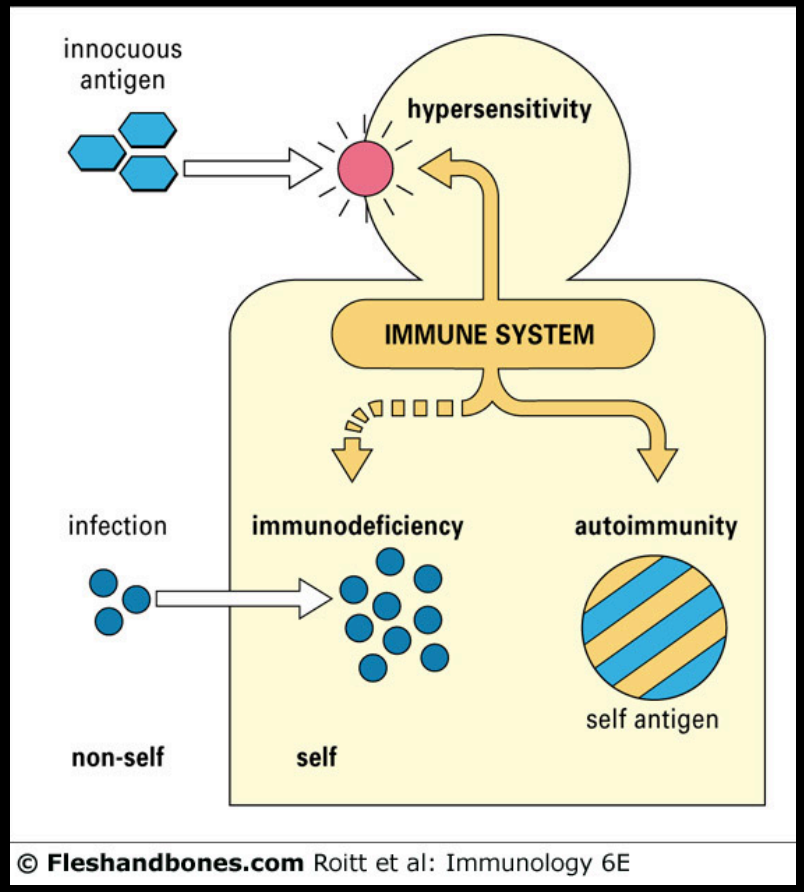
Allergy and the *'Hygiene Theory'*

Hypersensitivity, one of three major mechanisms of 'inappropriate' immunity



Allergy and the 'Hygiene Theory': fact or fiction?

- Observations leading to the hygiene theory
- The cellular and molecular basis for the hygiene theory
- What causes allergy?
- Types of allergic responses
- Allergy prevention, diagnostic, therapy and treatment

The hygiene hypothesis

The problem

Several types of allergies and chronic inflammatory diseases are increasing in prevalence in developed countries.

Why?

The hygiene hypothesis

The problem

Several types of allergies and chronic inflammatory diseases are increasing in prevalence in developed countries.

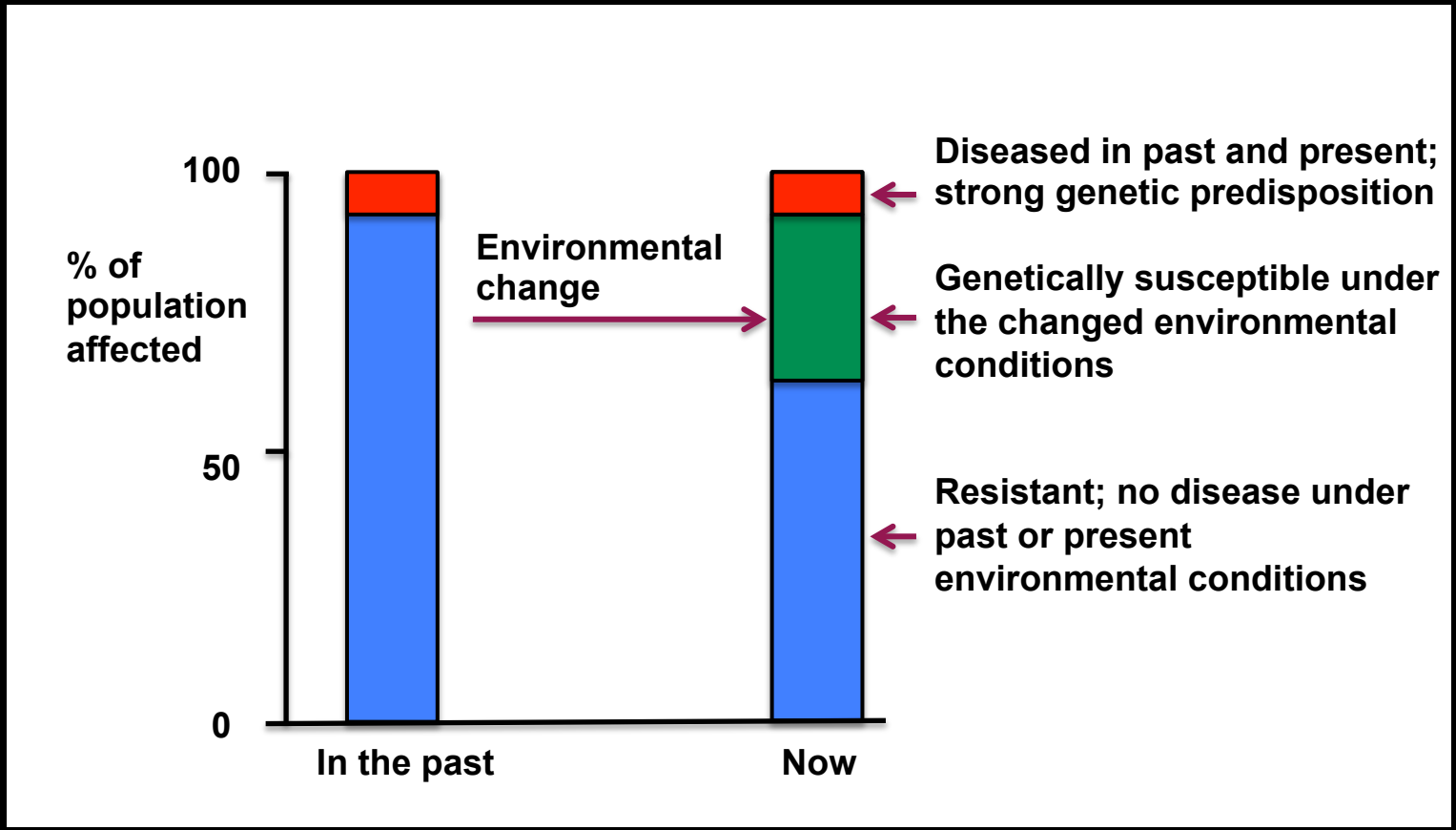
Why?

The hypothesis

The increase in allergies and chronic inflammatory disorders in developed countries is caused by a malfunction of the immune system attributable to diminished exposure to microorganisms that were present in the environment throughout mammalian evolutionary history.

Gene - environment interactions

Genetic susceptibility to a disease revealed under specific environmental conditions



Some epidemiological findings that support the hygiene hypothesis

You are less likely to have allergies if you:

- were brought up on a farm
- have older siblings (boys better than girls)
- rarely washed your face and hands as a child
- had infections via the oral-fecal route
- kept a dog
- lived in economically deprived regions
- had helminth infections
- lived in a home where dust was contaminated with bacteria

Farming conditions and resistance to allergy

The fact that contact with farming environment protects against allergy disorders has been demonstrated in Europe in several countries.

A typical farm house in Europe used to have two sections, one for the family and an adjacent one for the farm animals where the cowshed communicate directly with the living area.

Erika von Mutius and colleagues (Munich) found that if very young babies are placed in the cowshed while the mother milks the cows, they are protected from allergic disorders (Riedler et al., (2001) Lancet 358:1129).

In Bavaria, the house is very close to the barn. The relationship with animals is intimate. Animal-associated bacteria have been demonstrated in the children's bedding.

Farming, Bavarian Style

Growing up on a Farm Bavarian Style

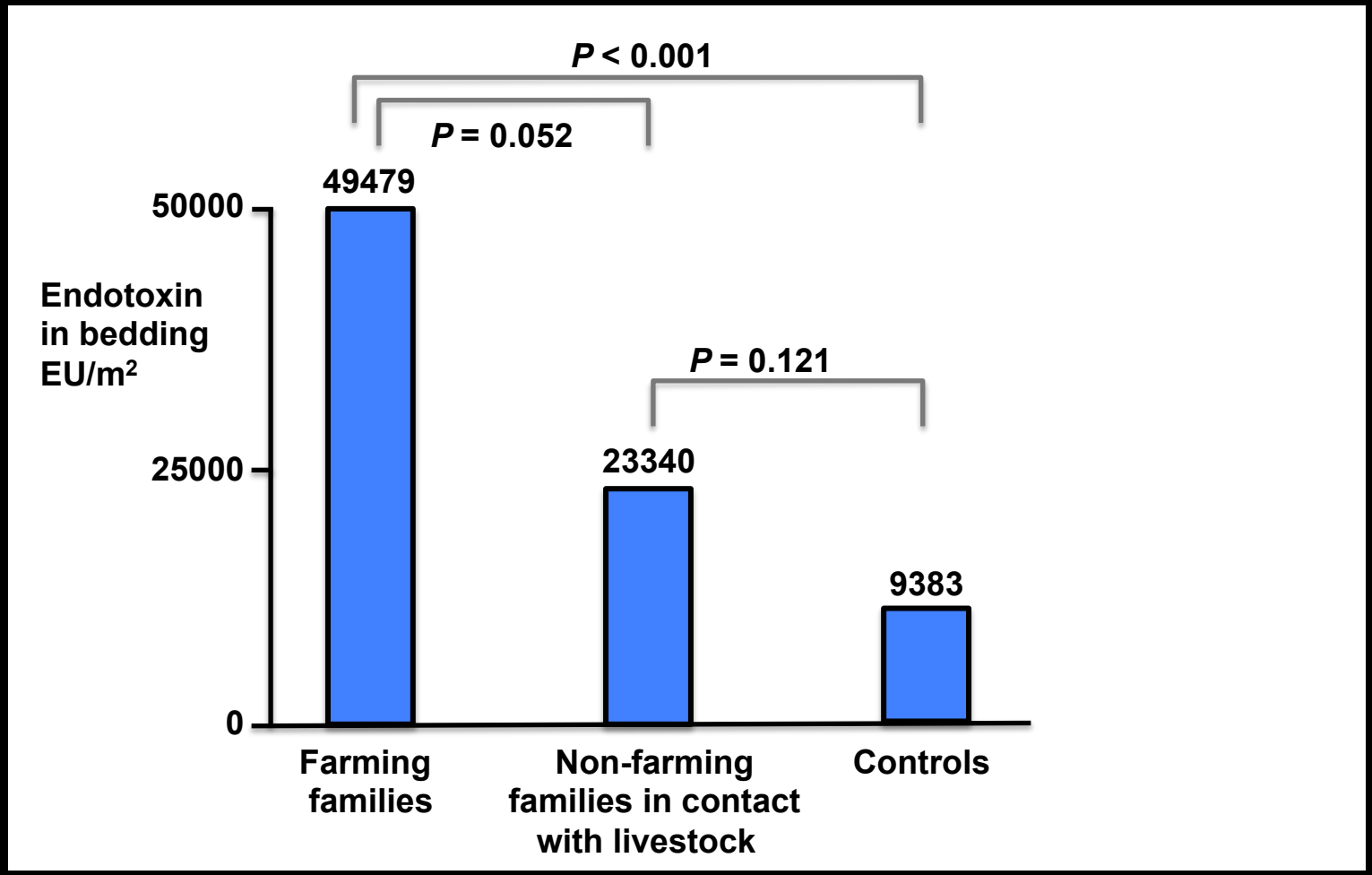
Farming, Bavarian Style

Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey

	Stables and farm milk in the 1st year of life (n=218)	Neither stables nor farm milk exposure (n=170)
Asthma allergy	1% (3)	12% (20)
Hay Fever	3% (6)	15% (25)
Atopic sensitization	12% (27)	33% (56)

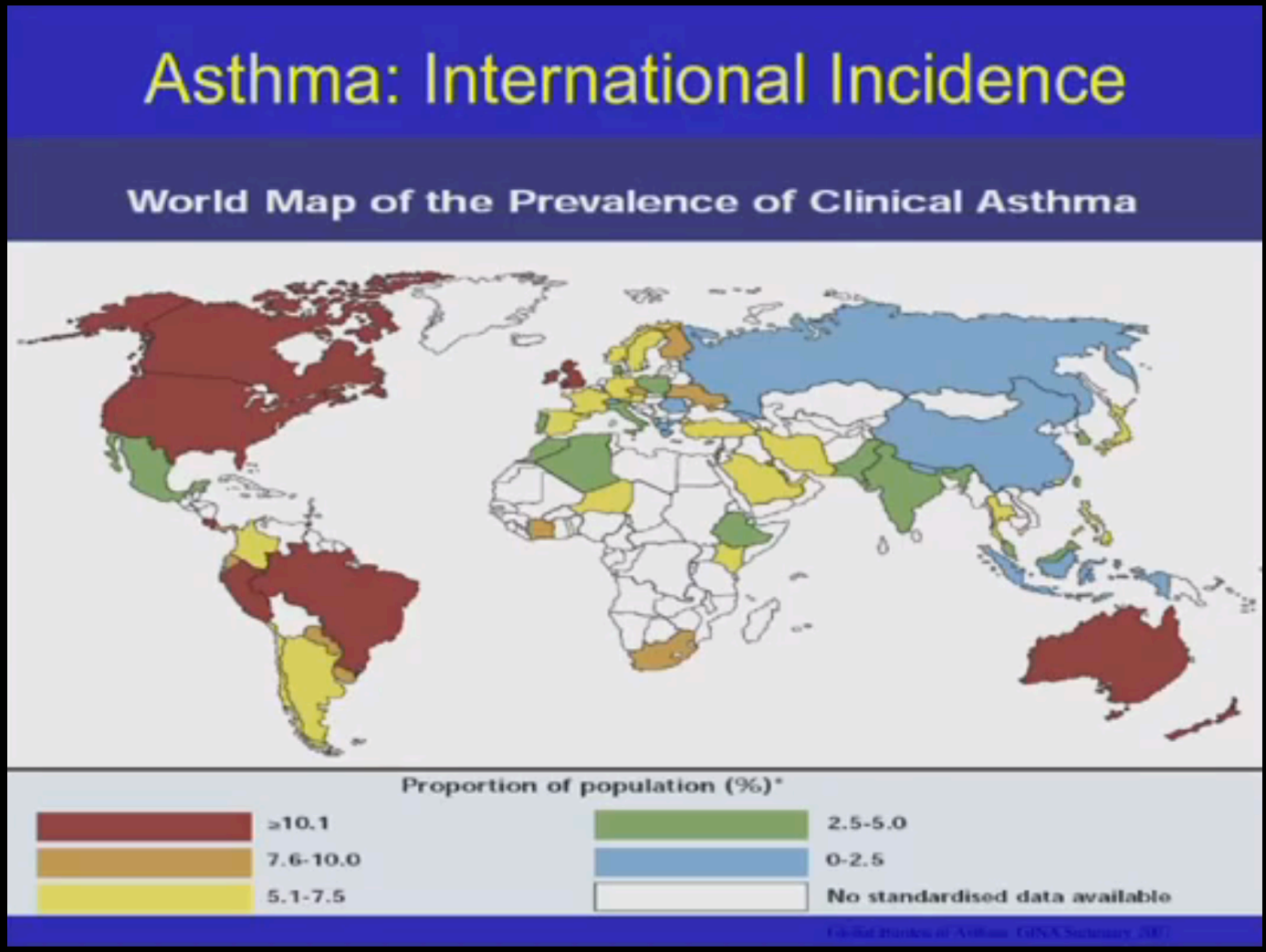
Riedler *et al.*, (2001) *Lancet* **358**:1129

Endotoxin in bedding can be used as a surrogate marker for exposure to bacterial products



Von Mutius *et al.*, (2000) *Clin Exp Allergy* **30**:1230

Prevalence of asthma in different countries

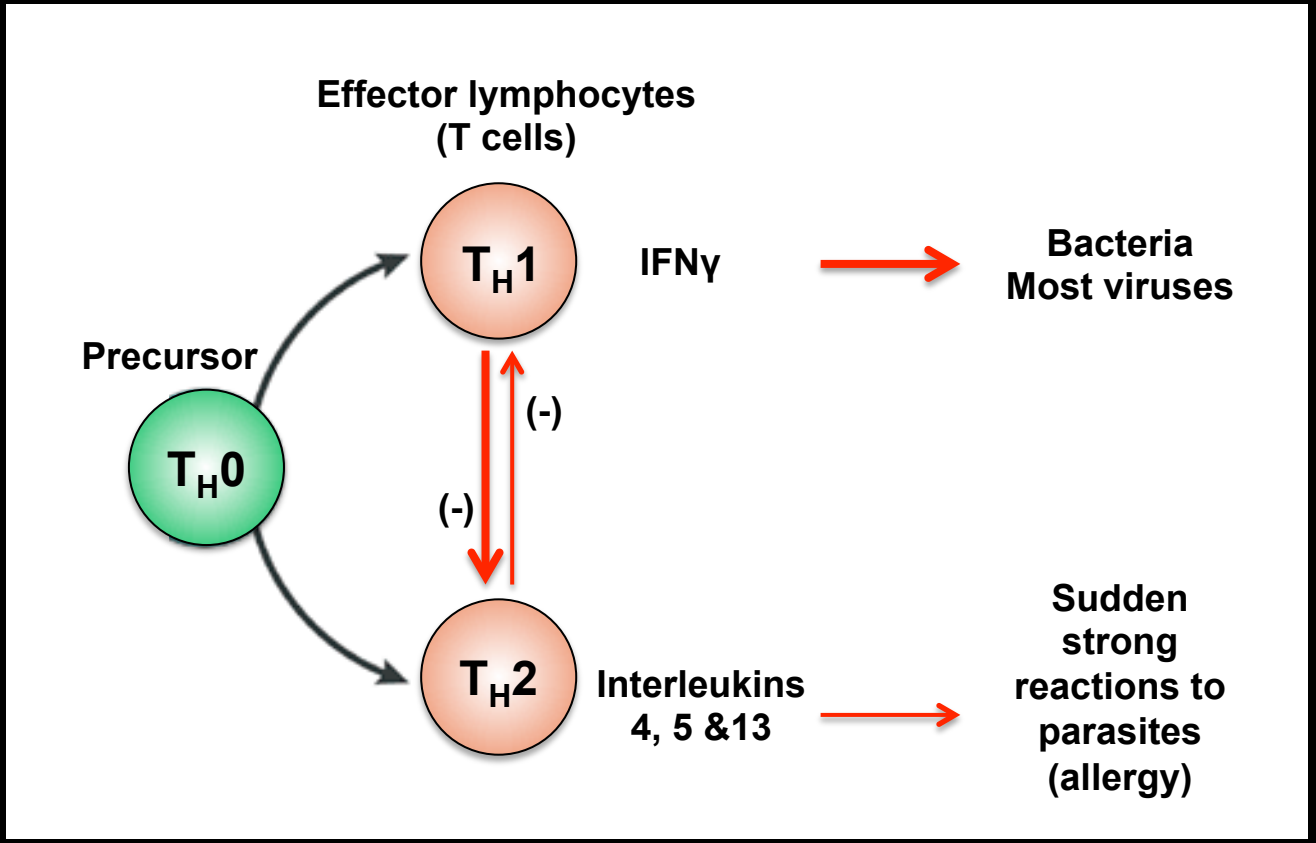


Explanation of the hygiene hypothesis was initially based on the existence in our immune system of two major subsets of effector T helper (T_H) lymphocytes:

