Food Allergy
Introduction, Etiology, and Mechanisms

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

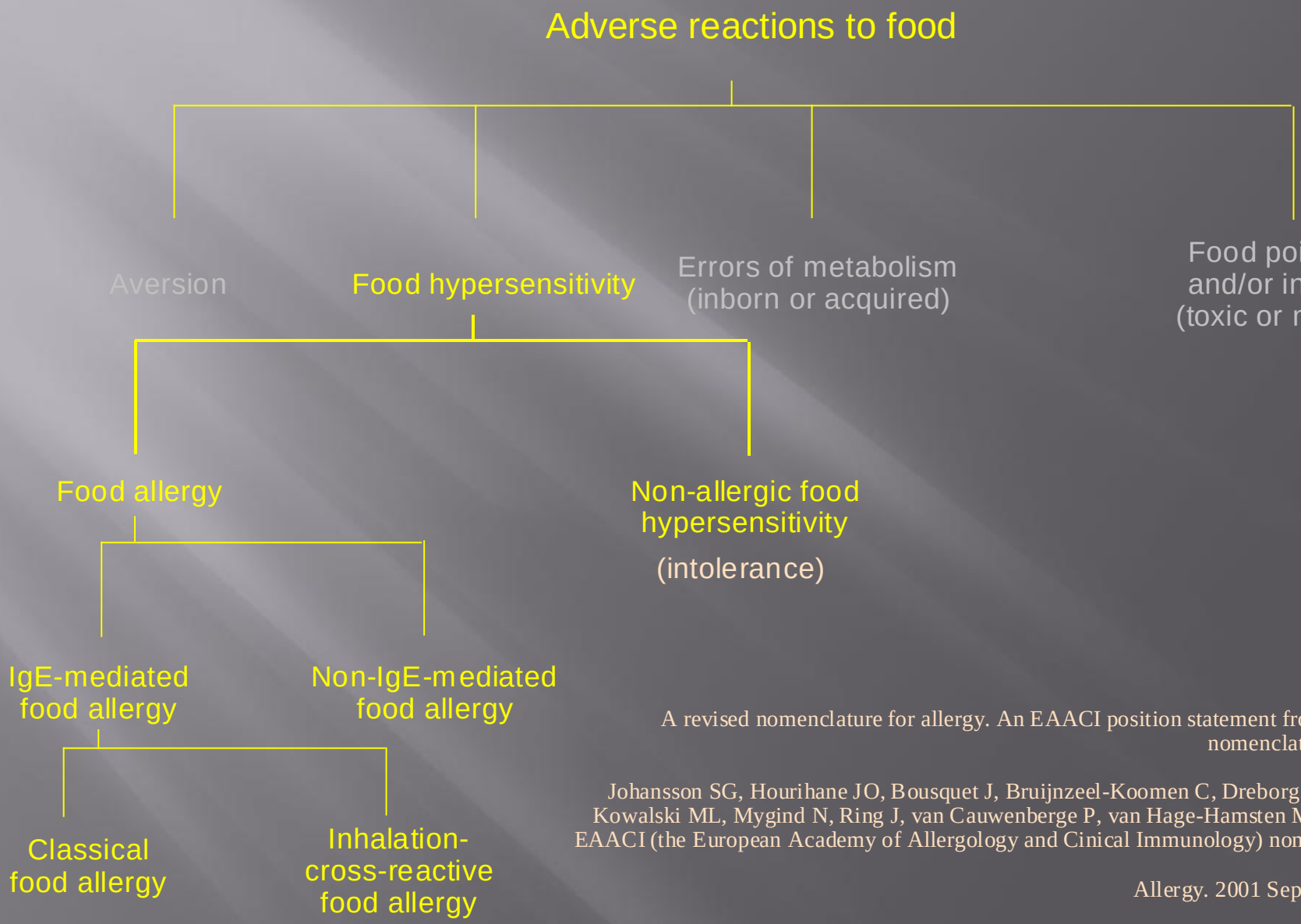
Conjunctivitis

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.

Food challenges

Review Article

Standardization of food challenges in patients with immediate reactions to foods - Position paper form the European Academy of Allergology and Clinical Immunology

C. Bindslev-Jensen, B.K. Ballmer-Weber, U. Bengtsson, C. Blanco, C. Ebner, J. Hourihane, A.C. Knulst, D.A. Moneret-Vautrin, K. Nekam, B. Niggeman, M. Osterballe, C. Ortolani, J. Ring, C. Schnopp, T. Werfel

Allergy 59:690-7; 2004

All patients with suspicion of an immediate, systemic food reaction: DBPCFC

Children < 3 y: open challenges

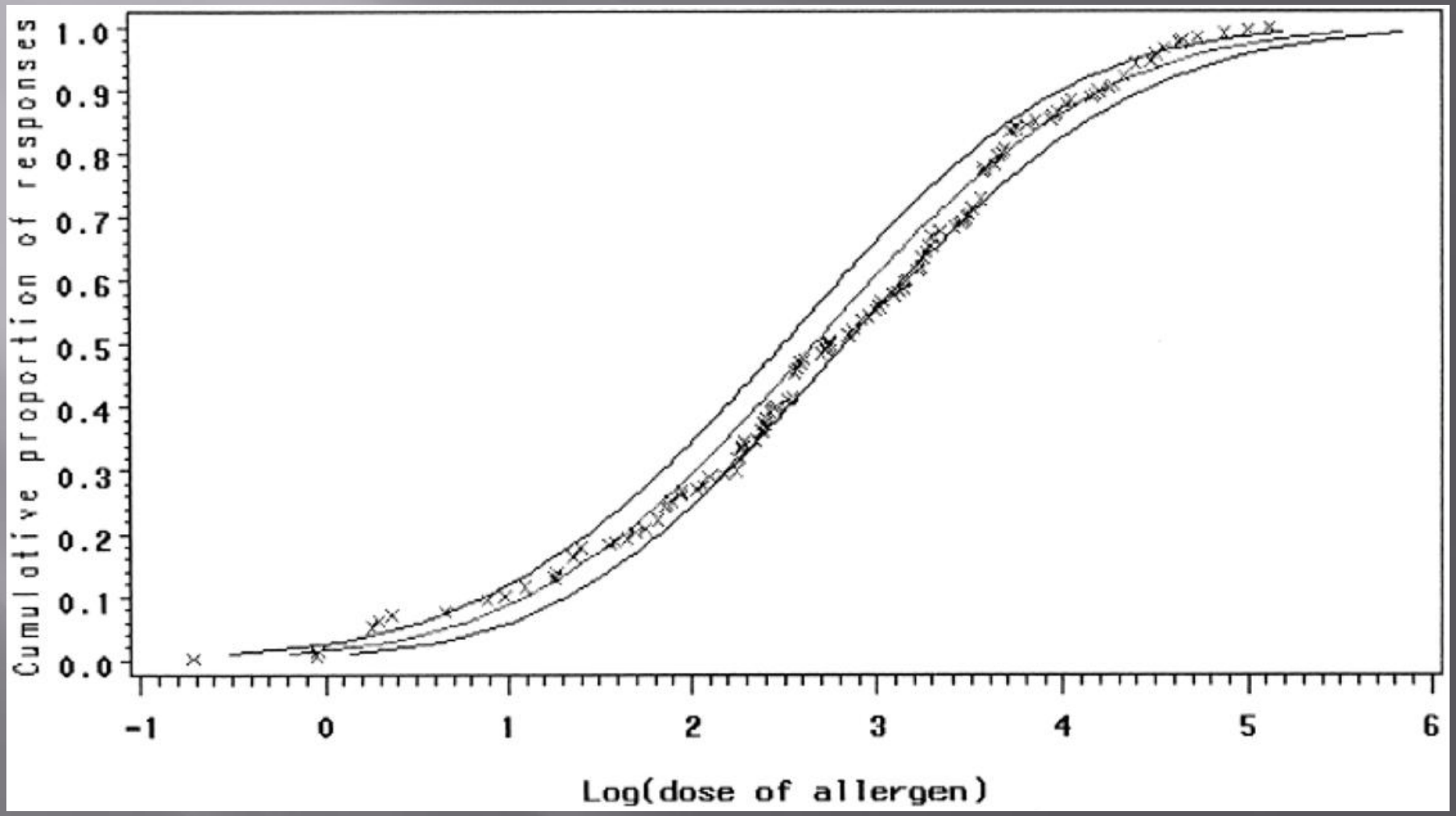
Pollen-related OAS: only in selected cases

Exclusion: anaphylaxis, patients with ongoing disease, interfering medications, specific IgE??

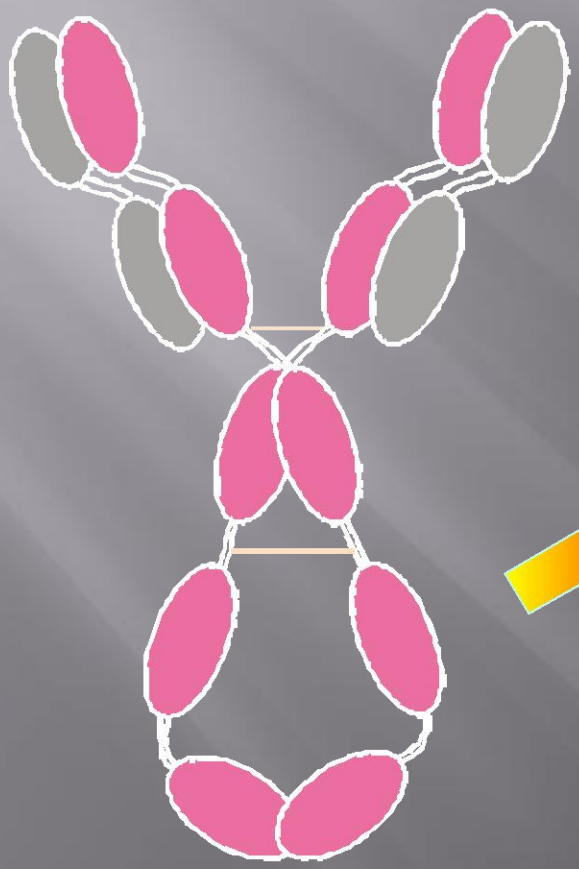
Use 2- or 10 fold titrations starting from 0.1 to 100 mg.

