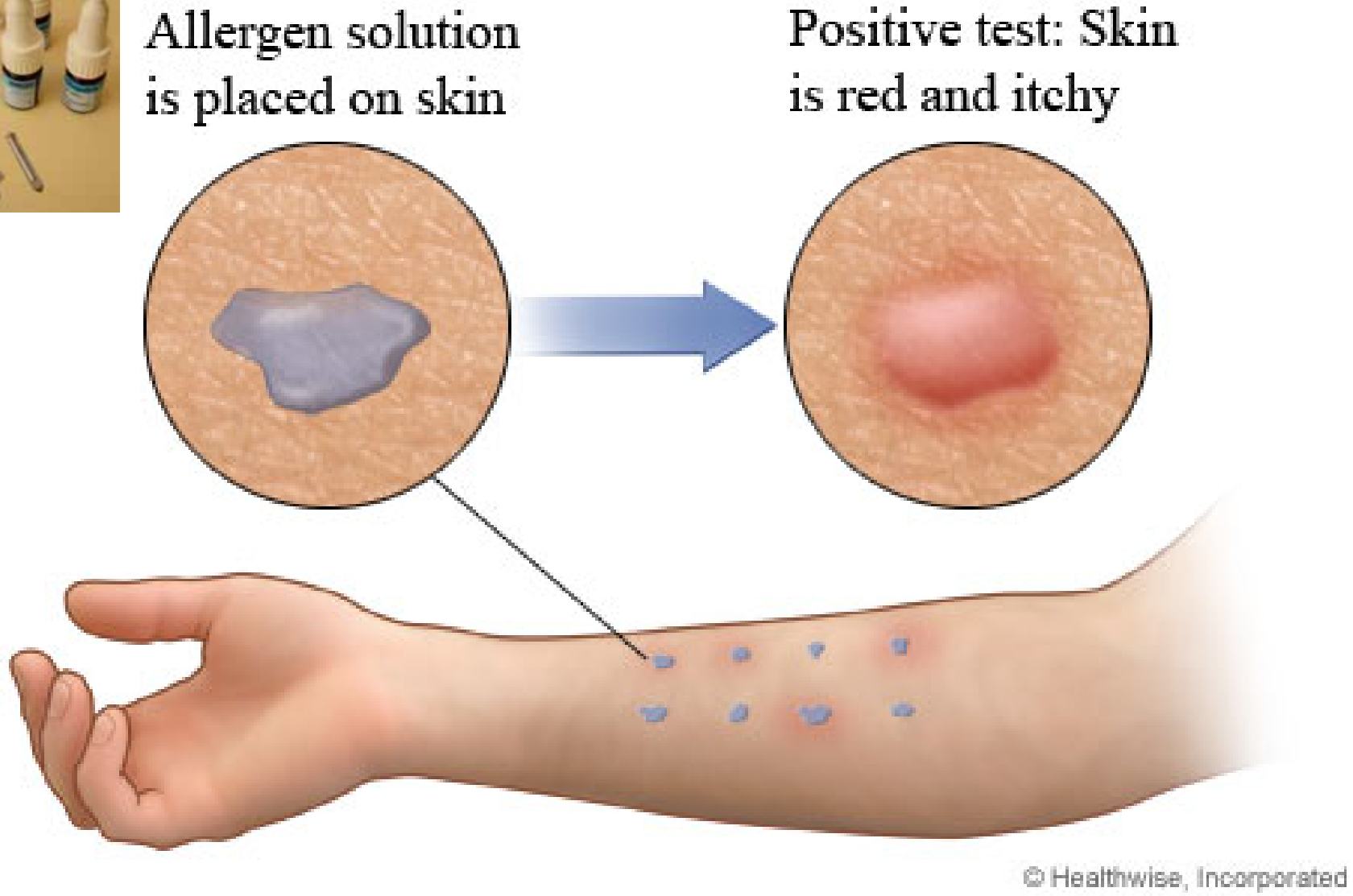
Acute Urticaria

- Common in both children and adults
- Self-limiting condition
- Prevalence of about 15% to 20% in the general population
- Complete resolution within 3 weeks in more than 90% of cases

Acute urticaria

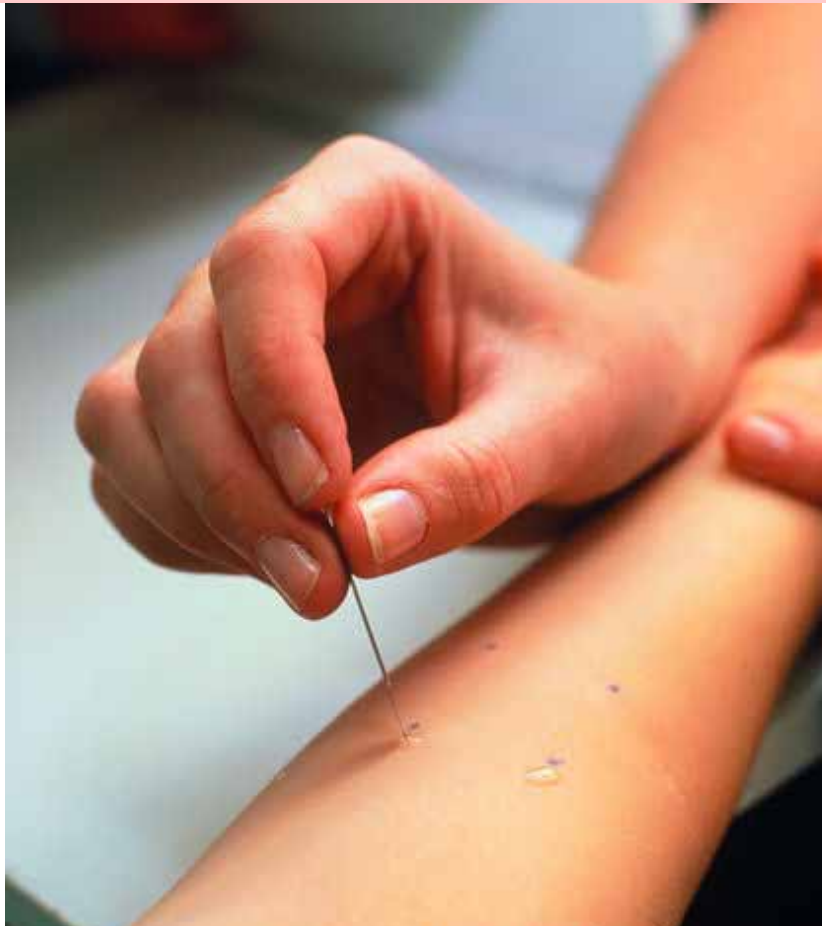
Acute Urticaria

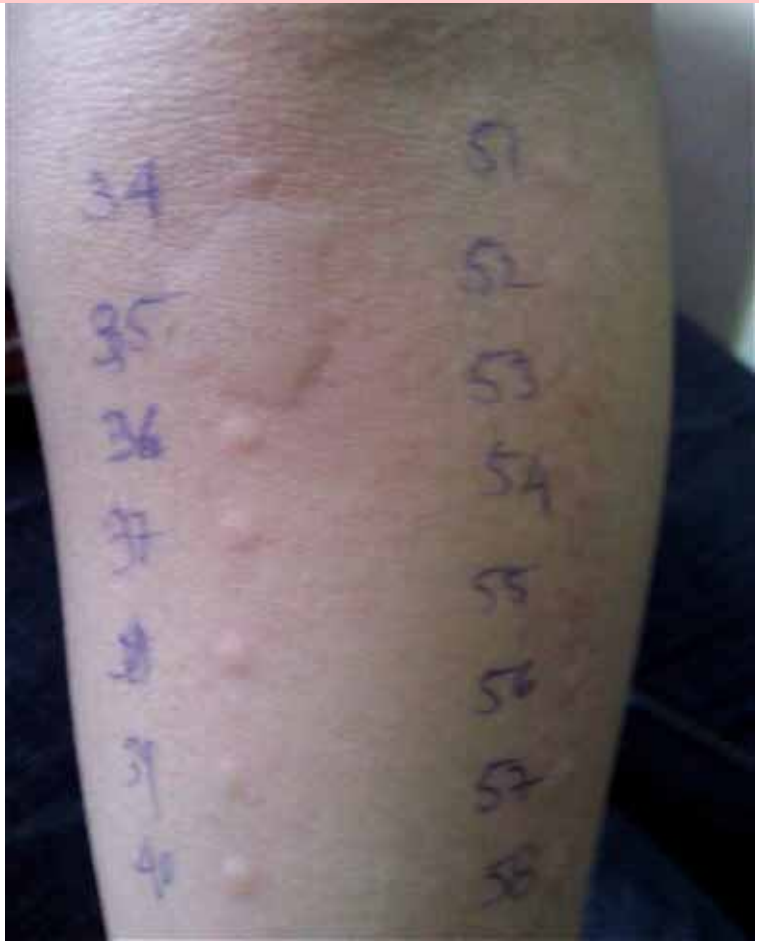
Prick Test



Acute Urticaria

Prick Test





- Implication for food and inhalant material
- Very little role for diagnosis of chronic urticaria

Food Allergy

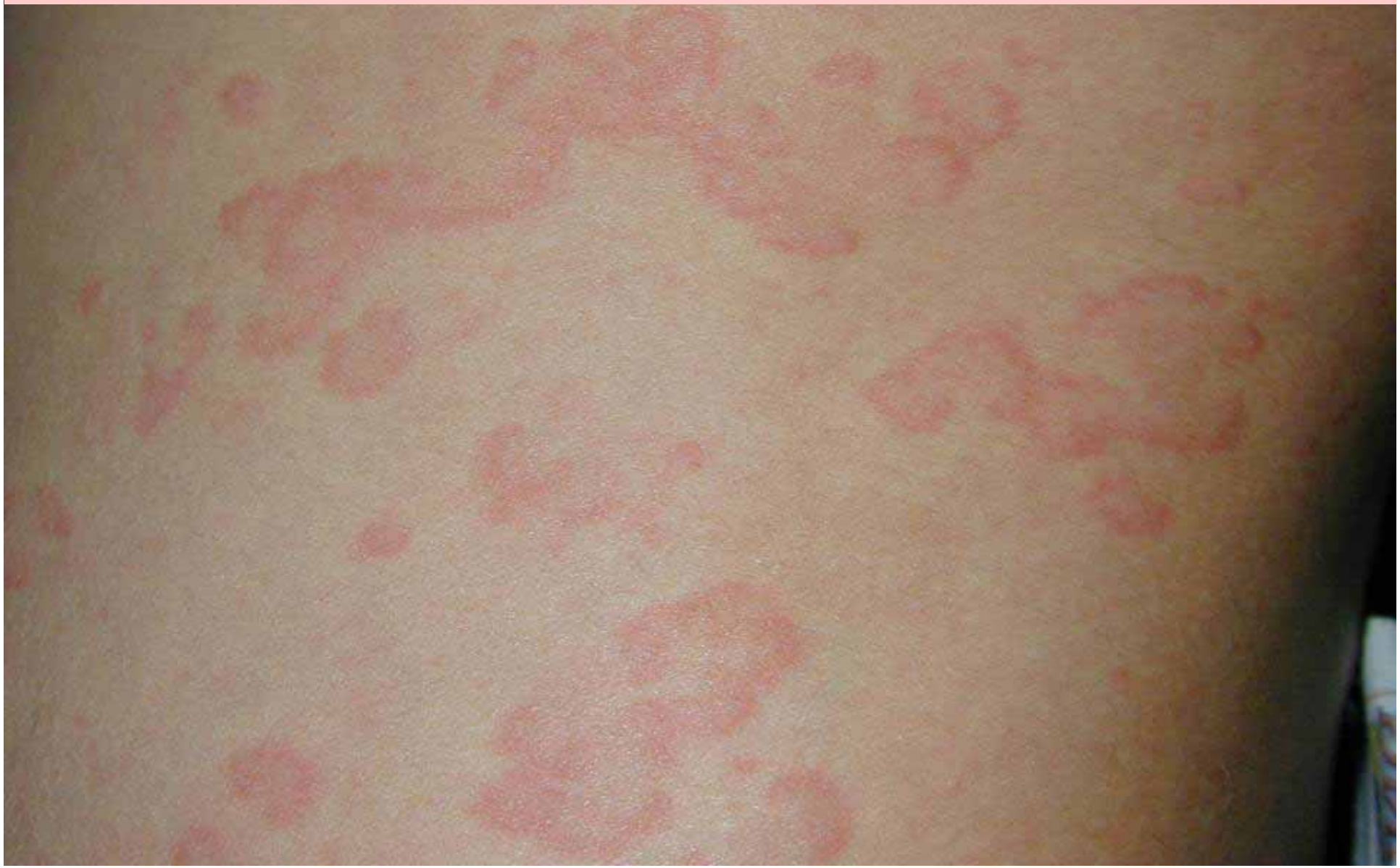
- 20-60% with acute urticaria
- <2% with chronic urticaria

Double-blinded placebo-controlled food challenge is the gold standard

Skin test false negativity due to instability of allergen in food extract used for skin testing

Acute Urticaria

Drug induced urticaria



Management of Acute Urticaria

- Identify and eliminate endogenous and exogenous cause

- Advice that it takes several weeks for the lesions to go away completely

- Other laboratory investigation eg CBC, complete metabolic panel, thyroid testing, UA NOT NECESSARY

Management of Acute Urticaria

- Specific Treatment

  Nonsedating antihistamine
  Sedating antihistamines is the mainstay

  Corticosteriods 60-80 mg/day for 3 days
  then taper 5-10 mg/day

  Epinephrine (severe, angioedema)

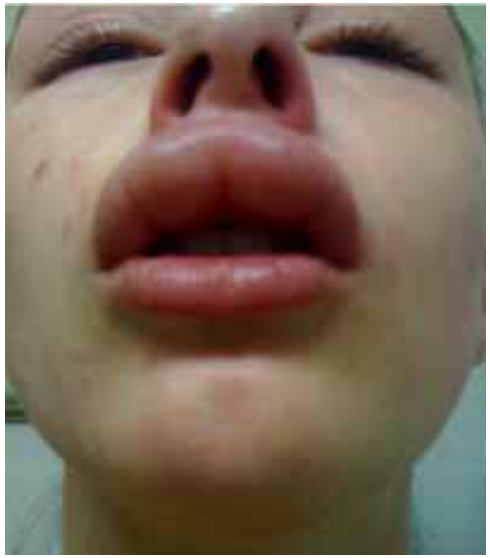
Case 3

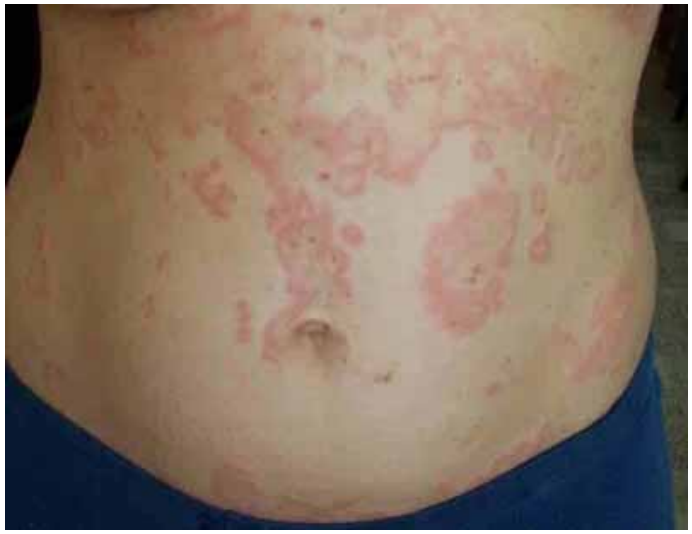
A 34 year-old woman with hives daily for 4 months

She occasionally has associated upper lip swelling but denies dyspnea or throat swelling

Review of systemic symptoms are otherwise negative

Diagnosis?





Chronic urticaria

Recurrent at least twice / week for > 6 weeks

Urticaria and angioedema (40%)

Uriticaria alone (40%)

Angioedema alone (20%)

Prevalence of 0.5% to 3% in the general population

Common in 3rd and 4th decades, rare in children

Not associated with food, pollens, dyes ect.

