What is Food Allergy?

Lars K. Poulsen, Ph.D. Professor

Allergy Clinic, Copenhagen University Hospital
Denmark

Symptoms of food hypersensitivity

Oral allergy syndrome (OAS):
Itching and swelling of the mouth and oropharynx

Skin: Urticaria, activation of atopic eczema

Respiratory system: rhinitis, asthma

Gastrointestinal system:
nausea, vomiting, abdominal pain, diarrhoea

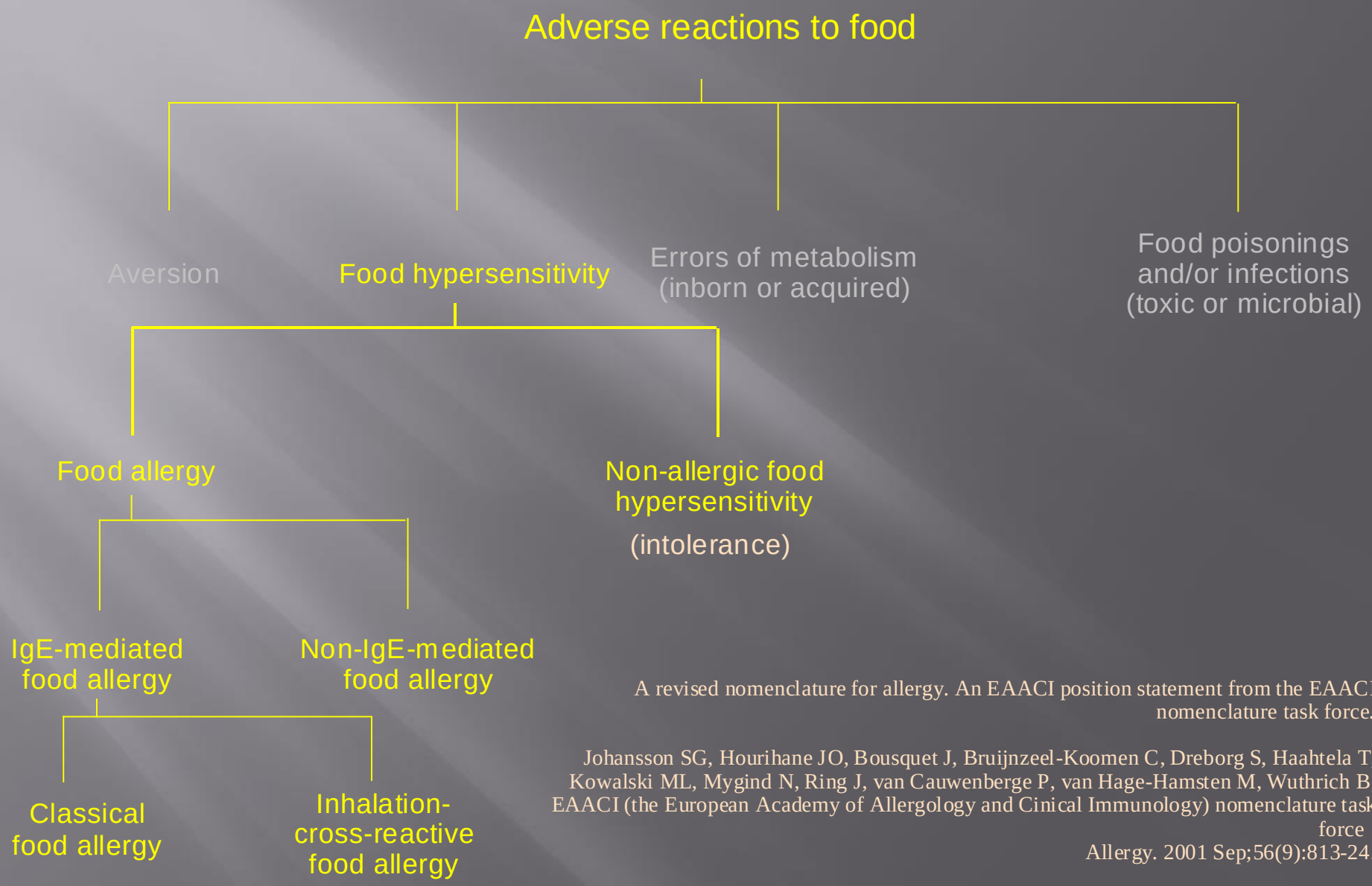
Conjunctivitis

Angio-oedema

Anaphylaxis

Often from two or more organ systems

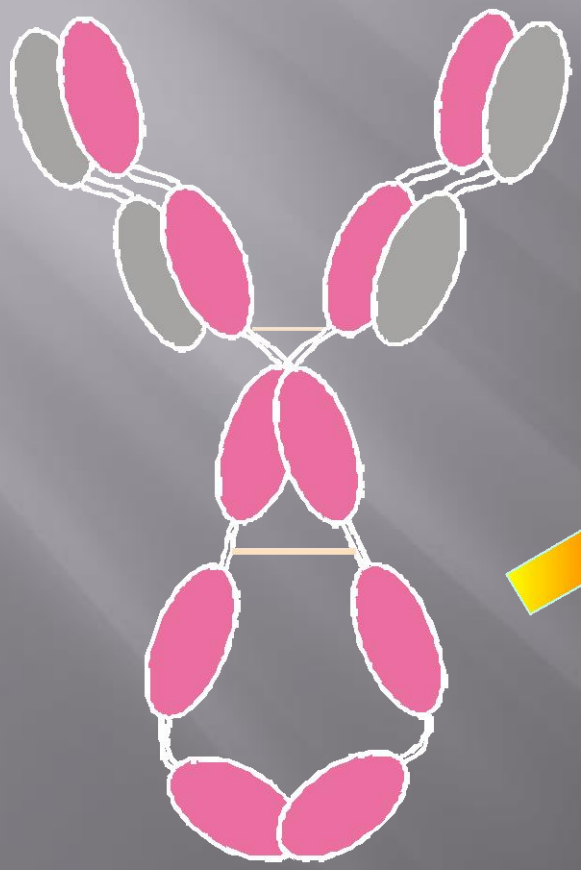
Classification of adverse reactions to food



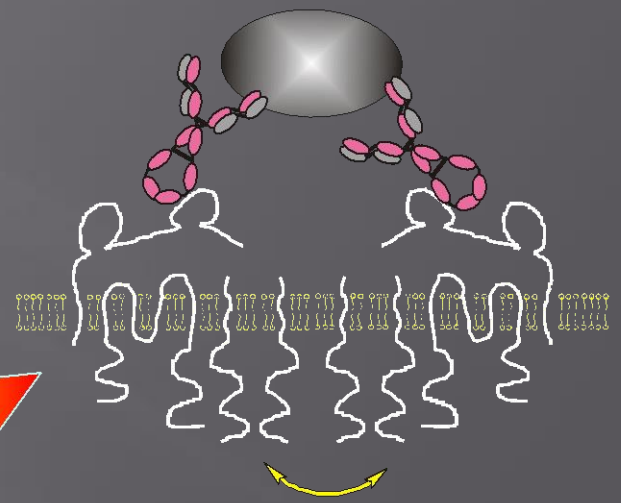
A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force.

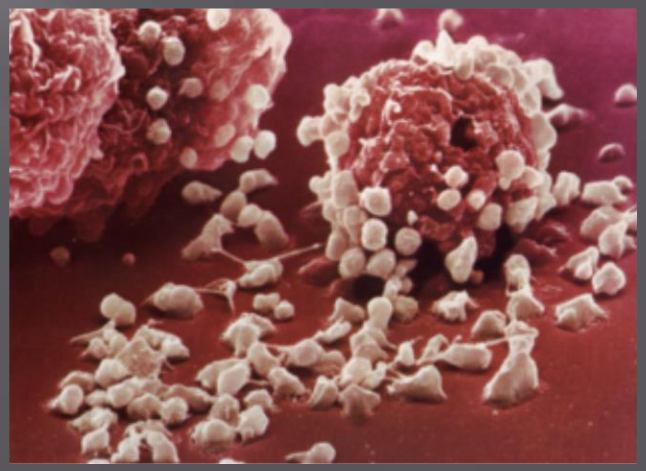
Johansson SG, Hourihane JO, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T, Kowalski ML, Mygind N, Ring J, van Cauwenberge P, van Hage-Hamsten M, Wuthrich B; EAACI (the European Academy of Allergology and Cinical Immunology) nomenclature task force
Allergy. 2001 Sep;56(9):813-24.