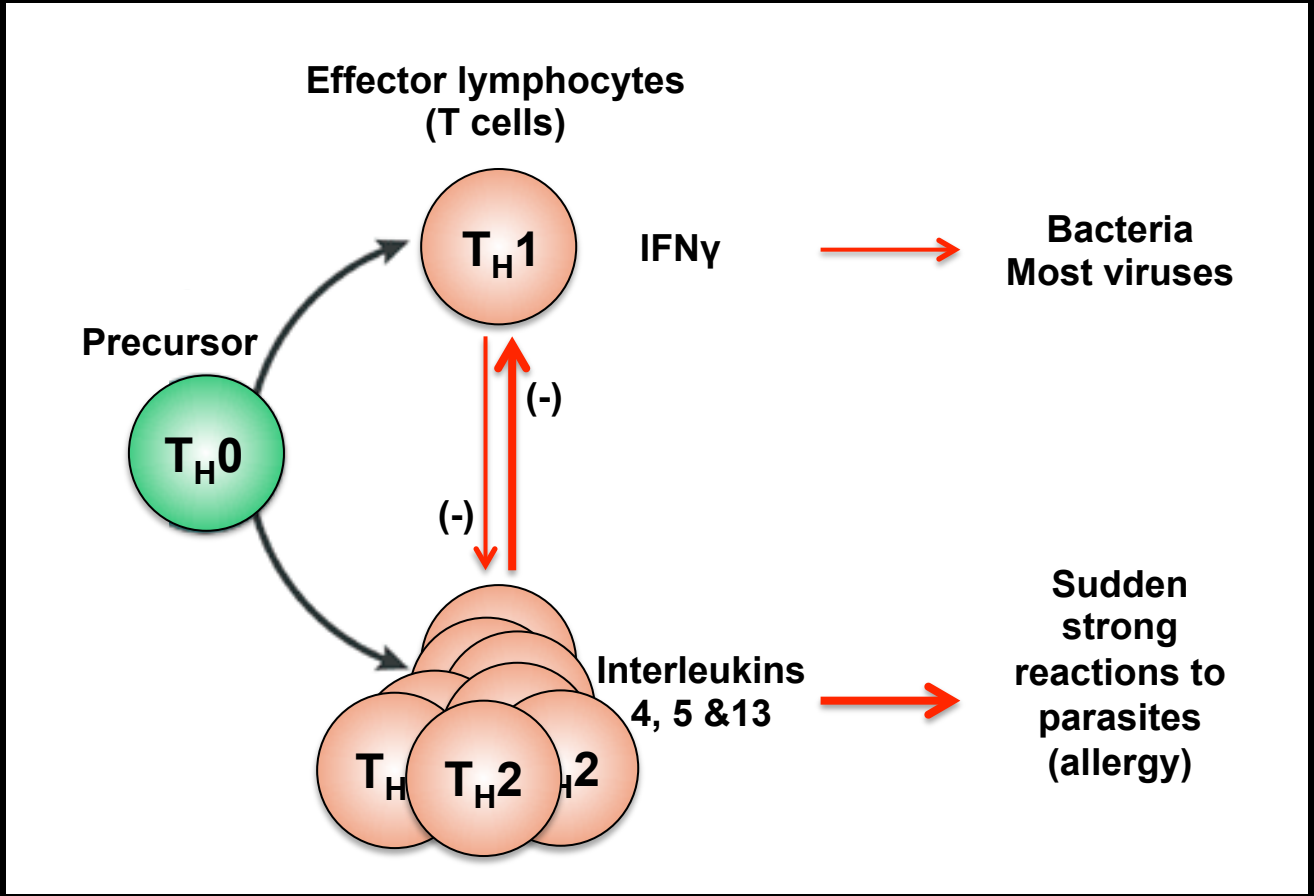
- The T_H1 lymphocytes, which protect us from various bacterial infections and most viral infections
- The T_H2 lymphocytes, which are responsible for strong and very rapid reactions to parasites and allergens

T helper (T_H) lymphocyte subsets

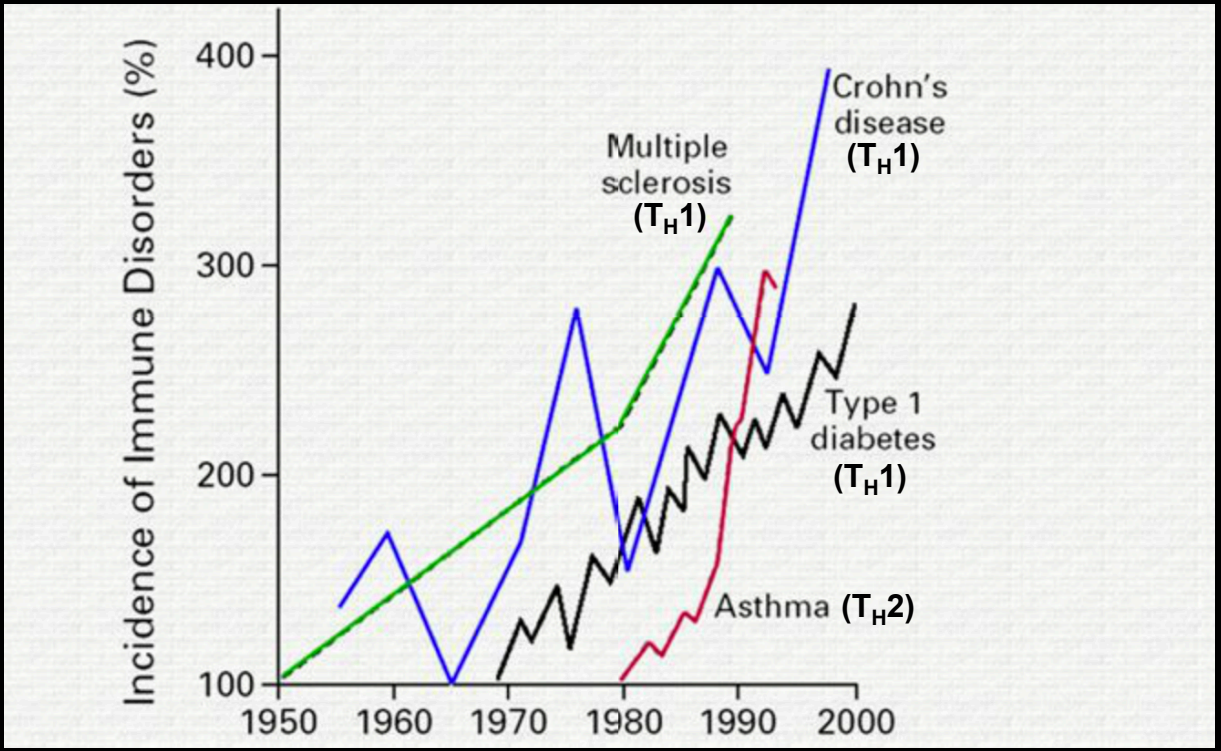
- Lymphocytes are the major mediators of the adaptive immune response
- T lymphocytes differentiate into two major distinct subsets that target different infections



Could lack of infections that drive T_H1 cells result in excessive production of T_H2 cells?



The increasing incidence of immunoregulatory disorders



This hypothesis would have made sense if only allergies mediated by T_H2 cells were increasing, such as asthma. But in the developed countries, not only are allergic disorders increasing, but also autoimmune disorders, such as MS, type I diabetes and other chronic inflammatory diseases, such as Crohn's disease, which are mediated by T_H1 cells.

So what we actually have in the developed countries is a simultaneous increase in allergies mediated by T_H1 cells, as well as chronic inflammatory- and autoimmune-disorders mediated by T_H1 cells.

These findings suggest a failure of regulation of both cell types rather than an imbalance between T_H1 and T_H2 cells.

Bach J-F. *New Engl J Med* (2002) **347**:911

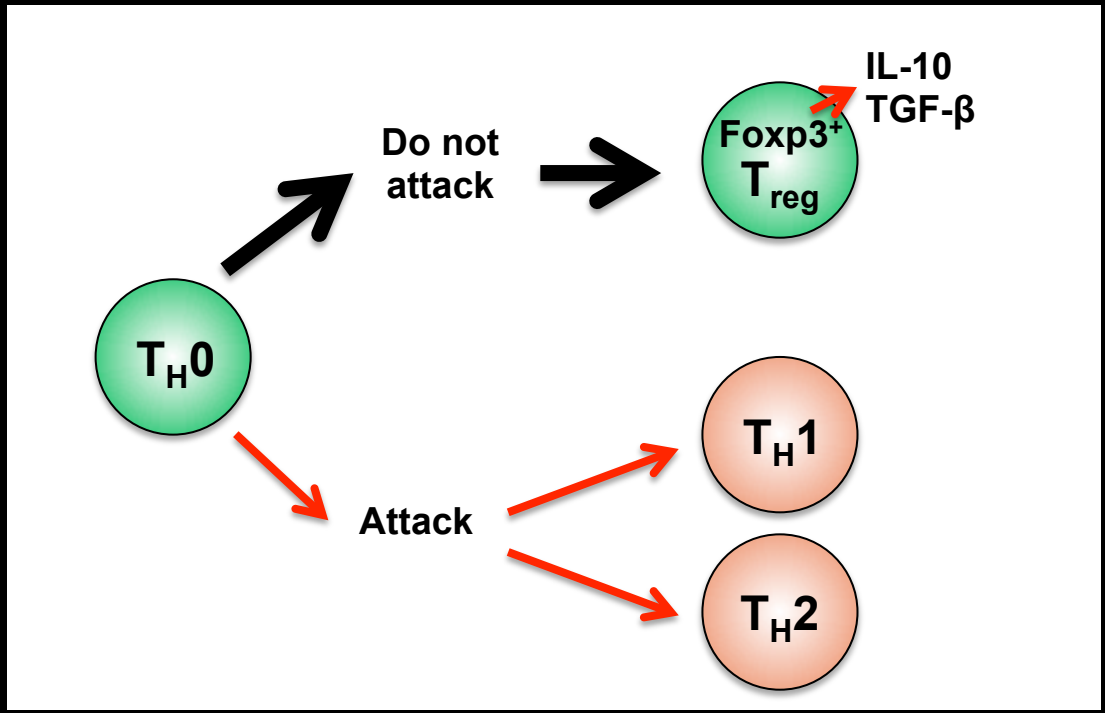
Three distinct types of diseases that increase with time in the developed countries

Disease group	Inappropriate target of immune system	Effector cell
• Allergies (Asthma)	Allergens (in air or food)	T_H2
• Chronic inflammatory bowel diseases (Crohn's disease, ulcerative colitis)	Gut contents	T_H1
• Autoimmunity (MS, Type I diabetes)	Self	T_H1

A regulatory defect rather than a defect of T_H1/T_H2 balance?

Bach J-F. *New Engl J Med* (2002) **347**:911

Most of the time the job of the immune system is NOT to attack. This is partly achieved by generating regulatory T cells (T_{reg})



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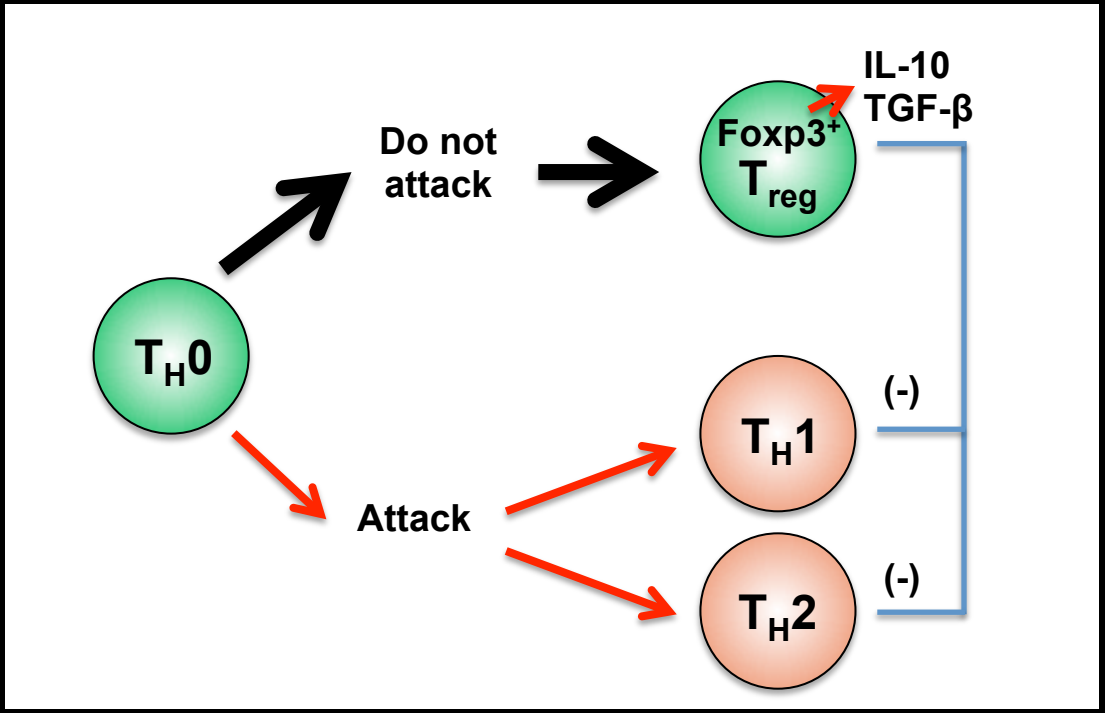
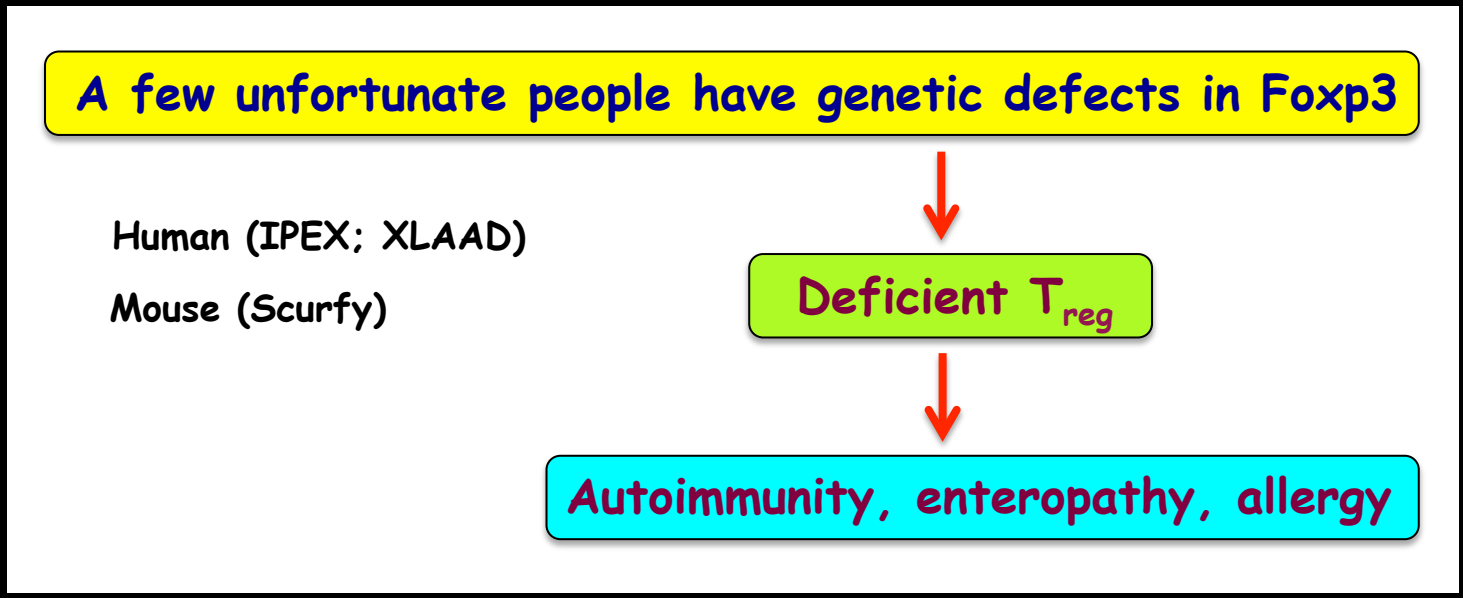


Treg produces regulatory cytokines which exert negative feedback on the activity of both T_H1 and T_H2 cells. If this is correct, then the increase in allergy, chronic inflammatory disorders and autoimmune diseases in developed countries may correlate with the failure of this type of regulatory circuit. Strong evidence support this assumption.

Development of regulatory T cells (T_{reg}) is controlled by the transcription factor, Foxp3



Hori, Nomura & Sakaguchi (2003) *Science* **299**:1057

People and mice with defects in Foxp$^+$ T_{reg} have a very severe syndrome which includes elements both of autoimmunity and of enteropathy, and of allergy. It is possible therefore to have increase of all three types of disorders, involving both T_H1 and T_H2 cells as a direct results of inadequate function of T_{reg}.