Bad news…….May last for years

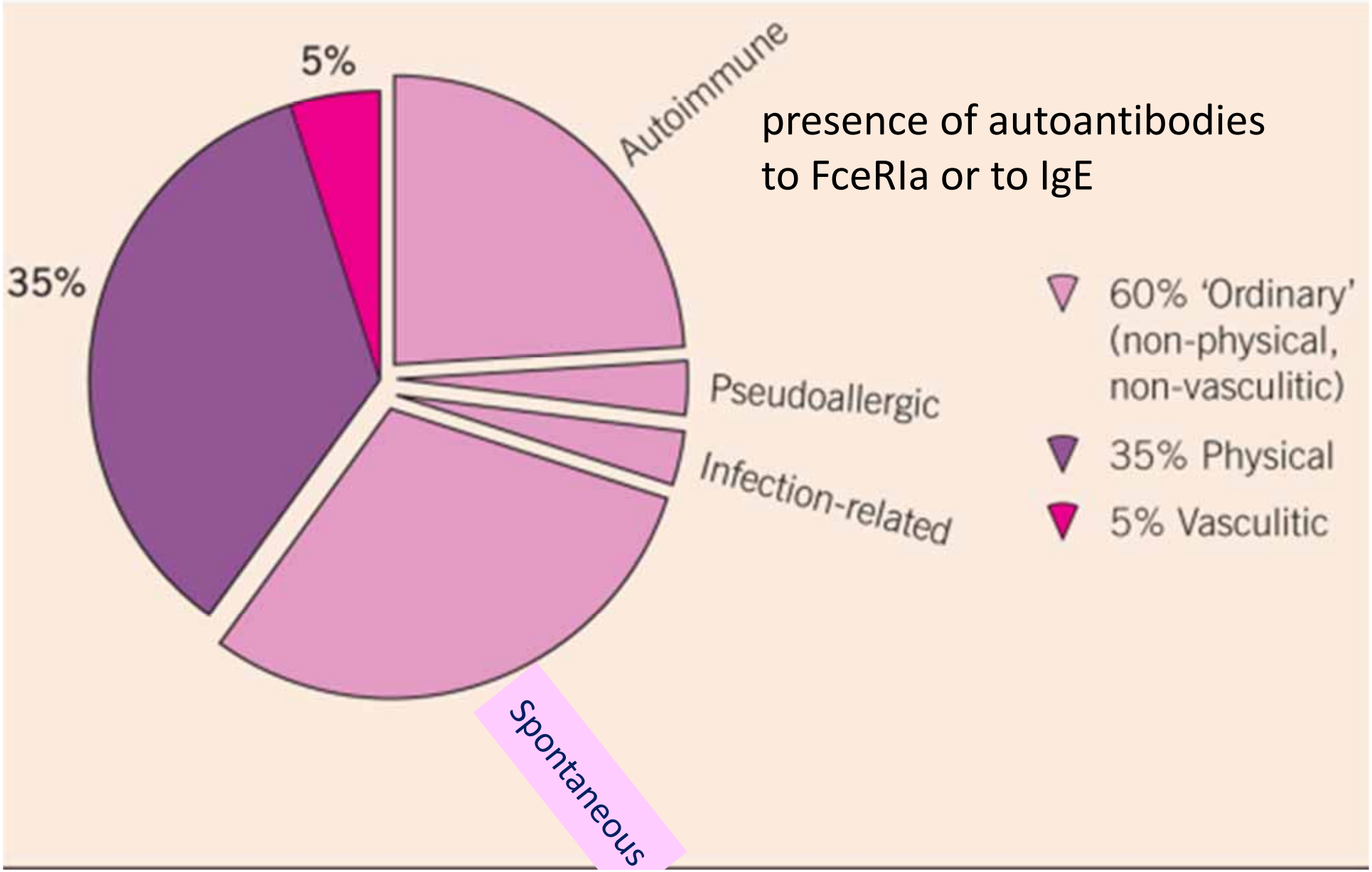
Chronic urticaria

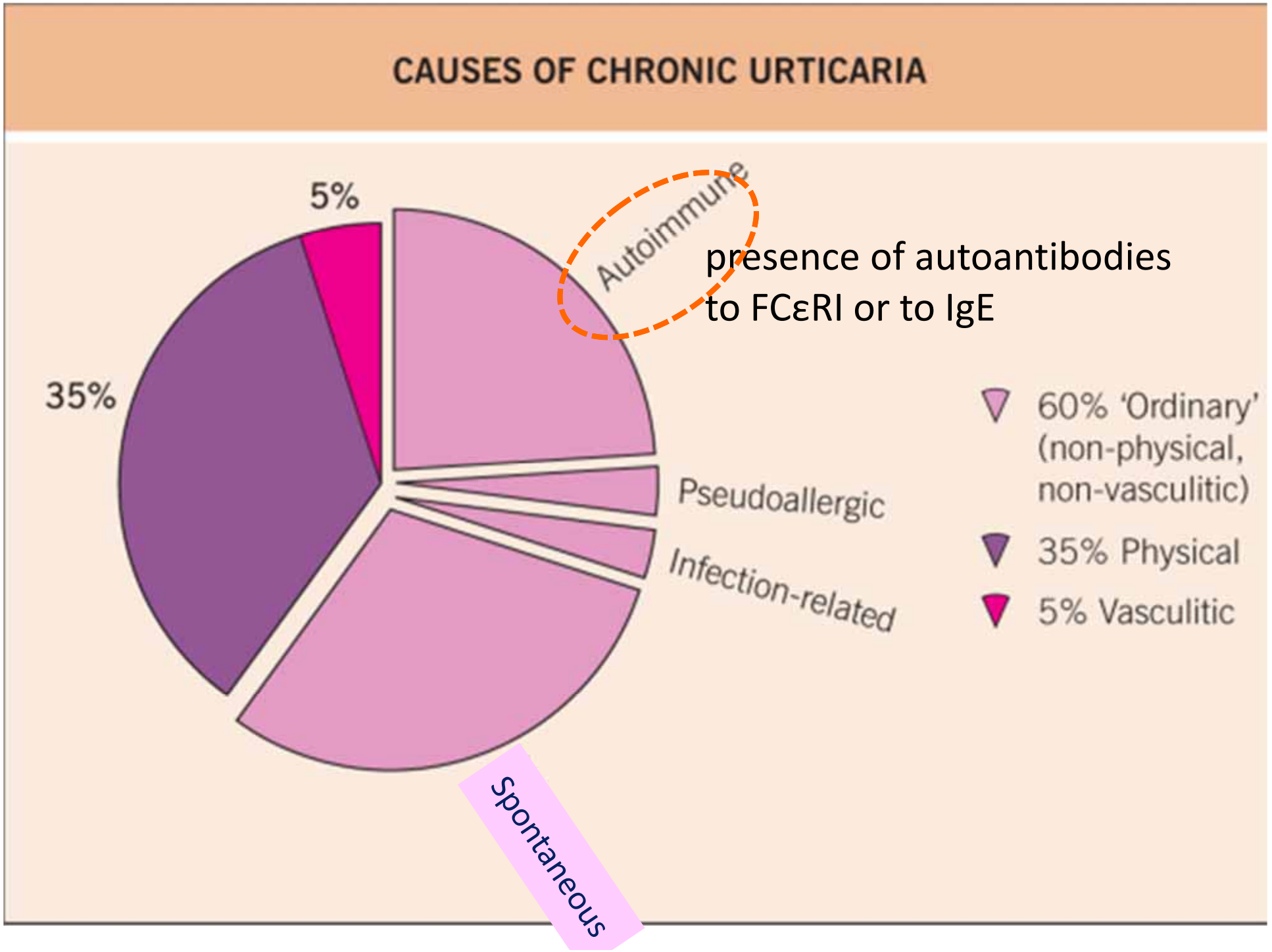
Persists for months or years

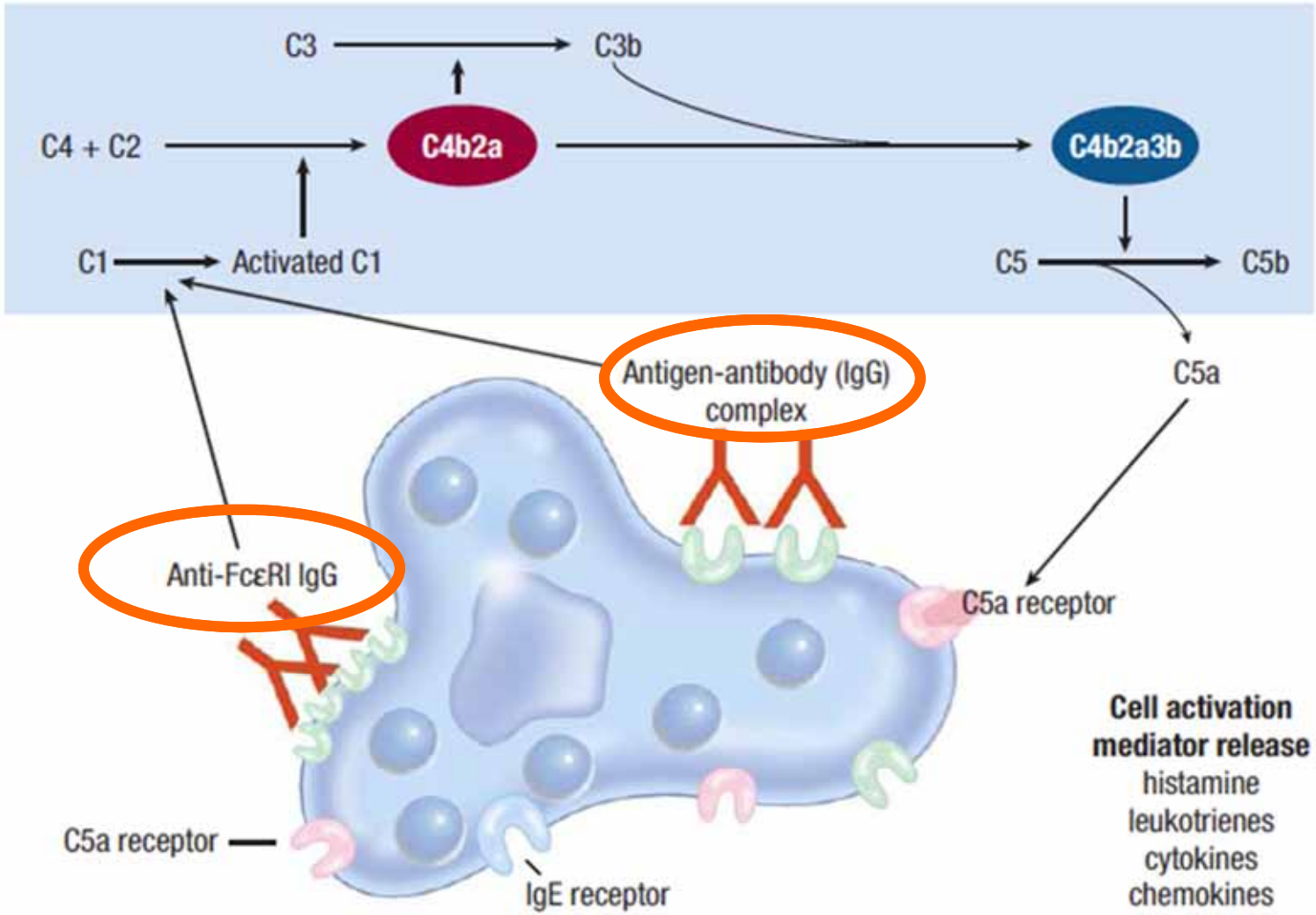
- 50% of pt. free of lesions within 1 year
- 65% " 3 years
- 85% " 5 years
- <5% of pt. lesions last >10 years

- Angioedema-25% clear in 1 year

CAUSES OF CHRONIC URTICARIA




CAUSES OF CHRONIC URTICARIA
5%
35%
Autoimmune
Pseudoallergic
Infection-related
Spontaneous
presence of autoantibodies
to FCεRI or to IgE
60% 'Ordinary'
(non-physical,
non-vasculitic)
35% Physical
5% Vasculitic



▲ **FIGURE 37-1** Schematic diagram of the activation of cutaneous mast cells by immunoglobulin G (IgG) antireceptor antibody, followed by activation of complement, release of C5a, and augmentation of mast cell release.

Chronic autoimmune urticaria

- Autoimmune thyroid disease
- Vitiligo
- Insulin dependent diabetes
- Rheumatoid arthritis
- Pernicious anemia
- HLA-DR4, HLA-DQ8