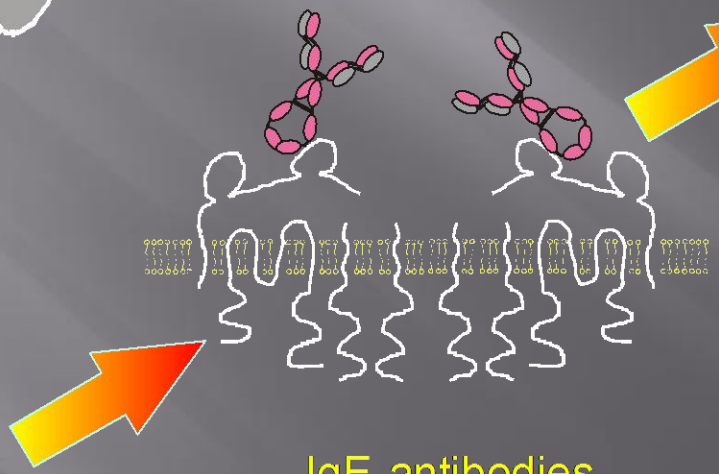
Negative DB always followed by OC

Threshold values: Egg as an example

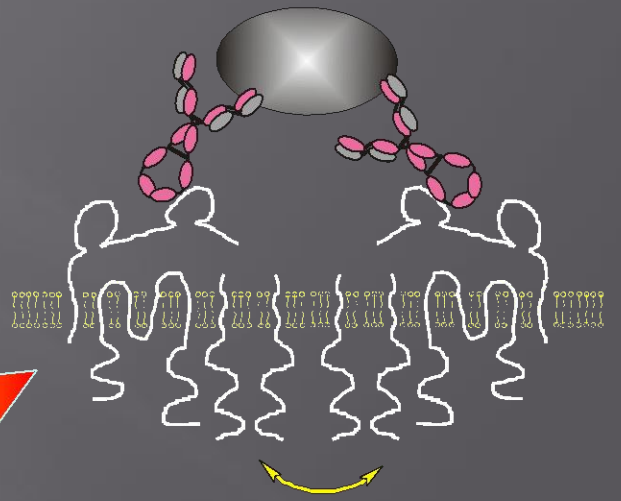


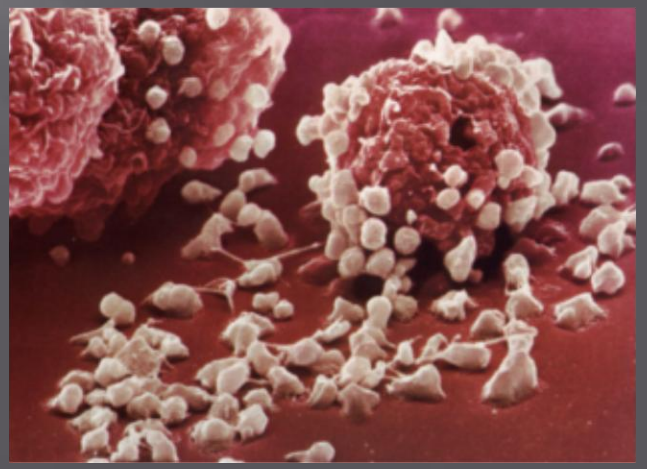
Immunoglobulin E (IgE)
Allergens cross-links IgE and activate mast cells



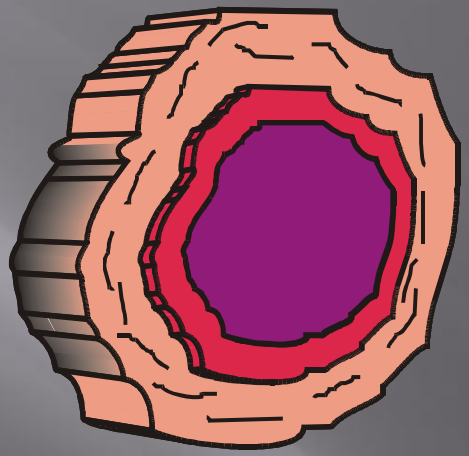


IgE-antibodies
bind to mast cells
(sensitization)



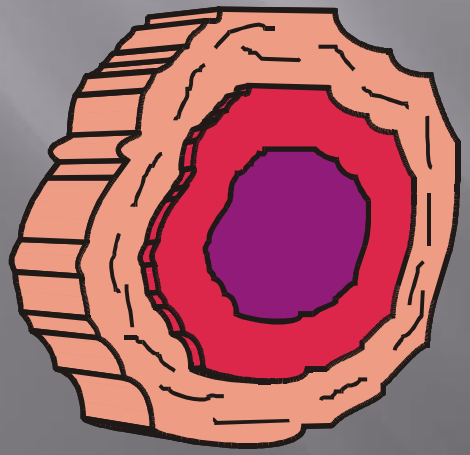


Acute asthma

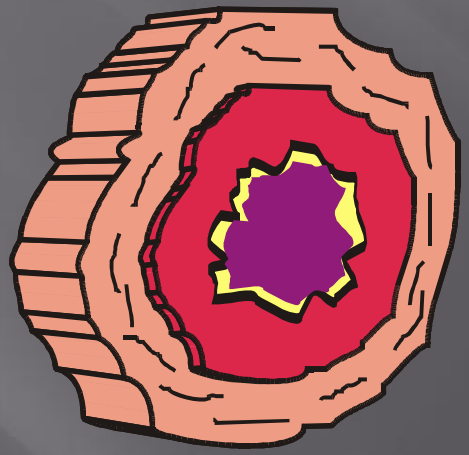


Cross-section of normal airway

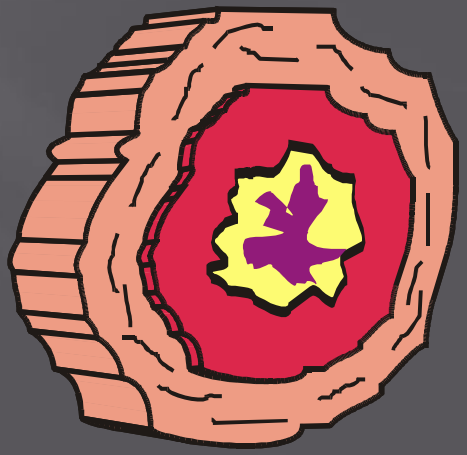
Smooth muscle contraction



Oedema formation



Mucus hypersecretion



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

ABSORPTION OF UNDIGESTED PROTEINS IN HUMAN BEINGS

IV. ABSORPTION OF UNALTERED EGG PROTEIN IN INFANTS AND IN CHILDREN

SAMPSON J. WILSON, M.D.
AND
MATTHEW WALZER, M.D.
BROOKLYN

It has been shown in previous communications [1] that following the ingestion of such proteins as those of fish and eggs, detectable amounts of these substances are absorbed into the circulation in most normal adults. Absorption from the rectum was also demonstrated by the same technic.[1c] The present communication deals with an investigation of these phenomena of absorption in infants and children.

Egg was chosen as the protein most suitable for study because it is a common constituent of the diet of the average child and is easily administered. The technic employed in this investigation was practically the same as that reported in the previous communications. A brief summary follows:

METHODS OF INVESTIGATION

Egg in any form was excluded from the diet of the subject on the day that passive local sensitization was induced. This procedure consisted of an intracutaneous injection into the flexor surface of the forearm of about 0.05 cc. of a special serum obtained from a person who was sensitive to eggs (K 4 serum). On the following morning the test meal, containing egg, was taken by the fasting subject. No attempt was made to clear the intestinal tract before the test. Following the meal, the sensitized cutaneous site was kept under observation. The appearance of erythema or a wheal marked the onset of the local reaction, which indicated that unaltered egg protein had entered the circulation.

The K 4 serum used for producing passive local sensitization was the same as that employed in the series of adults. It was obtained from a patient 2½ years of age, suffering from eczema, asthma and urticaria, who was extremely sensitive

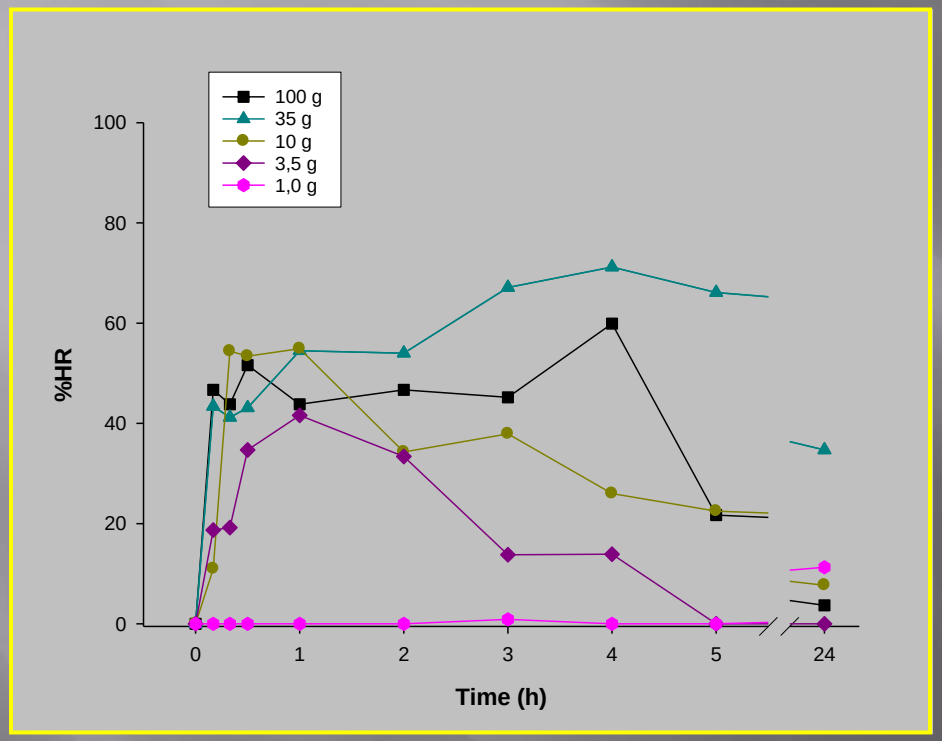
From the Jewish Hospital.