Defective T_{reg} in chronic inflammatory disorders

Allergies

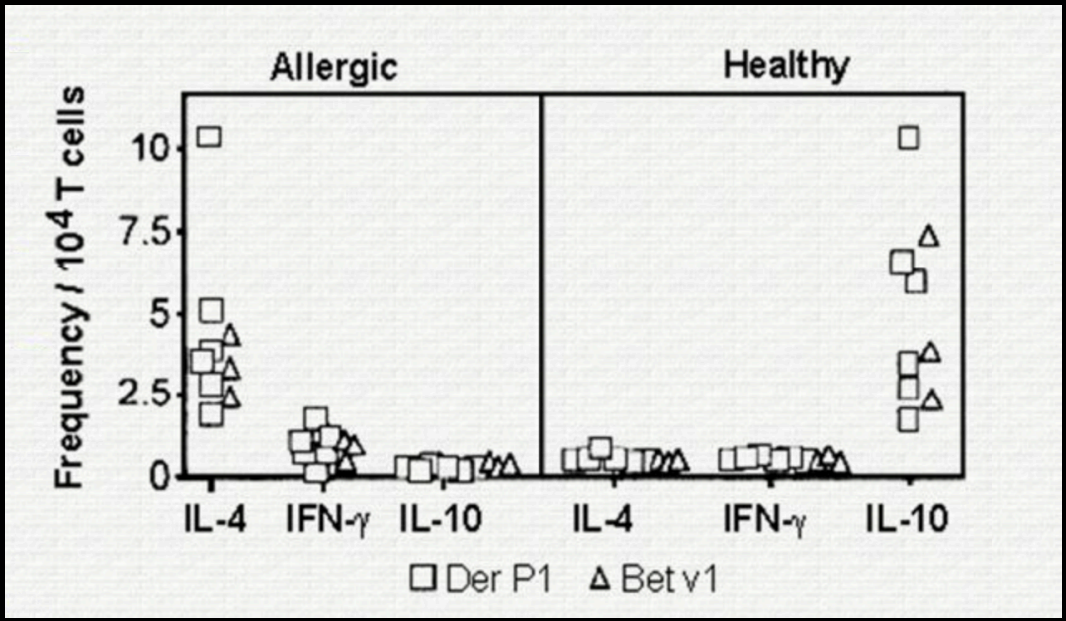
Food allergy

MS

Autoimmune polyglandular syndromes

Inflammatory bowel disease

Deficiency of IL-10-secreting regulatory T cells in allergic individuals



Der P1 - house dust mite allergen
Bet v1 – a pollen allergen

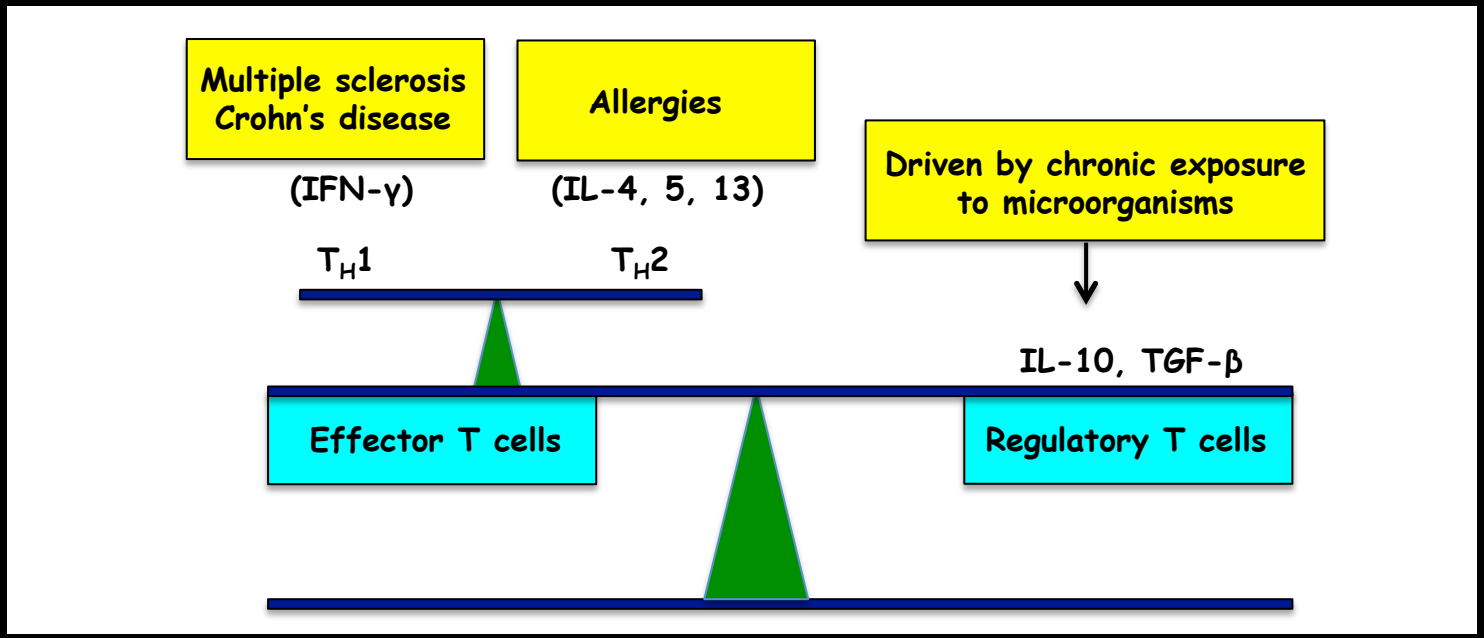
Akdis M. et al., *J Exp Med* (2004) **199**:1567

Frequencies of T lymphocytes in the peripheral blood of allergic and healthy people that either produce the cytokine IL-4, which is one of the mediators of allergic responses, or produced the cytokine IL-10, which is associated with a regulatory response.

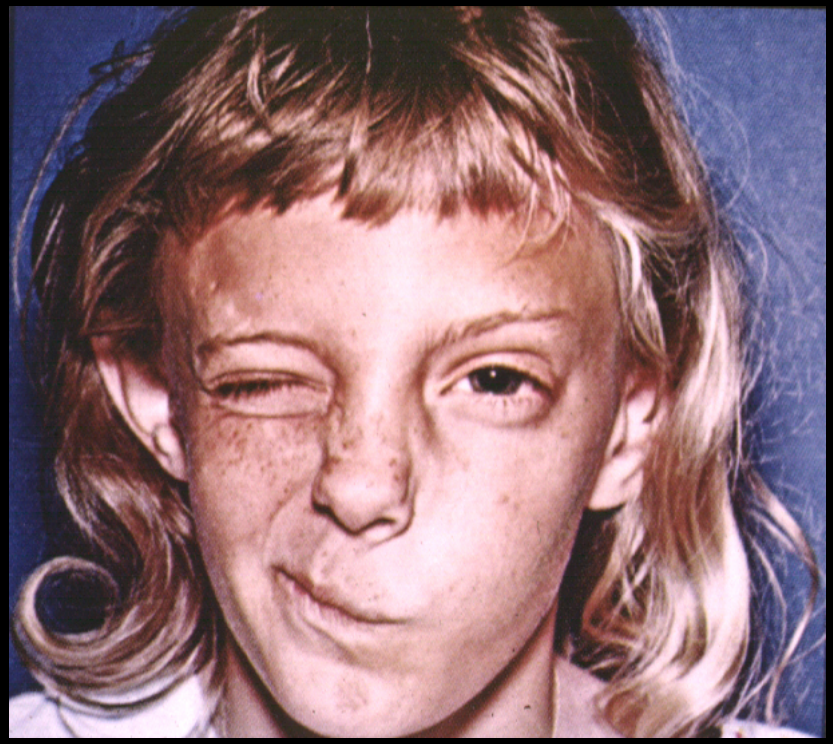
T cells of healthy people are responding with an IL-10 upon exposure to DerP1 or Betv1 and they are not making IL-4. In contrast, the allergic individuals are producing IL-4in response to Der P1 and Bet v1, whereas they do not have circulating T cells that respond by IL-10 productions.

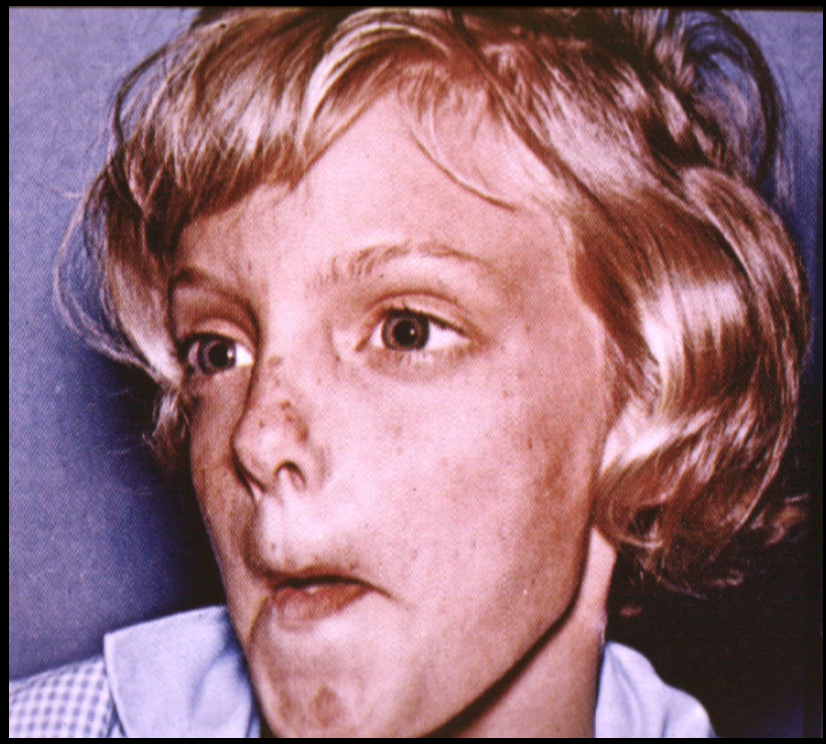
This is in close agreement with the notion that allergic individuals are producing an effector cell response that recognizes the allergen but have a defective response in terms of regulatory T cells.

Disregulation of the immune system is linked by epidemiological studies to diminished exposure to microorganisms



Common allergy, also termed type I hypersensitivity

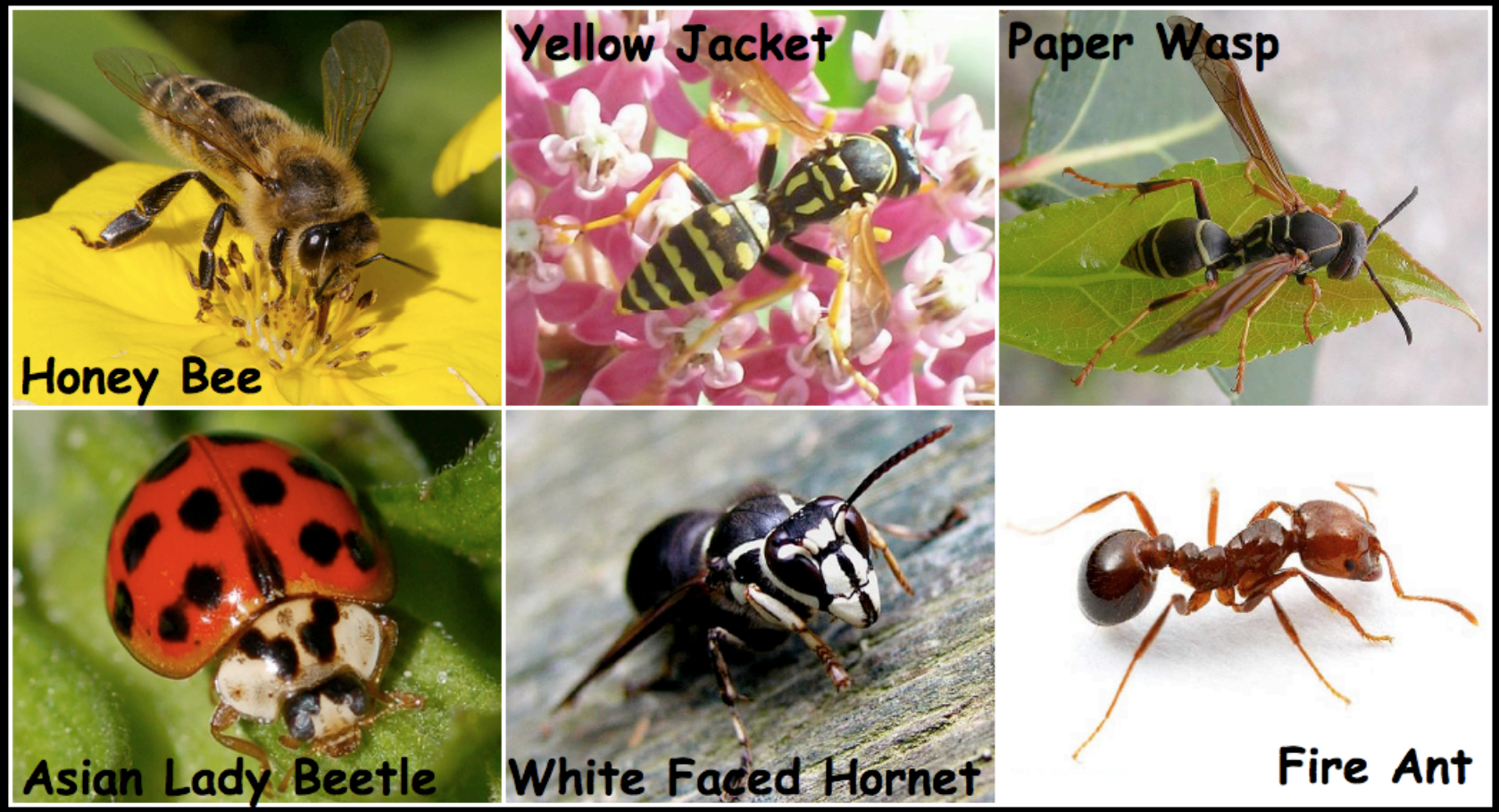




The common allergy is mediated by a specific type of antibody, termed IgE

IgE-mediated reactions to extrinsic antigens and the routes of allergen entry

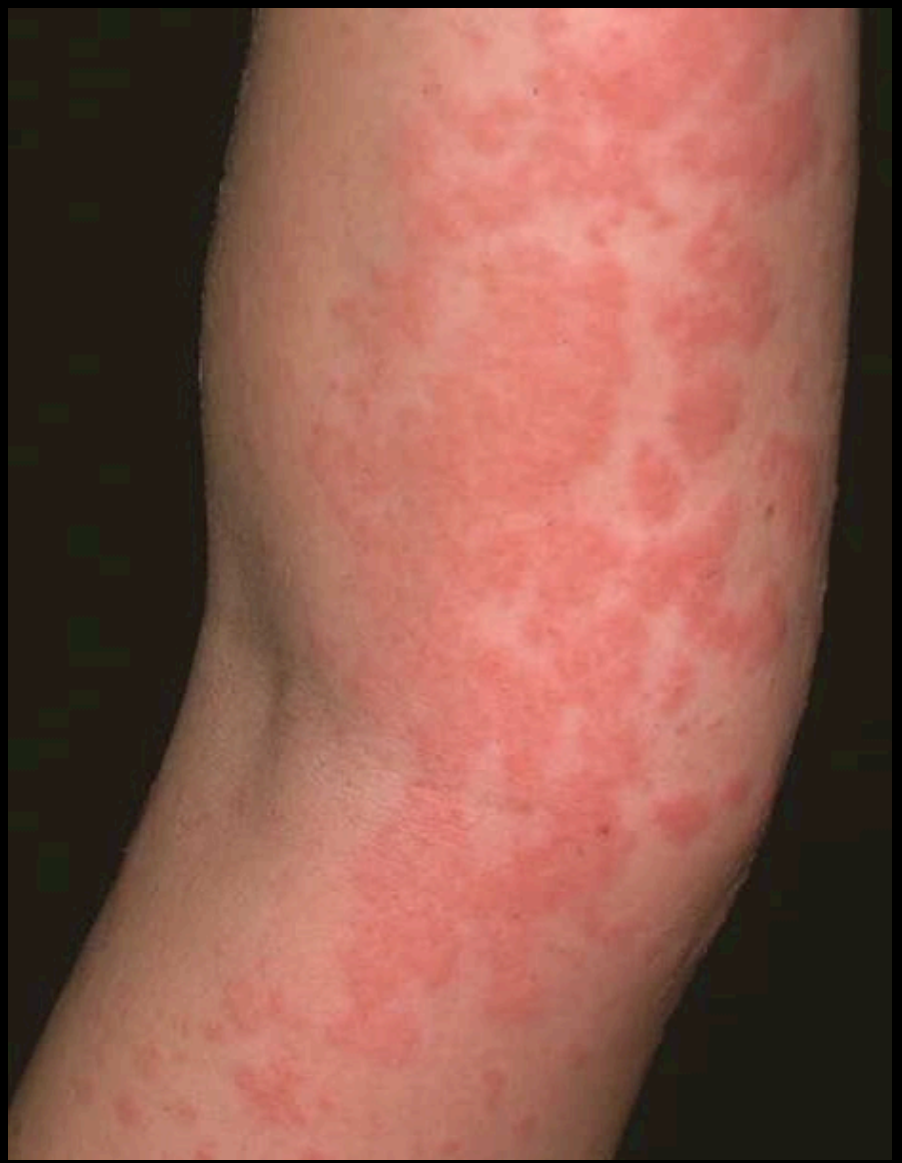
	IgE-mediated allergic reactions			
	Syndrome	Common allergens	Route of entry	Response
A.	Acute urticaria (wheal-and-flare)	Animal hair Insect bites Allergy testing	Through skin Systemic	Local increase in blood flow and vascular permeability



Insect allergy can be a life-threatening condition. About 50 people die from insect venom allergy each year in the US

Urticaria

(red hives and itchy skin welts)



IgE-mediated reactions to extrinsic antigens and the routes of allergen entry

B.