Chronic autoimmune urticaria: Methods of detecting autoantibody

- Basophil histamine release assay is the Gold Standard
- Direct immunoassays

  Western blotting

  Immunoprecipitation

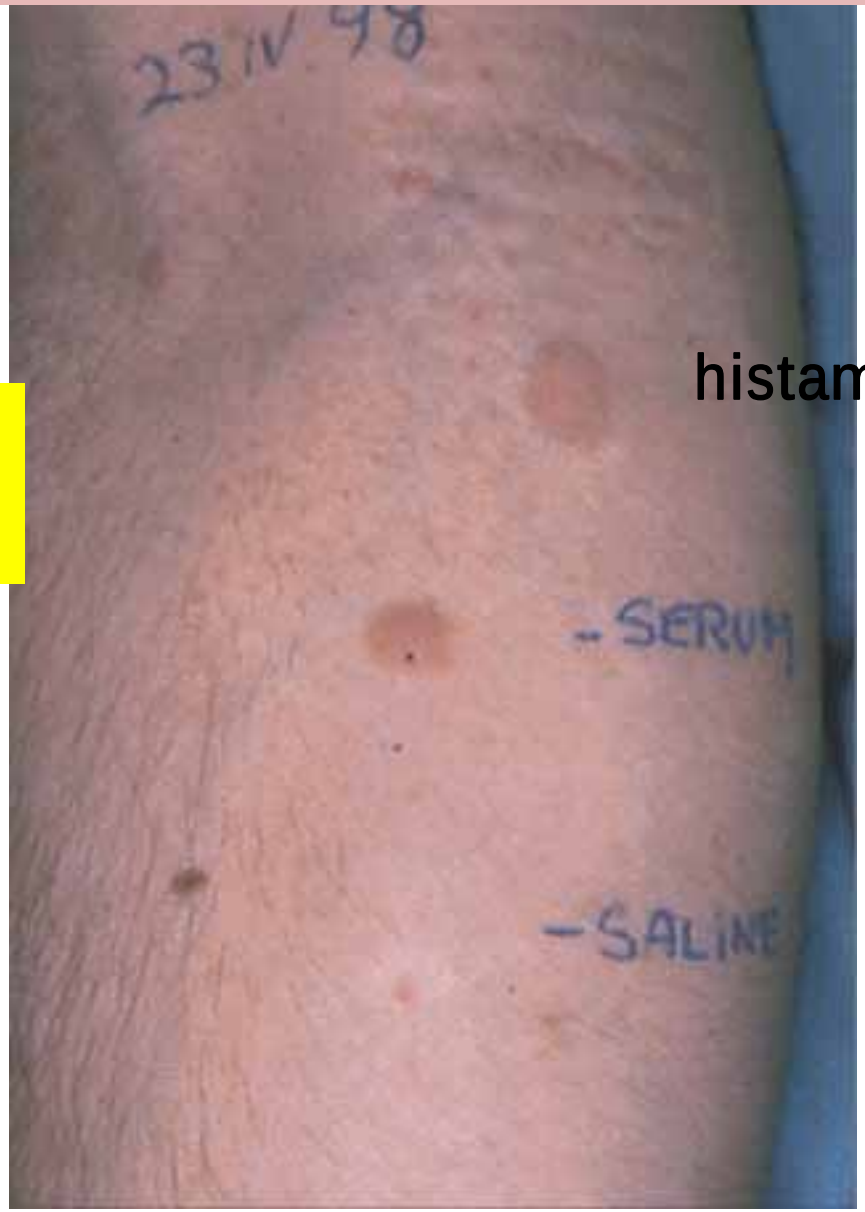
  ELISA

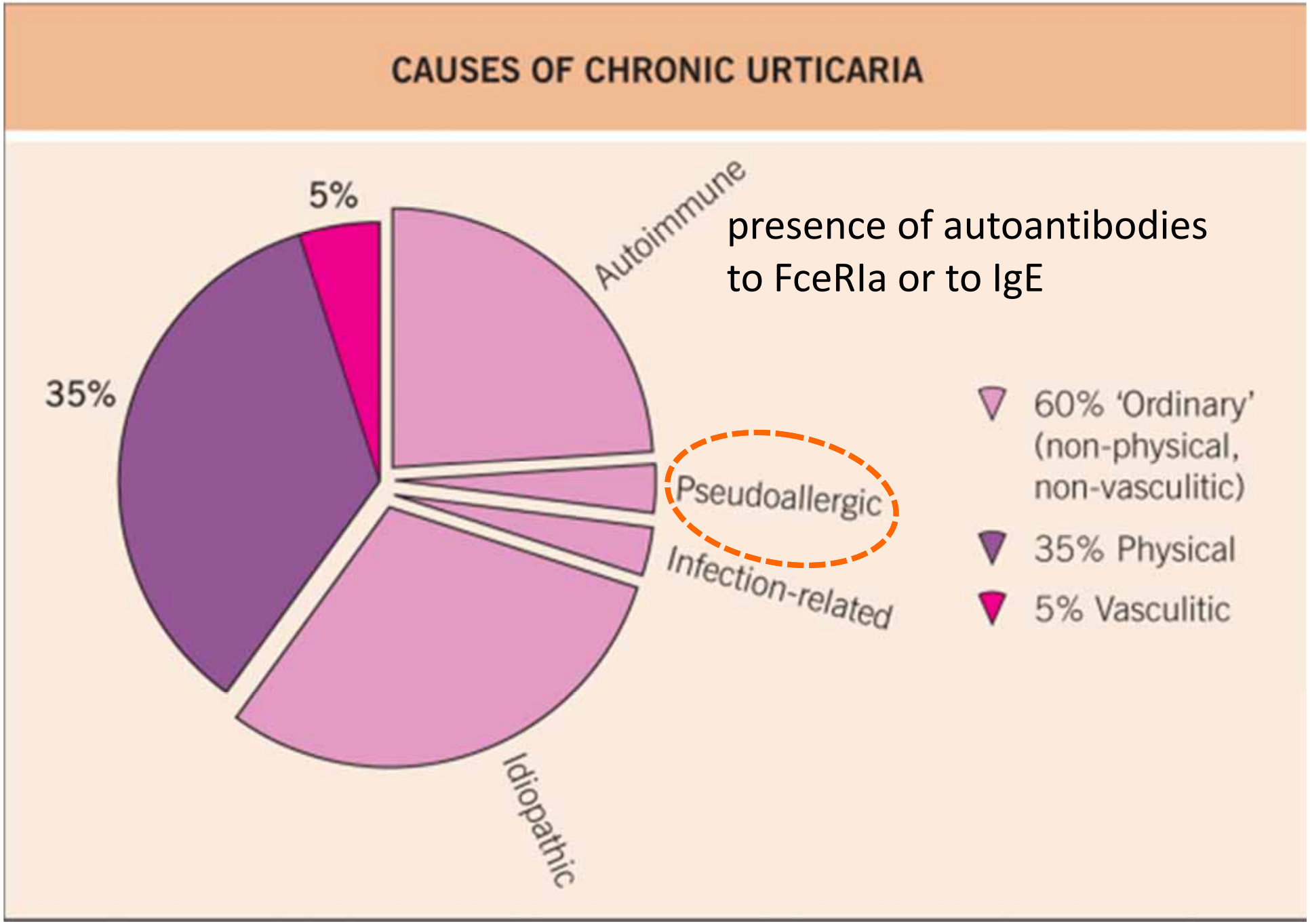
  Flow cytometry
- ASST (sensitivity 70%, specificity 80%)

Chronic Autoimmune Urticaria

Autologous Serum Skin Test

Response within 30 mins
At least 1.5 mm

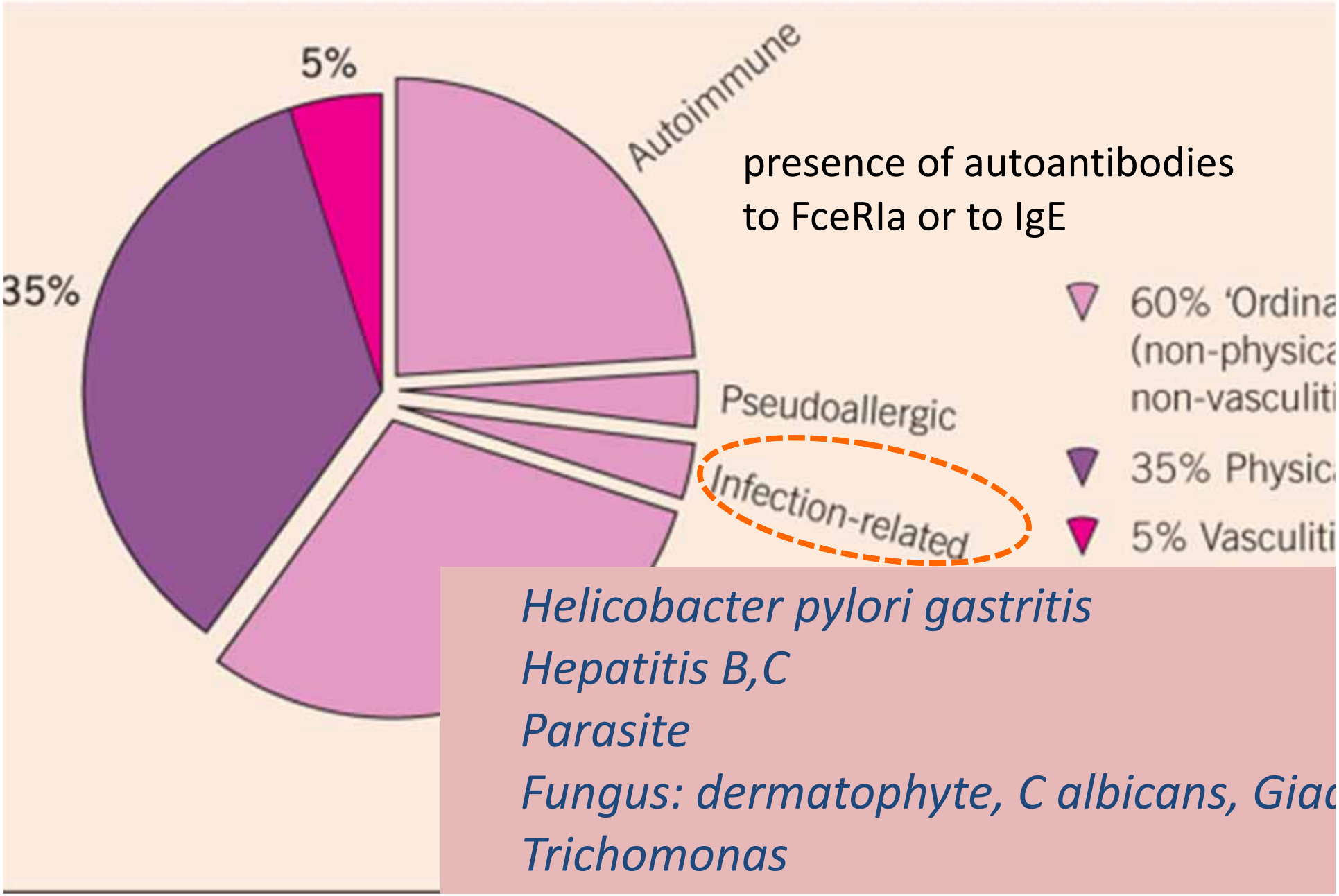



CAUSES OF CHRONIC URTICARIA
5%
Autoimmune
35%
Pseudoallergic
Infection-related
Idiopathic
presence of autoantibodies
to FceRIa or to IgE
60% 'Ordinary'
(non-physical,
non-vasculitic)
35% Physical
5% Vasculitic

Pseudoallergic reaction

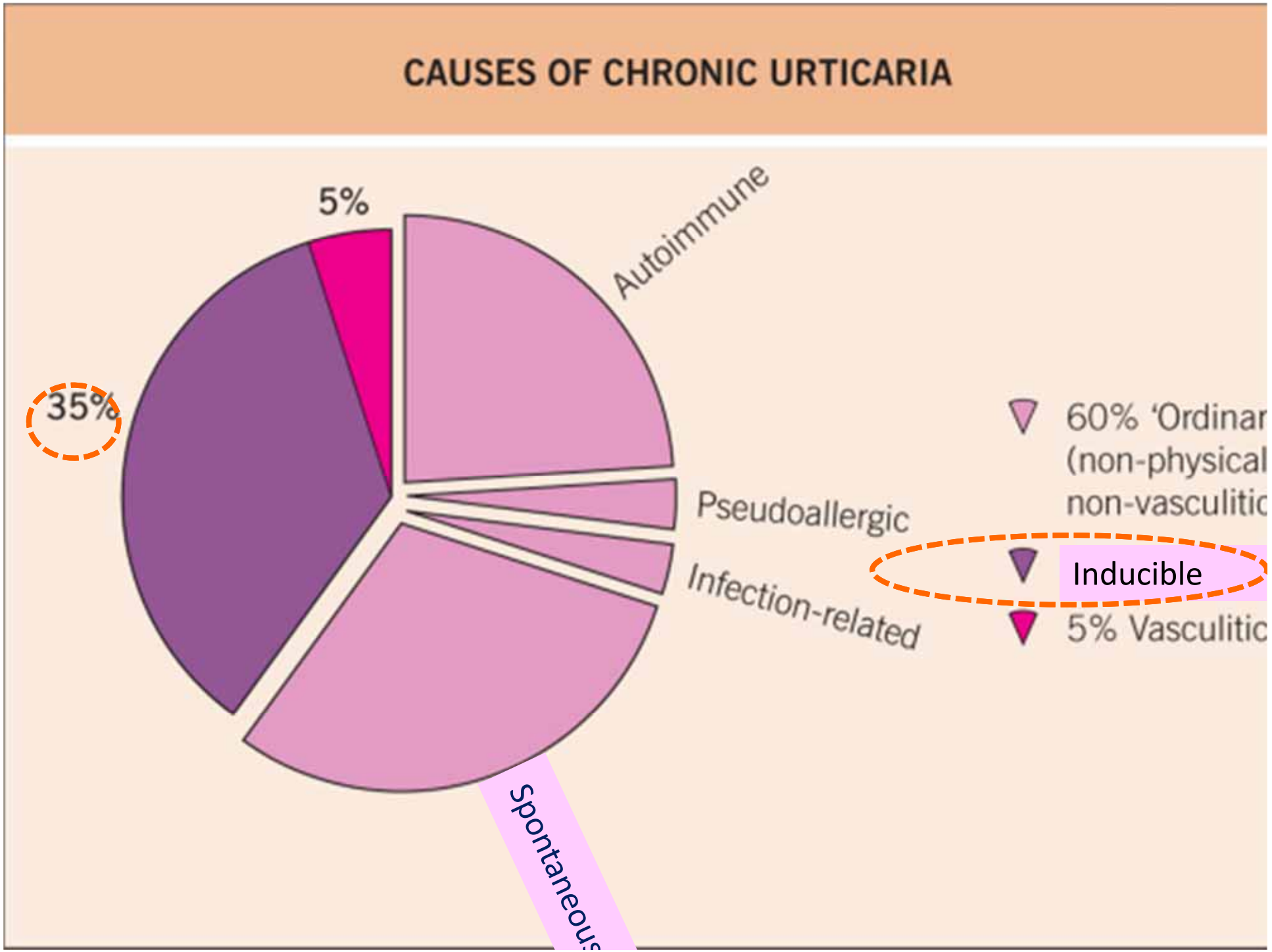
- Direct action of the substance on mast cells
  - opiates, radiocontrast media
- Interference of drugs
  - aspirin and other NSAIDs
  - inhibit cyclooxygenase (COX) 1 and 2 with arachidonic acid metabolism
  - increased synthesis of cysteinyl leukotrienes
  - induces vasodilatation and edema

CAUSES OF CHRONIC URTICARIA



presence of autoantibodies to FceRIa or to IgE

Helicobacter pylori gastritis
Hepatitis B,C
Parasite
Fungus: dermatophyte, C albicans, Giac
Trichomonas


CAUSES OF CHRONIC URTICARIA
5%
Autoimmune
35%
Pseudoallergic
Infection-related
Spontaneous
60% 'Ordinar
(non-physical
non-vasculitic
Inducible
5% Vasculitic

Inducible urticaria

Types of physical urticaria

Individual lesions last< 2 hours

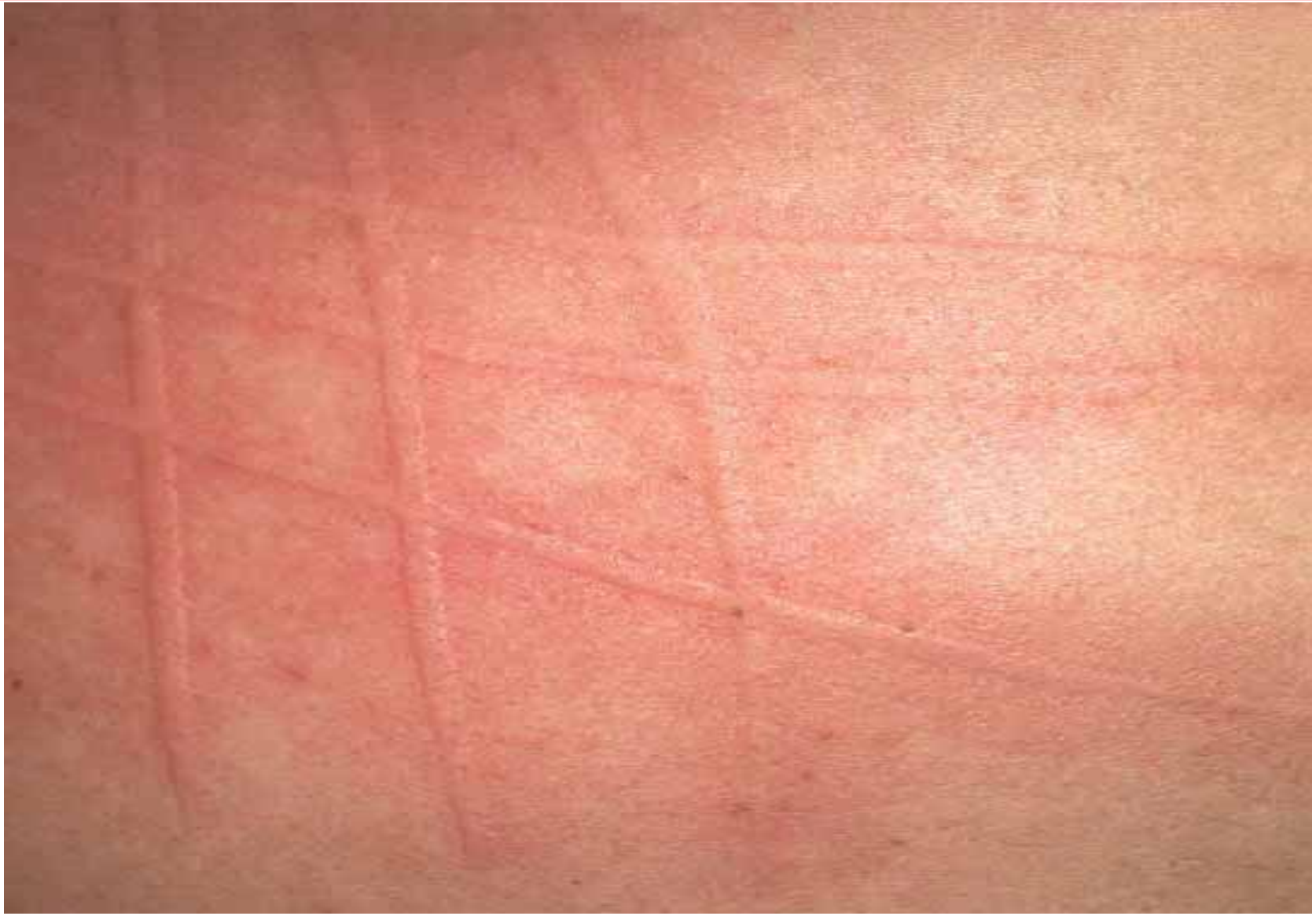
- Cold urticaria
- Cholinergic urticaria
- Dermographism
- Heat contact urticaria
- Aquagenic urticaria
- Solar urticaria
- Vibratory urticaria