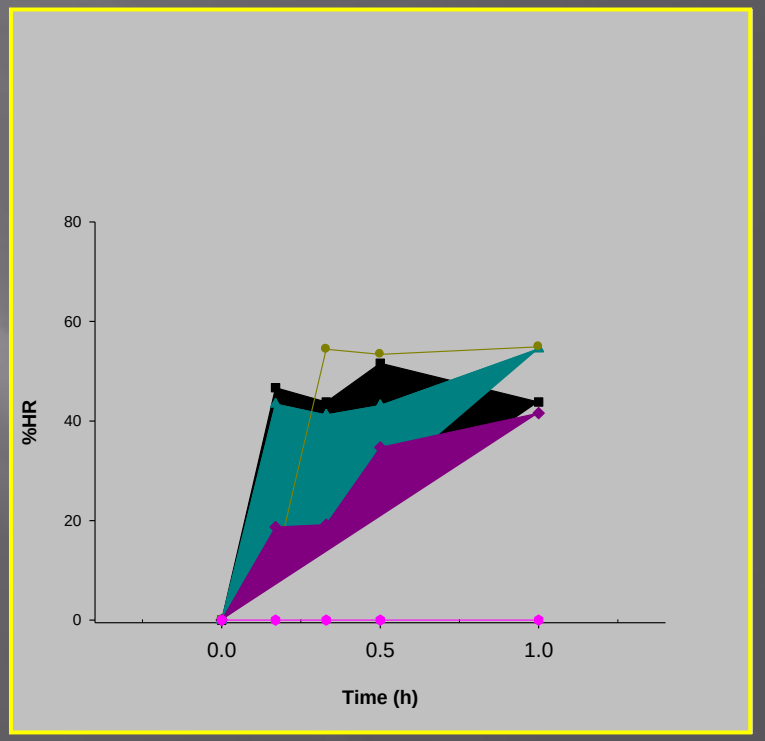
Read before the Brooklyn Pediatric Society, Oct. 17, 1929.

1. (*a*) Walzer, M.: Studies in Absorption of Undigested Proteins in Human Beings: I. A Simple Direct Method of Studying the Absorption of Undigested Proteins, J. Immunol. **16**:143 (Sept.) 1927. (*b*) Brunner, M., and Walzer, M.: Absorption of Undigested Proteins in Human Beings: The Absorption of Unaltered Fish Proteins in Adults, Arch. Int. Med. **42**:172 (Aug.) 1928. (*c*) Sussman, H.; Davidson, A., and Walzer, M.: Absorption of Undigested Proteins in Human Beings: III. The Absorption of Unaltered Egg Protein in Adults, ibid. **42**:409 (Sept.) 1928.

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

Dose response study



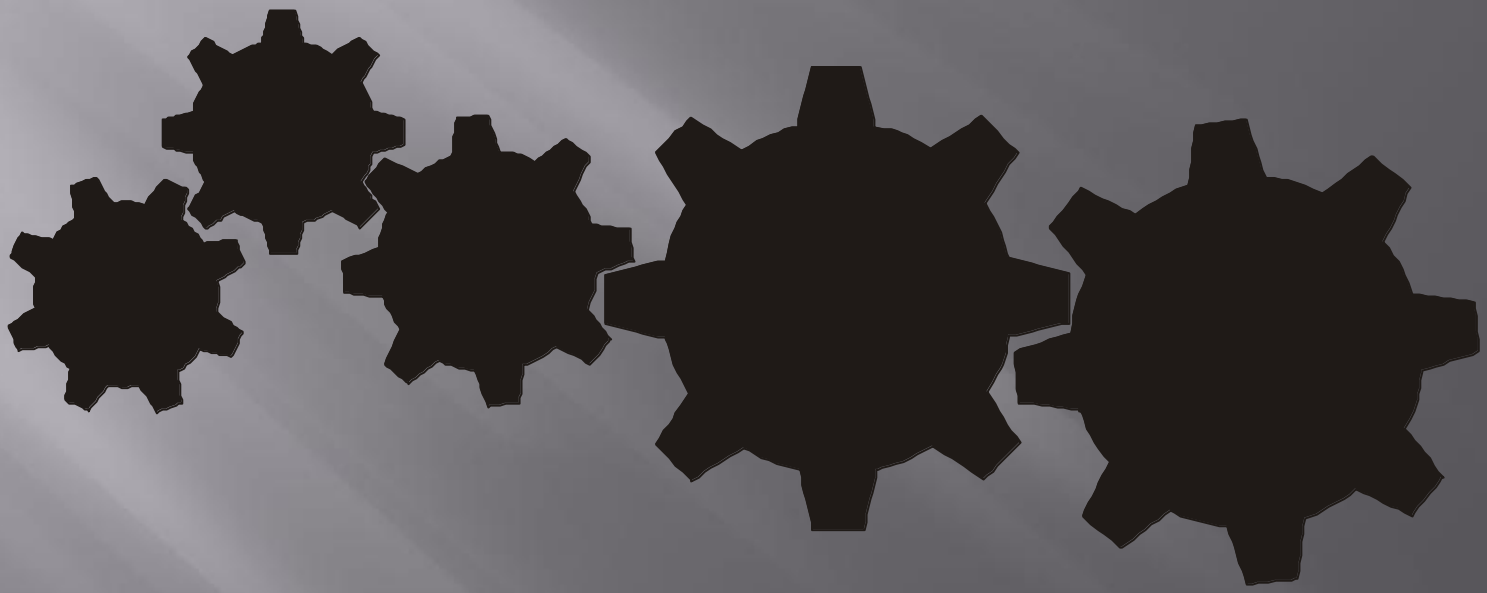


Allergenic activity determined by histamine release (% HR) using passive sensitization of basophils with a serum from a strongly peanut allergic person

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

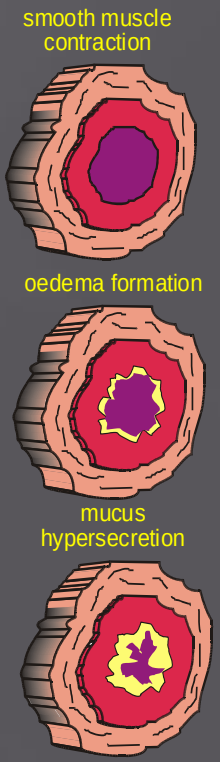
Classification of hypersensitivity

Antigen	Immune response	Eliciting mechanism	Initial cellular processes	Disease examples



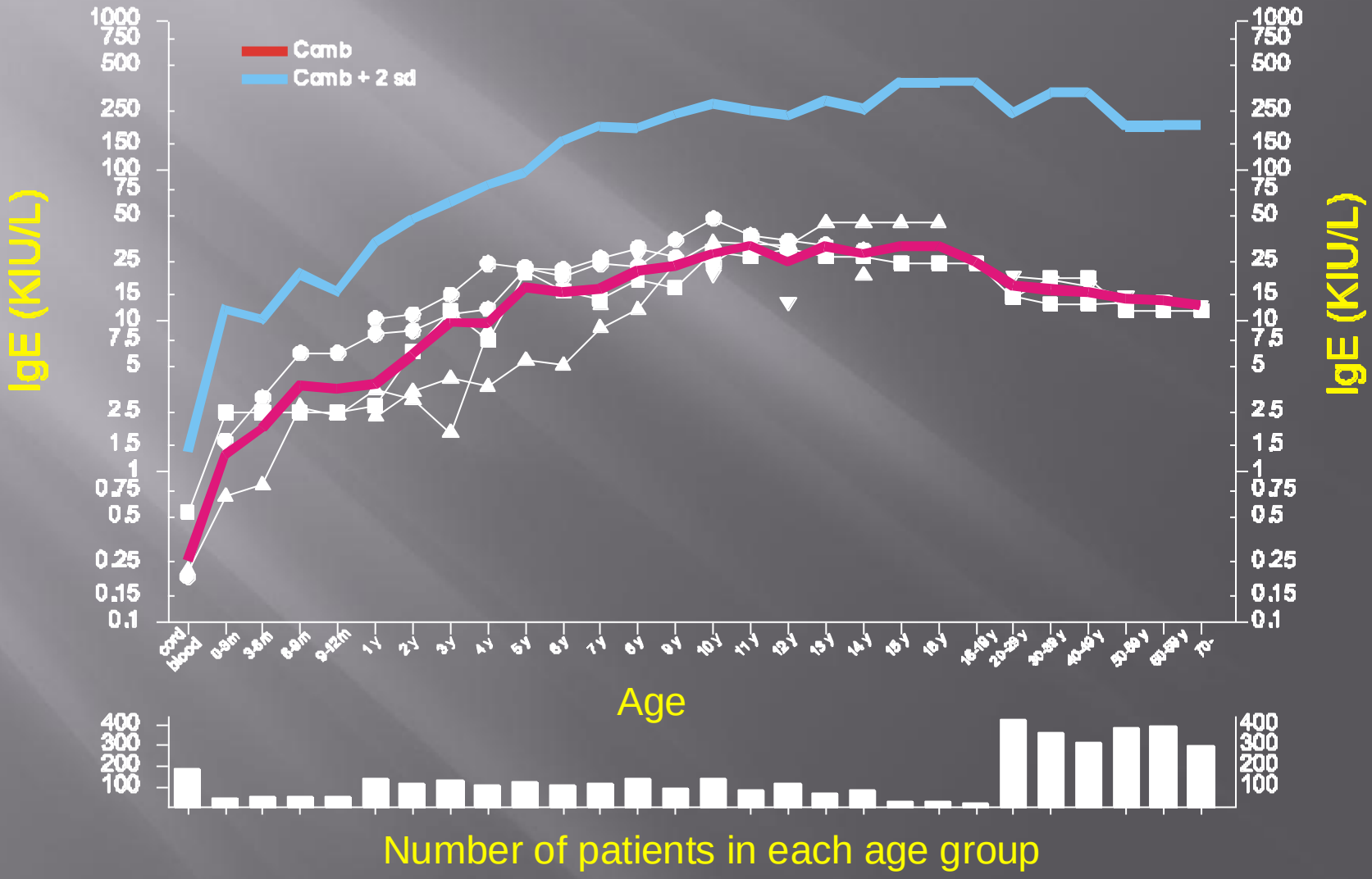
Classification of hypersensitivity: type I