IgE-mediated allergic reactions			
Syndrome	**Common allergens**	**Route of entry**	**Response**
Food allergy	Tree nuts Shellfish Peanuts Milk Eggs Fish Soy Wheat	Oral	Vomiting Diarrhea Pruritis (itching) Urticaria (hives) Anaphylaxis (rarely)

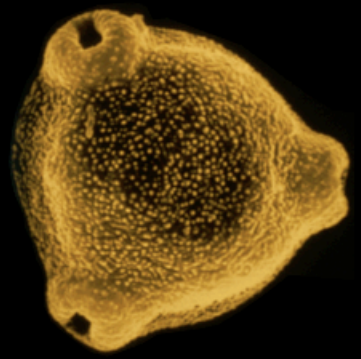
Immunobiology, Janeway et al., 4th Ed. Fig. 12.1, p. 462 (5th, Fig. 12.1, p.471)

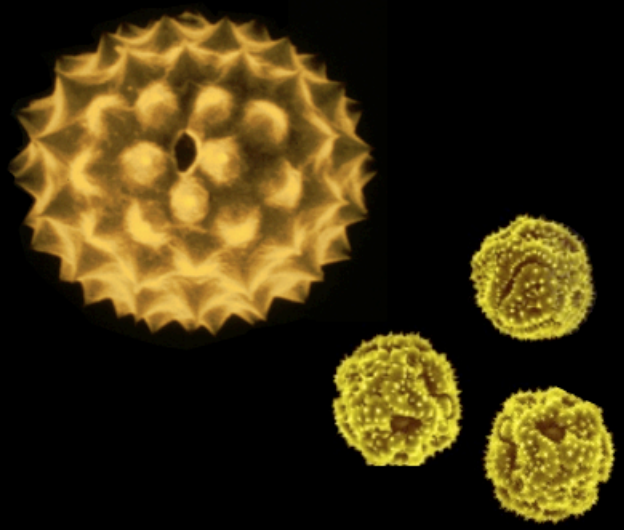
IgE-mediated reactions to extrinsic antigens and the routes of allergen entry

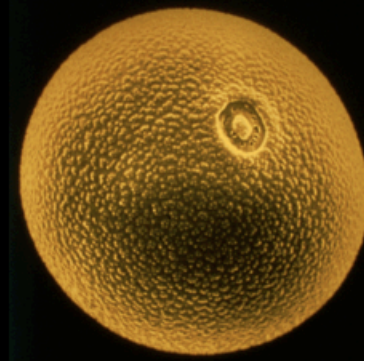
C.

IgE-mediated allergic reactions			
Syndrome	**Common allergens**	**Route of entry**	**Response**
Seasonal rhinoconjunctivitis (hay fever)	Pollens (ragweed, trees, grasses) Dust-mite feces	Inhalation	Edema of nasal mucosa Sneezing







Immunobiology, Janeway et al., 4th Ed. Fig. 12.1, p. 462 (5th, Fig. 12.1, p.471)

IgE-mediated reactions to extrinsic antigens and the routes of allergen entry

D.

IgE-mediated allergic reactions			
Syndrome	**Common allergens**	**Route of entry**	**Response**
Asthma	Danders (cat) Pollens Dust-mite feces	Inhalation	Bronchial constriction Increased mucus production Airway inflammation

Common allergens :

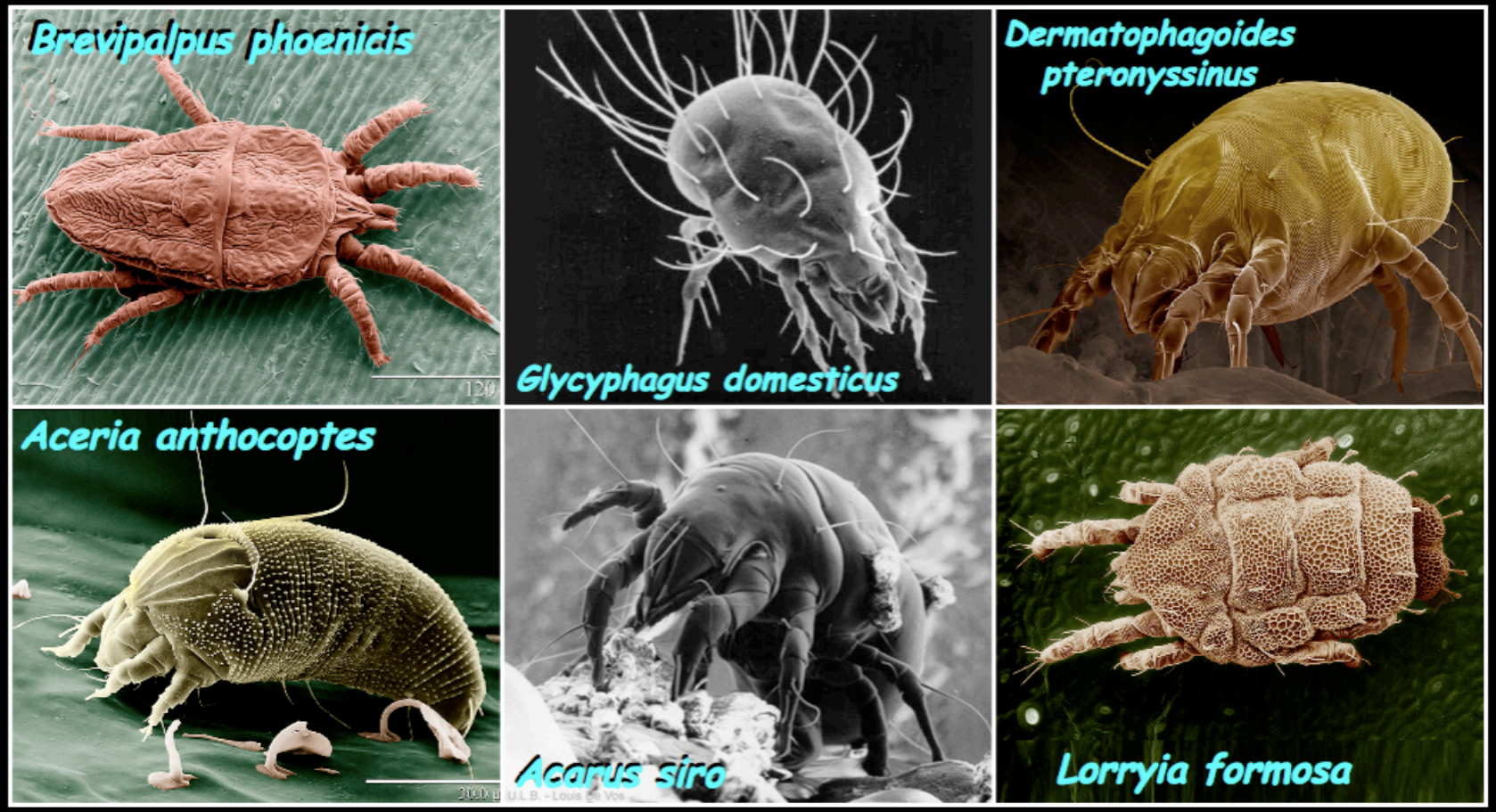
Animal dander

House dust: mite

IgE-mediated reactions to extrinsic antigens and the routes of allergen entry

D.

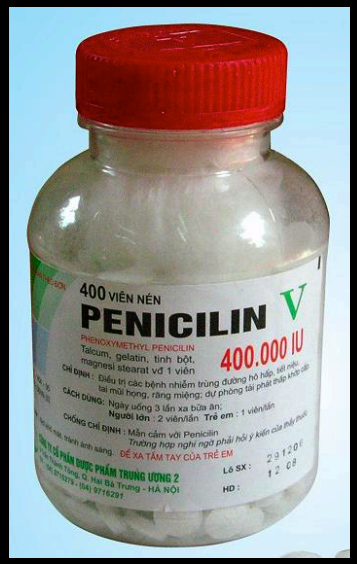
IgE-mediated allergic reactions			
Syndrome	**Common allergens**	**Route of entry**	**Response**
Asthma	Danders (cat) Pollens Dust-mite feces	Inhalation	Bronchial constriction Increased mucus production Airway inflammation

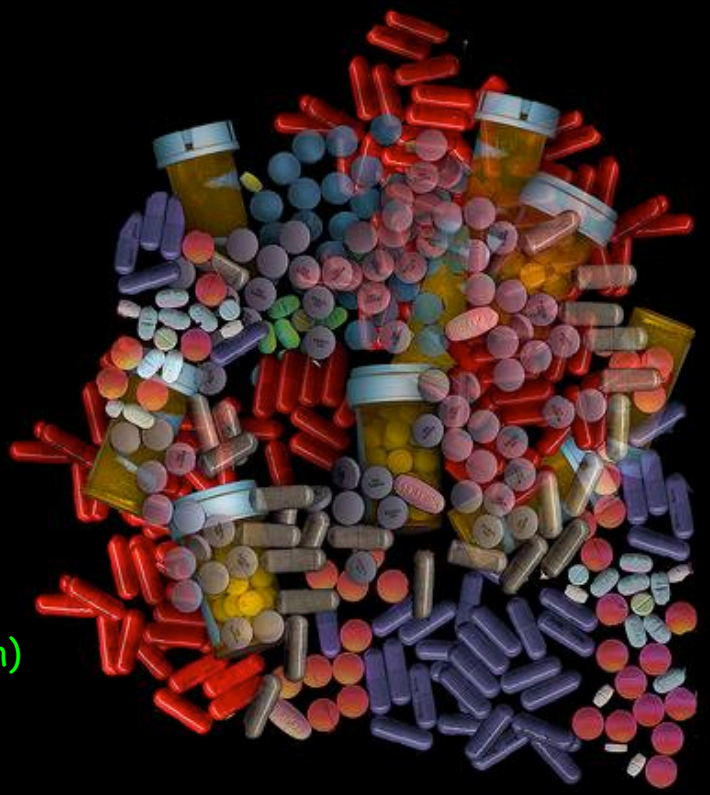


IgE-mediated reactions to extrinsic antigens and the routes of allergen entry

E.

IgE-mediated allergic reactions			
Syndrome	**Common allergens**	**Route of entry**	**Response**
Systemic anaphylaxis	Drugs Serum Venoms Food, e.g. peanuts	Intravenous (either directly or following oral absorption into the blood)	Edema Increased vascular permeability Laryngeal edema Circulatory collapse Death





Antibiotics
- Penicillin
- Sulfa drugs
- Tetracycline

Analgesics
- Codeine
- Non-steroidal anti-inflammatory drugs (aspirin, ibuprofen)

Antiseizure
- Dilantin
- Tegretol

IgE-mediated reactions to extrinsic antigens and the routes of allergen entry

Additional materials and conditions, which may cause allergy:

Latex allergy. Allergy caused by contact to latex materials. Common latex materials that cause allergic reaction are:

- Rubber bands
- Carpet backing
- Hospital and dental equipment
- Rubber (latex) gloves
- Balloons
- Condoms

Exercise induced Anaphylaxis (EIA): Allergy reaction that develops after doing some strenuous exercise.

Hypersensitivity of females to seminal plasma (semen allergy).

Allergic reaction to henna and tattoo.

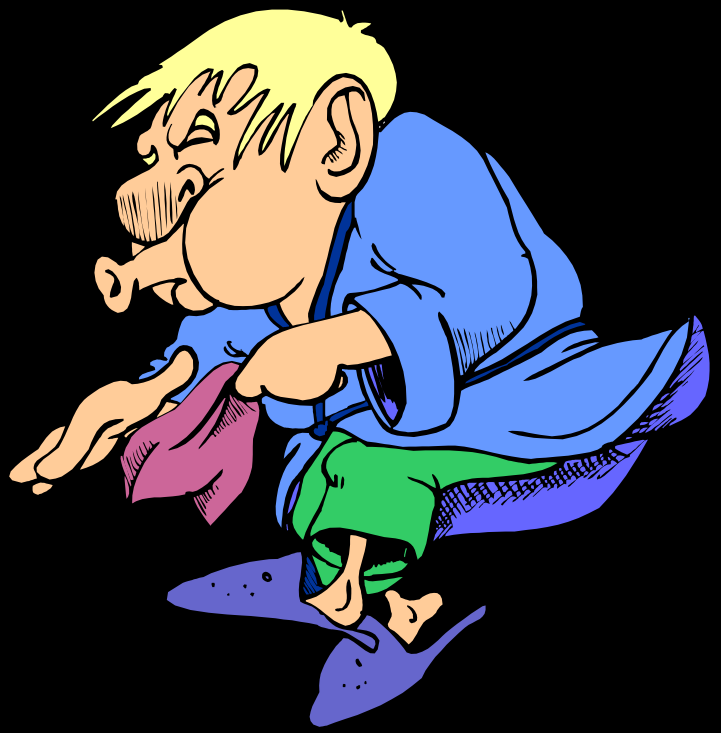
Cold weather allergy.

Other names for IgE-mediated allergy

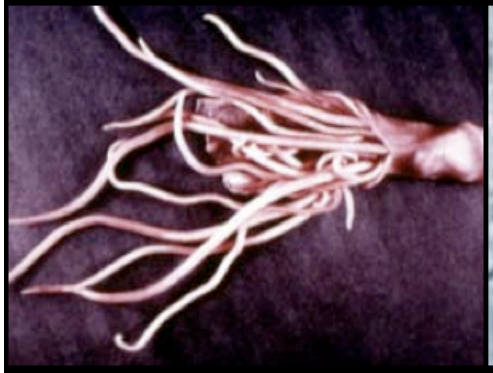
- Allergy
- Immediate type hypersensitivity
- Type I hypersensitivity
- Type I allergy
- Atopy

When a substance (antigen) is capable of producing allergic symptoms, it is known as an allergen.

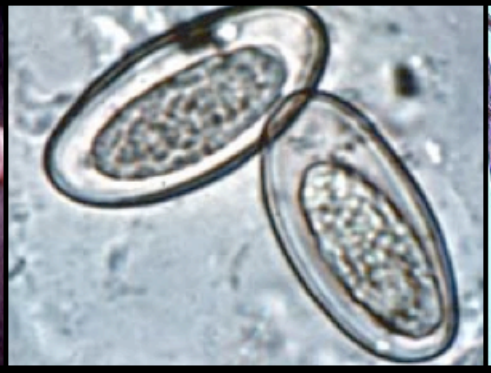
People who suffer from Hay fever, asthma, and some types of eczema, usually have an immune system that reacts in an inconvenient way to one or more common substances in the environment.



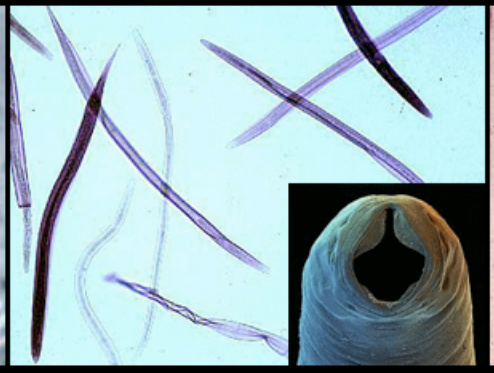
What are allergic immune responses really for?