Lesions last > 2hours

- Delay pressure urticaria

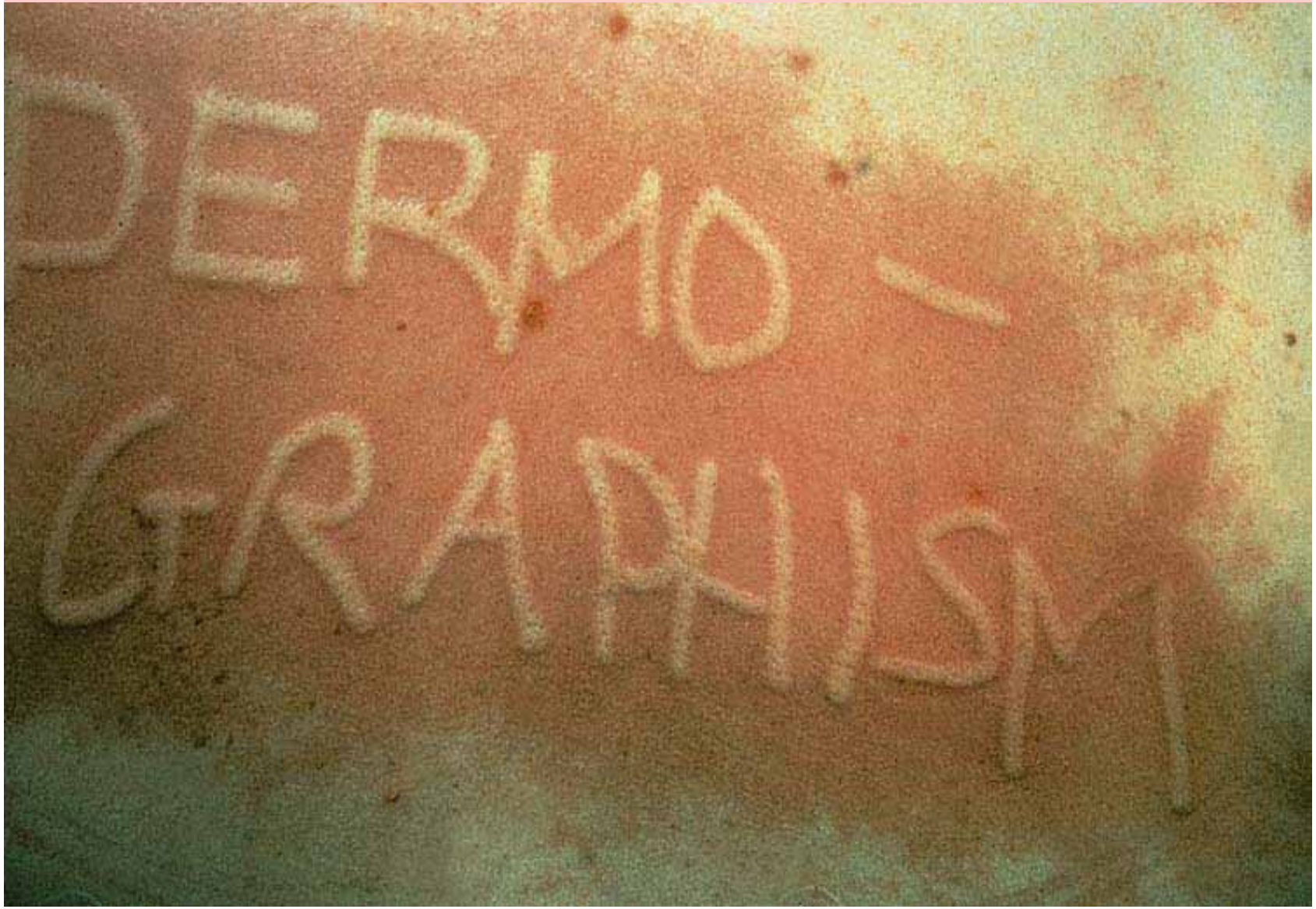
Inducible urticaria

Urticaria due to mechanical stimuli



Inducible urticaria

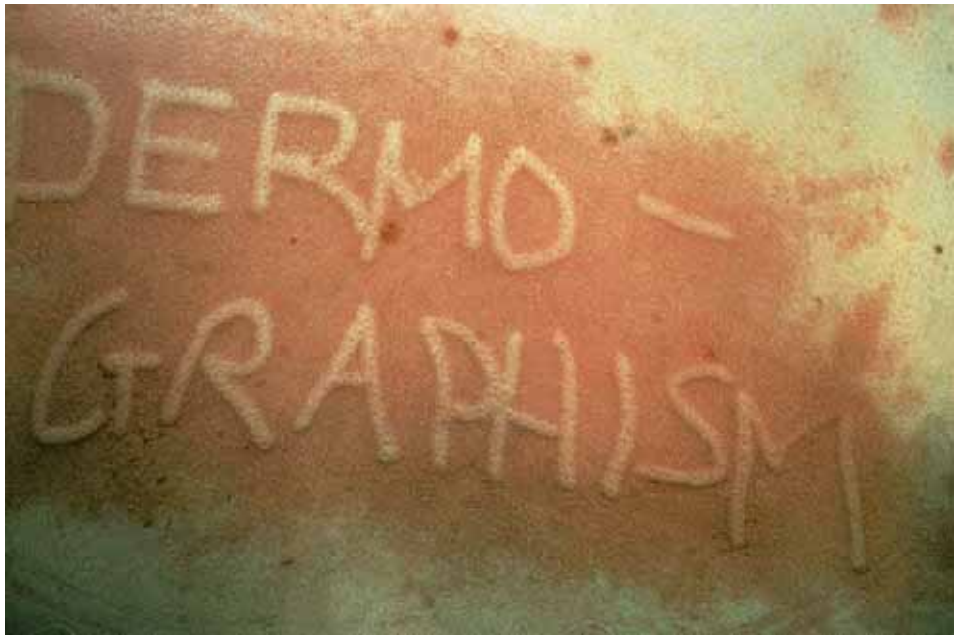
Urticaria due to mechanical stimuli



Inducible urticaria

Dermographism

- Most common form of physical urticaria
- Linear wheal with a flare where the skin is briskly stroked with a firm object
- 1.5 - 4.2% in the general population
- No association with systemic disease, atopy, food allergy or autoimmunity.
- Mean duration 5-7 years



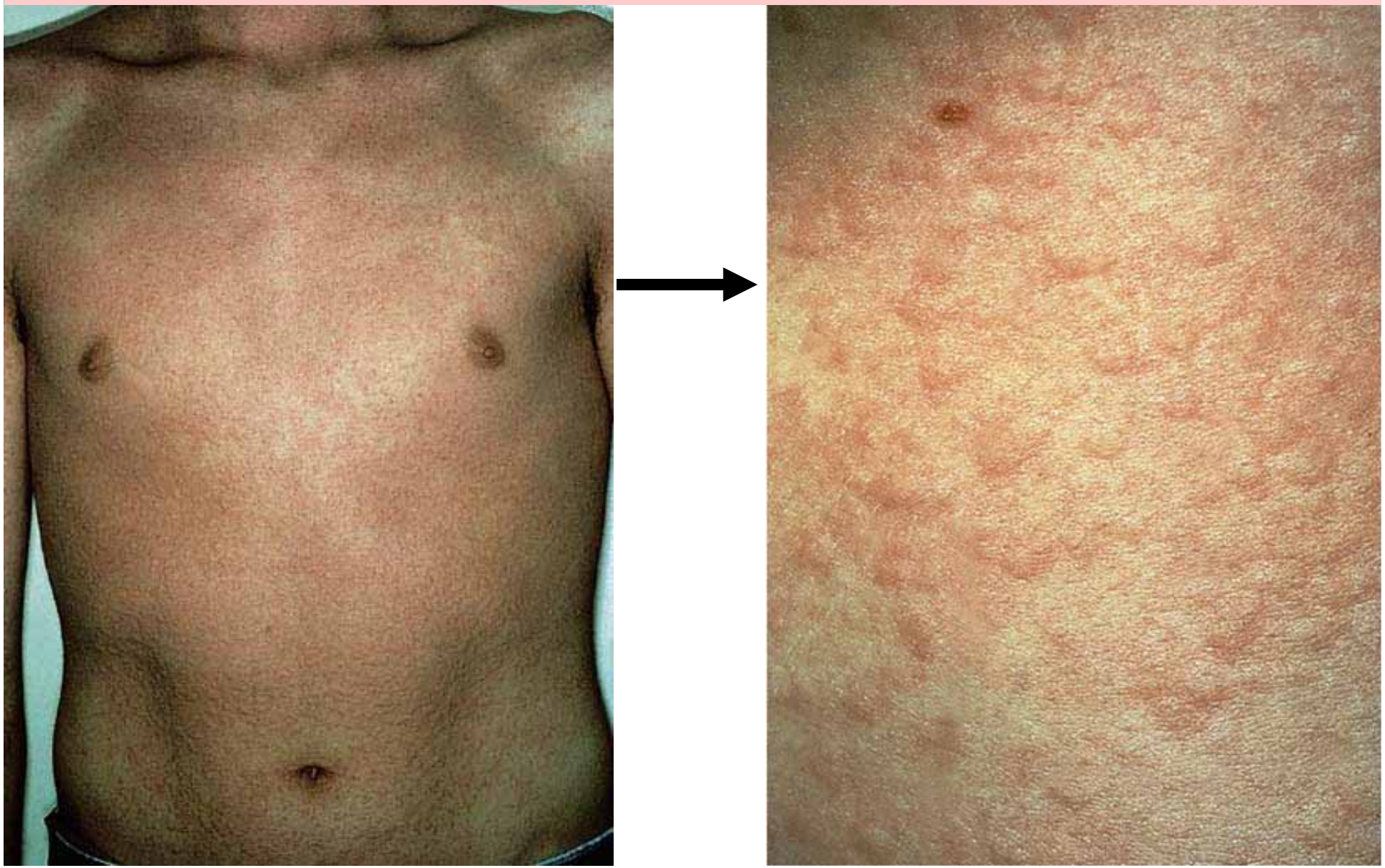
Dermographism

Delayed dermographism

- Lesions develop 3 to 6 hours after stimulation, either with or without an immediate reaction, and last 24 to 48 hours.
- May be associated with delayed pressure urticaria

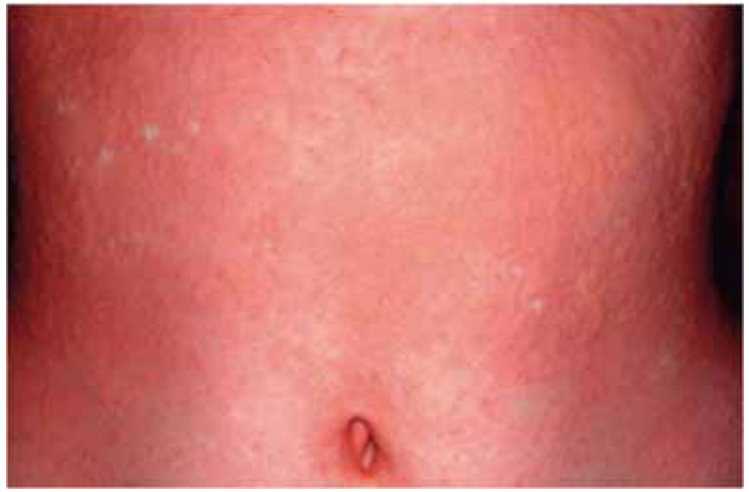
Inducible urticaria

Cholinergic Urticaria



Cholinergic urticaria

- Develops after an increase in core body temperature
- Multiple transient papular wheals 2–3 mm surrounded by flare.
- Occur within 15 minutes
- More frequently in young adults with an atopic tendency
- The intracutaneous injection of cholinergic agents, methacholine chloride, produces a wheal with satellite lesions in 1/3 of patients.



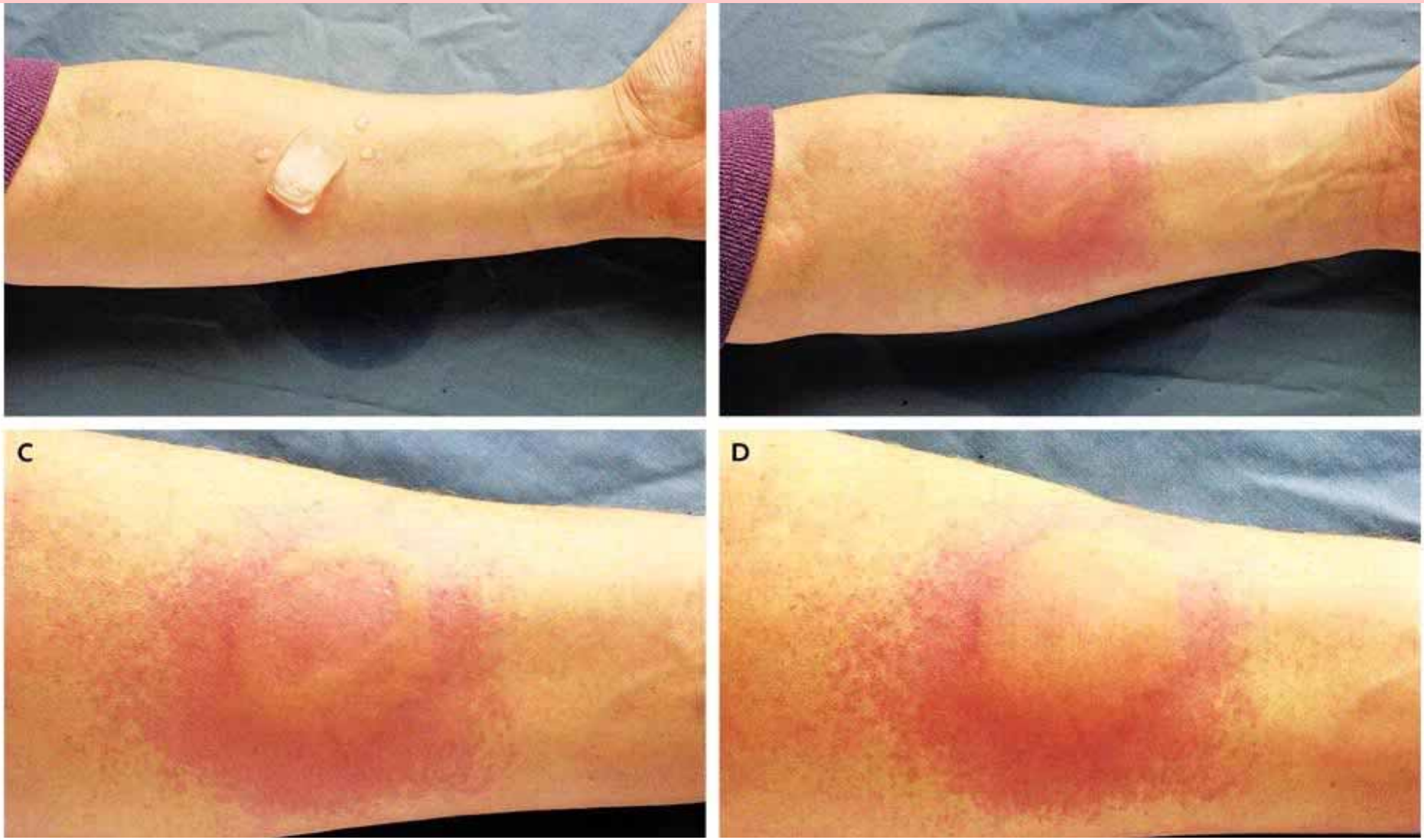
Inducible urticaria

Heat contact urticaria

- Rarest from of urticaria
- Within minutes of contact with heat from any source
- Systemic symptoms may occur if urticaria is extensive

Inducible Urticaria

Cold Urticaria



Positive wheal at the test site within 20-30 minutes

Cold urticaria

- Whealing occurs within minutes of rewarming after cold exposure.

Primary cold contact urticaria

- Follow respiratory infections, or arthropod bites or stings, HIV infection
- Cold baths and swimming should be avoided.

Secondary cold contact urticaria

- Cryoglobulinemia or cryofibrinogenemia
- Associated with manifestations such as Raynaud's phenomenon or purpura
- May have underlying HBV or HCV infections, lymphoproliferative disease or infectious mononucleosis.