Immunoglobulin E (IgE)
Allergens cross-links IgE and activate mast cells

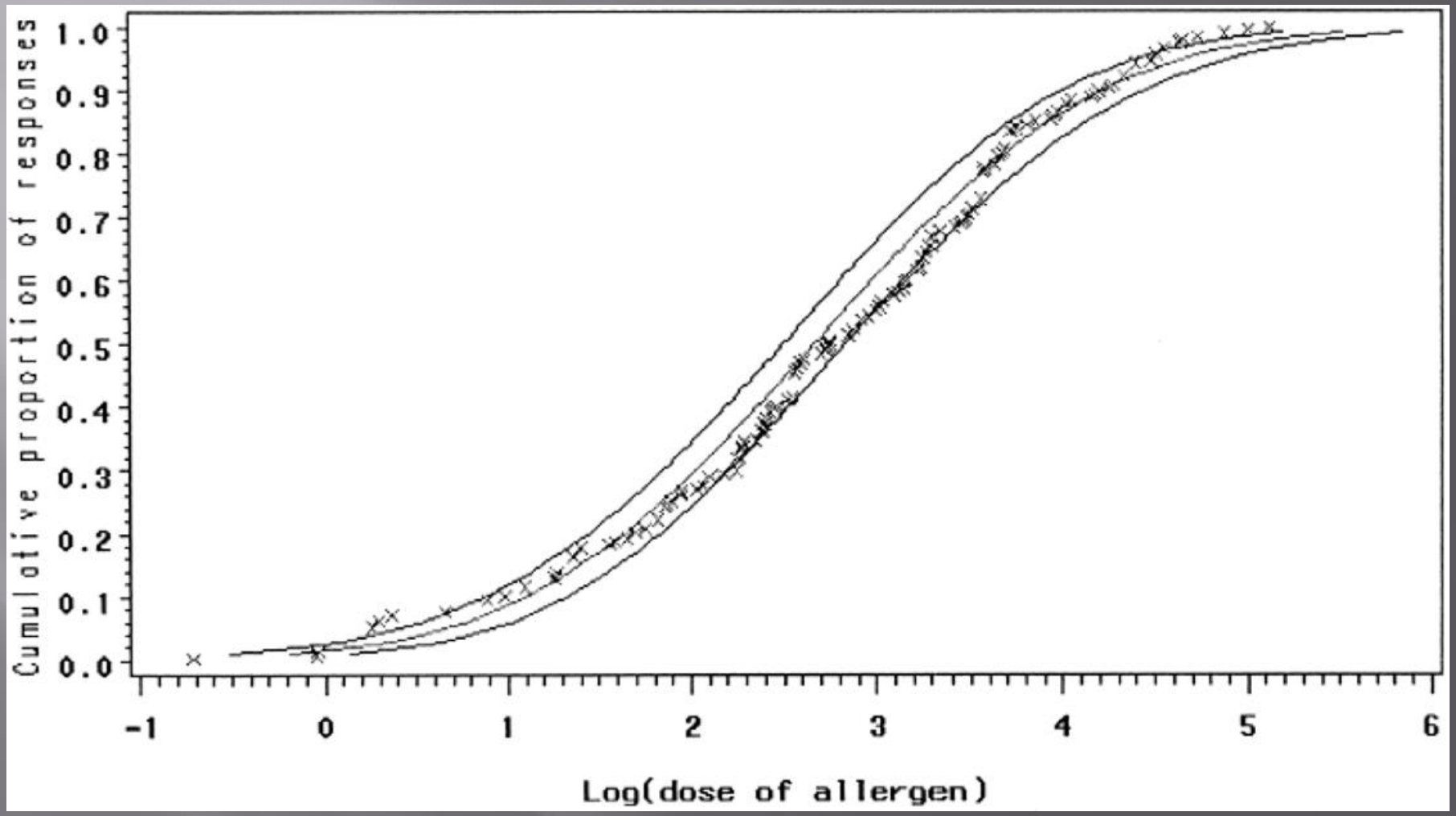


IgE-antibodies
bind to mast cells
(sensitization)





Threshold values: Egg as an example



Uptake and distribution of whole food proteins

The technique for demonstrating absorption of unaltered fish protein was as follows: A site on the skin of the subject to be tested is passively and locally sensitized with 0.05 cc. of serum obtained from a certain fish-sensitive patient. On the following day the subject is fed 50 gm. of raw herring on an empty stomach. Development of a wheal at the sensitized site is proved to indicate absorption of fish into the circulation in an unaltered state. The phenomenon occurred in 93.8% of 65 cases tested.

In 50% of the subjects the reaction occurred within 15 min. after the fish meal; in 83.3%, within 1/2 hr.

Atopic patients and families show a lower percentage of positive reactions than normals. In a patient with hookworm disease, who failed to show a positive reaction, a true lack of permeability to unaltered proteins was demonstrated throughout the entire alimentary tract.

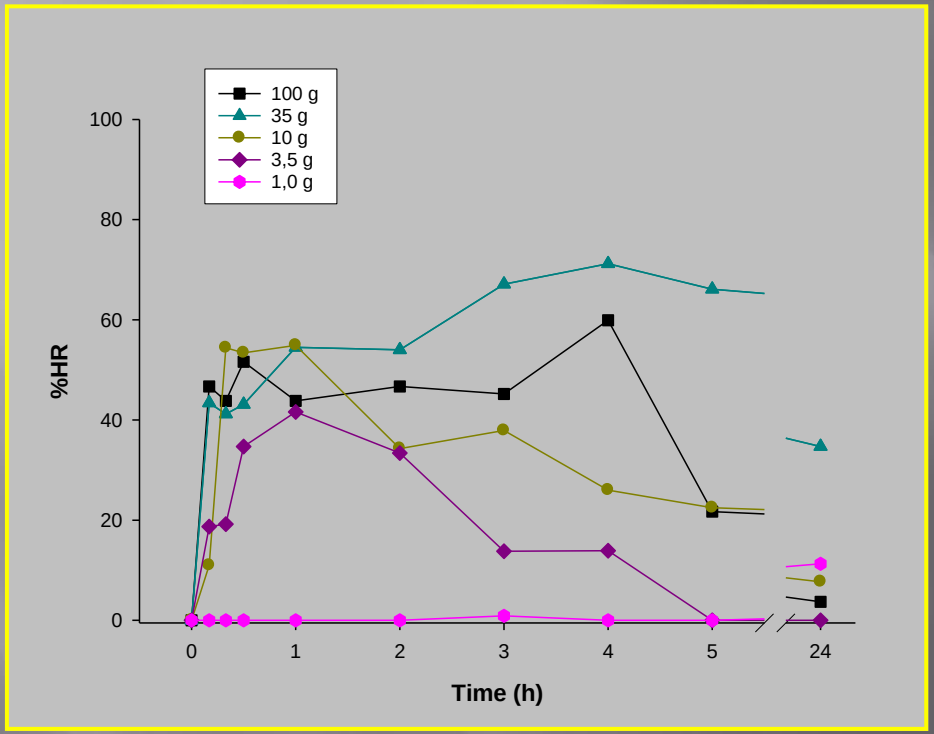
ABSORPTION OF UNDIGESTED PROTEINS IN HUMAN BEINGSTHE ABSORPTION OF UNALTERED FISH PROTEINS IN ADULTS