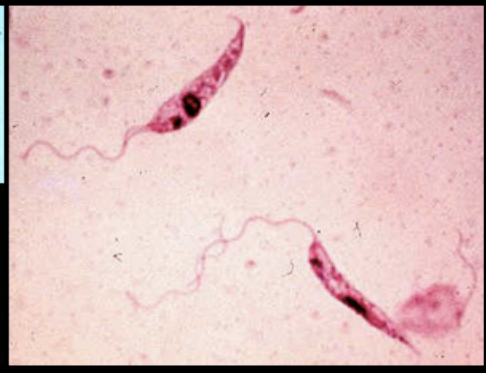
Ascaris



Enterobious

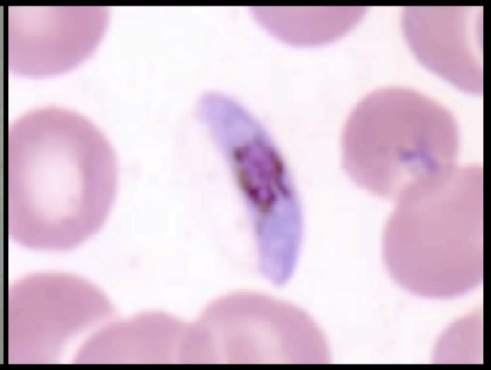


Hookworm



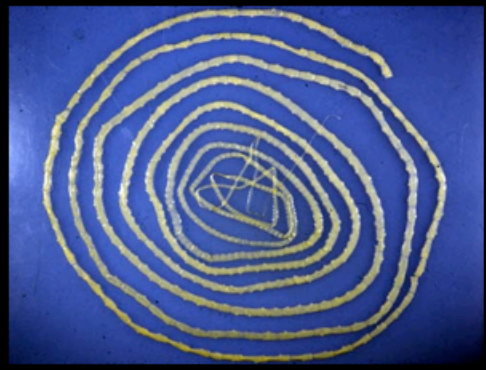
Leishmania

Onchocerca

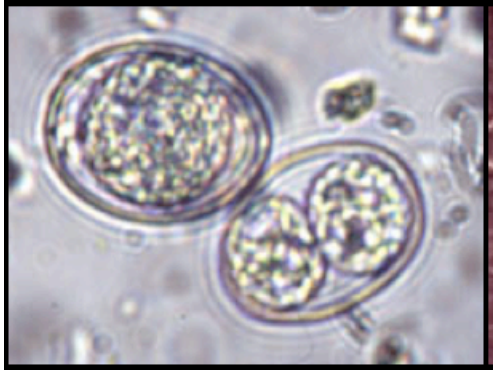


Plasmodium

Schistosome

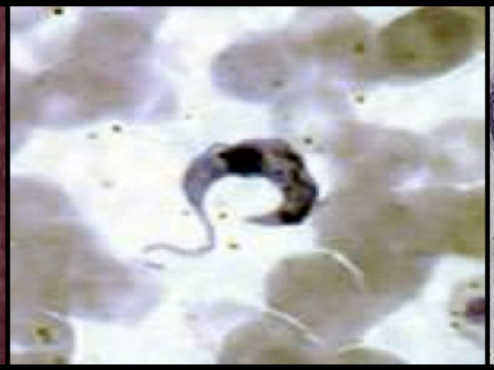


Taenia

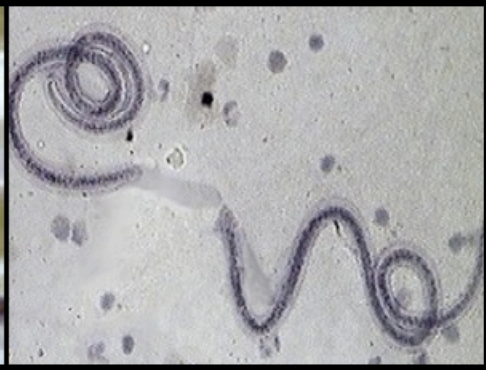


Toxoplasma

Trichuris

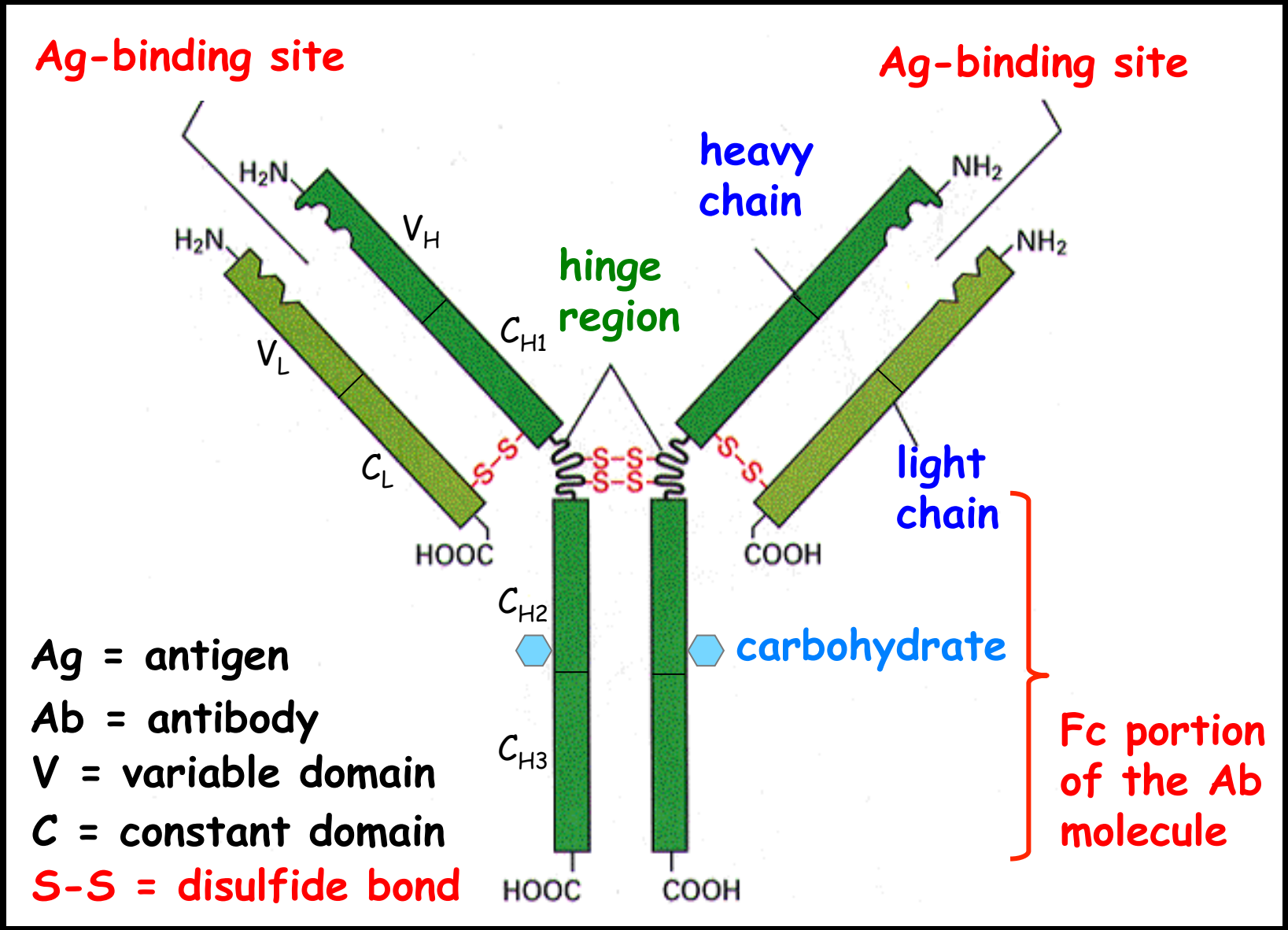


Trypanosoma

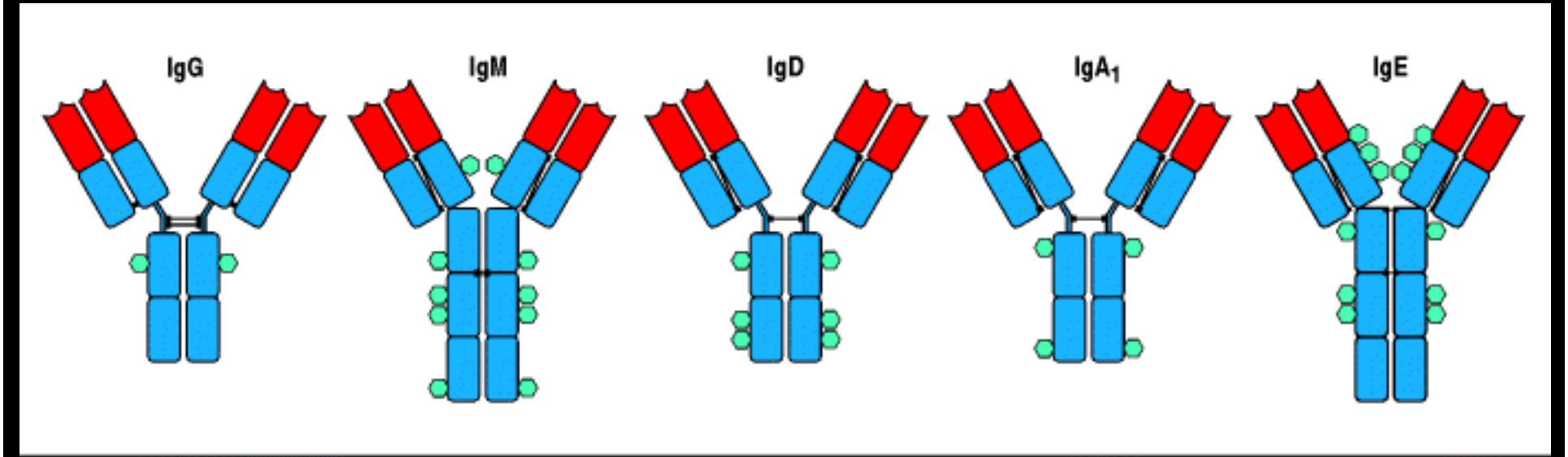


Wuchereria

Antibody (immunoglobulin) structure



The structural organization of the main human immunoglobulin isotype monomers

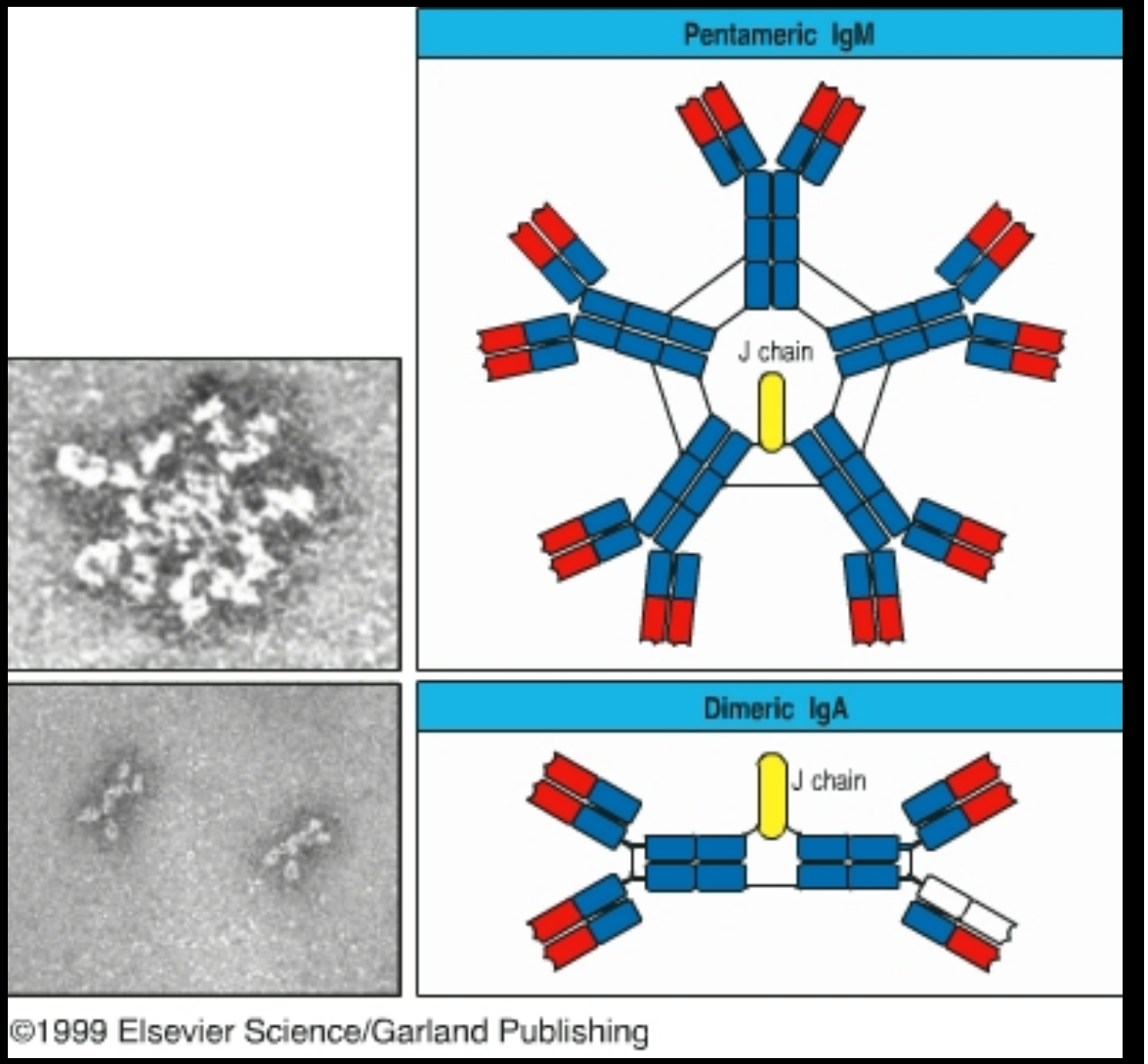


Both IgM and IgE lack a hinge region but each contains an extra heavy-chain domain. Note the differences in the numbers and locations of the disulfide bonds (black lines) linking the chains. The isotypes also differ in the distribution of N-linked carbohydrate groups, shown as turquoise hexagons.

Immunobiology, Janeway et al., 4th Ed. Fig. 3.21, p. 102. (5th, Fig. 4.17)

The IgM and IgA molecules can form multimers

IgM and IgA are usually synthesized as multimers in association with an additional polypeptide chain, the J chain. In pentameric IgM, the monomers are cross-linked by disulfide bonds to each other and to the J chain. The top left panel shows an electron micrograph of an IgM pentamer, showing the arrangement of the monomers in a flat disc. IgM can also form hexamers that lack a J chain but are more efficient in complement activation. In dimeric IgA, the monomers have disulfide bonds to the J chain as well as to each other. The bottom left panel shows an

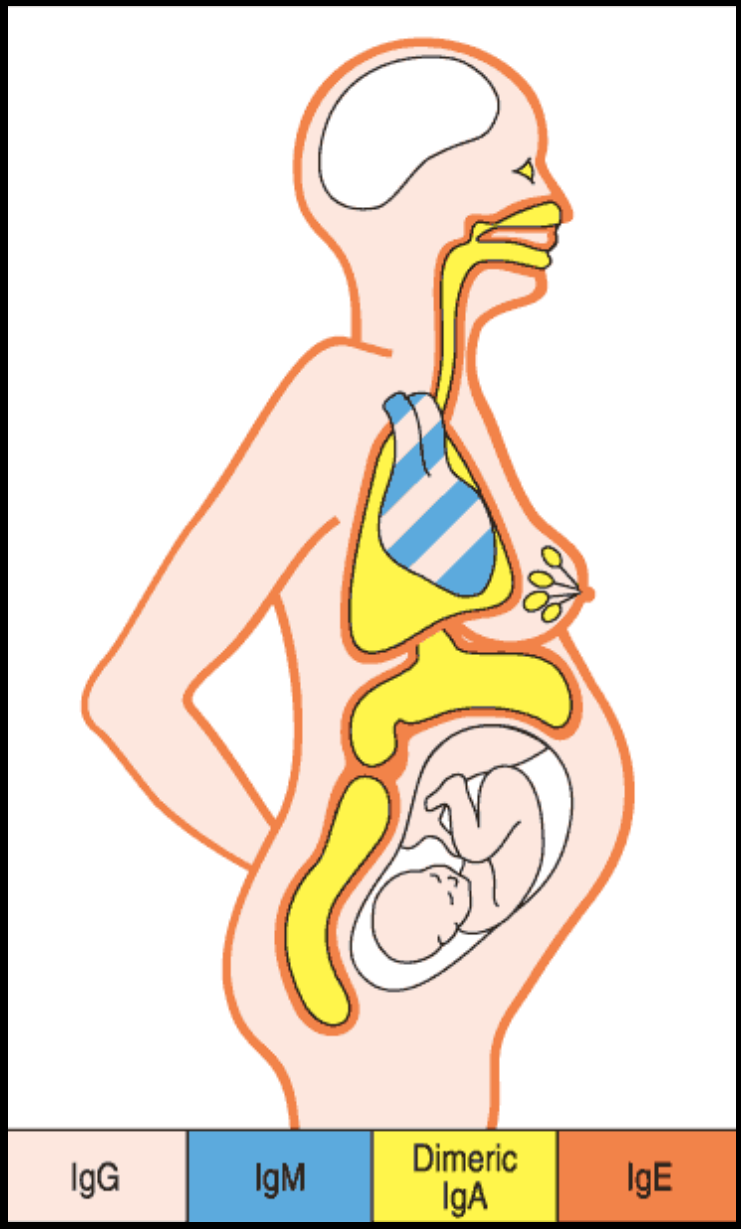


Transmission electron micrograph of dimeric IgA (x900,000)

Immunobiology, Janeway et al., 4th Ed. Fig. 3.22, p. 104. (5th, Fig. 4.23)

Immunoglobulin isotypes are selectively distributed in the body

IgG and IgM predominate in plasma, whereas IgG and monomeric IgA are the major isotypes in extracellular fluid within the body. Dimeric IgA predominates in secretions across epithelia, including breast milk. The fetus receives IgG from the mother by transplacental transport. IgE is found mainly associated with mast cells just beneath epithelial surfaces (especially of the respiratory tract, gastro-intestinal tract, and skin). The brain is normally devoid of immunoglobulin.



Immunobiology, Janeway *et al.*, 5th Ed,. Fig. 9.22

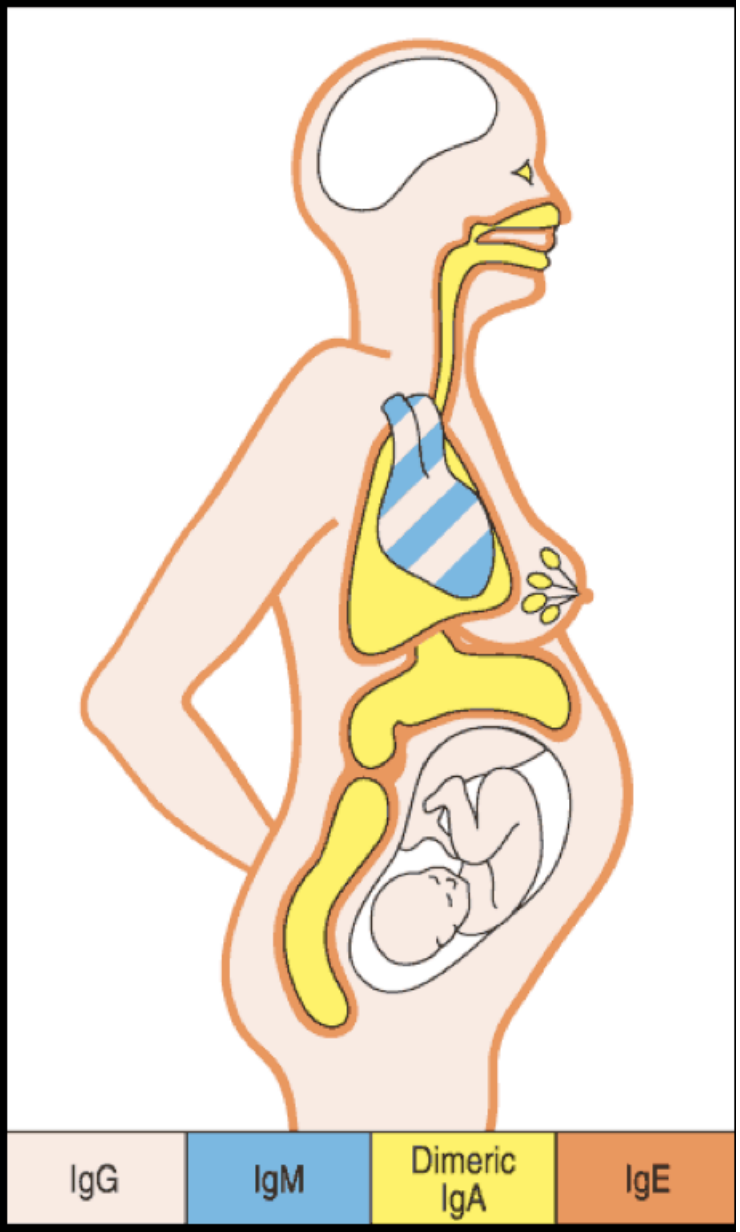
IgE concentration in the serum is extremely low

IgE is found mainly associated with mast cells just beneath epithelial surfaces (especially of the respiratory tract, gastrointestinal tract, and skin). It is also found on the surface of blood basophils.