Inducible urticaria

Exercise-induced anaphylaxis (EIA)

Food- and exercise-induced anaphylaxis (FEIA)

- Angioedema and/or anaphylaxis occur within minutes of exercise if it follows either prior ingestion of a specific food (e.g. wheat), or within 4 hours of a heavy meal.
- Due to priming of the mast cell by prior exposure to an allergen, or to an unknown mechanism.

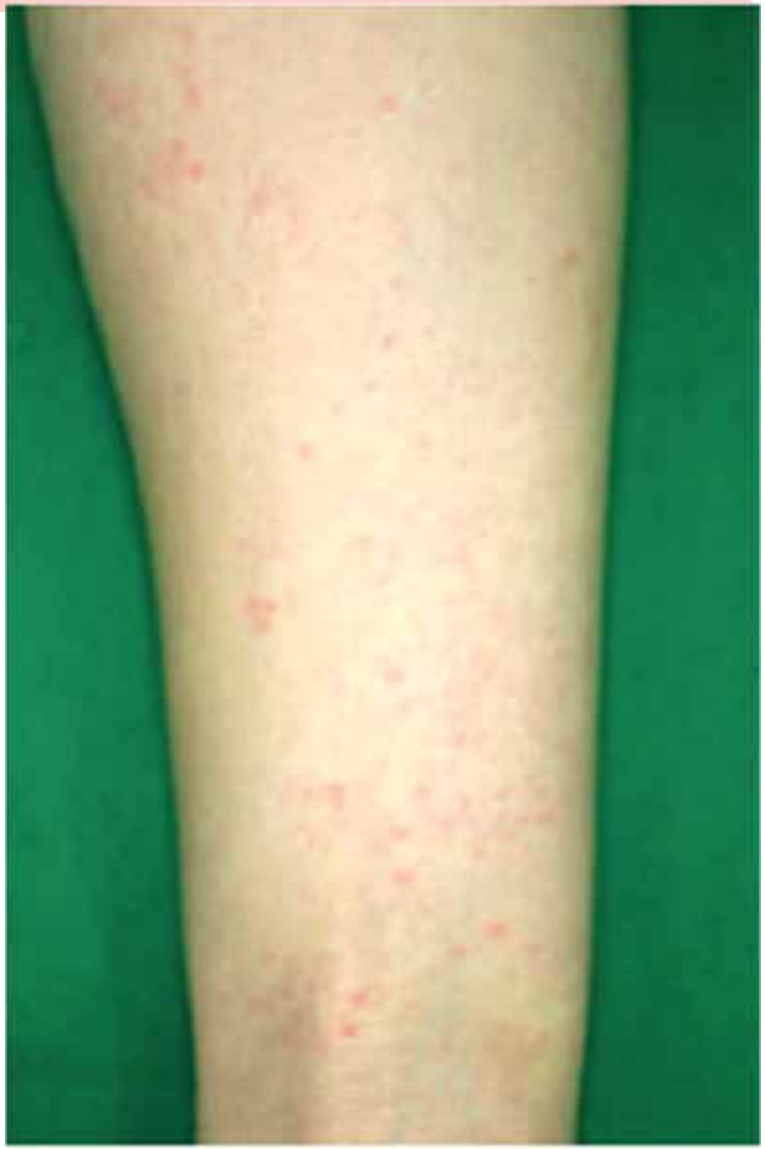
Exercise-induced anaphylaxis (EIA)

- Produced by exercise
- Not associated with increase in core temperature like cholinergic urticaria

Inducible urticaria

Adrenergic urticaria

- Presence of blanched vasoconstricted skin surrounding small pink wheals
- Induced by sudden stress
- The lesions can be reproduced by intradermal injections of norepinephrine.

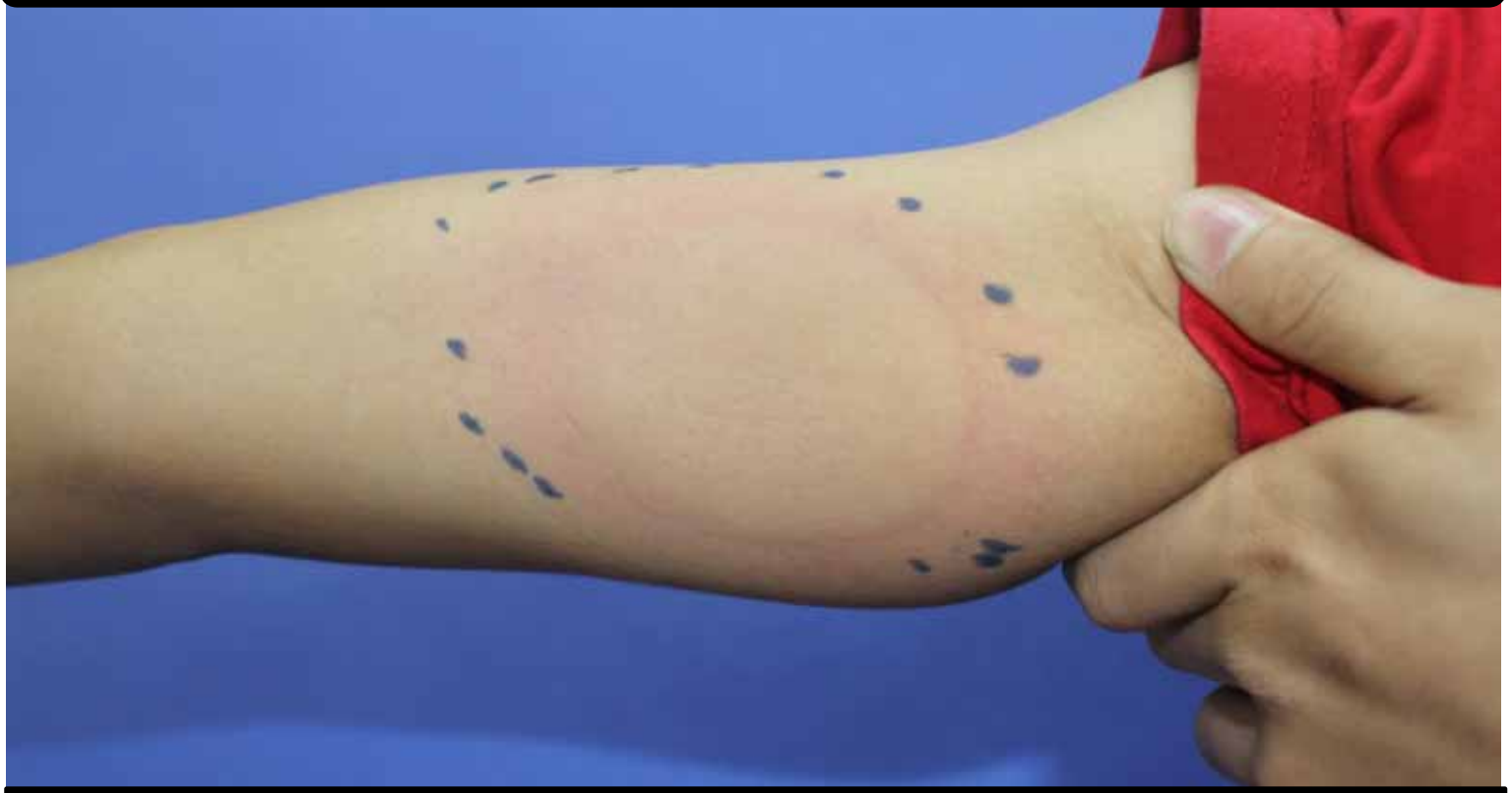


Inducible urticaria

Solar Urticaria

Phototest

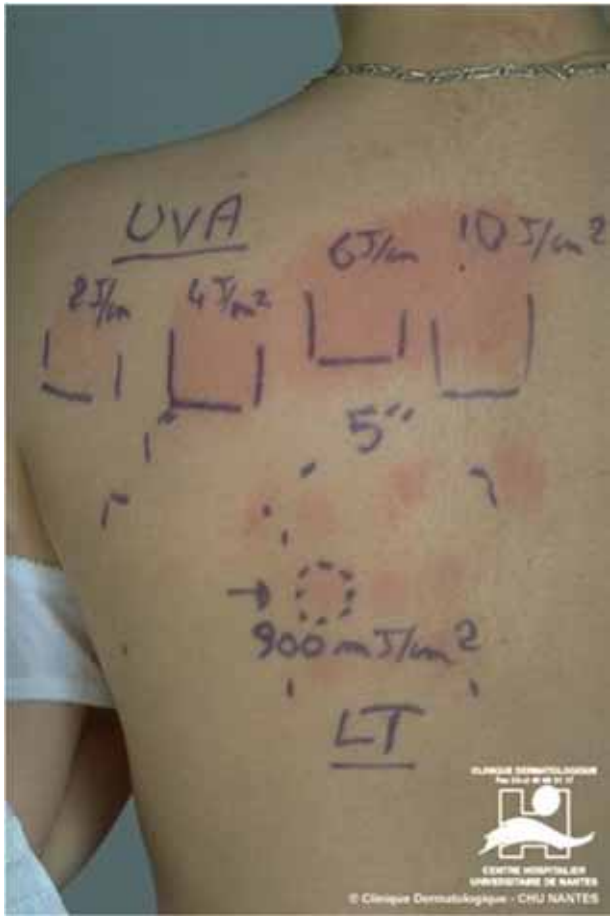
Visible light : immediately after test



Wheal and erythematous flare on test site

Solar urticaria

- Itching and whealing occur within minutes of exposure to UV or visible wavelengths
- Solar radiation may penetrate light clothing.
- Wheals last< 1 hr
- Headache and syncope can accompany severe reactions.



Inducible urticaria

Aquagenic urticaria

- Contact with water of any temperature induces smalll wheals urticarial eruption
- Occur most frequently on the upper part of the body
- Last for < 1 hr.
- Must be differentiated from aquagenic pruritus (HD, PV, MDS)

Inducible urticaria

Contact urticaria

- Development of urticaria at the site of contact with skin or mucosa
- Percutaneous or mucosal penetration of the urticant may have distant effects, including acute urticaria or even anaphylaxis

Contact urticaria

Immunologic

- IgE-independent
  - Grass
  - Animals
  - Foods
  - Latex

Non-immunologic

- Direct effects of urticants on blood vessels
  - Sorbic acid
  - Benzoic acid
  - Cinnamic aldehyde (PGD2)
  - Nettle stings (histamine, acetylcholine, serotonin)
  - Dimethylsulfoxide
  - Cobalt chloride
- Inhibited by NSAIDs.

Inducible urticaria

Vibratory urticaria

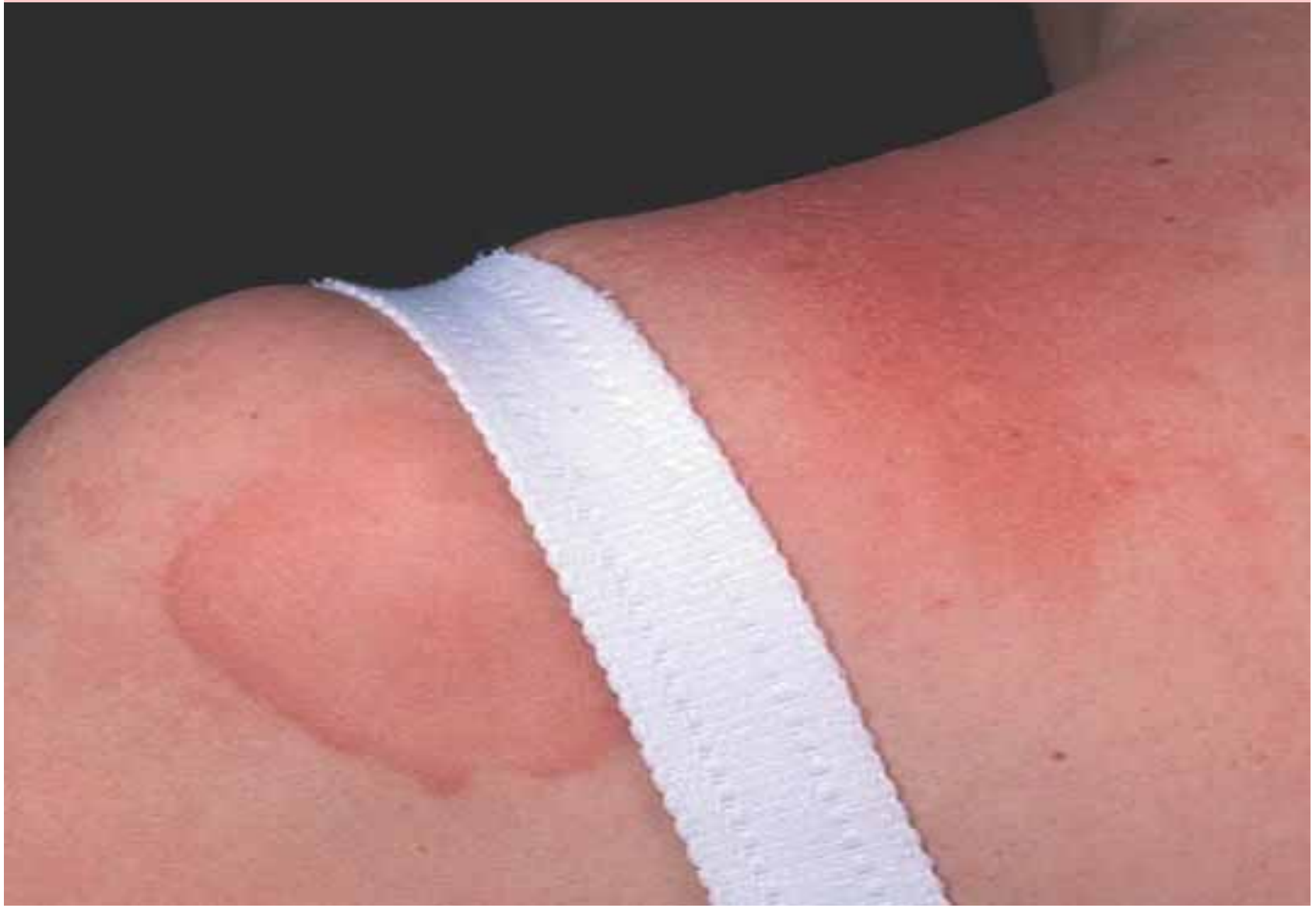
- Very rare form of urticaria
- Vibratory stimulus induces localized swelling and erythema within minutes, lasting 30 minutes.