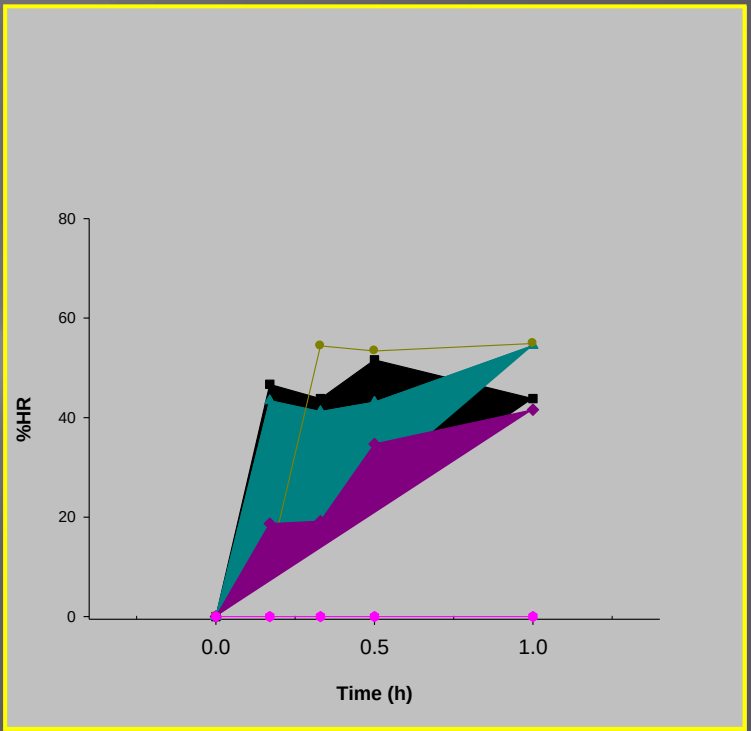
MATTHEW BRUNNER, M.D.; MATTHEW WALZER, M.D.

Arch Intern Med (Chic). 1928;42(2):172-179

Allergenic activity recovered in serum of a non- allergic person after ingestion of peanuts

Dose response study



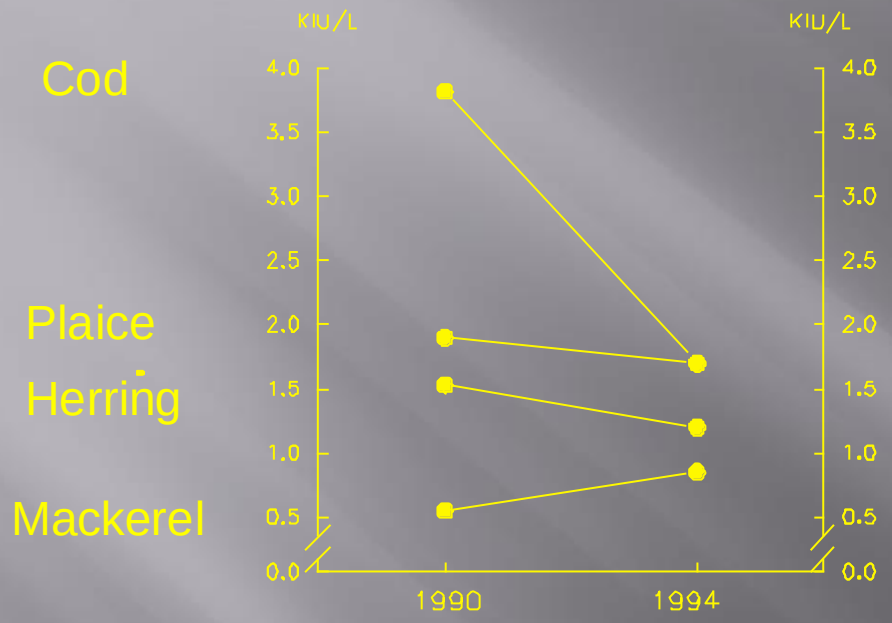


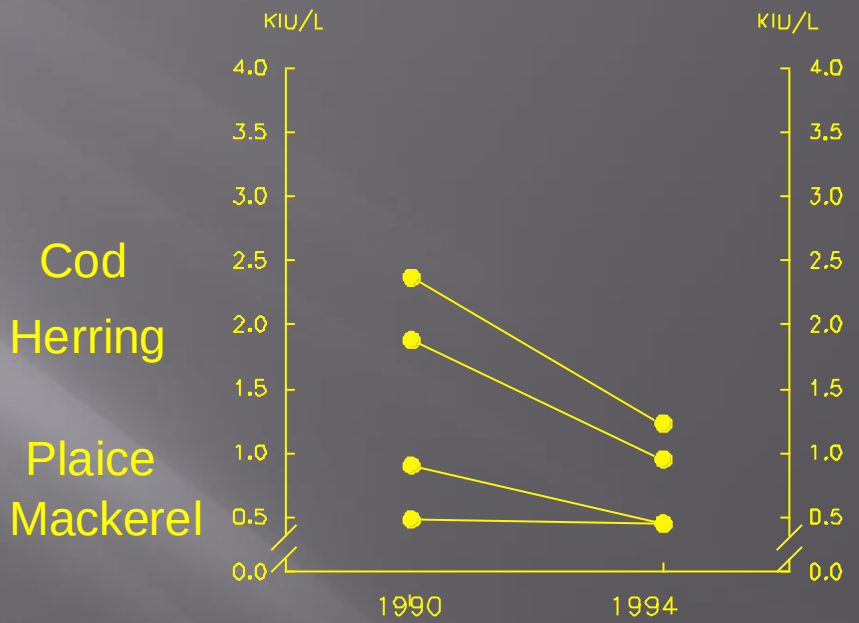
Allergenic activity determined by histamine release (% HR) using passive sensitization of basophils with a serum from a strongly peanut allergic person

Abstract #1017: C G Dirks, M H Pedersen, M H Platzer, C Bindslev-Jensen, P S Skov, L K Poulsen
Systemic absorption of biologically active peanut allergens in non-allergic volunteers following oral intake