Antigen	Immune response	Eliciting mechanism	Initial cellular processes	Disease examples
Allergen i.e. a soluble, environ-mental antigen Helmint antigens	IgE	FceRI-mediated activation of mastcells or basophils Degranulation with release of pre-formed mediators Release of lipid mediators Cyto & chemokine synthesis	Receptor-mediated (histamine, leukotriene, prostaglandin) activation of smooth muscle vessels glands	Anaphylaxis Acute asthma

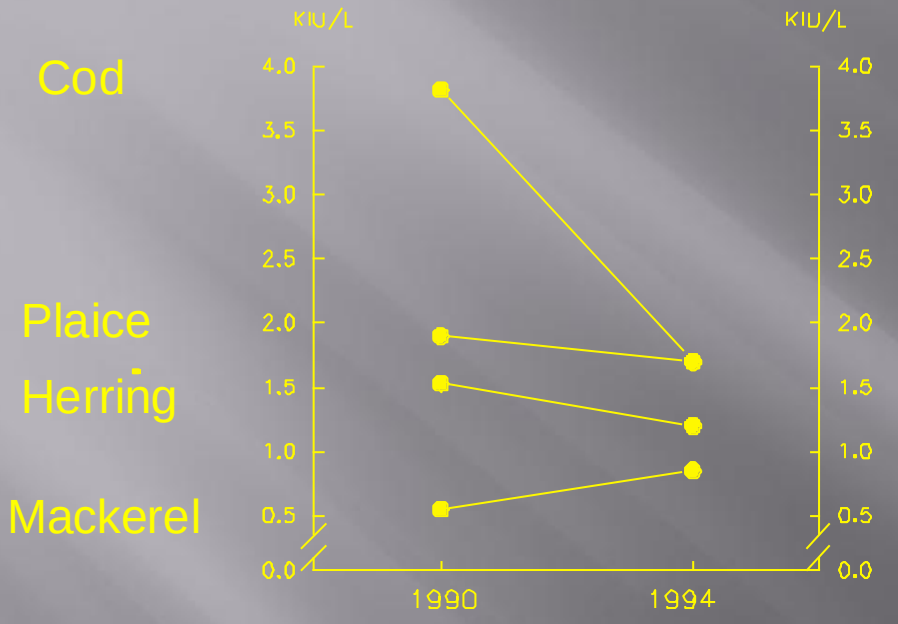


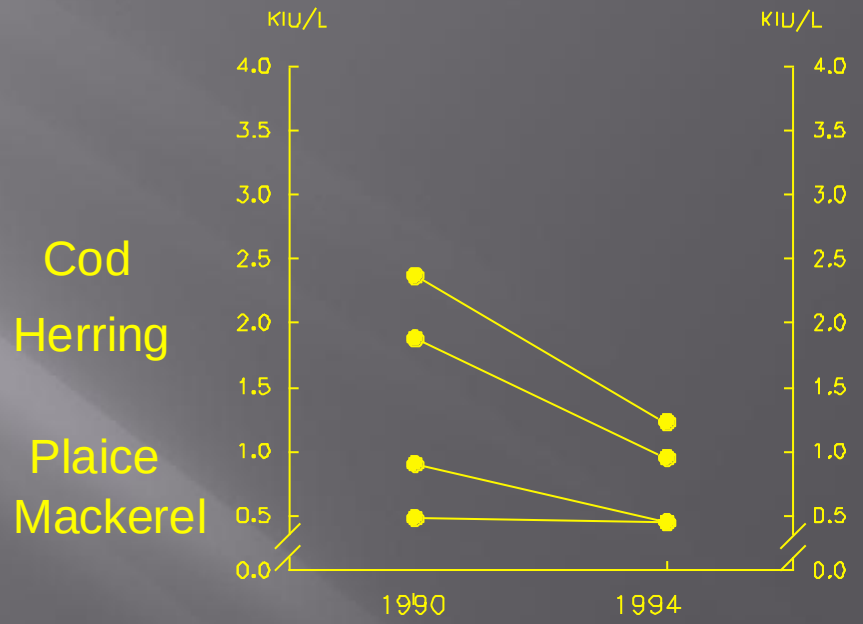
Immunological regulation of the IgE production

Levels of serum IgE in a non-allergic population



Natural history of specific IgE



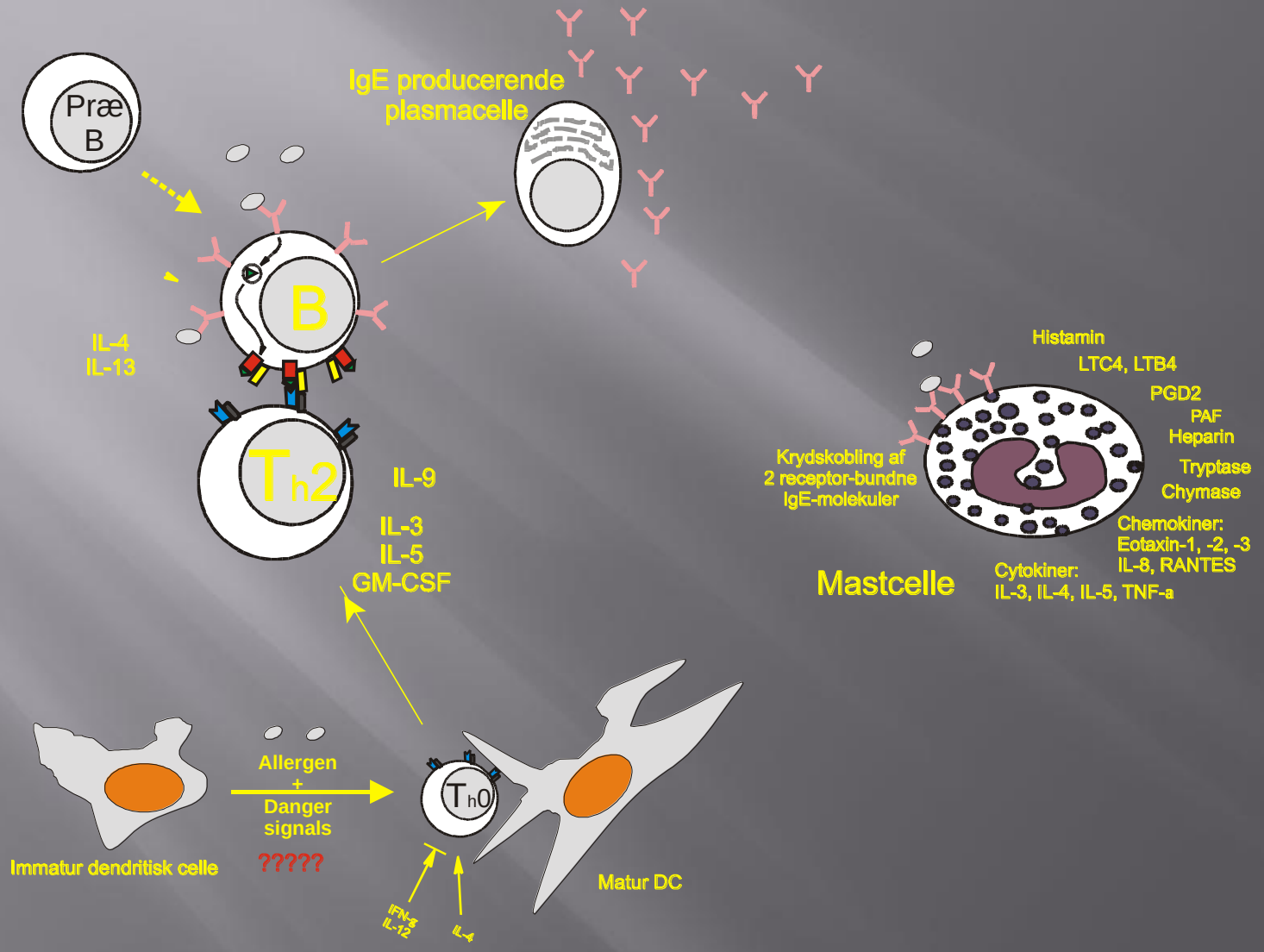


Female, age: 33
Last exposure to codfish in 1970. SPT positive.
Reponse to challenge: Asthma