Vibratory angioedema

- The acquired form
  - milder
  - associated with DPU and symptomatic dermographism.
- The familial form
  - dominantly inherited
  - intense vibratory stimuli may induce generalized erythema and headache

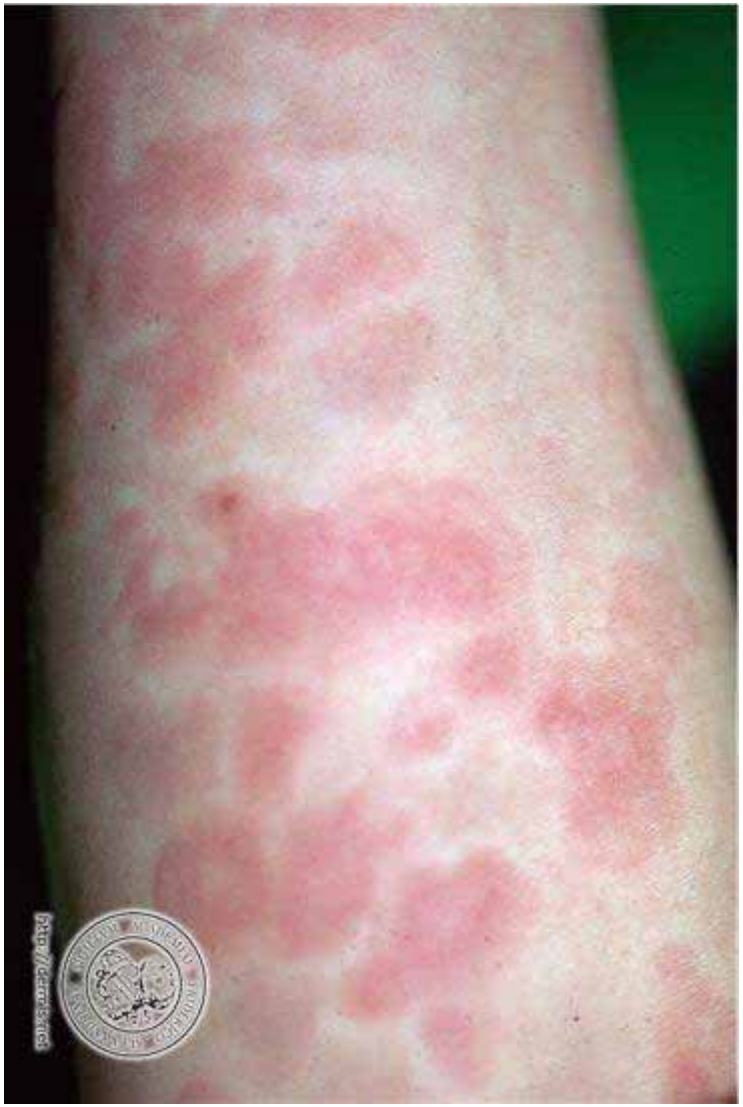
Physical Urticaria

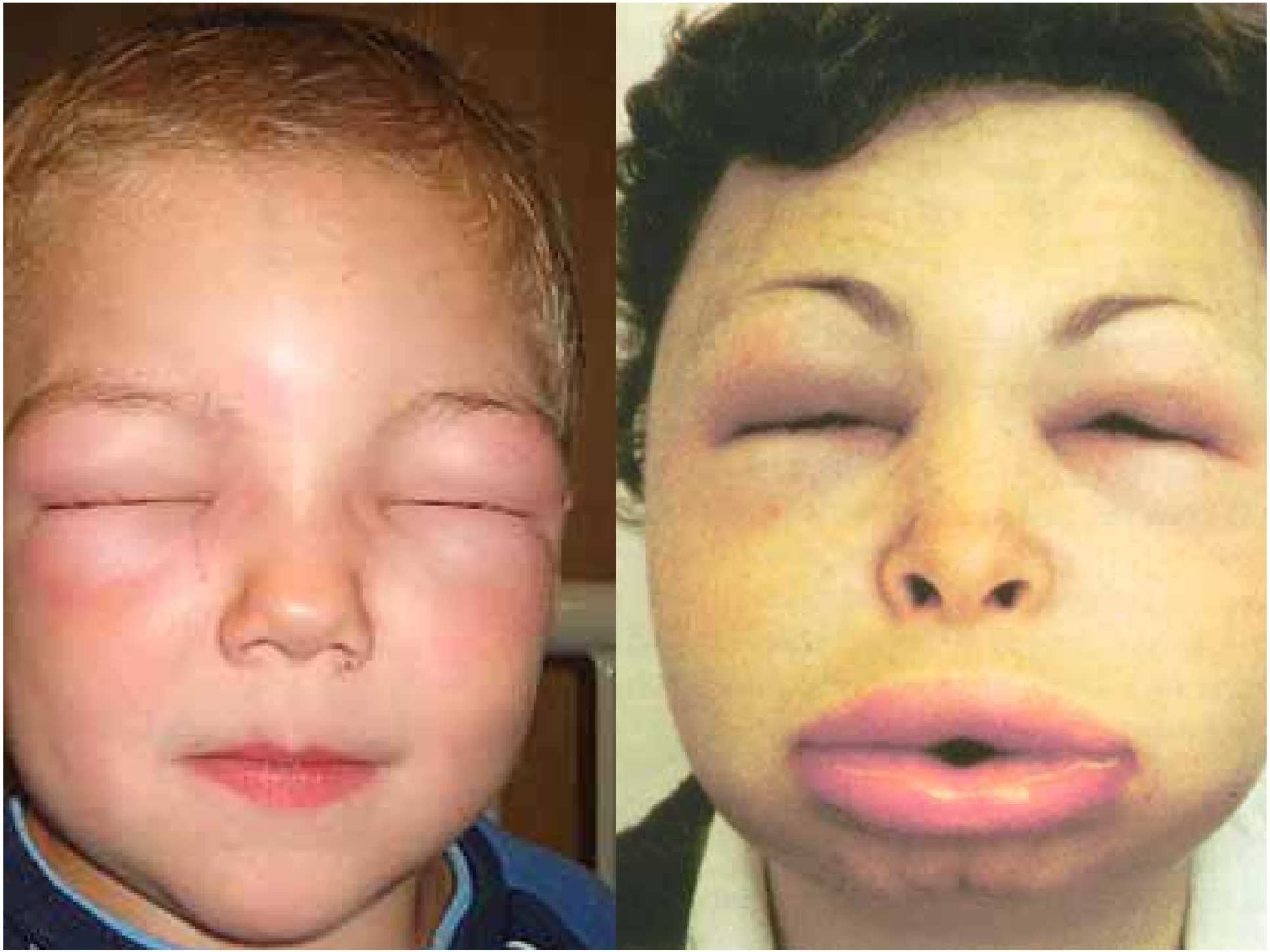
Delayed pressure urticaria



Urticarial vasculitis

- Resemble urticaria
- Histologically show evidence of leukocytoclastic vasculitis
- Lesions persist for >24 hours
- Burn ,painful with pruritus
- Resolve with residual purpura
- Angioedema up to 40% of patients
- Arthralgias in 50%





Angioedema without Wheals

- Idiopathic
- Drug reaction:
  - Aspirin, NSAIDs
  - ACE inhibitor: African-American polymorphism enzymes catabolize bradykinin contraindicated in pt. with history of angioedema
- C1 esterase inh deficiency

Direct mast cell degranulation

- Radiocontrast media
- Opiate
- Analgesics
- Polymyxin B
- Curare
- D- tubocurarine

Inducible Urticarias

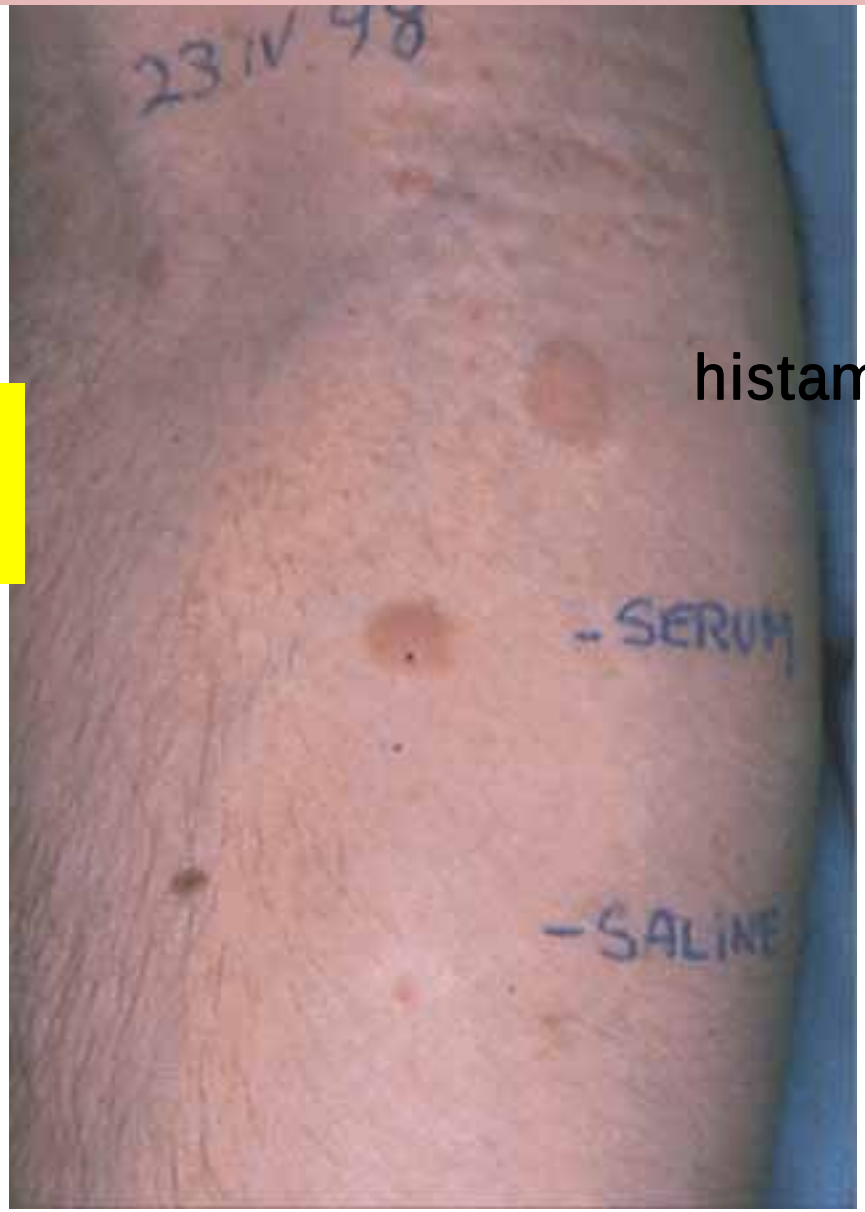
- Dermatographism
- Cold
- Cholinergic
- Local heat
- Delayed pressure
- Solar
- Aquagenic
- Vibratory

- Stroke with tongue blade (36g/mm2)
- Ice cube in thin bag 5 minutes
- Exercise til sweat, hot bath 42C, 10 min
- 44 C 5 minutes
- Sandbags 15 lbs 15 minutes
- Specific wavelengths
- 35 C water compress
- Vortex 4 minutes

Chronic Autoimmune Urticaria

Autologous Serum Skin Test

Response within 30 mins
At least 1.5 mm



Invesgations of Chronic Urticaria

Exclude physical urticaria

Exclude urticarial vasculitis

Exclude thyroid disease by screening thyroid antibody test

- If positive: perform thyroid function test
- Positive result strengthens the likelihood of an underlying autoimmune process

Invesgations of Chronic Urticaria

WBC count for eosinophilia

Stool exam requested in the presence of eosinophilia

Investigate for autoimmune urticaria

Management of Chronic Urticaria

- Identify and eliminate endogenous and exogenous cause

- Advice that it takes months to years for the lesions to go away completely

Laboratory examinations

- CBC, Stool exam, HBsAg, CXR
- Antinuclear antibodies
- ESR, C-reactive protein
- Complement
- Antithyroperoxidase antibodies and thyroid function tests
- Autologous serum or plasma skin test

What would be your first prescription?

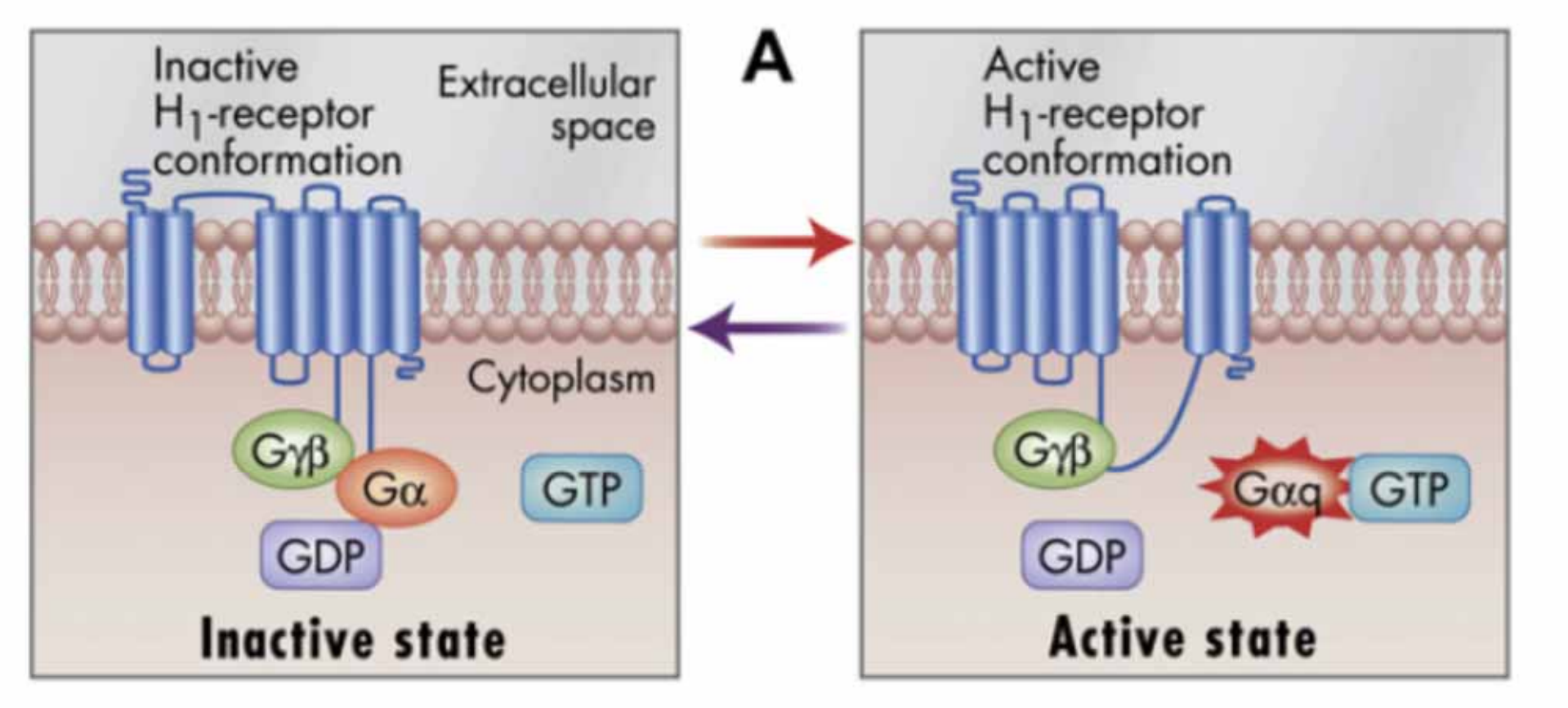
a) Topical steroids
b) Oral steroids
c) Topical antihistamines
d) Oral antihistamines

H_1 antihistamine

- Inverse agonists

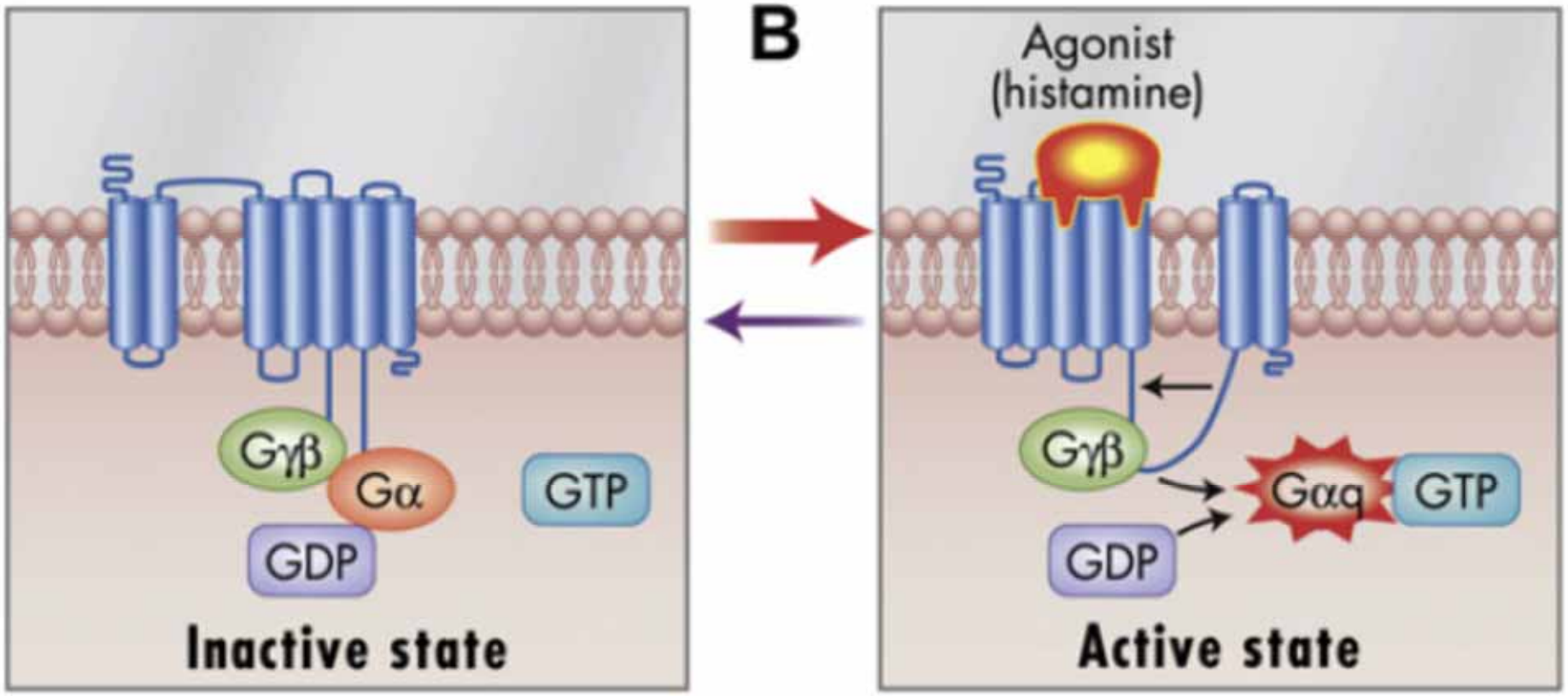
  "agent that binds to the same receptor as an agonist but induces a pharmacological response opposite to that agonist"
- Combine and stabilize the inactive conformation of histamine receptor

