50 år med IgE

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Some allergy history highlights

1870ies  **Blackley**: skin tests, nasal provocation tests, pollen counts

1911   **Noon**: Allergen Specific Immune Therapy

1919  **Ramirez**: horse dander allergy asthma via blood transfusion

1921  **Prausnitz & Küstner**: passive transfer of positive skin test to fish
Reagins belong to $\gamma$A globulins

- Augustin R, Hayward BJ. *Immunology* 1960;3:45-73
Blocking of Prausnitz-Küstner sensitization with reagin by ‘A chain’ of human γ1A-globulin

K. Ishizaka, T. Ishizaka & E.M. Hathorn.

“Normal human γ1A-globulin blocked passive sensitization of non-allergic human skin with reagin. The blocking ability of the protein remained after reduction and alkylation. It was also indicated that the blocking ability was associated with A chain rather than B chain in γ1A-globulin molecules”

Immunochemistry 1964;1:197-207.
Immunelectrophoresis of serum ND, June 1965

Johansson and Bennich, *Immunology* 1967;13:381
Properties of IgND as of 1967

Mol. weight, sedimentation constant, unique antigens  
Johansson & Bennich, Immunology 13:381, 1967

Dose-response blocking of PK-reaction  
Stanworth, Humphrey, Bennich & Johansson,  
The Lancet ii:330, 1967

Increased levels of IgND in atopic allergy  

Allergen-specific anti-IgND antibody by RAST  
Wide, Bennich & Johansson,  
The Lancet ii:1105, 1967
### Data on "reagin", February, 1968

<table>
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<tr>
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<th>$\gamma$E</th>
<th>IgND</th>
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<td>Physico-chemical properties</td>
<td>-</td>
<td>++</td>
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<td>Immunological characteristics</td>
<td>(+)</td>
<td>++</td>
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<tr>
<td>Biological activity</td>
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Immunoglobulin E, a new class of human immunoglobulin*


*Bull. Wld Hlth Org. 1968;38:151

* This memorandum was drafted by the signatories following discussions held at the WHO International Reference Centre for Immunoglobulins in Lausanne, February 1968.
To unge svenske Jahre-prisvinnere

Overrekkelse i Universitetets aula idag
The impact of IgE

Acceptance of ”allergy”
Allergen characterization
*In-vitro* allergy diagnosis
Inflammation of ”atopic allergy”
Immunomodulation of allergy
Asthma

Allergic asthma

IgE-antibody mediated allergic asthma

(Non-IgE antibody mediated allergic asthma)

Non-allergic asthma
IgE-antibody  Lymphocyte  Unknown

Inflammation

Eosinophils-Lymphocytes-Cytokines

Asthma  Rhinitis  Eczema
Allergen, hapten

Low mol. weight ”chemical” immunogenic when linked to carrier

- Carrier, e.g. HSA
- hapten
- epitope

IgE-haptens
  - Isocyanates
  - Formaldehyde
  - Patent Blue V

Lymphocyte-haptens
  - nickel
  - chromium
  - other
Allergy diagnosis

Case history
Skin prick test (SPT)
IgE testing
Allergen provocation
Basophil allergen threshold sensitivity, CD-sens
The hypersensitivity sequence

Allergen → IgE-antibody → Mast cell Basophil → Mediators → Inflammation → Symptoms & Signs

Unknown → ?
Bronchial allergen sensitivity and SPT wheal size

Dahlén, Nopp, Johansson et al. unpublished.
Some non-allergic disorders with raised IgE

- Helminth infestation, e.g. Ascaris, Schistosoma
- Bacterial infections, e.g. Staphylococcal strains containing enterotoxins, so called “super-antigens”, pertussis
- Virus infections, e.g. cytomegal virus (CMV)
- Exposure to air pollutants, e.g. tobacco smoke
- Increased consumption of alcohol
- Certain cough syrups, e.g. pholcodine
- GVHD, Graft Versus Host Disease
The principle of RAST

Insoluble polymer-allergen conjugate + Allergen antibody of the IgE class (reagin) →

\[^{125}\text{I}\text{-labelled antibody to IgE} \] →
The hypersensitivity sequence

Allergen

IgE-antibody

Mast cell
Basophil

Mediators

Inflammation

Unknown

Symptoms & Signs
Mast cell / Basophil triggering

- **Allergen**
- **Anti-IgE**
- **Anti-FcεRI**

- Histamine, Cytokines
- IL4, IL-5 m.m.

- CD63
- CD203c

Basophil
Allergen threshold sensitivity, CD-sens

Nopp et al, Allergy 2006;61:298
CD-sens in asthmatics with a low (left) and a high (right) bronchial hyperreactivity.

(r=0.88; P<0.0001)  
(r=0.38; P<0.3)

Dahlén, Nopp, Johansson, CEA 2011;41:1091
Basophil reactivity and bronchial allergen sensitivity

Dahlén, Nopp, Johansson et al. CEA 2011;41:1091.
CD-sens before (■--■) and after (□--□) washing. ABA is the CD-sens ratio after/before.
CD-sens to Patent Blue V after anaphylaxis

Nopp et al, Allergy 2006;61:298
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- Symptoms & Signs

Unknown
Relation between IgE and airway hyper responsiveness

![Graph showing the relation between serum IgE levels and airway responsiveness.](image)
Sera with high and low percentages of IgE antibodies before and after omalizumab
Omalizumab effect on multiple IgE-sensitization
A 16 year old boy with severe allergic asthma and milk allergy. CD-sens became negative and all symptoms disappeared at double dose Xolair.
Anaphylaxis related to Neuro Muscular Blocking Agents, NMBA

France >1: 6 500
Norway ~1: 5 000
Sweden ~1: 83 000
Denmark ~1:180 000
USA ~1:500 000
Pholcodine (PHO) är monovalent för den allergena epitopen, QAI, medan NMBA, t.ex. suxamethonium, är bivalenta.
PHO-sirap, 1 tesked om dagen, stimulerer en polyklonal IgE syntes

Florvaag et al., Allergy 2006;61:49
Serum-IgE nivåer vid Graft Versus Host Disease

Norwegian cough syrup containing pholcodine

26 March, 2007
EMA and pholcodine

1. The benefits of pholcodine continue to outweigh its risks.
2. No new risks have been identified with pholcodine.
3. Although a cross-sensitization between pholcodine and NMBAs is biologically plausible the available data are weak and not fully consistent.
4. Patients taking pholcodine-containing medicines can continue to do so.
PHO financial turn-over

- Annual PHO production: approx. 6 tons
- One Tuxi-bottle is 200 mg PHO
  i.e. 30 000 000 vials per year
  Over-the-counter price per vial: approx. 10 USD
  i.e. 300 000 000 USD annual turn-over
Beneficial function of IgE?

- Clearance, of airways and GI tract by an "allergic reaction"
- Gatekeeper, immunological surveillance
- Immune protection, helminth defence
- Sensitization potentiation, enhance antibody production