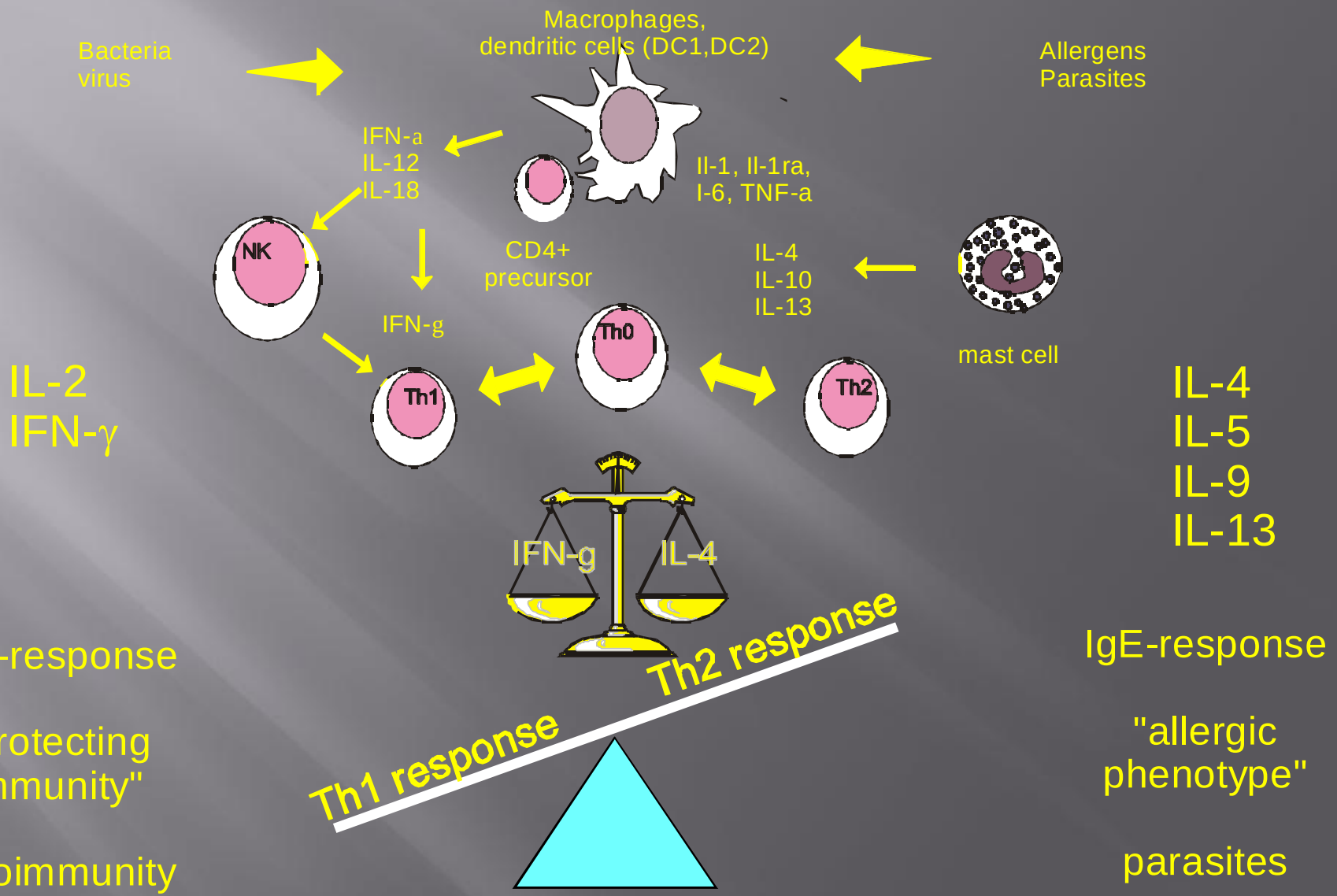
Male, age: 26
Last exposure to codfish in 1988. SPT positive.
Reponse to challenge: Asthma + G.I. symptoms

Data from TK Hansen

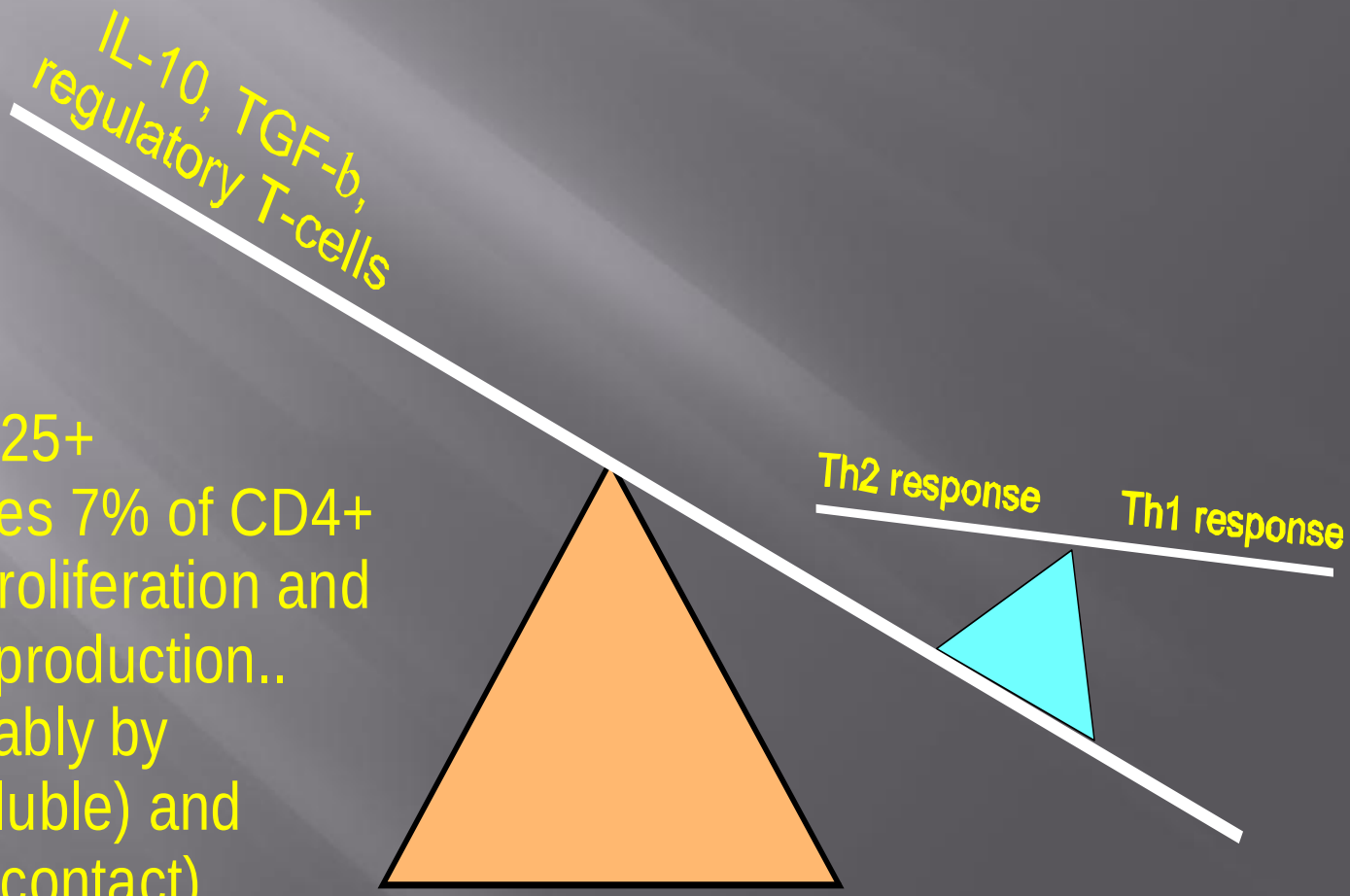
Sensitization phase of the allergic immune response



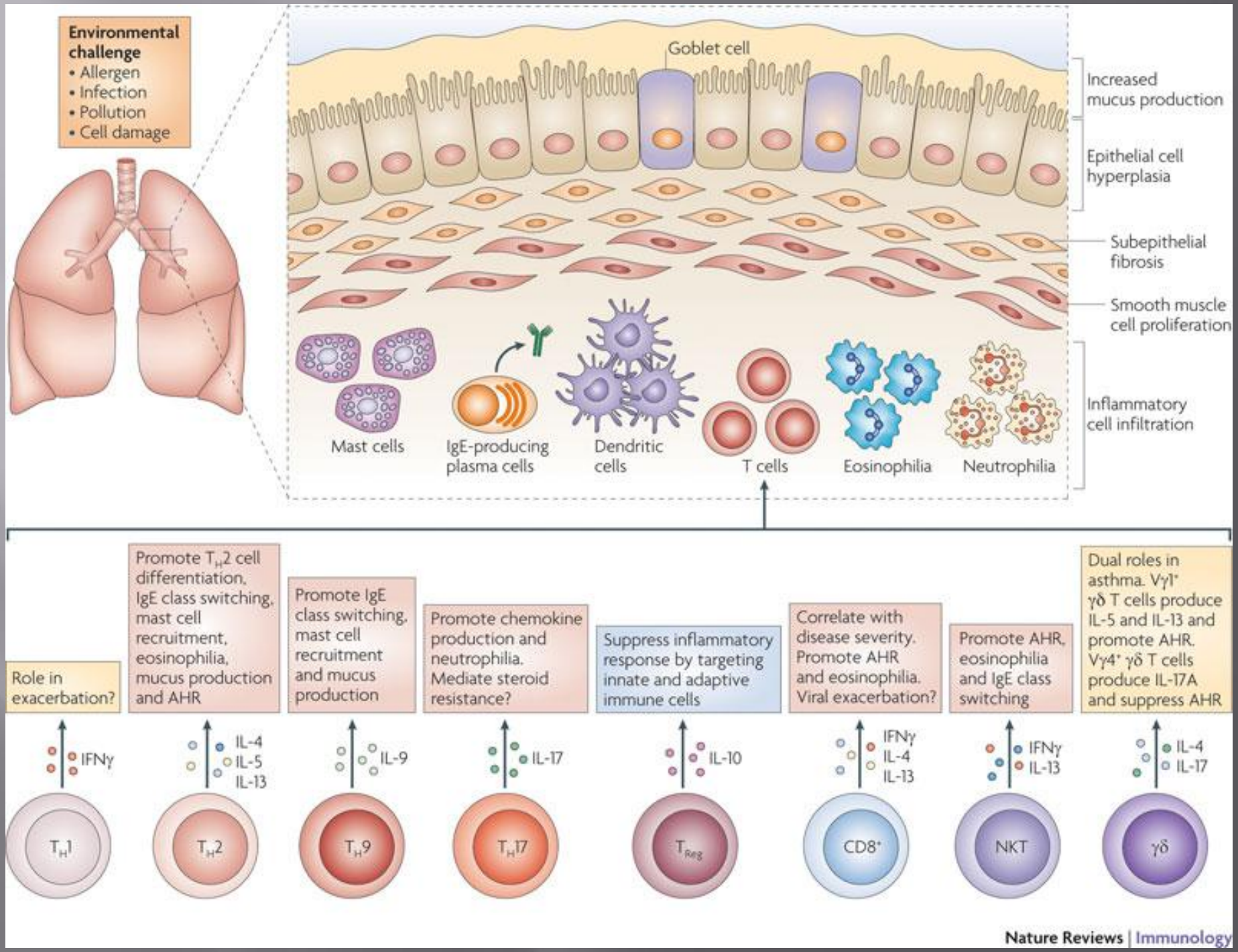
Differentiation of CD4+ T-cells into Th1 or Th2 cells