Equilibrium
In-active state



Estelle F et al. J Allergy Clin Immunol;128:1139

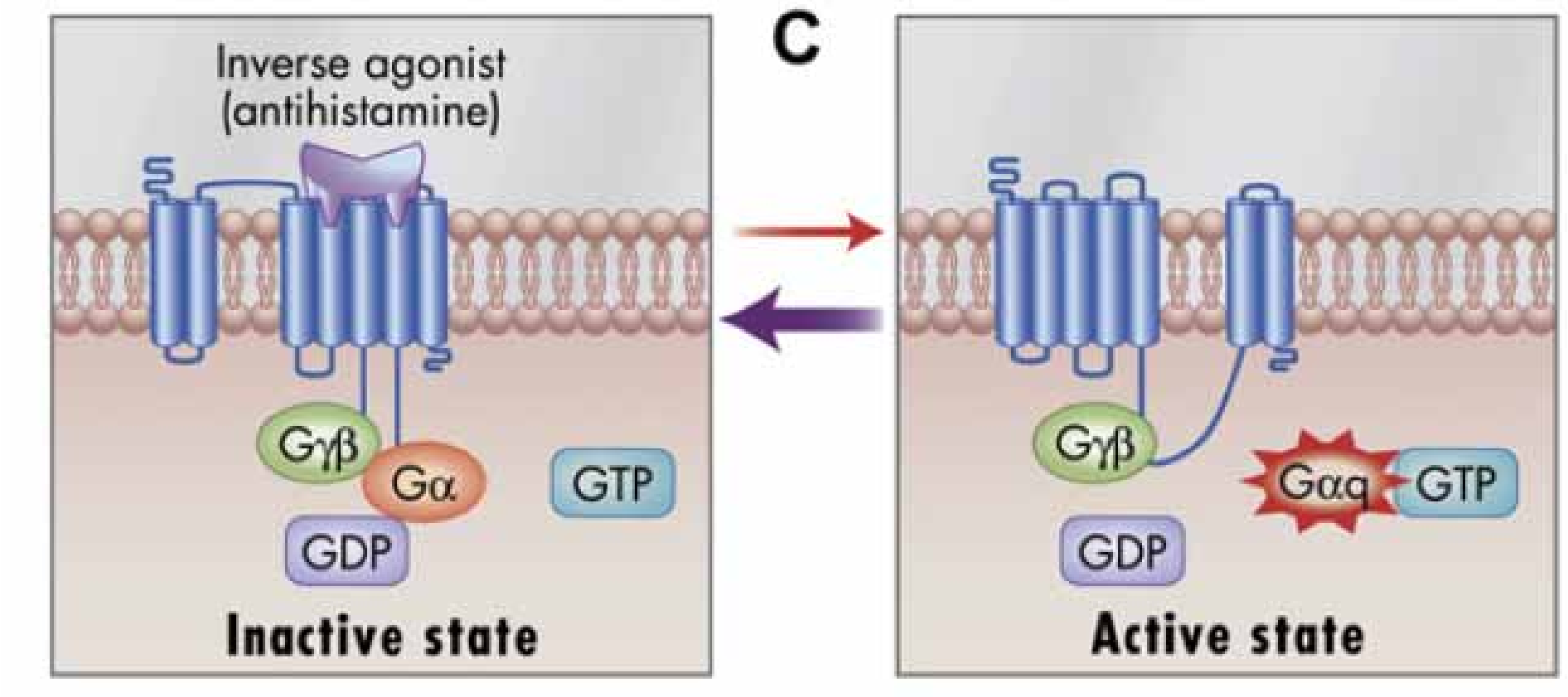
Histamine



Histamine has affinity for the active state and shifts the equilibrium toward the active state

Estelle F et al. J Allergy Clin Immunol;128:1139

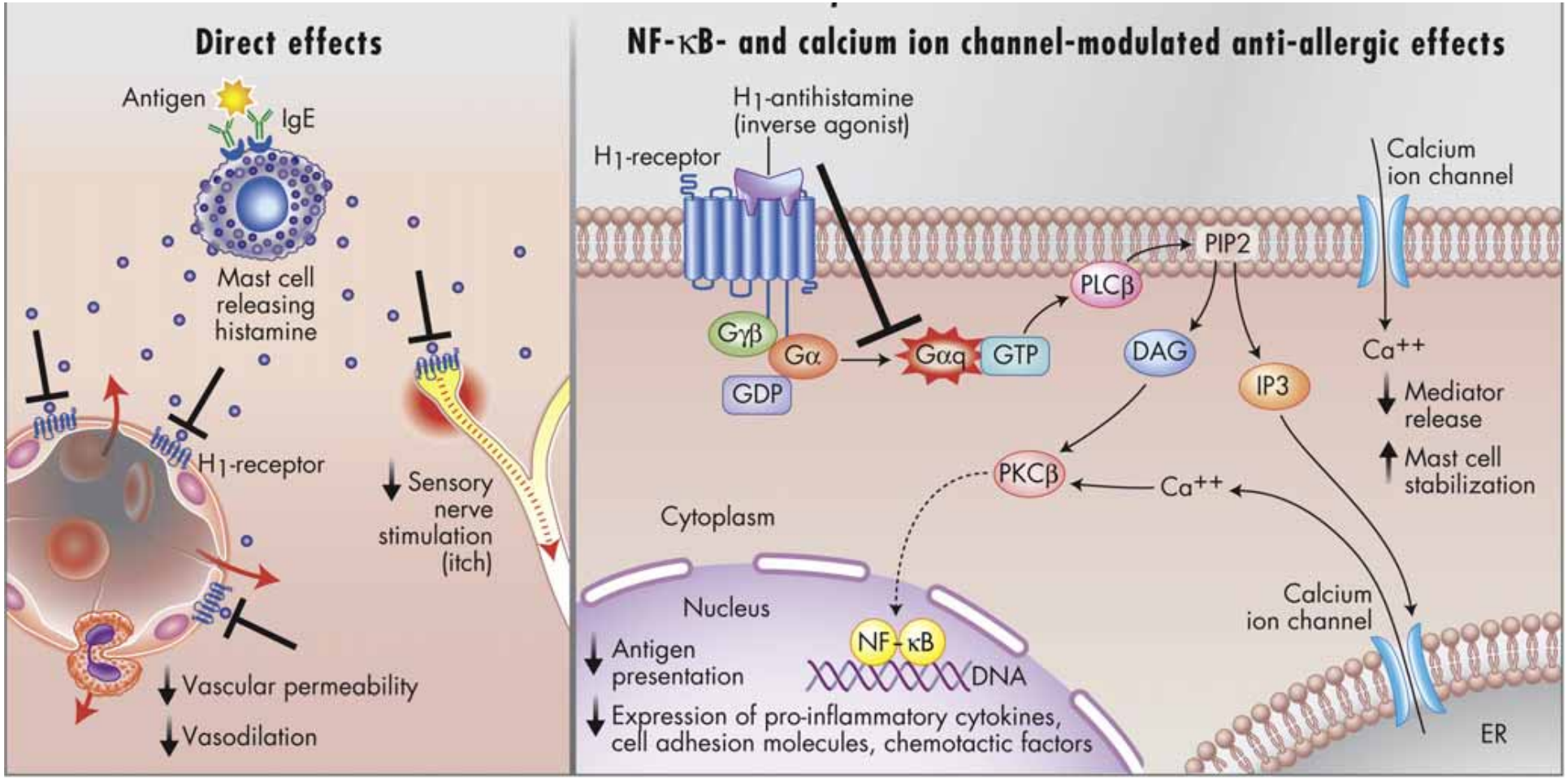
H_1 antihistamine



Antihistamine has preferential affinity for the inactive state, and shifts the equilibrium toward the inactive state

Estelle F et al. J Allergy Clin Immunol;128:1139

Beneficial effects of H1-antihistamines



- Directly interfere H1 receptor on sensory neuron, small blood vessels esp post-capillary venules
- Down regulates inflammation: ↓NF-κB

Wheal and flare suppression correlate(s) best with

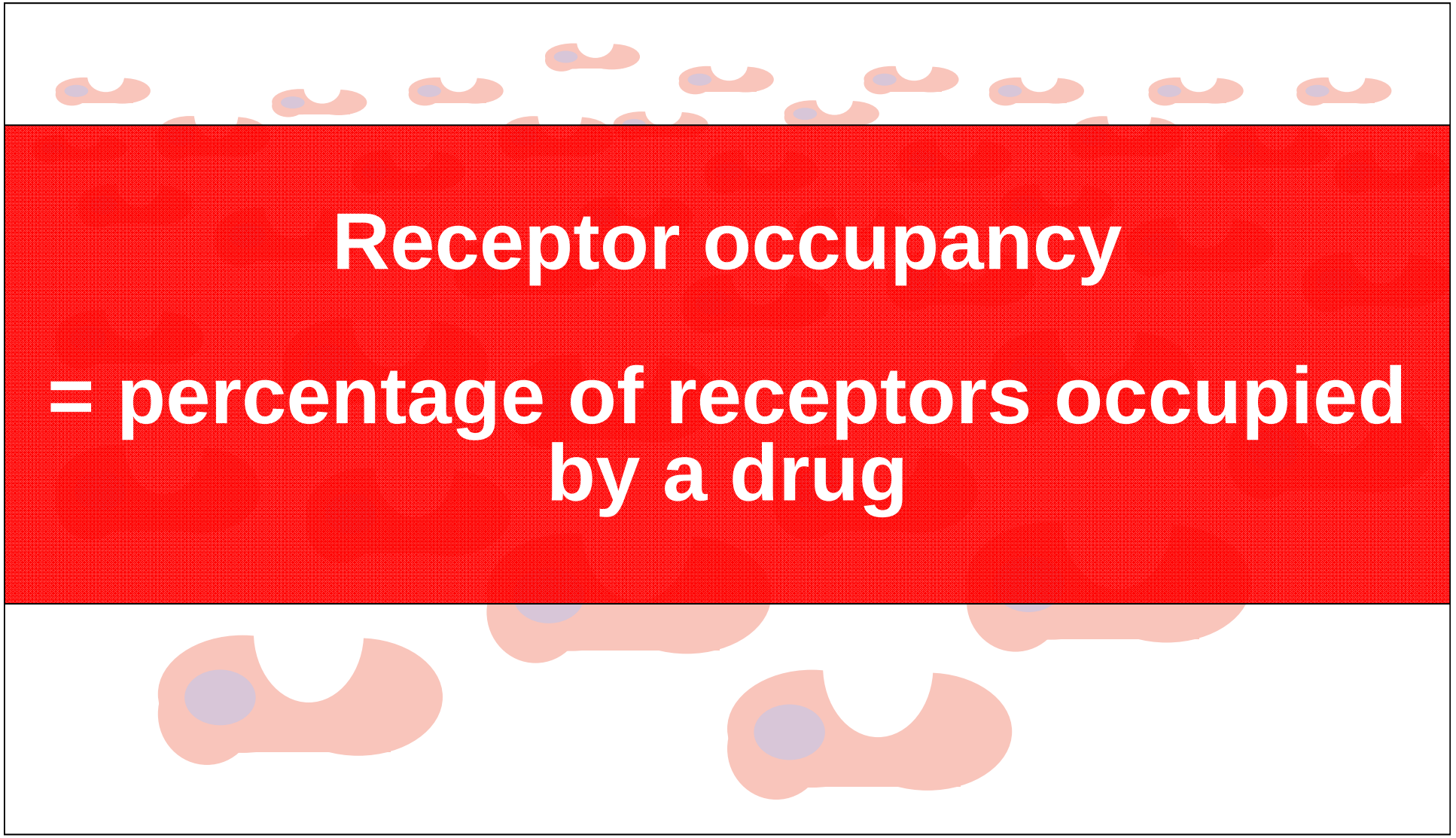
a. H_1 antihistamine receptor occupancy of unbound drug
b. H_1 antihistamine concentrations in plasma
c. H_1 antihistamine concentrations in tissue
d. All of above

The Receptor Occupancy Concept

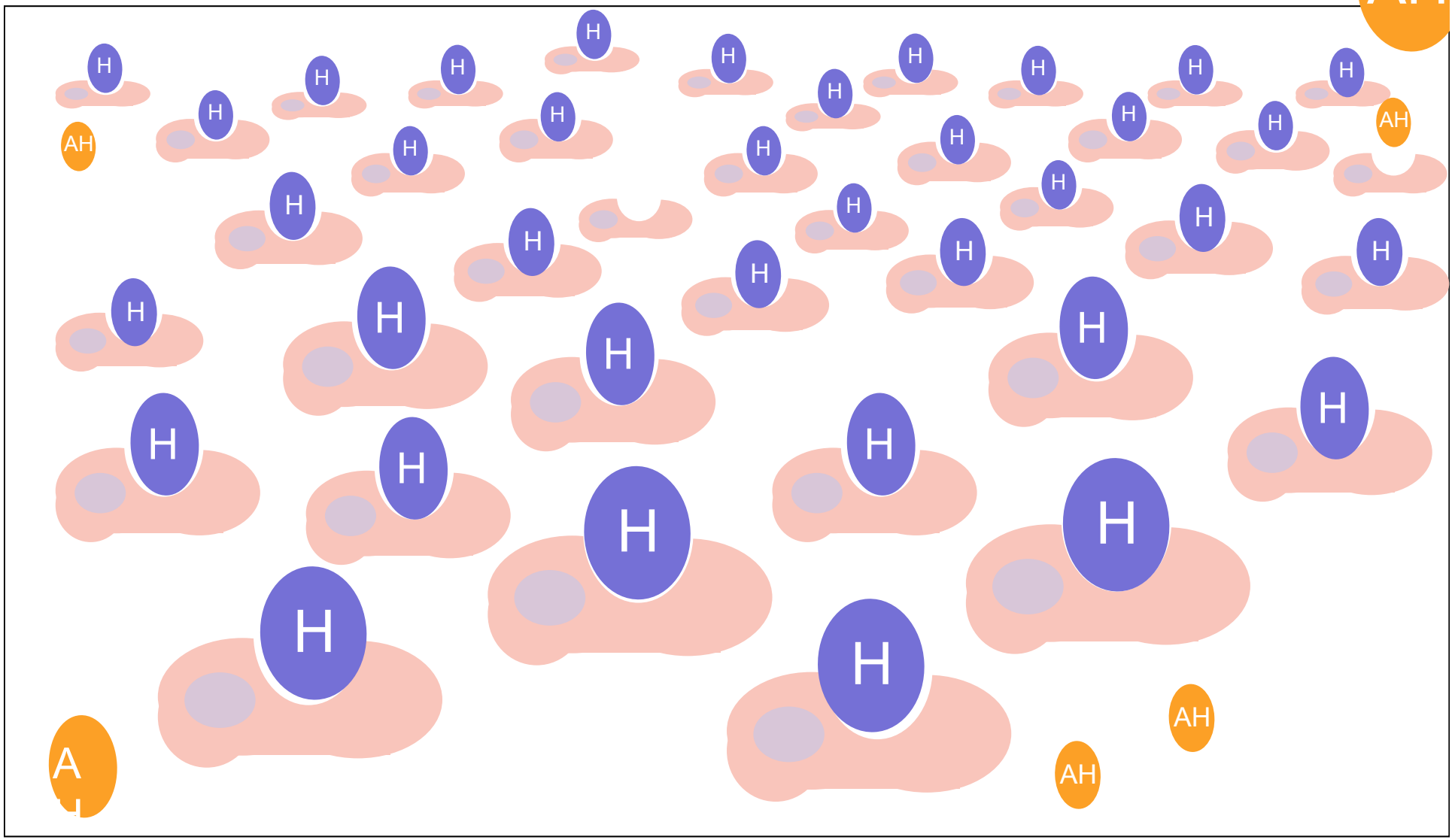
Receptor Occupancy

- Antihistamine do not displace histamine once it is bound
- Having antihistamine on the receptor before histamine arrives offers best result.
- Prescription around the clock