Immunological regulation of the IgE production

Natural history of specific IgE



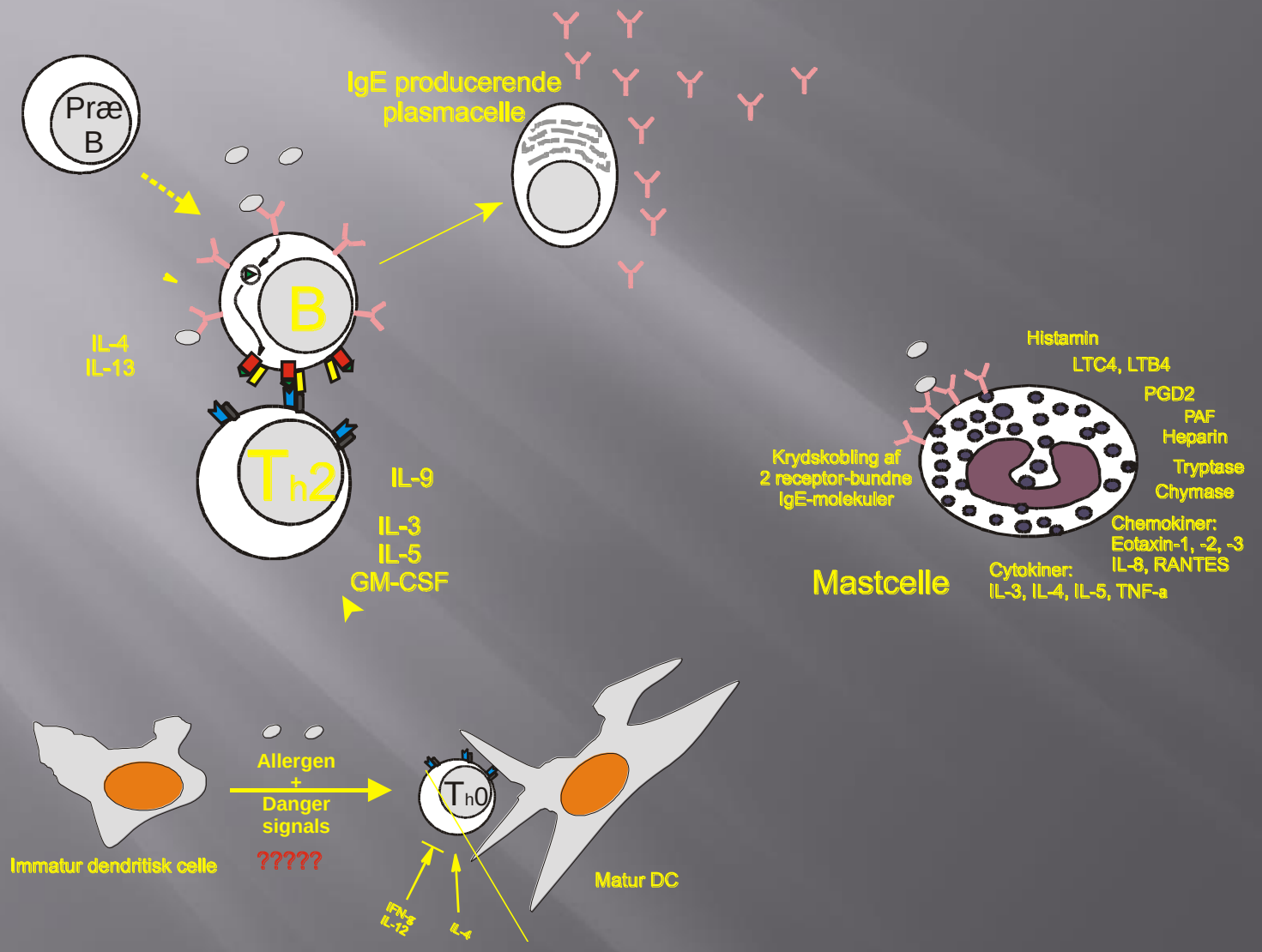


Female, age: 33
Last exposure to codfish in 1970. SPT positive.
Reponse to challenge: Asthma

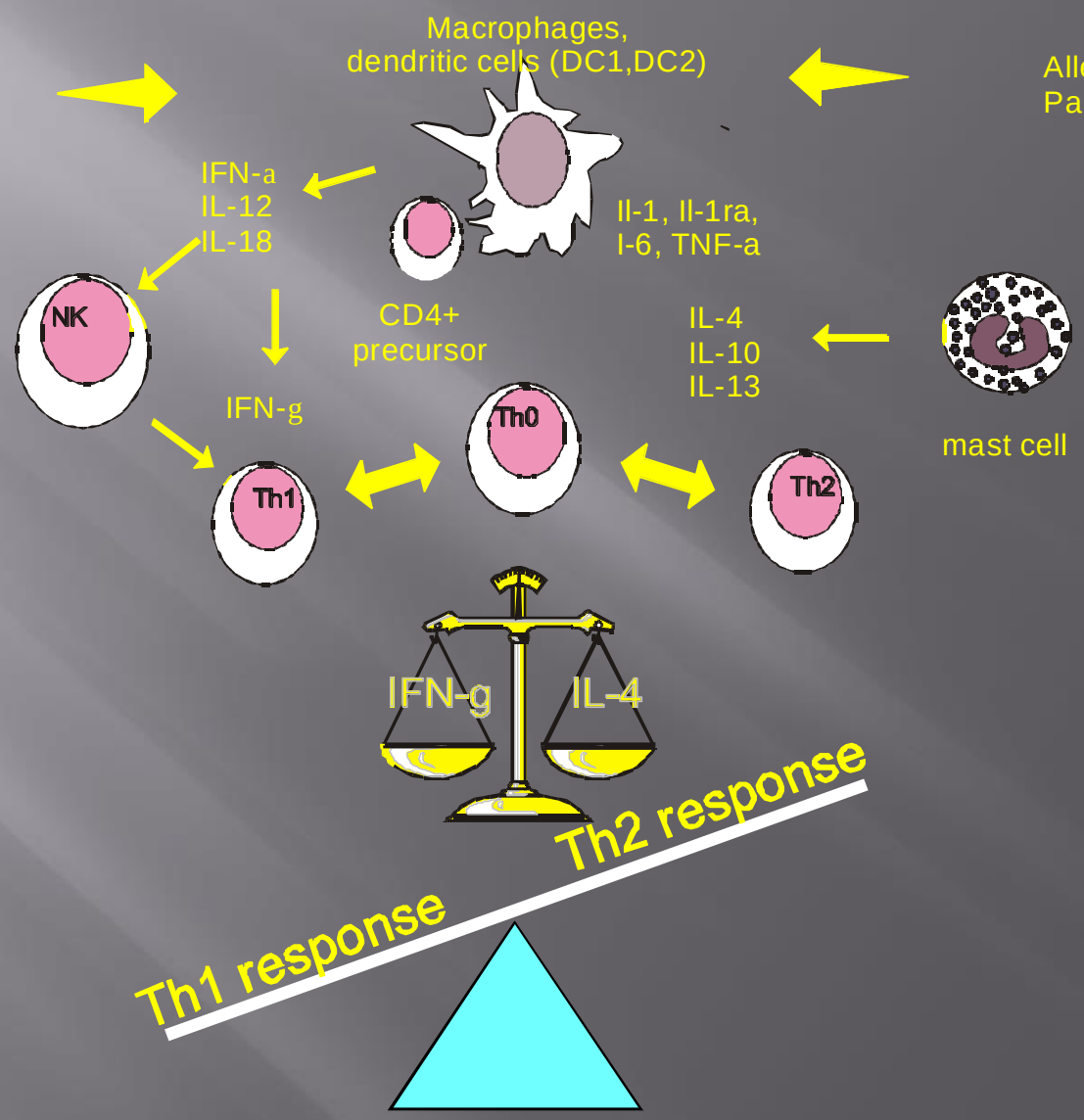
Male, age: 26
Last exposure to codfish in 1988. SPT positive.
Reponse to challenge: Asthma + G.I. symptoms

Data from TK Hansen

Sensitization phase of the allergic immune response



Differentiation of CD4+ T-cells into Th1 or Th2 cells



IL-2
IFN-γ

IL-4
IL-5
IL-9
IL-13

IgG-response

"protecting immunity"

