



Karolinska
Institutet

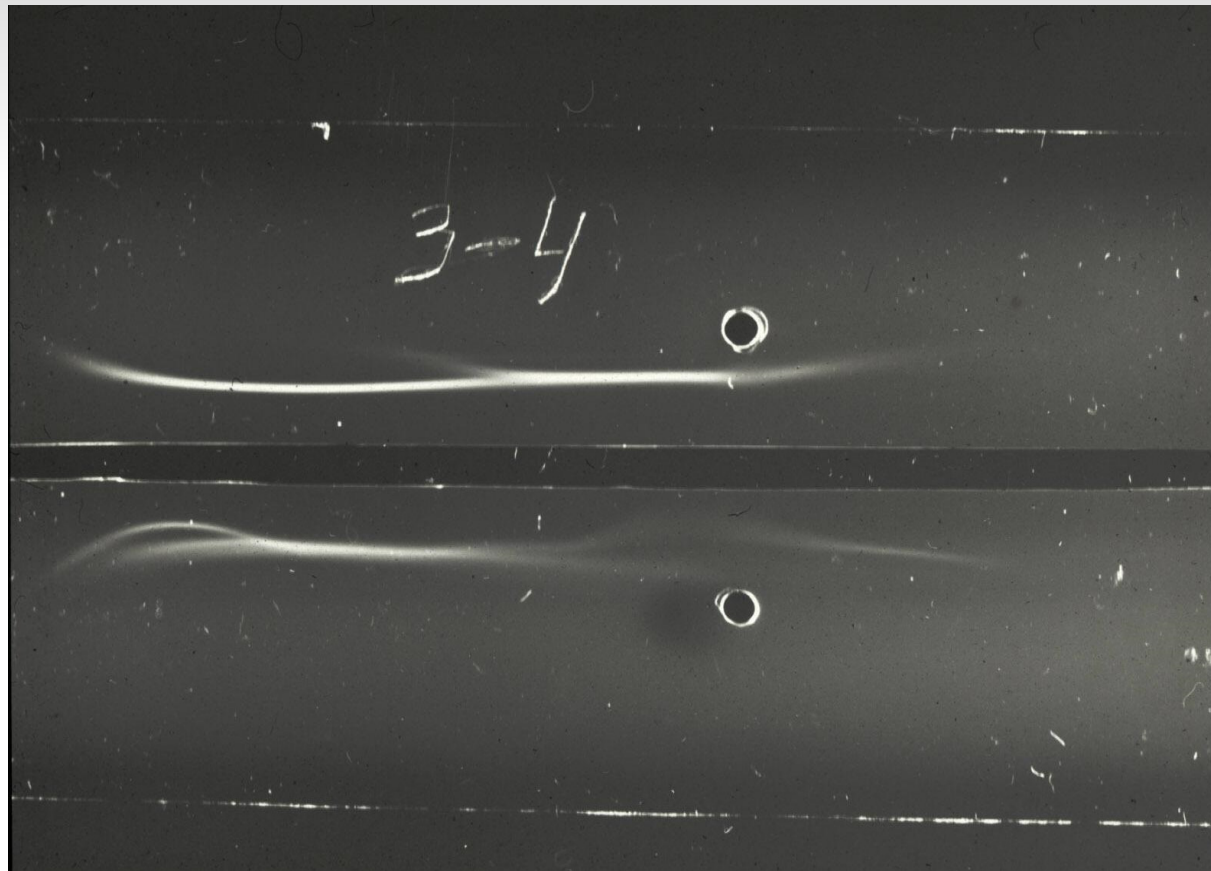
50 år av IgE

En spännande resa

S.G.O. Johansson
Department of Medicine
Immunology and Allergy Unit
Karolinska Institutet

Immunelectrophoresis of serum ND, June 1965

Anti-sera
against →
Igs and LCs



“Normal serum”

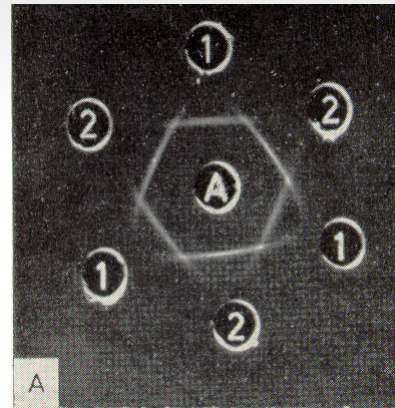
“Serum from ND”



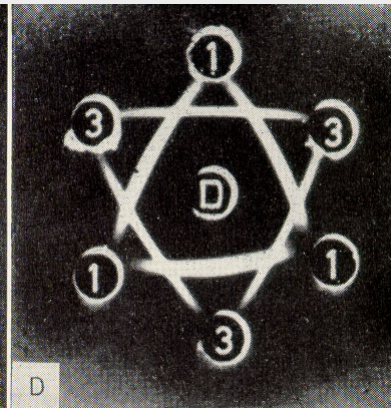
Purified IgND (well 1), IgA (well 2), IgD (well 3), IgG (well 4) and IgM (well 5)