Concentration of antibody classes in the serum:

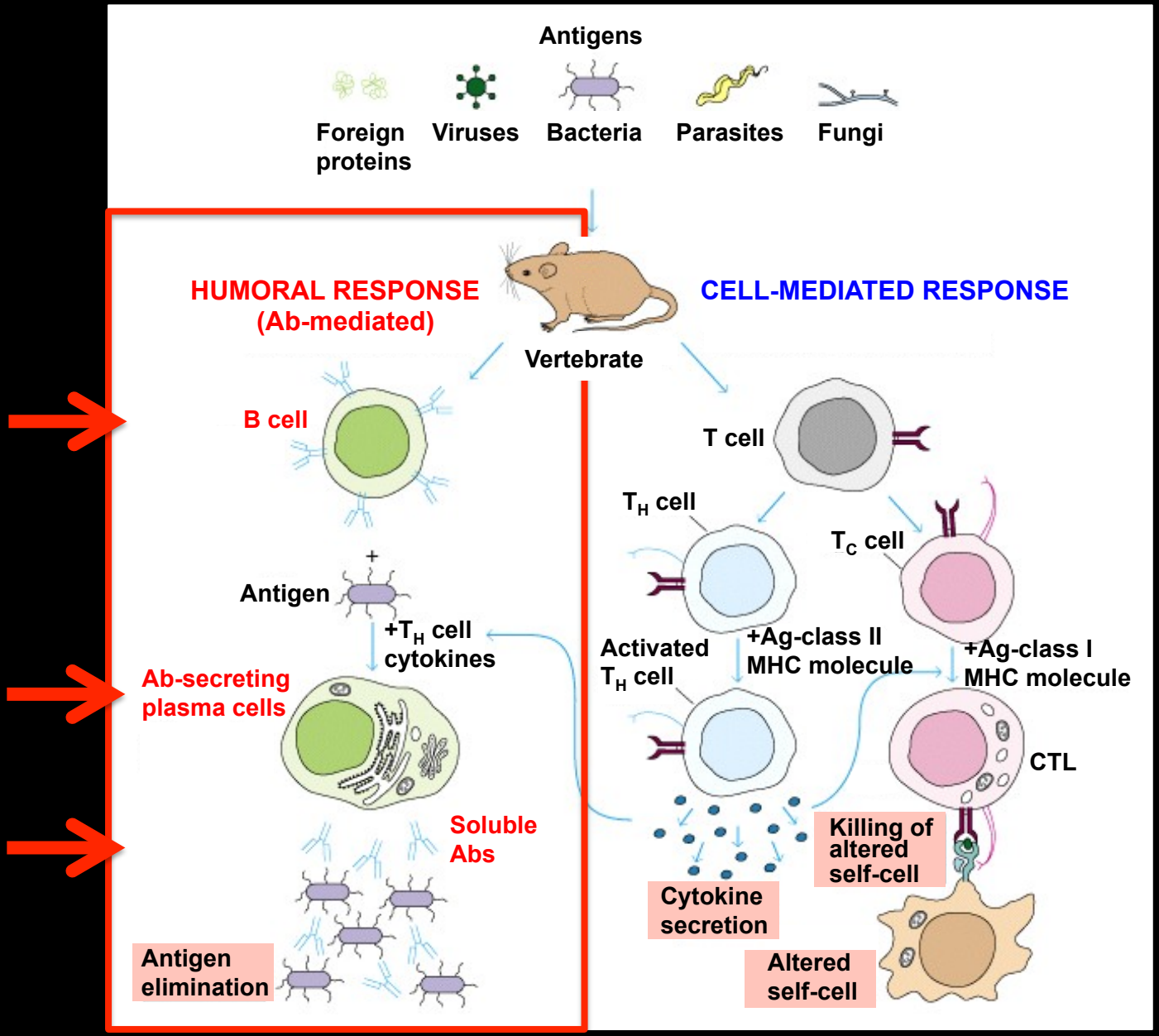
No.	Ab Class	mg/ml
1.	IgG	13.5
2.	IgA	3.5
3.	IgM	1.5
4.	IgD	0.03
5.	IgE	0.00005

IgE bind to speciallized receptors on the surface of mast cells and basophils, termed FcεRI.

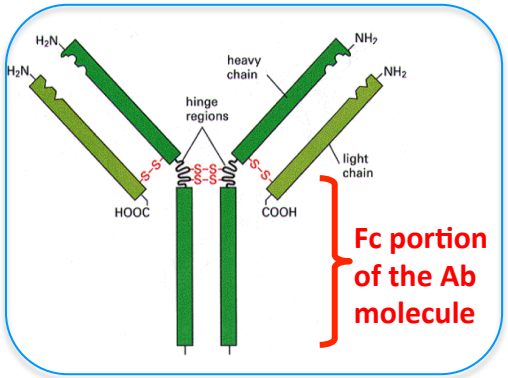


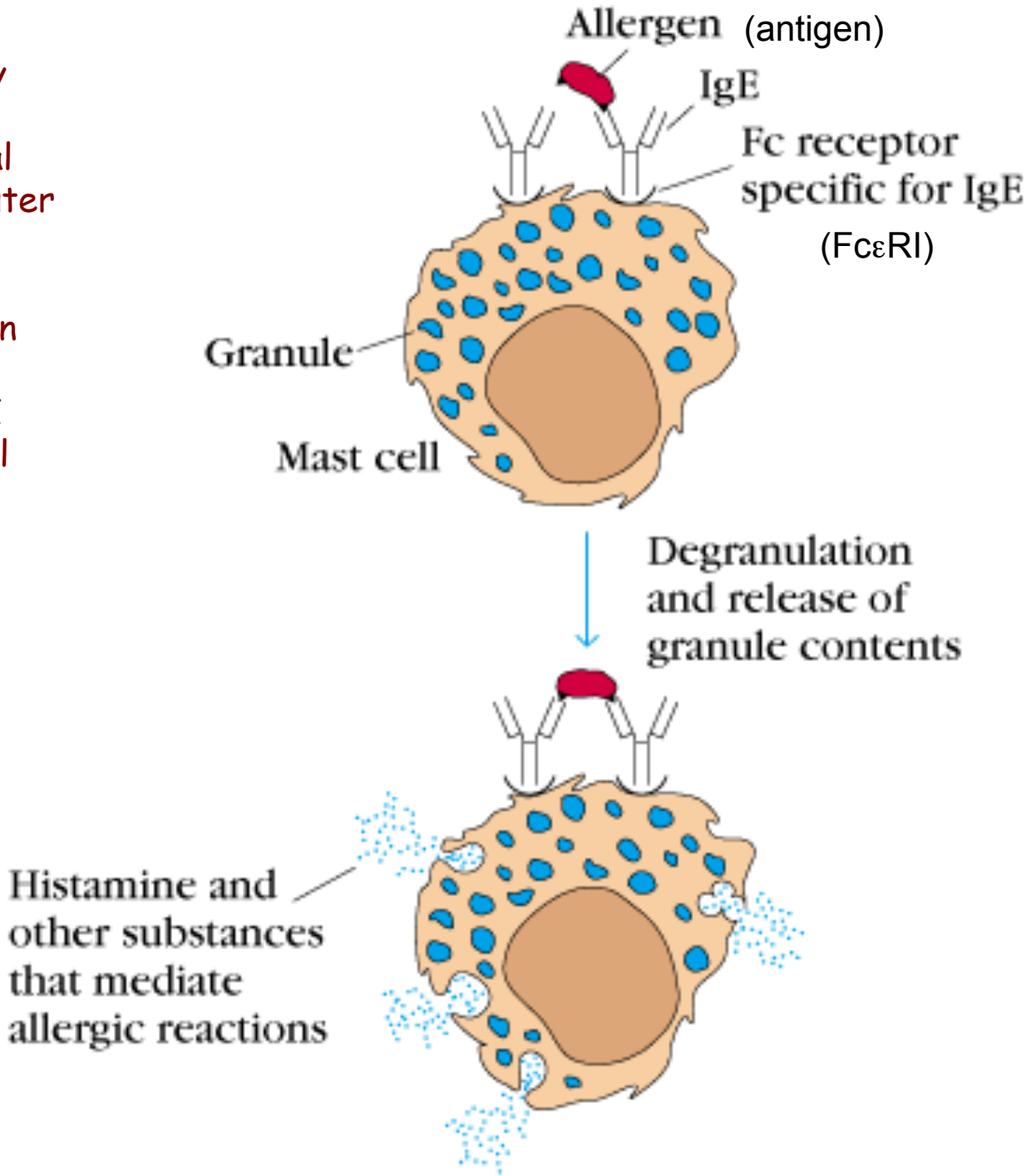
Immunobiology, Janeway *et al.*, 5th Ed,. Fig. 9.22

Where does the IgE come from ?

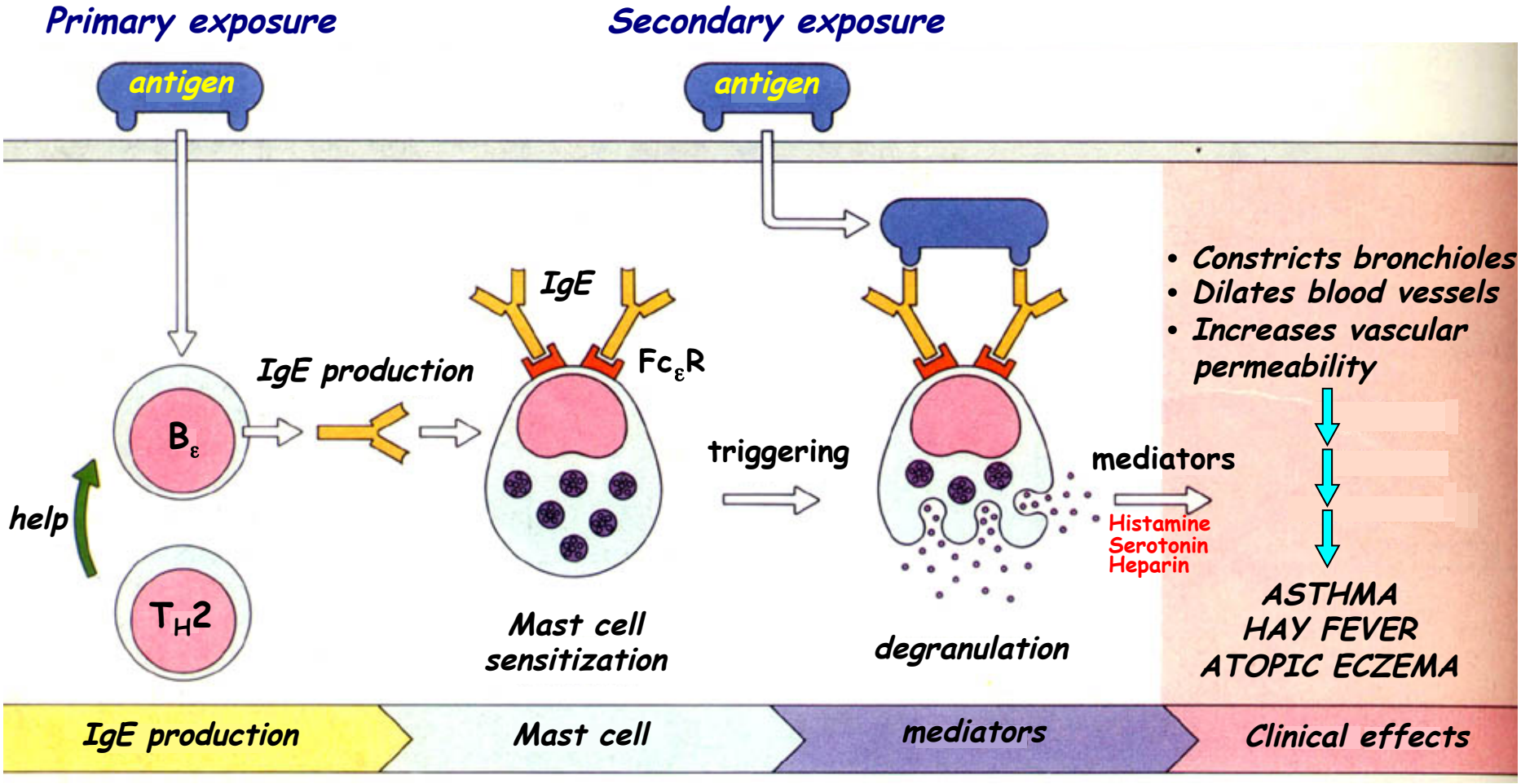


IgE antibody is produced by plasma cells in response to allergens. It binds to special receptors (FcεRI) on the outer surface of mast cells. Upon challenge with the same allergen, the soluble allergen binds to and cross-links the surface IgE bound to FcεRI thereby triggering mast cell degranulation.



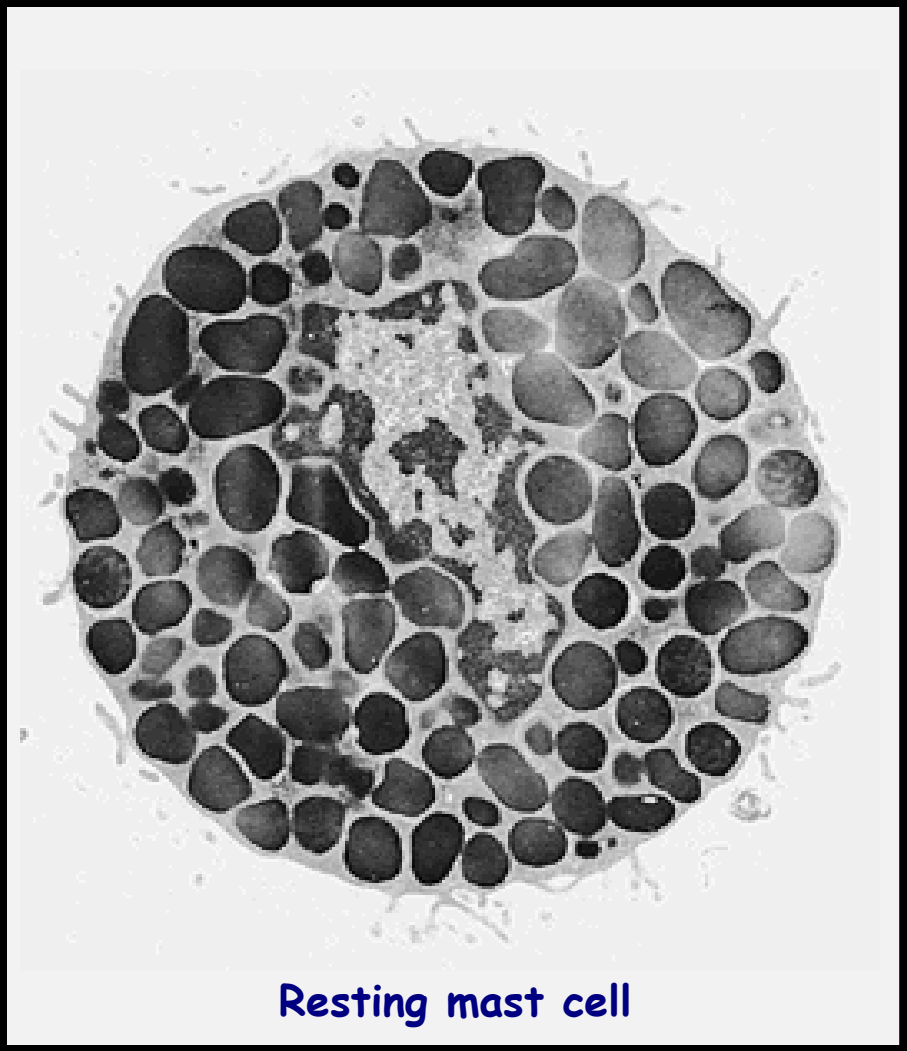


Mechanisms of Mast cell activation

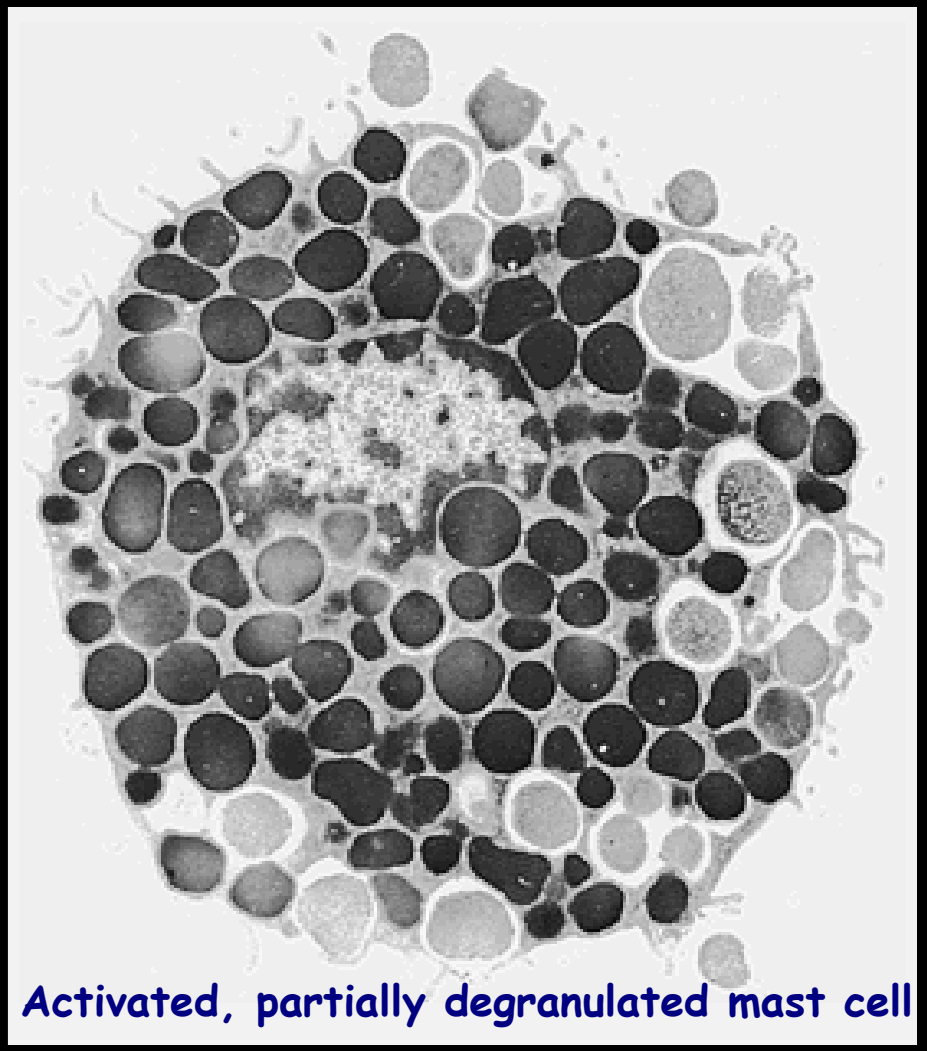


IgE is a "cytophilic" Ab. It binds to FcεRI surface receptor on mast cells in the tissues and basophils in the blood.