CD4+ T-cells can be regulatory or inflammatory cells

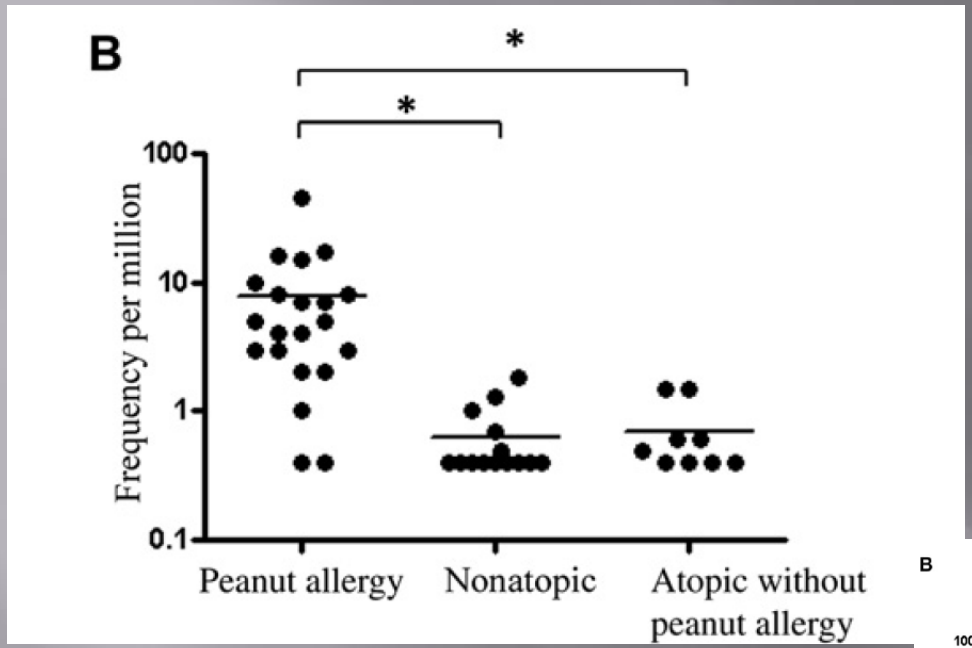


Treg:
CD4+CD25+
Constitutes 7% of CD4+
Inhibits proliferation and cytokine production..
..presumably by
IL-10 (soluble) and
CTLA-4 (contact)

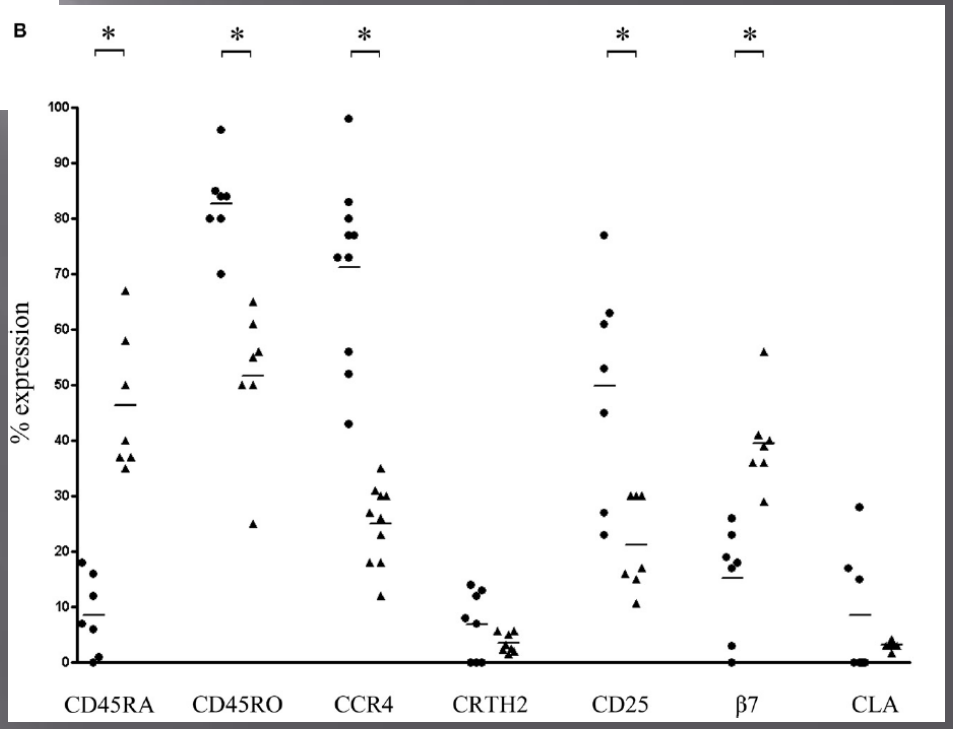

Environmental challenge
• Allergen
• Infection
• Pollution
• Cell damage
Goblet cell
Increased mucus production
Epithelial cell hyperplasia
Subepithelial fibrosis
Smooth muscle cell proliferation
Inflammatory cell infiltration
Mast cells
IgE-producing plasma cells
Dendritic cells
T cells
Eosinophilia
Neutrophilia
Role in exacerbation?
Promote T_H2 cell differentiation, IgE class switching, mast cell recruitment, eosinophilia, mucus production and AHR
Promote IgE class switching, mast cell recruitment and mucus production
Promote chemokine production and neutrophilia. Mediate steroid resistance?
Suppress inflammatory response by targeting innate and adaptive immune cells
Correlate with disease severity. Promote AHR and eosinophilia. Viral exacerbation?
Promote AHR, eosinophilia and IgE class switching
Dual roles in asthma. Vγ1+ γδ T cells produce IL-5 and IL-13 and promote AHR. Vγ4+ γδ T cells produce IL-17A and suppress AHR
IFNγ
IL-4
IL-5
IL-13
IL-9
IL-17
IL-10
IFNγ
IL-4
IL-13
IFNγ
IL-13
IL-4
IL-17
T_H1
T_H2
T_H9
T_H17
T_{Reg}
CD8+
NKT
γδ

Studies of food-specific T-cell in human food allergy

Peanut specific T-cells detected by tetramers



Specific T-cells vs. total T-cells



DeLong, JACI 2011

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

Allergy

ORIGINAL ARTICLE EXPERIMENTAL ALLERGY AND IMMUNOLOGY

Cutaneous lymphocyte antigen and α4β7 T-lymphocyte responses are associated with peanut allergy and tolerance in children

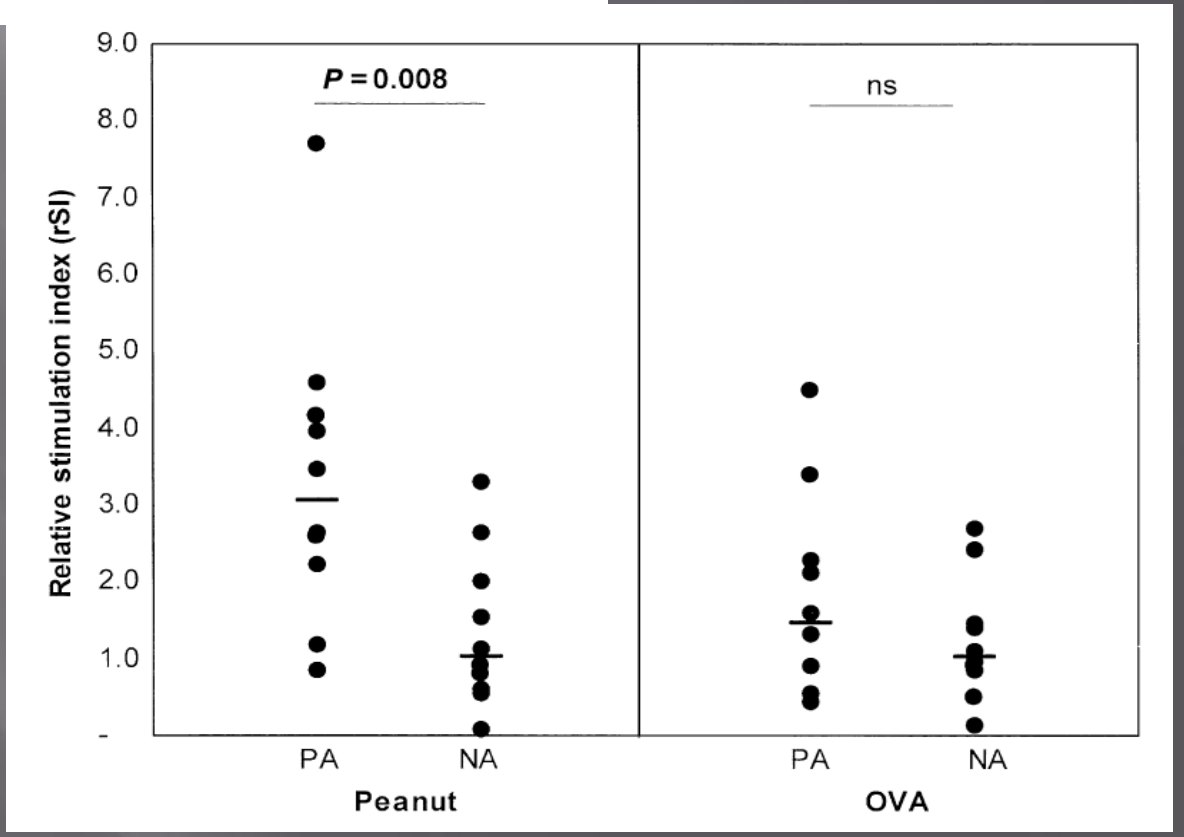
S. M. H. Chan[1,2], V. Turcanu[1], A. C. Stephens[1], A. T. Fox[1], A. P. Grieve[3,4] & G. Lack[1]