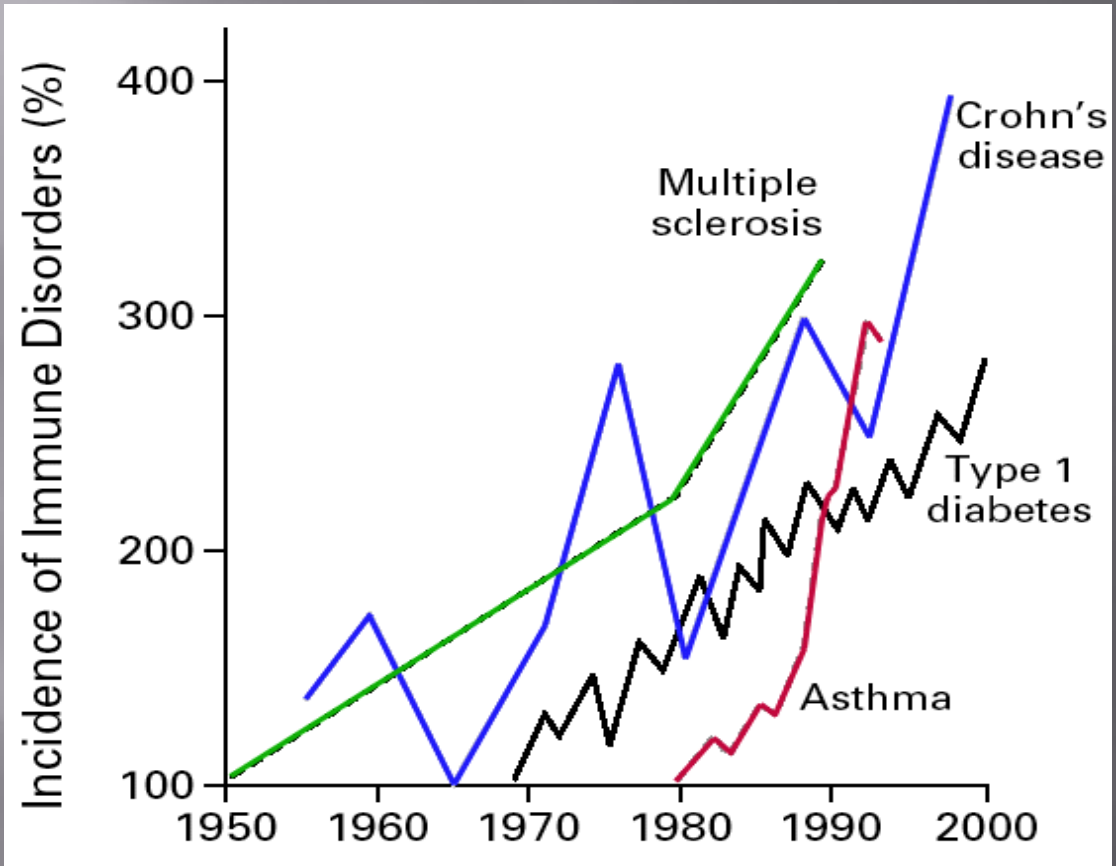
autoimmunity

IgE-response

"allergic phenotype"

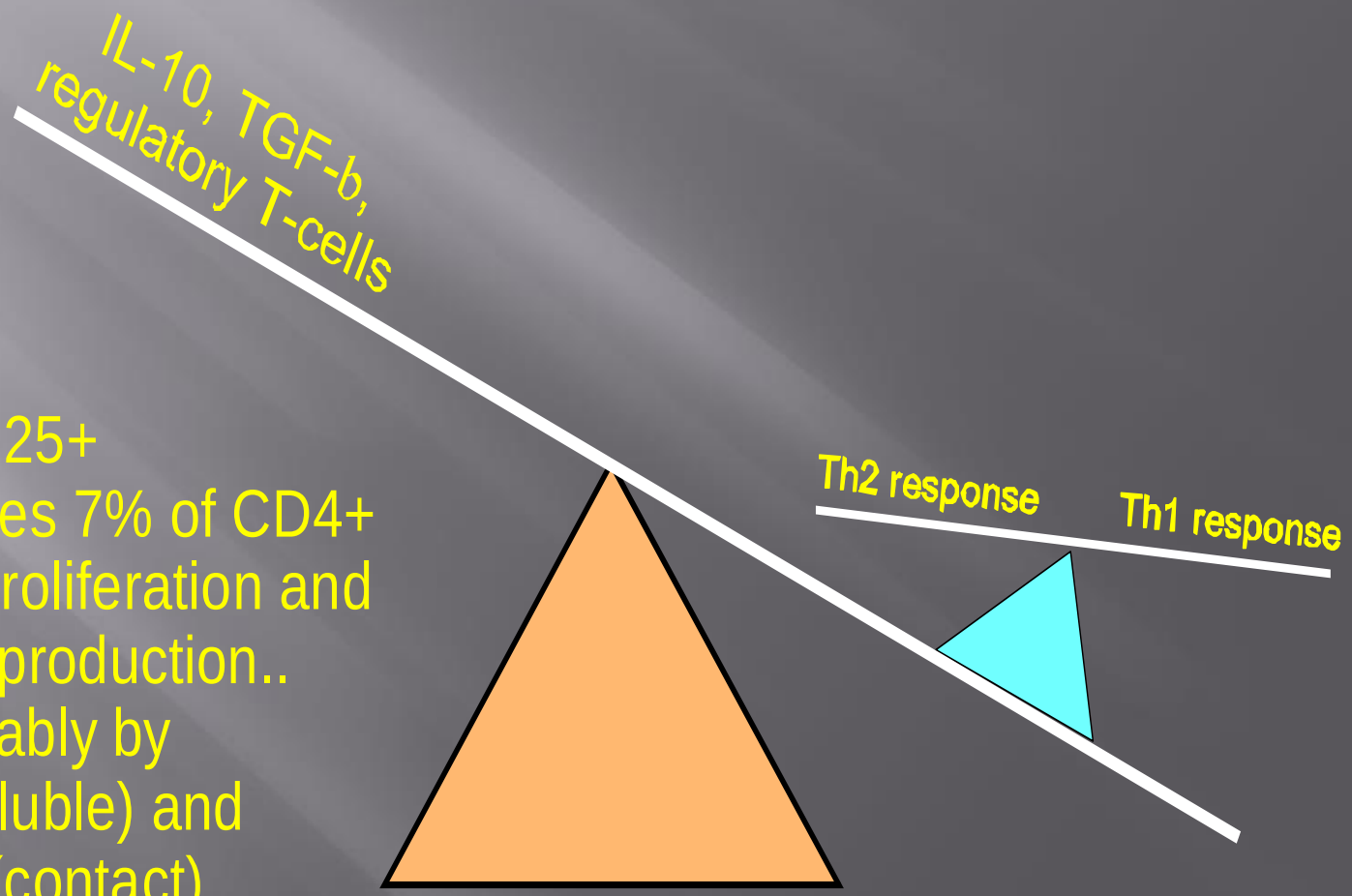
parasites

The Increasing Incidence of Immune Regulatory Disorders



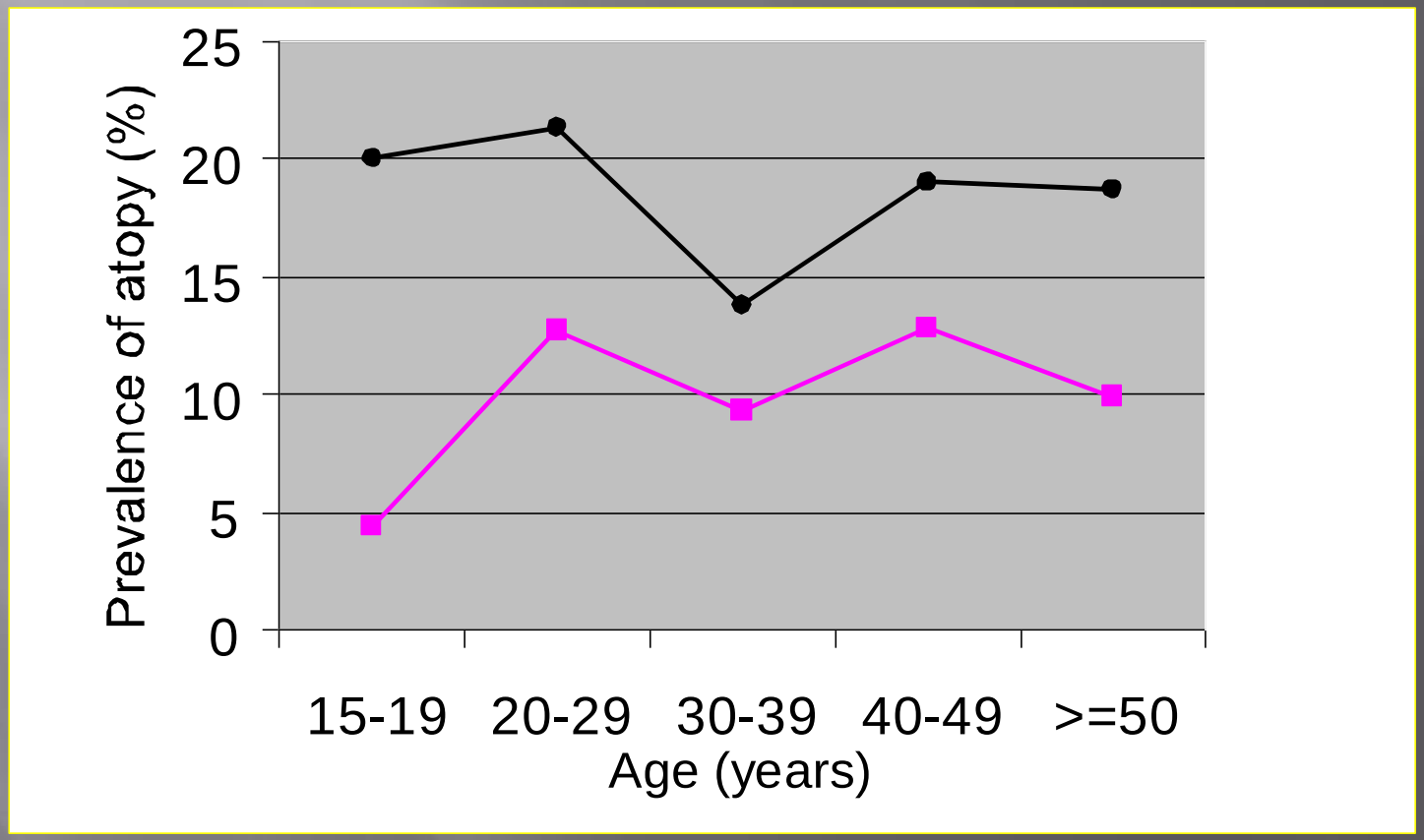
Bach J-F., (2002)
N.Engl.J.Med. 347:911-920

