Food Allergy
Introduction, Etiology, and Mechanisms

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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

Adverse reactions to food

- Aversion
  - Food allergy
    - IgE-mediated food allergy
      - Classical food allergy
    - Non-IgE-mediated food allergy
      - Inhalation-cross-reactive food allergy
  - Food hypersensitivity
    - Non-allergic food hypersensitivity (intolerance)
    - Errors of metabolism (inborn or acquired)
  - Food poisonings and/or infections (toxic or microbial)

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

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


Allergy 59:690-7; 2004

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

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

Children < 3 y: open challenges

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

Pollen-related OAS: only in selected cases

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
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 communications¹ 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.¹⁰ 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 eggs, 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 24 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.

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

- Allergen, i.e., a soluble, environmental antigen
- Helmint antigens

Immune response

- IgE

Eliciting mechanism

- FcεRI-mediated activation of mastcells or basophils

Initial cellular processes

- Degranulation with release of preformed mediators
- Release of lipid mediators
- Cyto & chemokine synthesis
- Receptor-mediated (histamine, leukotriene, prostaglandin) activation of smooth muscle vessels, glands

Disease examples

- Anaphylaxis
- Acute asthma

Smooth muscle contraction
- Oedema formation
- Mucus hypersecretion
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.
Response to challenge: Asthma

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

Data from TK Hansen
Sensitization phase of the allergic immune response

Præ B

Th0

Allergen
+
Danger signals

IgE producerende plasmacelle

IL-4
IL-13

IL-9
IL-3
IL-5
GM-CSF

Mastcelle

Histamin
LTC4, LTB4
PGD2
PAF
Heparin
Tryptase
Chymase
Chemokin:
Eotaxin-1, -2, -3
IL-8, RANTES
Cytokiner:
IL-3, IL-4, IL-5, TNF-a

Immatur dendritisk celle

Allergen
Danger signals

Th0

Matur DC

IL-12

Præ B

B

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

- **Bacteria**
  - IFN-α
  - IL-12
  - IL-18

- **Virus**
  - IFN-γ

- **Macrophages, dendritic cells (DC1,DC2)**
  - IL-1, IL-1ra, IL-6, TNF-α
  - IL-4
  - IL-10
  - IL-13

- **NK cell**
  - IFN-γ

- **CD4+ precursor**
  - IL-2
  - IL-4
  - IL-5
  - IL-9
  - IL-13

- **Th1 cell**
  - IFN-γ

- **Th0 cell**
  - IL-4
  - IL-12
  - IL-18

- **Th2 cell**
  - IL-4
  - IL-13

- **Mast cell**
  - IL-4
  - IL-5
  - IL-9
  - IL-13

IgG-response
- "protecting immunity"
- autoimmunity

IgE-response
- "allergic phenotype"
- parasites

**Th1 response**

**Th2 response**
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)
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
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

<table>
<thead>
<tr>
<th>Chromosome</th>
<th>Candidate gene</th>
<th>Function</th>
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<tbody>
<tr>
<td>1p31.2</td>
<td>IL-12 receptors beta2 chain</td>
<td>Signal transducer of IL-12</td>
</tr>
<tr>
<td>2p33</td>
<td>CD28</td>
<td>Co-stimulator in T-cell activation</td>
</tr>
<tr>
<td>2q33</td>
<td>CTLA-4</td>
<td>Co-stimulator in T-cell activation</td>
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<td>3p24.2-p22</td>
<td>CC chemokine receptor</td>
<td>Signal transducer of chemokine</td>
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<tr>
<td>3p27</td>
<td>BCL6</td>
<td>Repression of Stat6-activated transcription</td>
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<tr>
<td>3q31</td>
<td>IL-4</td>
<td>Differentiation of Th2 cells/induction of IgE production</td>
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<tr>
<td>3q32</td>
<td>IL-5</td>
<td>Eosinophils growth and activation/Promotion of IgE production</td>
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<td>3q33</td>
<td>IL-9</td>
<td>Mast cell growth factor</td>
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<tr>
<td>3q31-33</td>
<td>IL-13</td>
<td>Induction of IgE production</td>
</tr>
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<td>3q33</td>
<td>IL-12 p40</td>
<td>Inhibition of Th2 activity</td>
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<td>5q31</td>
<td>T-cell membrane proteins (TIMs)</td>
<td>Induction of IL-4 and IL-13 production</td>
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<td>5q35</td>
<td>Leukotriene C4 synthase</td>
<td>Synthesis of leukotriene</td>
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<tr>
<td>6p21</td>
<td>Major histocompatibility complex (HLA)</td>
<td>Presentation of antigenic peptide</td>
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<td>6p21</td>
<td>Tumour necrosis factors</td>
<td>Induction of inflammation</td>
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<tr>
<td>7p15</td>
<td>IL-6</td>
<td>Transportation of antigenic peptide</td>
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<td>7q35</td>
<td>T-cell receptor gamma chain</td>
<td>Promotion of IgE production</td>
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<tr>
<td>9q34</td>
<td>Complement factor 5</td>
<td>Recognition of antigen</td>
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<td>10p14</td>
<td>GATA3</td>
<td>Induction of IL-12 production</td>
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<tr>
<td>11q13</td>
<td>FcepsilonRI beta subunit</td>
<td>Amplifier of IgE signalling</td>
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<tr>
<td>12q13-14</td>
<td>STAT6</td>
<td>Transcription factor in IL-4 signalling</td>
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<tr>
<td>12q14</td>
<td>Stem cell factor</td>
<td>Mast cell growth factor</td>
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<tr>
<td>12q21</td>
<td>IFN-gamma</td>
<td>Inhibition of Th2 activity/Inhibition of IgE isotype classswitch</td>
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<tr>
<td>12q22</td>
<td>Leukotriene A4 hydrolase</td>
<td>Synthesis of leukotriene</td>
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<td>14q11.2-q13</td>
<td>T-cell receptor alpha/delta chain</td>
<td>Recognition of antigen</td>
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<td>16p12</td>
<td>IL-4 receptor alpha chain</td>
<td>Signal transducer of IL-4</td>
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<td>17p11</td>
<td>CC chemokine</td>
<td>Recruitment and activation of inflammatory cells</td>
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<td>19q13.3</td>
<td>Complement factor 5a receptor</td>
<td>Induction of IL-12 production</td>
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<td>Xq13</td>
<td>IL-13 receptor alpha1/alpha2 chain</td>
<td>Signal transducer of IL-13</td>
</tr>
</tbody>
</table>

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

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 catalogue 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
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 spectrometry 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

<table>
<thead>
<tr>
<th>Year</th>
<th>Unique sequences</th>
<th>Homologues, isoforms etc.</th>
<th>Total sequences</th>
<th>New</th>
<th>%New</th>
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<tbody>
<tr>
<td>1985</td>
<td>12</td>
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<td>1990</td>
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<td>2005</td>
<td>185</td>
<td>900</td>
<td>1085</td>
<td>5</td>
<td>0.5</td>
</tr>
</tbody>
</table>
### 3. Identification of cross-reactive patterns

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

### Example: Food allergy - cross-reacting foods

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

65 grass-pollen allergics who tolerate 25 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 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.
European Academy of Allergy and Clinical Immunology
7 – 11 June 2014
Copenhagen, Denmark

EAACI Congress 2014

www.eaaci2014.com

Abstract Submission Deadline: 15 January 2014