Mast cell activation & degranulation



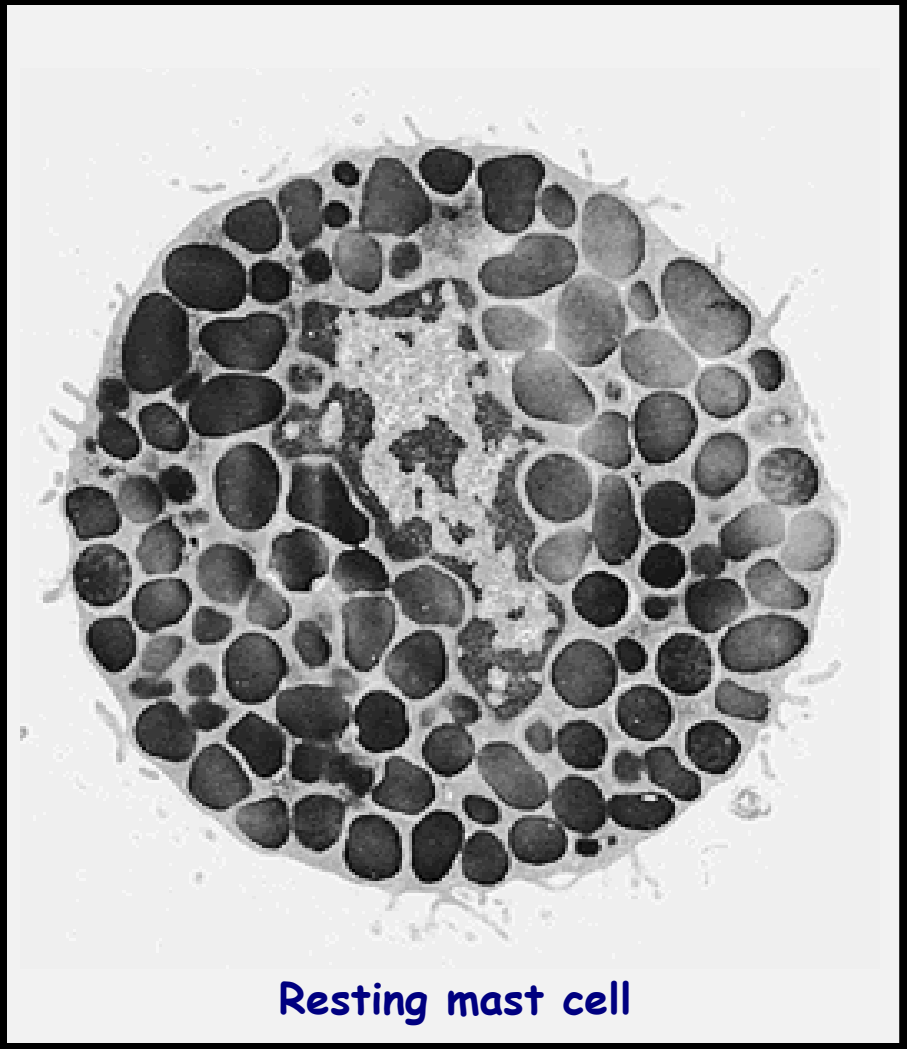
Resting mast cell



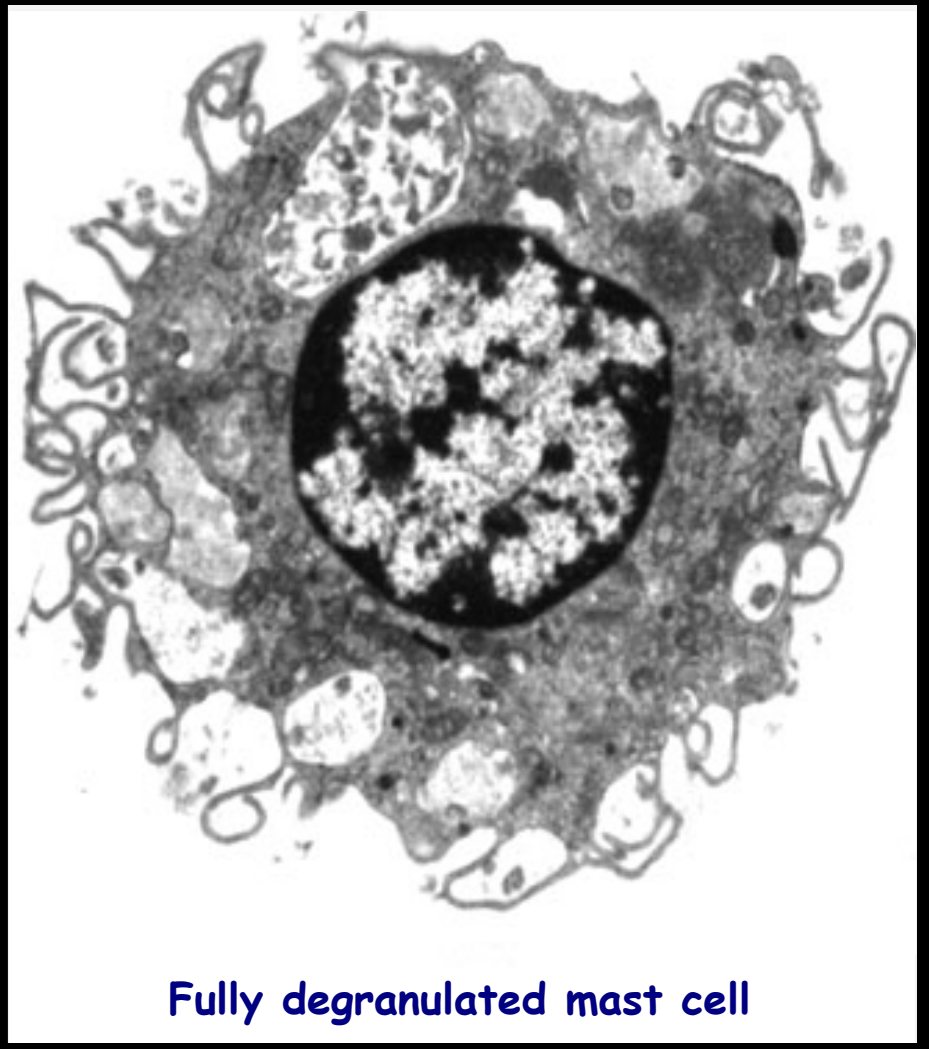
Activated, partially degranulated mast cell

A. Electron micrograph of a mast cell illustrating the large monocyte- like nucleus and the electron-dense granules. B. Activation induces the release of the content of its granules, as seen by their decrease in opacity and the formation of vacuoles connecting with the exterior.

Mast cell activation & degranulation



Resting mast cell



Fully degranulated mast cell

A. Electron micrograph of a mast cell illustrating the large monocyte- like nucleus and the electron-dense granules. B. Activation induces the release of the content of its granules, as seen by their decrease in opacity and the formation of vacuoles connecting with the exterior.

Molecules released from activated mast cells and basophils

Histamine - toxic to many parasites.

Histamine exerts its actions by combining with specific cellular histamine (H) receptors. Four receptors have been discovered thus far, termed H1 through H4.

Type	Location	Function
H1	Smooth muscle, endothelium, central nervous system tissue.	Causes vasodilation, increases vascular permeability, promotes bronchoconstriction, bronchial smooth muscle contraction, separation of endothelial cells (responsible for hives), pain and itching due to insect stings; H1 are the primary receptors involved in allergic rhinitis symptoms and motion sickness.
H2	Located on parietal cells.	Primarily stimulate gastric acid secretion.
H3	Found on central nervous system and to a lesser extent peripheral nervous system tissue.	Decreased neurotransmitter release: histamine, acetylcholine, norepinephrine, serotonin.
H4	Found primarily in the basophils and in the bone marrow. It is also found on thymus, small intestine, spleen, and colon.	Plays a role in chemotaxis.

Molecules released from activated mast cells and basophils

Prostaglandins

Prostaglandins are potent but have a short half-life before being inactivated and excreted. Therefore, they send only paracrine (locally active) or autocrine (acting on the same cell from which it is synthesized) signals.

There are currently ten known prostaglandin receptors expressed on different cell types. The diversity of receptors means that prostaglandins act on an array of cells and have a wide variety of effects. Among others, prostaglandins can:

- cause constriction or dilation in vascular smooth muscle cells
- cause aggregation or disaggregation of platelets
- sensitize spinal neurons to pain
- decrease intraocular pressure
- regulate inflammatory mediation
- regulate calcium movement
- control hormone regulation
- control cell growth

Molecules synthesized and released by mast cells on stimulation by antigen binding to IgE

Class of product	Examples	Biological effects
Enzyme	Tryptase, chymase, cathepsin G, carboxypeptidase	Remodel connective tissue matrix
Toxic mediator	Histamine, heparin	Toxic to parasites Increase vascular permeability Cause smooth muscle contraction
Cytokine	IL-4, IL-13	Stimulate and amplify T_H2 cell response
	IL-3, IL-5, GM-CSF	Promote eosinophil production and activation
	TNFα (some stored preformed in granules)	Promotes inflammation, stimulates cytokine production by many cell types, activated endothelium
Chemokine	MIP-1α	Attracts monocytes, macrophages and neutrophils
Lipid mediator	Leukotreins C4, D4, E4	Cause smooth muscle contraction Increase vascular permeability Stimulate mucus secretion
	Platelet-activating factor	Attracts leukocytes, amplifies production of lipid mediators, activates neutrophils, eosinophils, and platelets

Immunobiology, Janeway et al., 4th Ed. Fig. 12.11, p. 473 (5th, Fig. 12.10, p. 481)

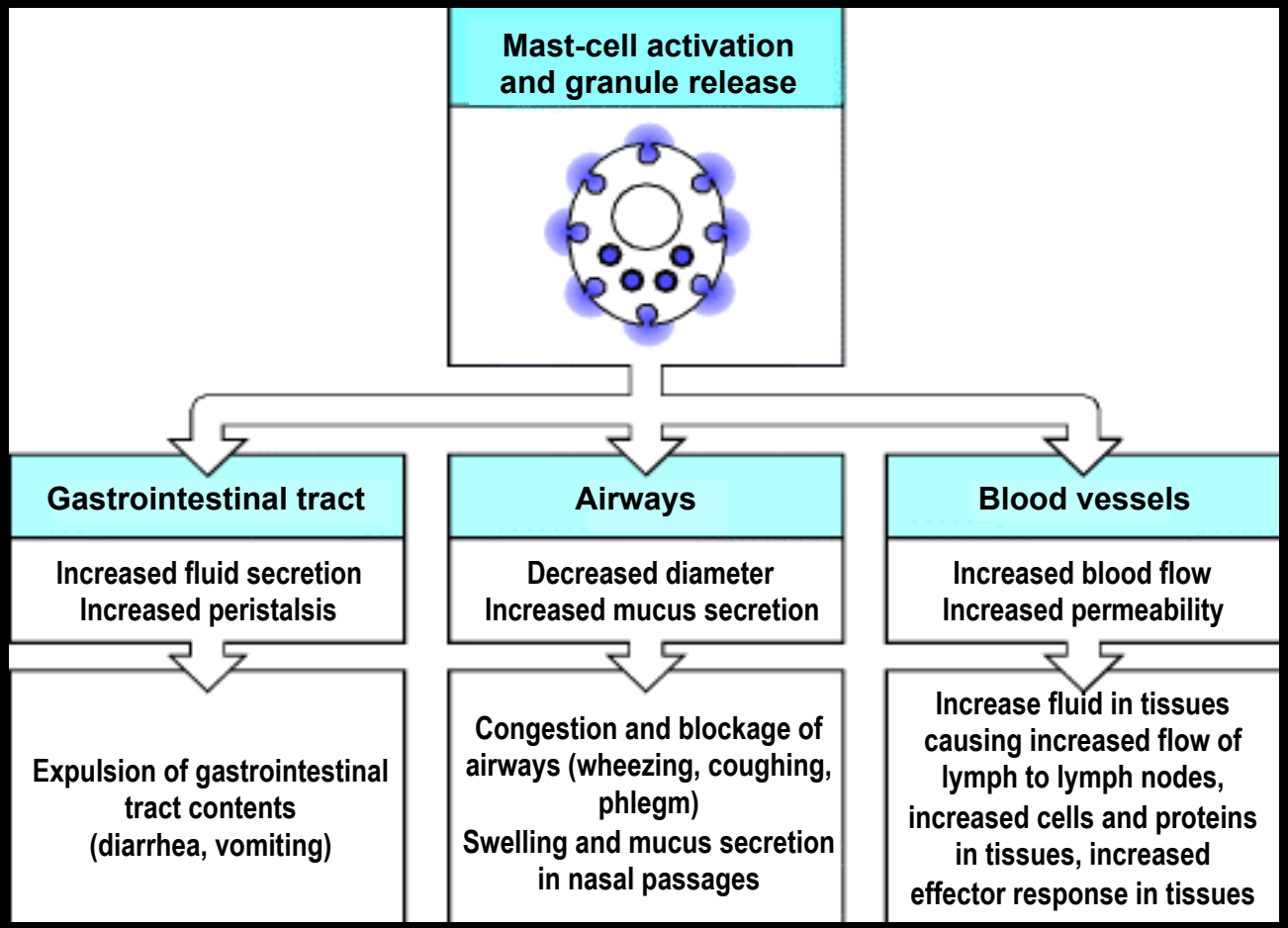
Major target organs in allergy

Smooth muscle → Contraction

Capillary → Dilation

Mucous gland → Increase secretion

Mast-cell products have different effects on different tissues



Immunobiology, Janeway et al., 4th Ed. Fig. 12.6, p. 468 (5th, Fig. 12.9, p. 479)

What is anaphylaxis?

- Anaphylaxis is the most severe form of IgE mediated allergy that exists
- It is an immediate life-threatening reaction that requires urgent treatment

The urgency of anaphylaxis

- The urgency of anaphylaxis is such that a patient could die before qualified help is available.
- It is very important therefore, that patients and also their relatives know how to observe, and if necessary, provide treatment before symptoms become life-threatening.

Anaphylaxis can be fatal

Garbanzos trigger fatal allergy

The Associated Press

ROYAL OAK, Mich.

Fumes from a pot of cooking garbanzos killed an 8-year-old girl who was allergic to the beans, her doctor said Thursday.

Nita Sekhri was at a friend's house Sunday when she inhaled mist from across the kitchen, Dr. Mark Goetting said. She had many food allergies and the beans were on her forbidden list.

"It was a fluke," Goetting said. "It's something no one could have predicted." Nita's medicated inhaler wasn't enough to combat the reaction. She went into a coma and died Wednesday.

Dr. John Yunginger, an allergies expert at the Mayo Clinic in Rochester, Minn., said fatal reactions from allergies are rare and death by fumes even more so. Each year, 50 to 100 people in the United States die from allergic reactions, mostly from foods, he said.

The girl's father, Suneel Sekhri, said: "Parents have to pay attention to small details. The more the parents know, the better prepared they will be."

Garbanzo beans, also known as chickpeas, are tossed in salads and often ground into a paste for hummus, a popular Middle Eastern dish.

Fortunately…

- The severest form of anaphylaxis is very uncommon
- Anaphylaxis responds very well to treatment with adrenalin
- Death from anaphylaxis is very rare

Symptoms that are often associated with anaphylaxis

- Usually only some of these symptoms will be experienced
- The symptoms at the "mild" end of the scale may require no treatment at all
- The symptoms at the severe end of the scale may become very serious

Mild to moderate

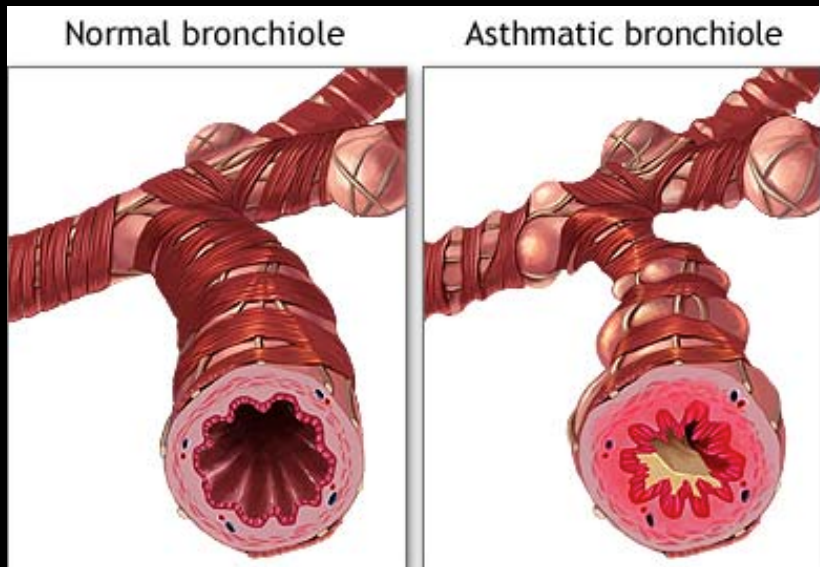
- Tingling or unusual taste in mouth
- Running nose and eyes, sneezing
- Itchy skin
- Hives – red, itchy nettle-rash, urticaria
- Swelling - puffiness of eyes, lips and limbs; Whole face may appear swollen

Moderate to severe

- Vomiting
- Abdominal cramps
- Uterine cramps
- Elevation of heart rate
- Mild wheezing

Severe to life-threatening

- Hoarseness or difficulty swallowing due to throat swelling
- Extreme distress, anxiety, panic, feeling of impending doom
- Difficulty breathing due to severe asthma or throat swelling
- Lips turn blue along with 'loss of colour'
- Weakness, dizziness, feeling faint, drop in BP
- Convulsions
- Collapse and/or unconsciousness



Can an anaphylactic reaction be prevented?