[1]King's College London, King's Health Partners, Asthma-UK Centre in Allergic Mechanisms of Asthma, Department of Asthma, Allergy and Respiratory Science, Guy's Hospital, London, UK; [2]National Institute for Health Research (NIHR), Biomedical Research Centre, Guy's and St. Thomas' NHS Foundation Trust, London, UK; [3]King's College London, Primary Care and Public Health Sciences, Guy's Hospital, London, UK; [4]AptivSolutions, Köln, Germany

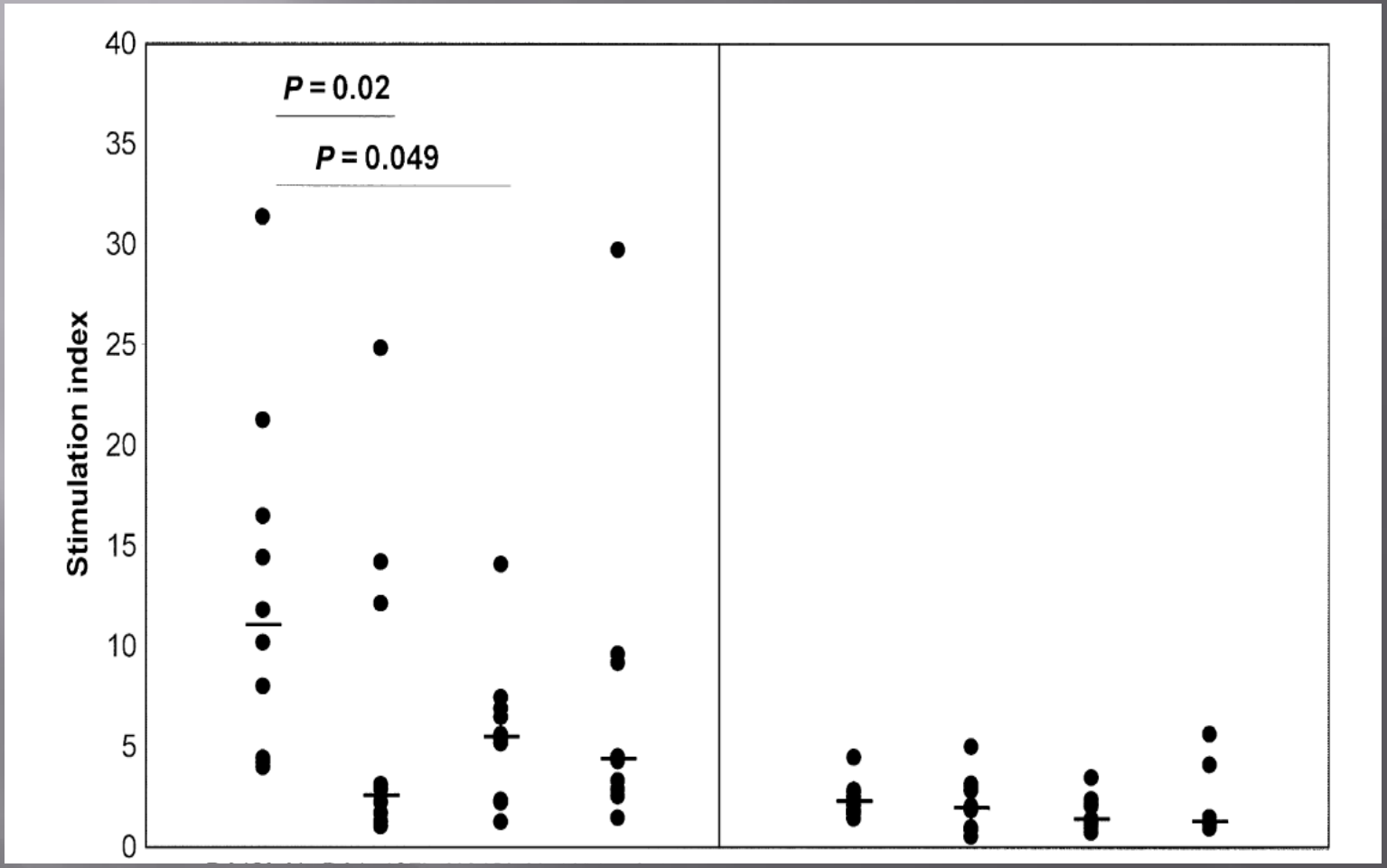
PBMCs from two groups were tested:

Peanut allergic, egg tolerant children (PA)

Peanut and egg tolerant children (NA)



Peanut-specific response dominated by skin-homing T-lymphocytes



Chan et al. Allergy 2012

Candidate genes for allergic diseases and their function

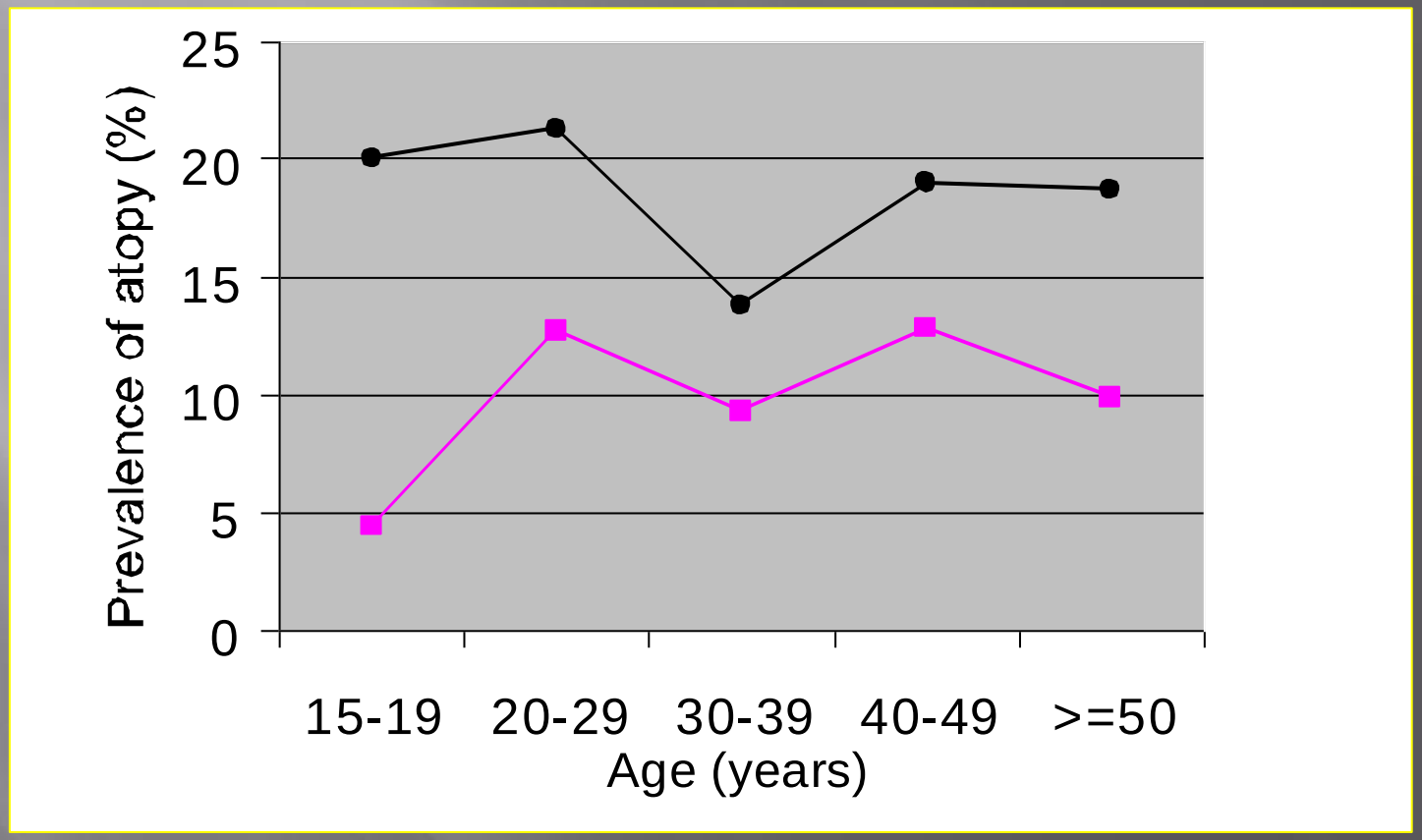
Chromosome	Candidate gene	Function
1p31.2	IL-12 receptors beta2 chain	Signal transducer of IL-12
2q33	CD28	Co-stimulator in T-cell activation
	CTLA-4	Co-stimulator in T-cell activation
3p24.2-p22	CC chemokine receptor	Signal transducer of chemokine
3q27	BCL6	Repression of Stat6-activated transcription
5q31	IL-4	Differentiation of Th2 cells/induction of IgE production
	IL-5	Eosinophils growth and activation/Promotion of IgE production
	IL-9	Mast cell growth factor
	IL-13	Induction of IgE production
5q31-33	IL-12 p40	Inhibition of Th2 activity
5q33	T-cell membrane proteins (TIMs)	Induction of IL-4 and IL-13 production
5q35	Leukotriene C4 synthase	Synthesis of leukotriene
6p21	Major histocompatibility complex (HLA)	Presentation of antigenic peptide
	Tumour necrosis factors	Induction of inflammation
	Transports involved in antigen processing and presentation (TAP-1 and TAP-2)	Transportation of antigenic peptide
7p15	IL-6	Promotion of IgE production
	T-cell receptor gamma chain	Recognition of antigen
7q35	T-cell receptor beta chain	Recognition of antigen
9q34	Complement factor 5	Induction of IL-12 production
10p14	GATA3	Transcription factor in Th2 differentiation
11q13	FcepsilonRI beta subunit	Amplifier of IgE signalling
12q13-14	STAT6	Transcription factor in IL-4 signalling
12q14	Stem cell factor	Mast cell growth factor
12q21	IFN-gamma	Inhibition of Th2 activity/Inhibition of IgE isotype classwitch
12q22	Leukotriene A4 hydrolase	Synthesis of leukotriene
14q11.2-q13	T-cell receptor alpha/delta chain	Recognition of antigen
16p12	IL-4 receptor alpha chain	Signal transducer of IL-4
17p11	CC chemokine	Recruitment and activation of inflammatory cells
19q13.3	Complement factor 5a receptor	Induction of IL-12 production
Xq13	IL-13 receptor alpha1/alpha2 chain	Signal transducer of IL-13