CD4+ T-cells can be regulatory or inflammatory cells



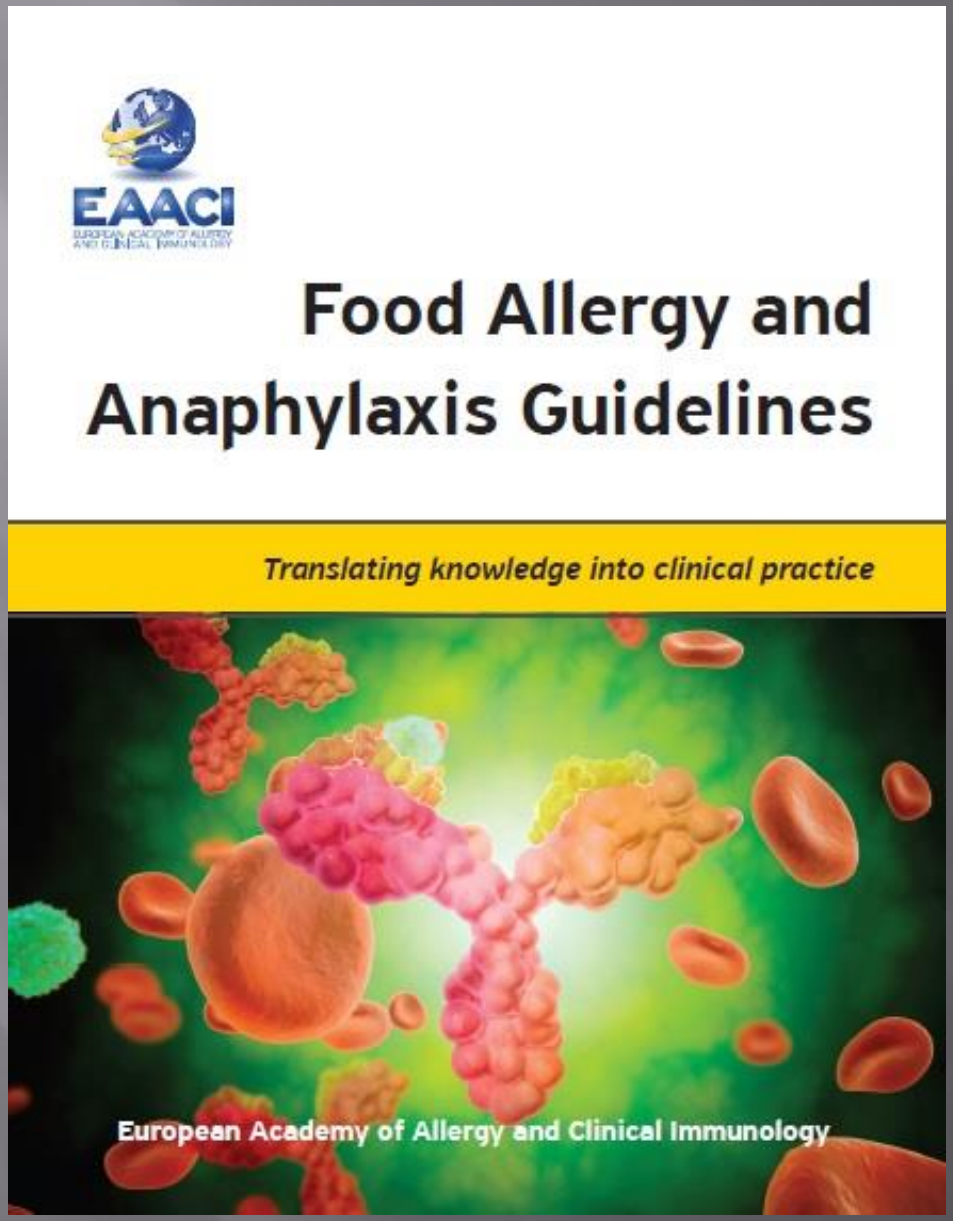
Treg:
CD4+CD25+
Constitutes 7% of CD4+
Inhibits proliferation and cytokine production..
..presumably by
IL-10 (soluble) and
CTLA-4 (contact)

Sensitization in Greenland



Krause TG, Koch A, Friborg J, Poulsen LK, Kristensen B & Melbye M
Increasing prevalence of atopy in the Arctic
The Lancet 360: 691-92 (2002)

Risk factors for becoming sensitized to foods


EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY
Food Allergy and Anaphylaxis Guidelines
Translating knowledge into clinical practice
European Academy of Allergy and Clinical Immunology

Four paradoxes in food allergy

Regional differences

Temporal changes of food allergy prevalence

Differential natural history of varying food allergies

Taxonomically related, but allergenically different foods

Poulsen LK
In search of a new paradigm: Mechanisms of sensitization and elicitation of food allergy
Allergy 60(5):549-58 (2005)

Prevalence of food allergy

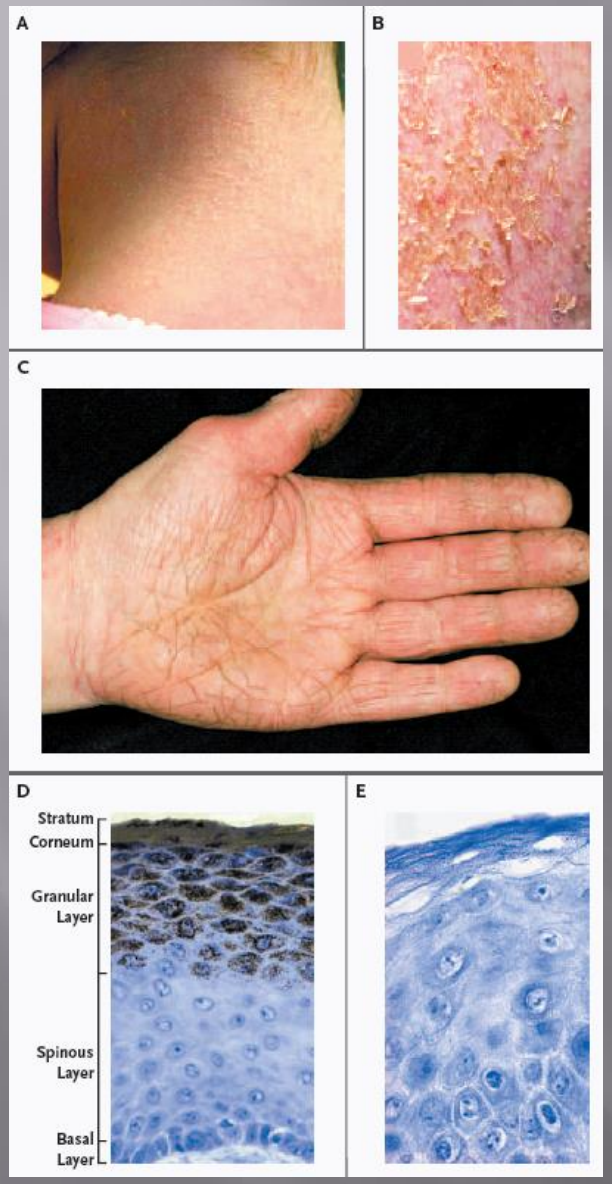
A selected pediatric population (<3Y)
Reported prevalence of food hypersensitivity: 28%
Confirmed by DBPCFC: 3.9 %