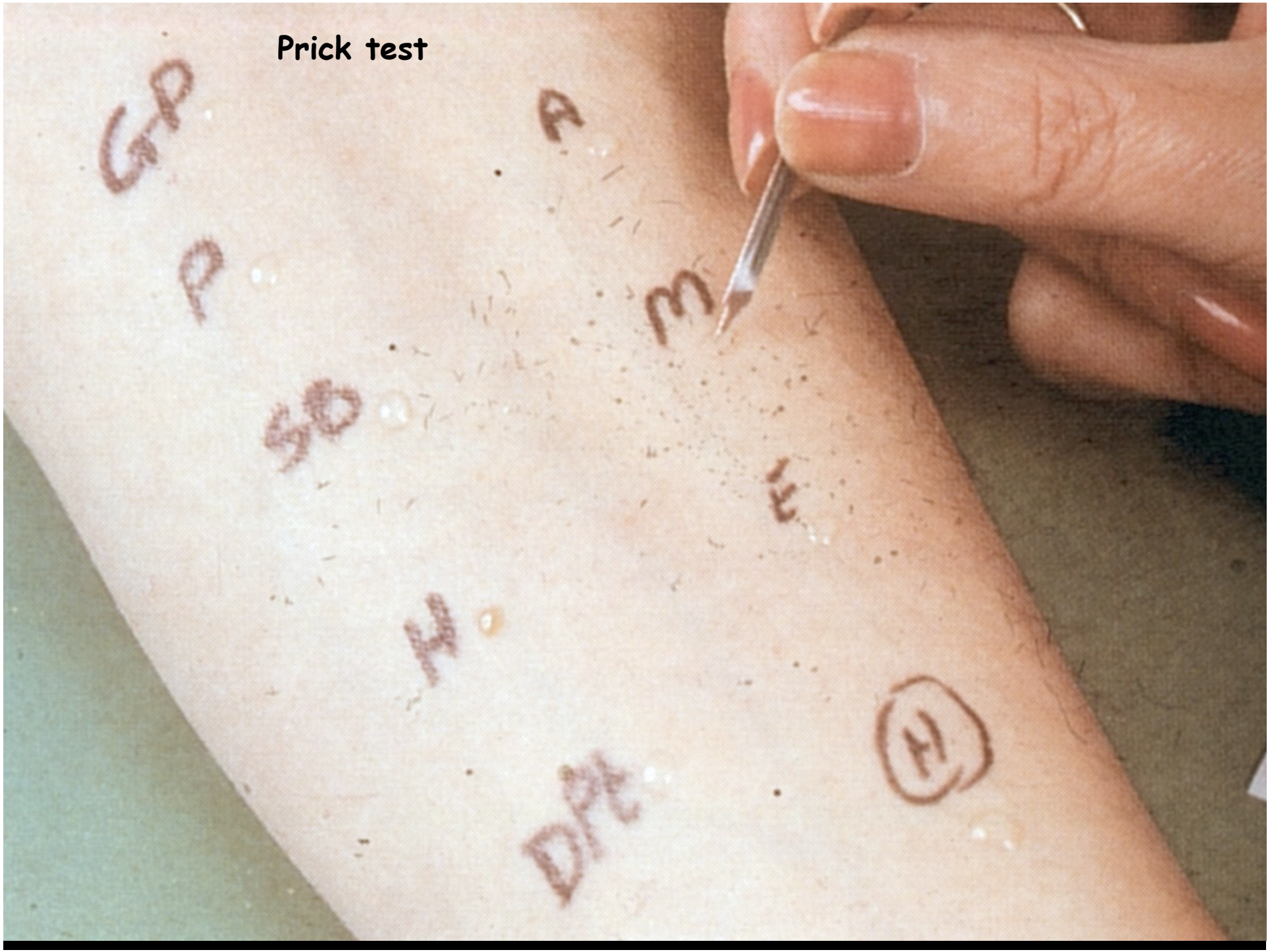
- Accurately identify the offending substance
- Avoid that substance as much as possible
- Have "rescue medication" available at all times and know when and how to use it
- Practice using the prescribed "rescue medication" frequently as directed by your doctor

How can the offending substances be accurately identified?

- A detailed medical history
- Skin tests
- Blood tests
- Sometimes, a challenge with the suspect allergen

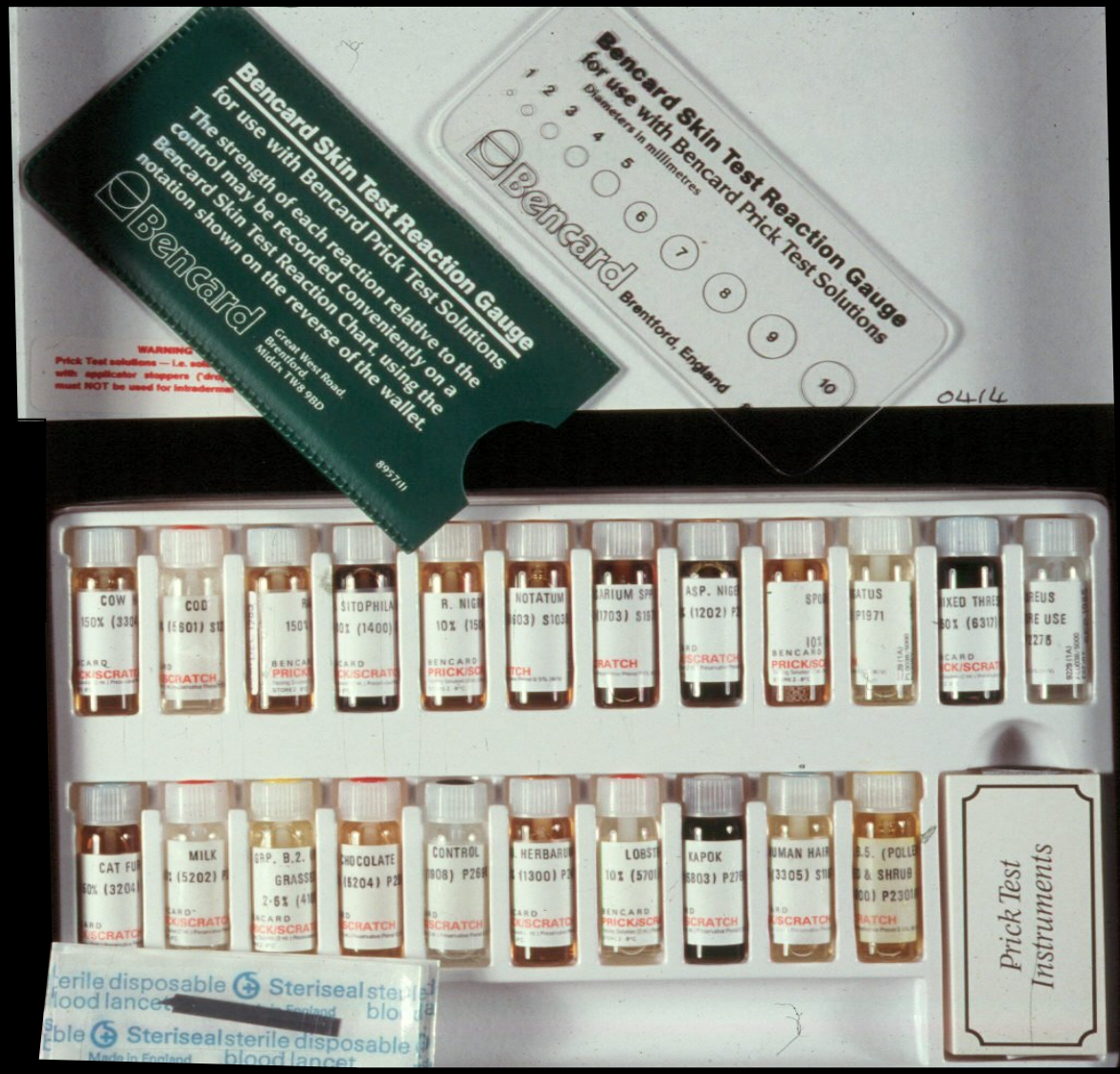
Types of skin testing

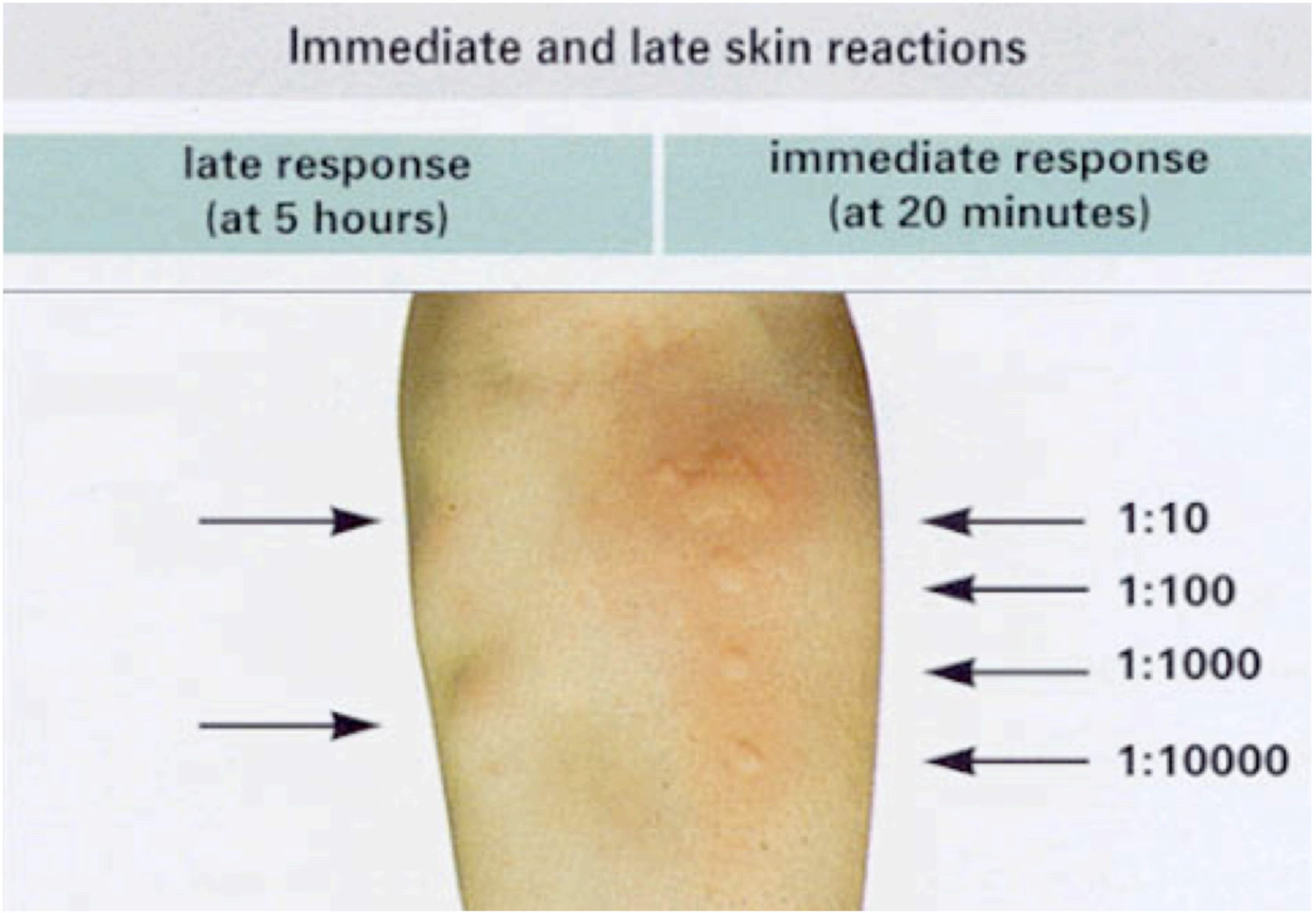
1. Prick tests with commercial antigens or fresh antigens
2. Intradermal testing
3. Patch testing for contact urticaria


Prick test
GP
A
P
M
SD
E
H
H
Dpt

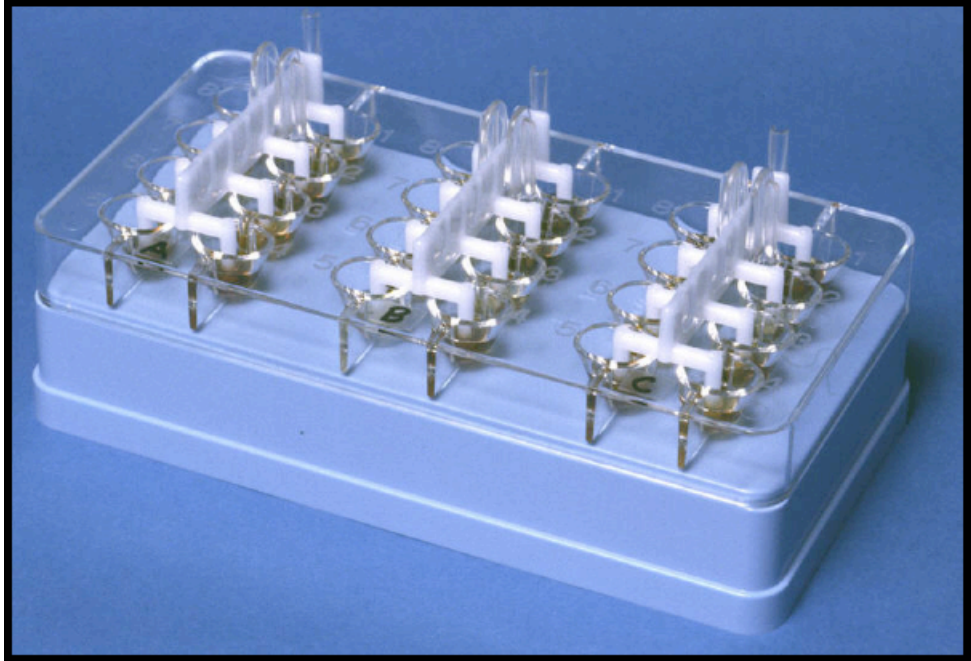
Prick test with commercial antigens

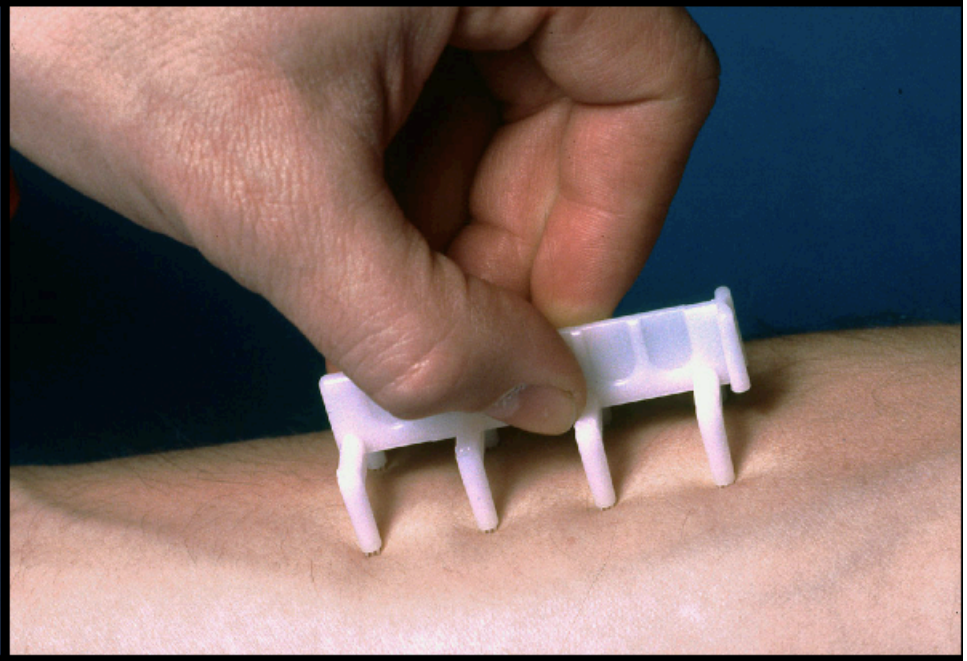
A variety of allergens are commercially available for skin tests as pure substances

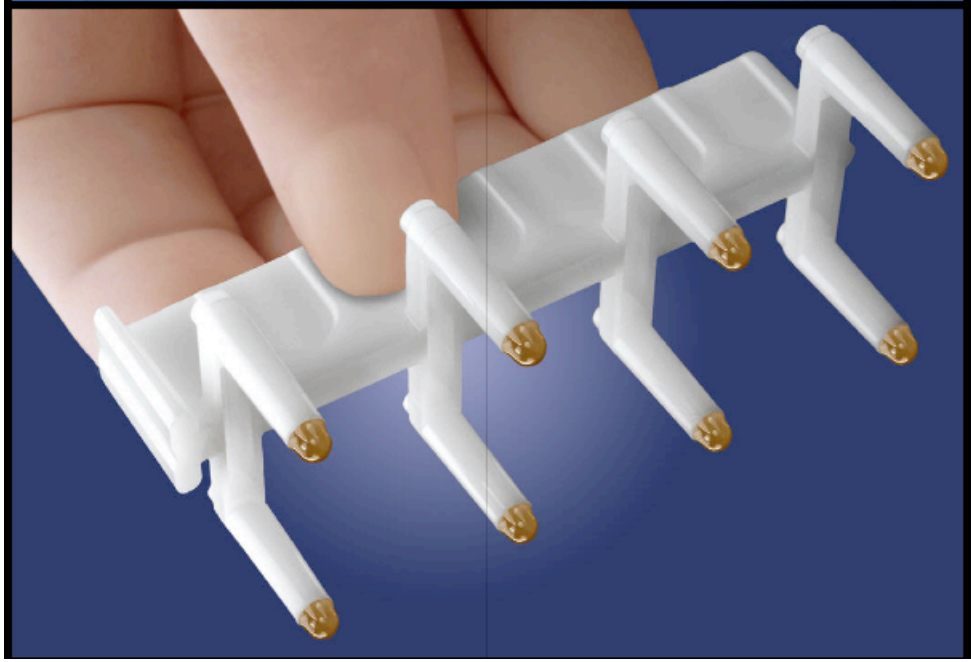


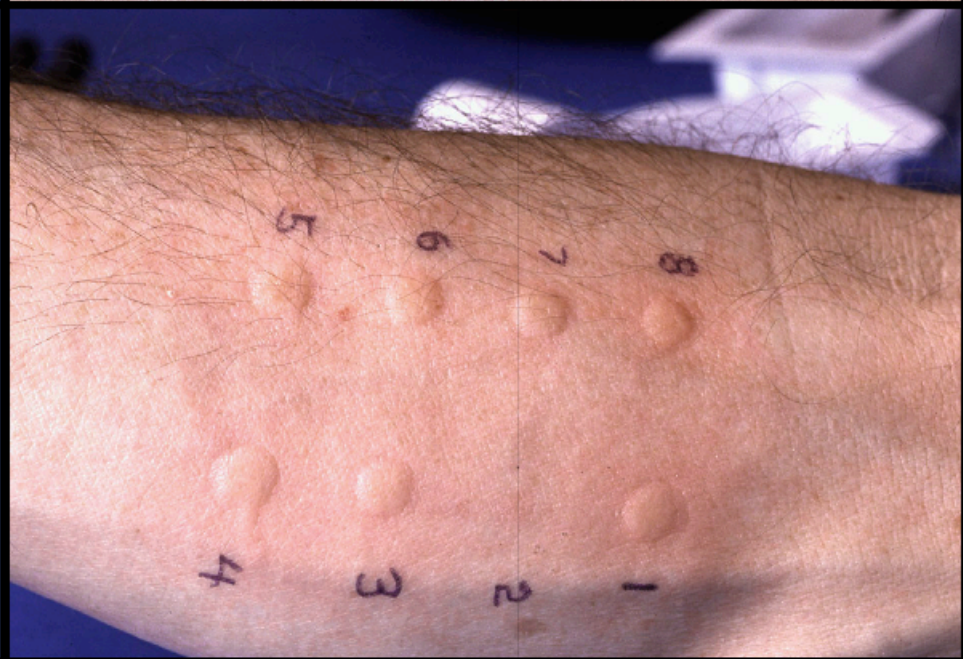

Immediate and late skin reactions
late response
(at 5 hours)
immediate response
(at 20 minutes)
1:10
1:100
1:1000
1:10000

The Multi-Test II enables to perform 24 skin tests in 30 seconds









Patch testing for contact urticaria