Toda, Masako & Ono, Santa Jeremy. Genomics and proteomics of allergic disease. Immunology 106 (1), 1-10.

Sensibilisering i Grønland

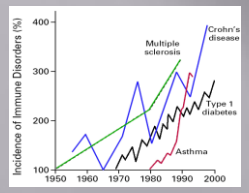
Raske:
- sensibiliseret
- symptomer

Sensibiliseret (eller allergisk)



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)

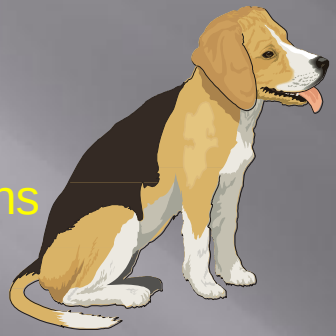
The Increasing Incidence of Immune Regulatory Disorders

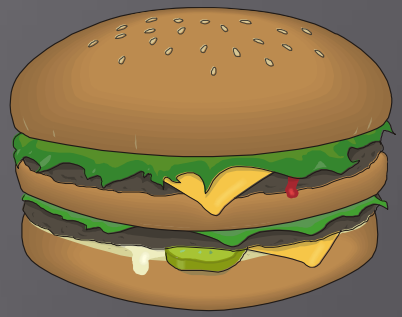


Bach J-F., (2002)
N.Engl.J.Med. 347:911-920

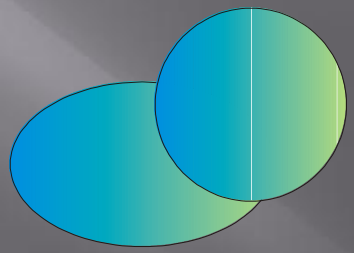
The allergens - terminology

Allergenic materials
- the sources of allergens

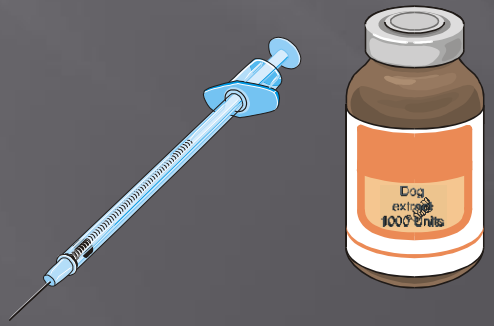




Allergens
- IgE-binding antigens
- normally proteins



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?

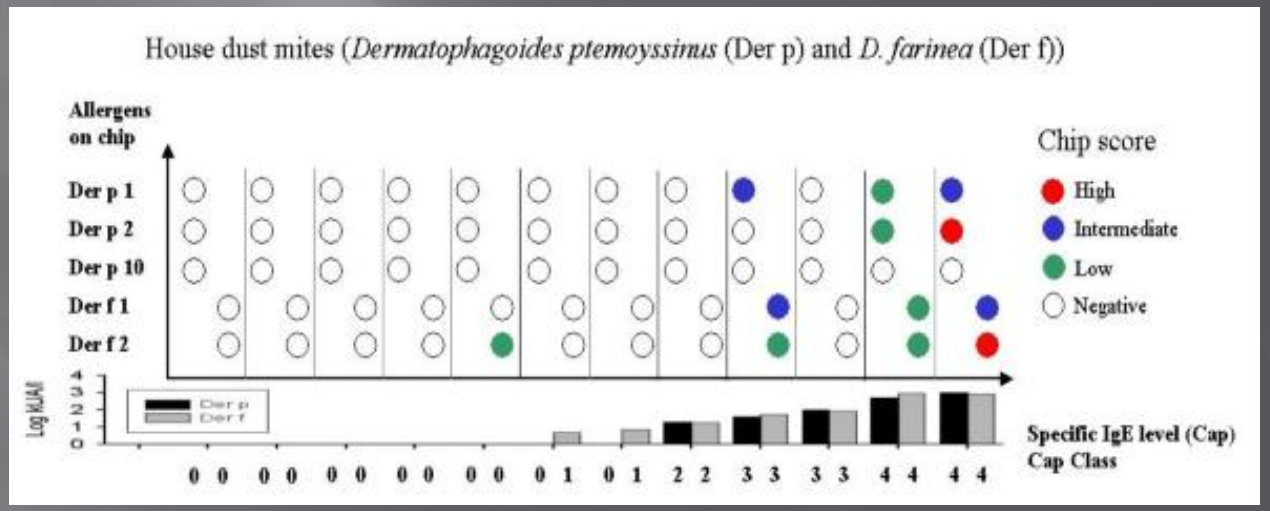
New allergenic sources due to climate changes?

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!

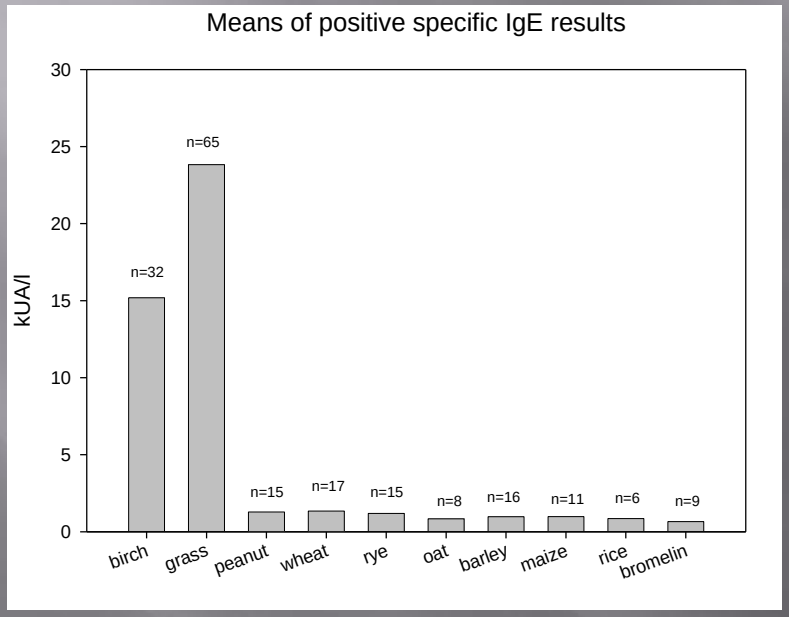
Example: Food allergy - cross-reacting foods

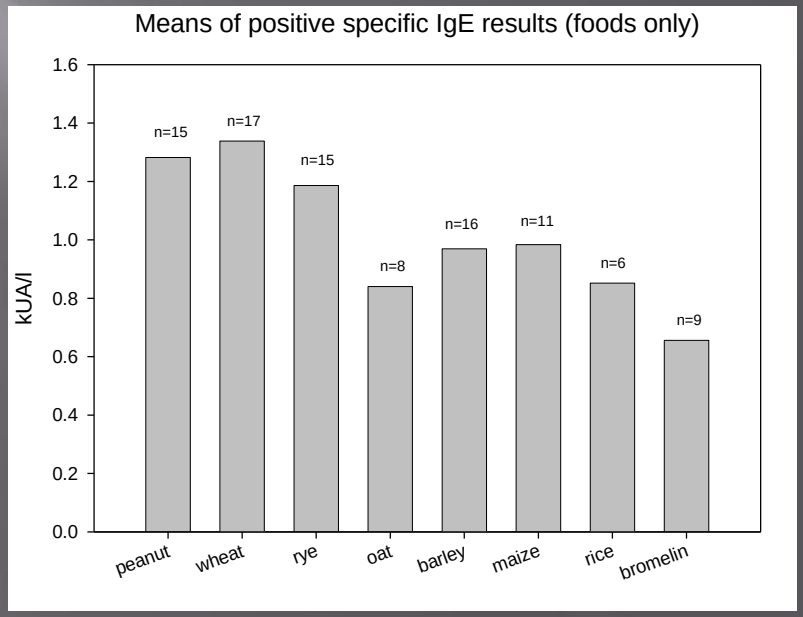
Food	Crossreaction
Cow's milk	Goat's milk, mare's milk, sheep's milk
Hen's egg	Eggs from goose, turkey, duck. Chicken meat. Bird feathers.
Codfish	Plaice, mackerel, herring other fishes
Peanut X)	Soy, green bean, pea
Shrimp	Crab, crayfish, lobster
Birch crossreacting foods	Hazelnuts, apple, potato, carrot, 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.

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