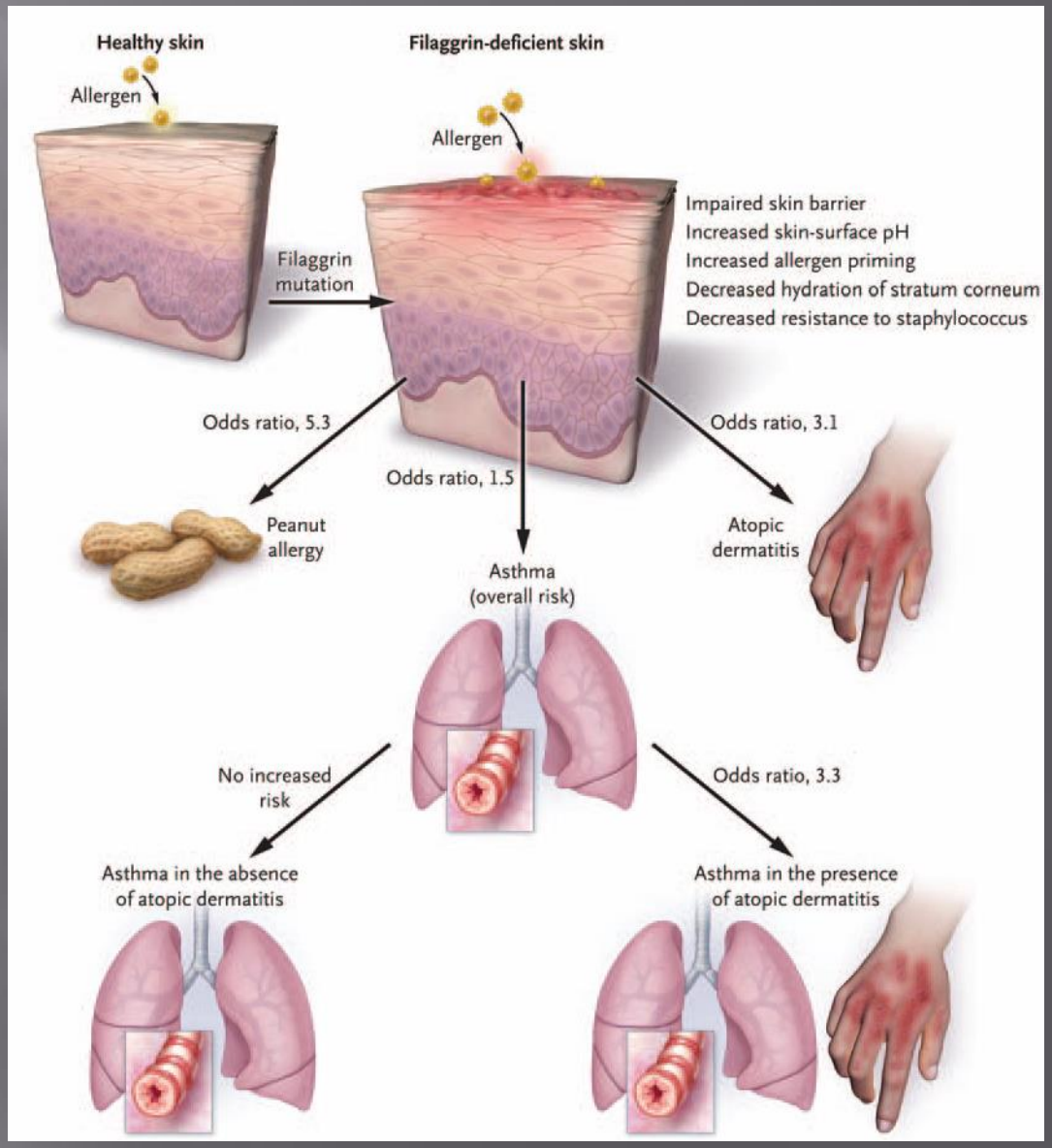
Bock, SA
Prospective appraisal of complaints of adverse reactions to foods in children durig the first 3 years of life.
Pediatrics 79, 683-8 (1987).

A population based study of 2 x 7500 households
Reported prevalence of food hypersensitivity: 20%
Confirmed by DBPCFC: 1.4 - 1.8 %

E. Young, M.D. Stoneham, A. Petruckevitch, J. Barton & R. Rona
A population study of food intolerance.
Lancet 343, 1127-1130 (1994).

Filaggrin mutations

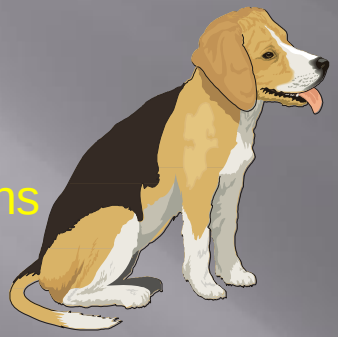


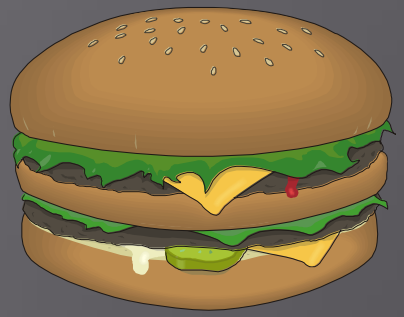


Irvine AD, McLean WH, Leung DY. Filaggrin mutations associated with skin and allergic diseases.N Engl J Med. 2011; 365(14):1315-27

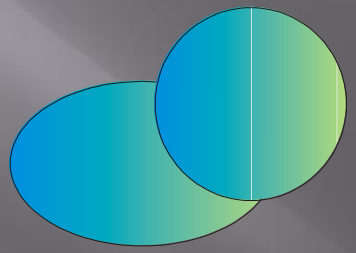
The allergens - terminology

Allergenic materials
- the sources of allergens

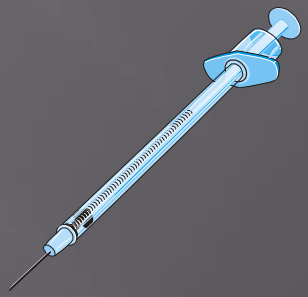




Allergens
- IgE-binding antigens
- normally proteins



Allergen extracts
- pharmaceutical preparations of allergens for diagnosis or treatment



Allergen research in the clinic: 3 waves

1. Identification of new allergenic sources

The ImmunoCAP catalogoue contains more than 600 different sources

Do we need more?

New allergenic sources due to climate changes?