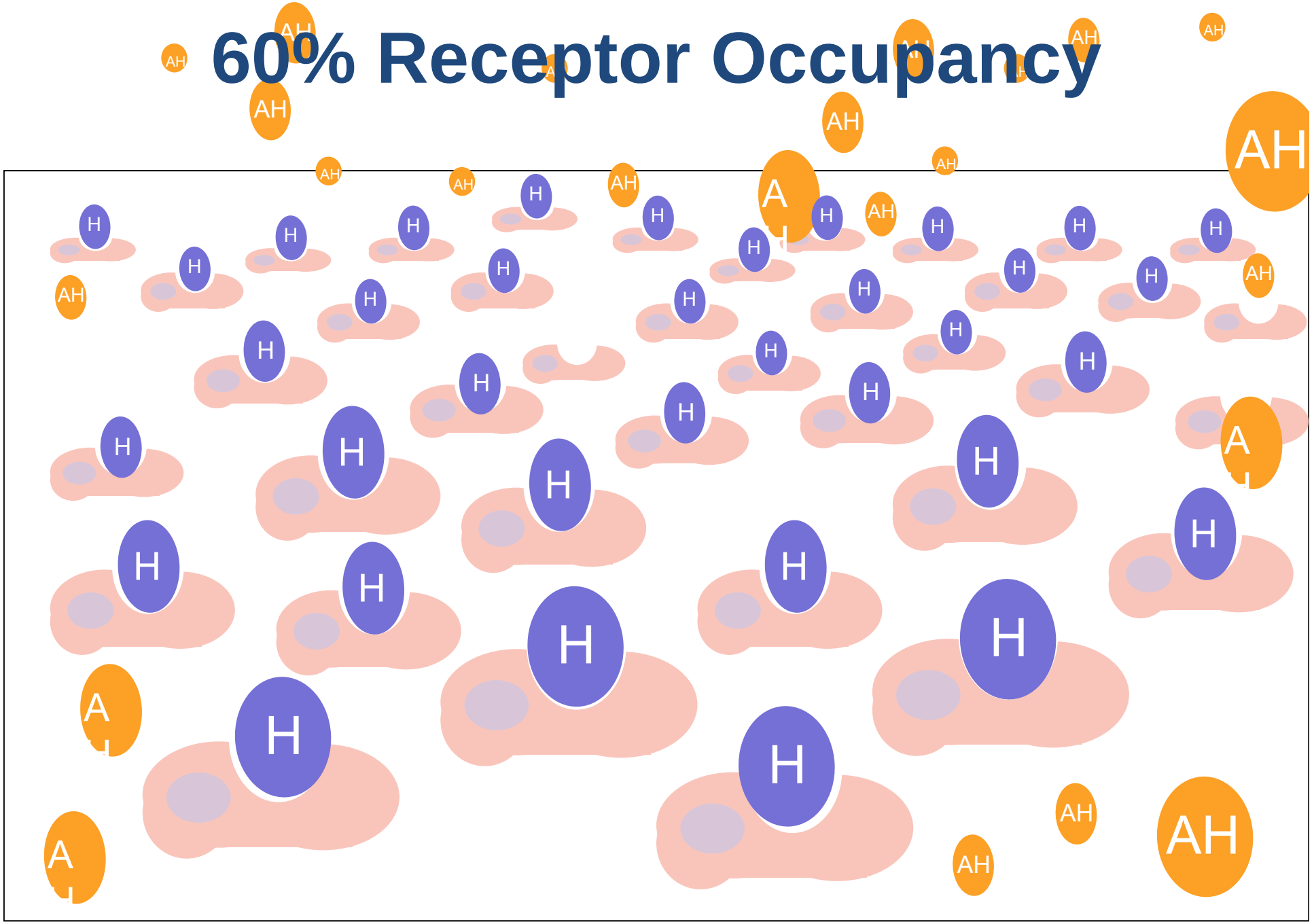
Histamine Release during an Allergic Reaction



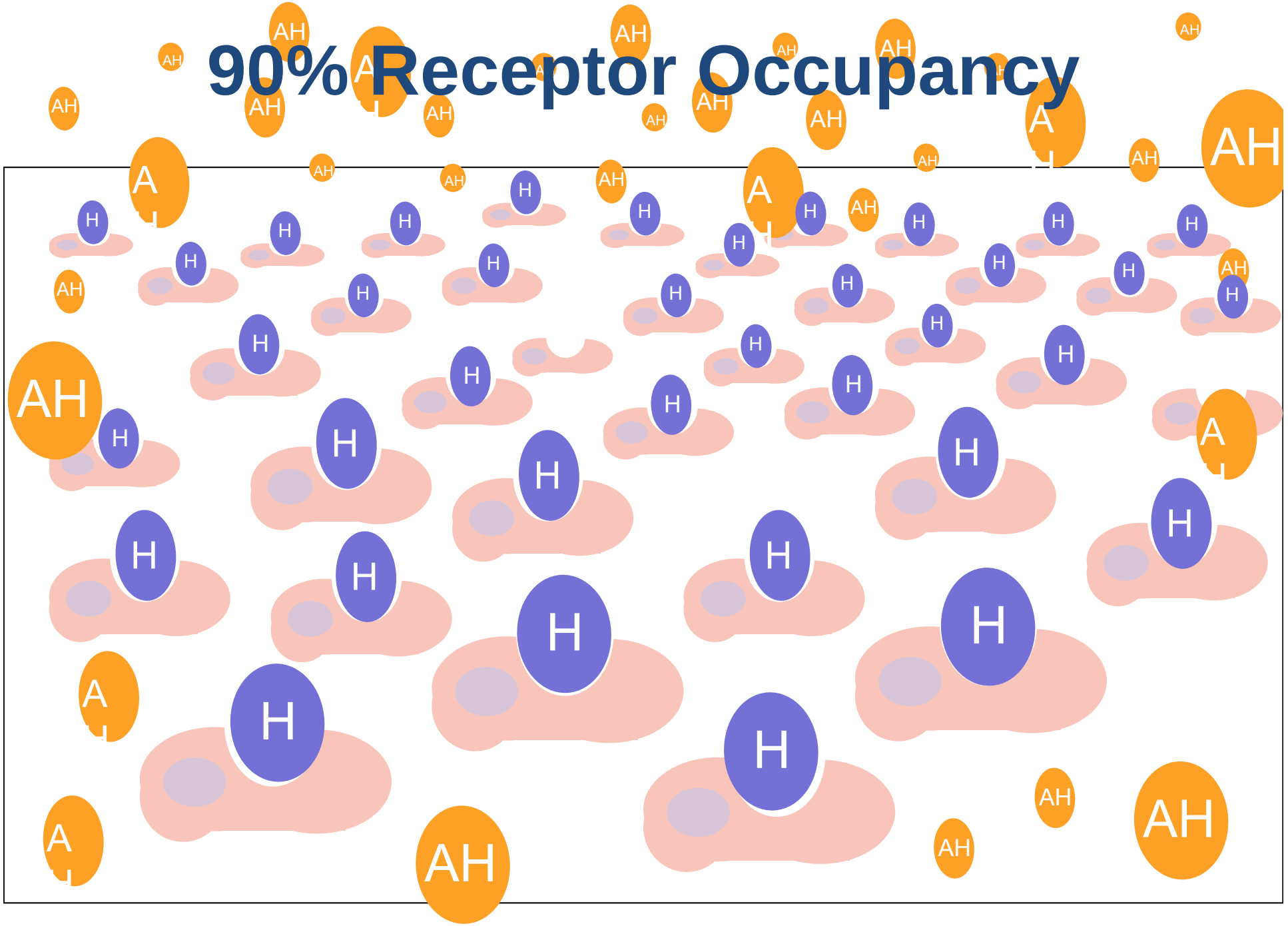
10% Receptor Occupancy



60% Receptor Occupancy



90% Receptor Occupancy



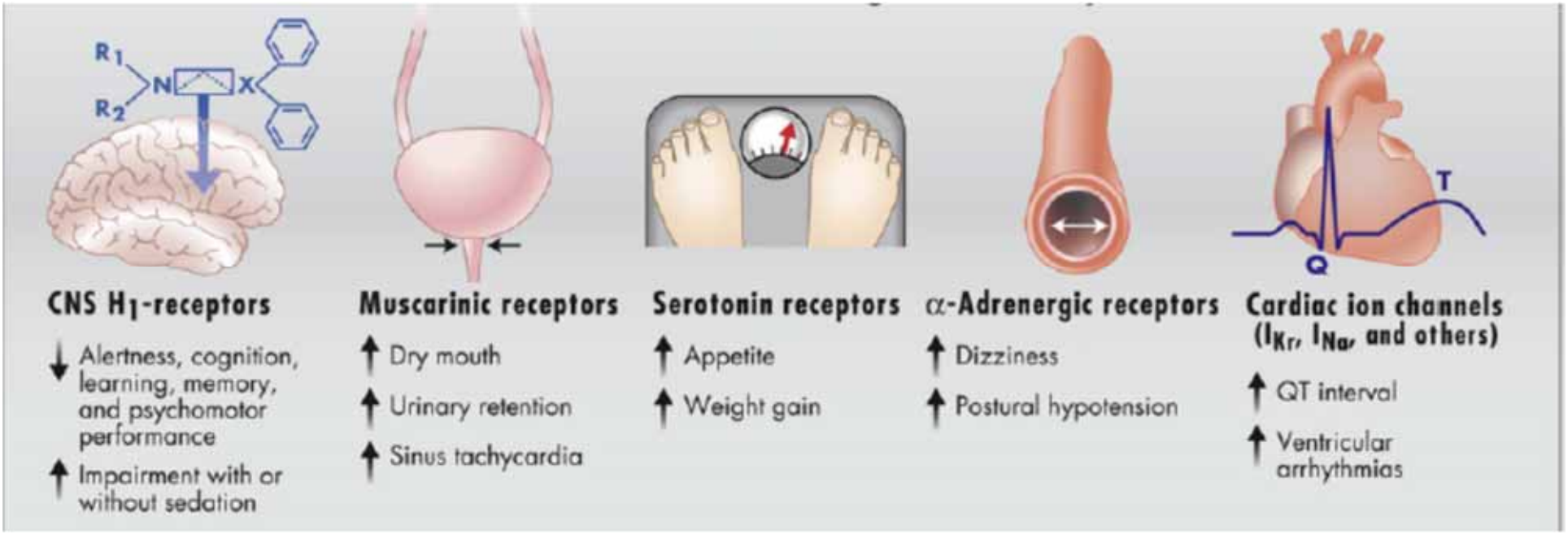
Antihistamine

- H_1 antihistamine
  - -1st generation
  - -2nd generation
- H_2 antihistamine

1st generation H_1-antihistamine

- Antihistamine
- Other properties

Adverse effects of 1st generation H1-antihistamine

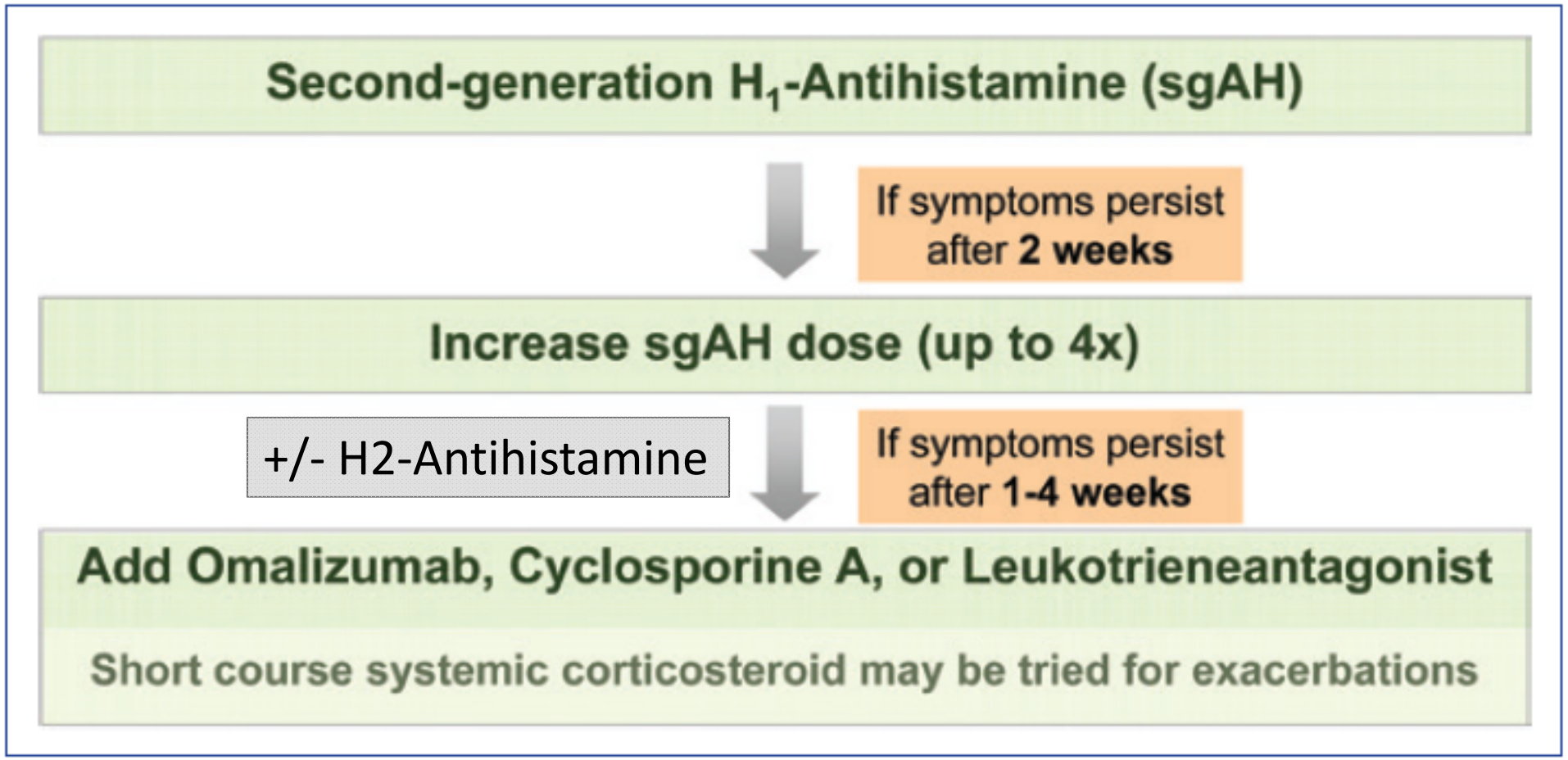


Multiple aromatic (heterocyclic ring) and alkyl substituents enhance lipophilicity → penetrates blood brain barrier

Oral H_1-antihistamines

First generation	Second generation
•short acting •more sedation •anticholinergic SE	•long acting •less sedation •less side effects
hydroxyzine, chlorpheniramine, diphenhydramine, cyproheptadine	ceterizine, loratadine, fexofenadine, levoceterizine, desloratadine

EAACI/GA2LEN/EDF/WAO guideline: management of CU: the 2013 revision and update



Zuberbier et al. *Allergy* 2014: 69: 868-87

Conclusion

Urticarias are very common

Acute Urticaria (<6 wks)

- History is the key
- Non-sedating antihistamine

Inducible Urticaria

- History and provocative challenges
- Non-sedating antihistamine

Chronic Uriticaria

- Ethiology rarely determined
- Therapy is difficult