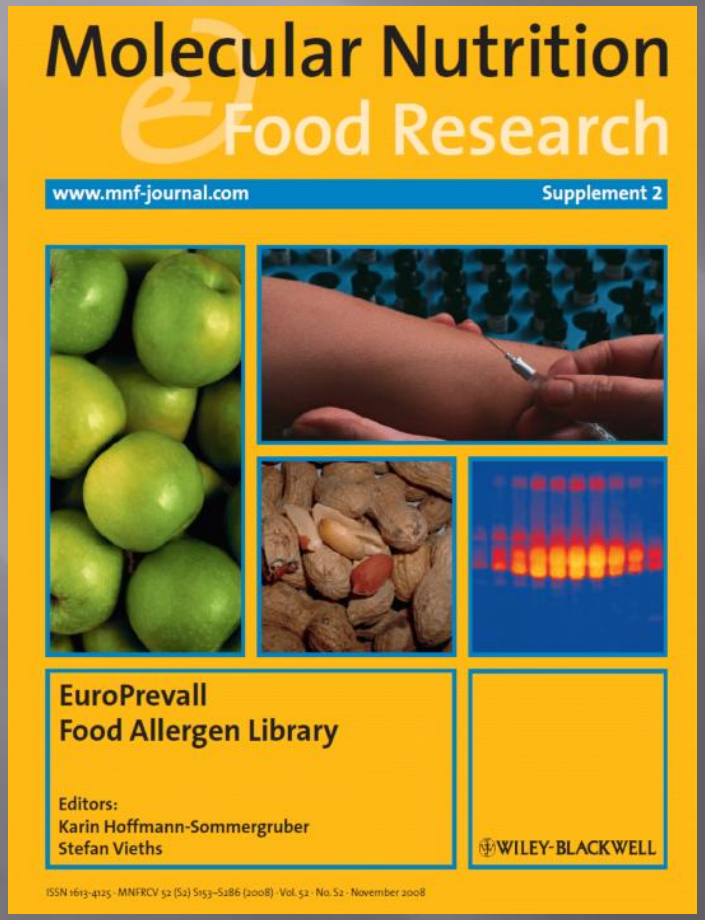
New allergenic sources due to globalization of food markets and habits?

New occupational allergens?

Allergen research in the clinic: 3 waves

2. Identification, characterization, and cloning of single allergens

EuroPrevall Food Allergen Library



From the editorial by Stefan Vieths & Karin Hoffman-Sommergruber:

...existing allergen purification protocols were improved and expression strategies for producing recombinant allergens were evaluated and optimized. Subsequently, authentication of the highly pure protein batches were performed using state of the art methods including MALDITOF mass spectrometry, tandem mass spectromenty and N-terminal amino acid sequencing. Tertiary structures were evaluated by high resolution one-dimensional 1H NMR spectroscopy; secondary structure was evaluated by far-UV circular dichroism spectroscopy. Allergenic activity was studied by IgE ELISA, IgE immunoblotting and cellular basophil activation tests, using selected sera from a panel of food allergic subjects. In the first round, 31 allergens from ten foods including many of the EC labelling list (apple, peach, hazelnut, peanut, celery, cow's milk, goat's milk, hen's egg, fish, and shrimp) were produced and purified by leading scientists in this field and for the first time characterised to a comparable extent.

131 pages, 11 original papers, 140 authors

"The golden age of new allergen discovery is over"

James D. Astwood

Year	Unique sequences	Homologues, isoforms etc.	Total sequences	New	%New
1985	12	0	12	12	100
1990	60	55	115	48	42
1995	140	79	219	80	36
2000	180	400	580	40	7
2005	185	900	1085	5	0.5

Allergen research in the clinic: 3 waves

3. Identification of cross-reactive patterns

For each n allergens, there are n x (n-1) possible cross-reactivities!

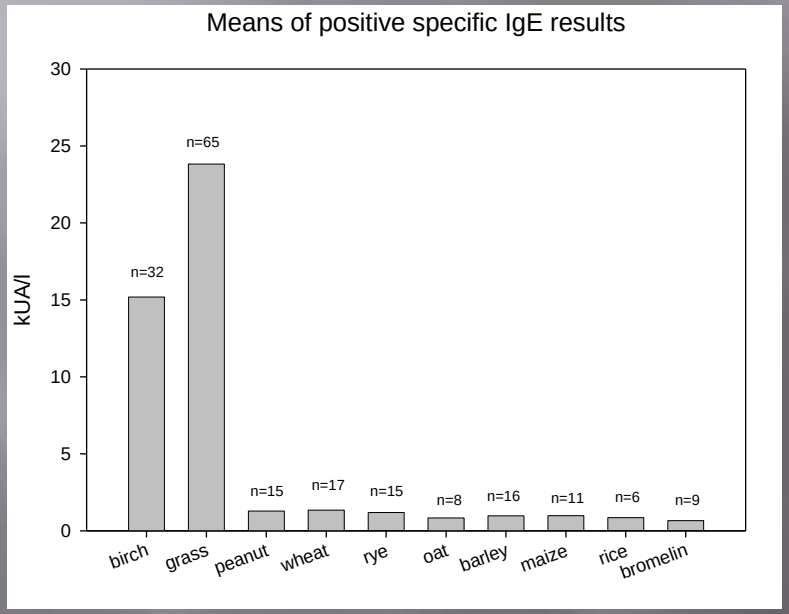
Example: Food allergy - cross-reacting foods

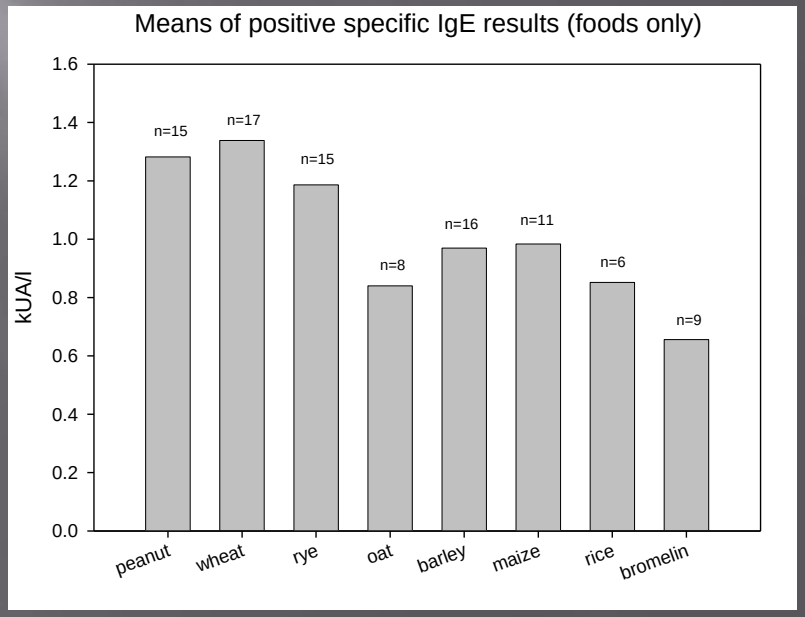
Food	Crossreaction
Cow's milk	Goat's milk, mare's milk, sheep's milk
Hen's egg	Eggs from goose, turkey, duck. Chicken meat. Bird feathers.
Codfish	Plaice, mackerel, herring other fishes
Peanut X)	Soy, green bean, pea
Shrimp	Crab, crayfish, lobster
Birch crossreacting foods	Hazelnuts, apple, potato, carrot, cherry, kiwi almond and other tree nuts
Wheat X)	Grass pollen, rye, sesame, buckwheat, oats
Banana	Latex, avocado, pear

Clinical non-relevant cross-reactions

65 grass-pollen allergics who tolerate25 grams of 6 cereal products plus peanut were tested in skin test and specific IgE (ImmuLite® & ImmunoCAP®).

46% (SPT), 37% (ImmunoCAP) and 20% (Immulite) reacts the the tolerated foods





Martens M, Schnoor HJ, Malling H-J & Poulsen LK
The clinical relevance of in vivo/in vitro tests for cereal and peanut sensitisation in grass pollen allergic patients
Clinical and Translational Allergy 2011, 1:15

New proteins in the food chain: Is there evidence of new sensitization and allergies?

Largest increases in sensitization rates comes from allergenic sources already known to be allergens.

New sources may be allergenic, but most often this happens because of cross-reactivity to allergens already well-established in society.

Individual novel proteins can - and should - be screened for potential cross-reactivity before their entry into the food chain.

Hidden allergens and unknown cross-reactivities are probably the largest allergy-related public health problem.

New processing technologies may cause new problems.