This sera could not be typed (ie, it was not IgM, IgG, IgA or IgD)

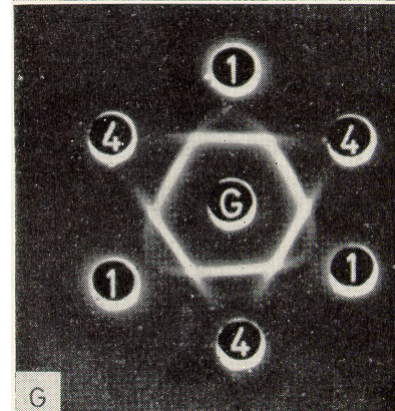
Anti-IgA



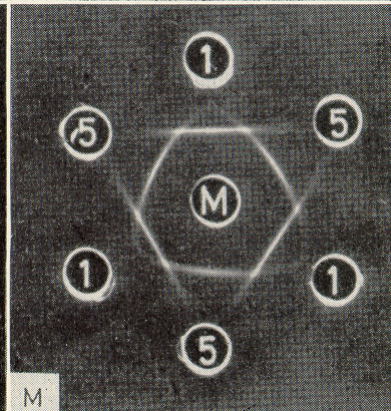
Anti-IgD



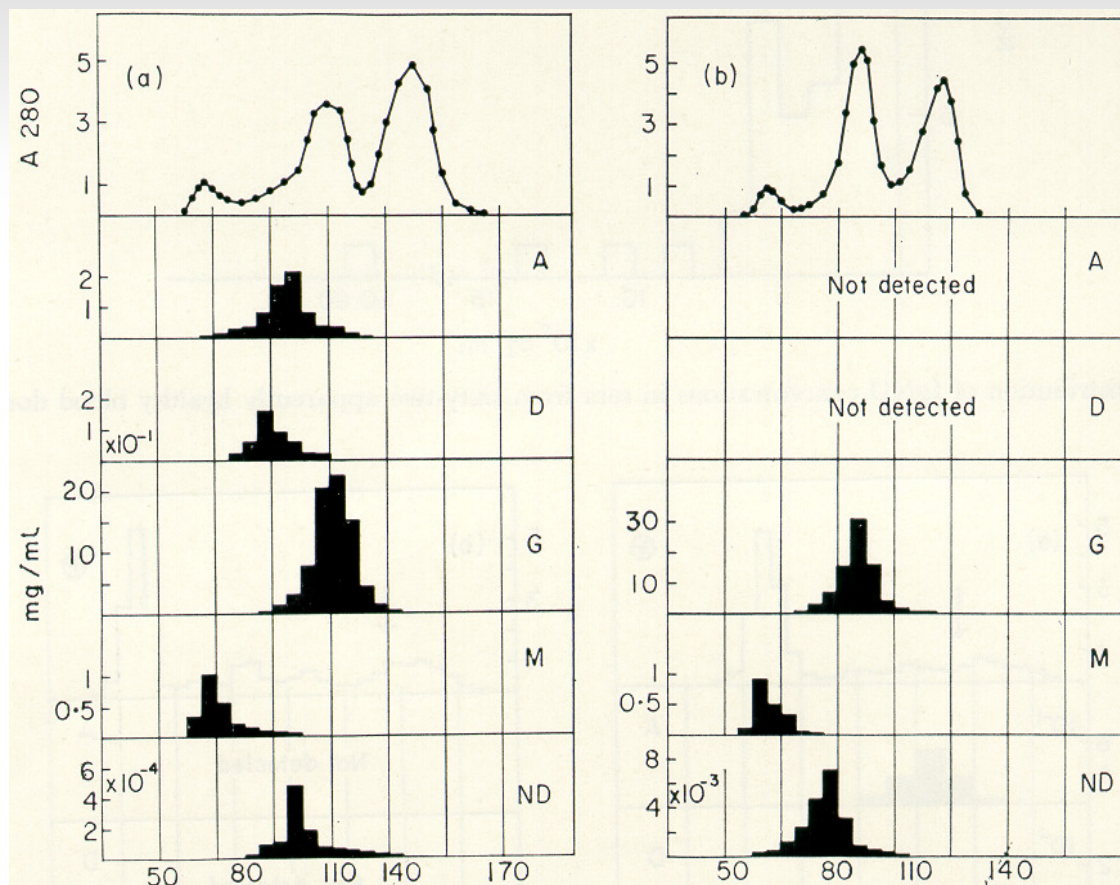
Anti-IgG



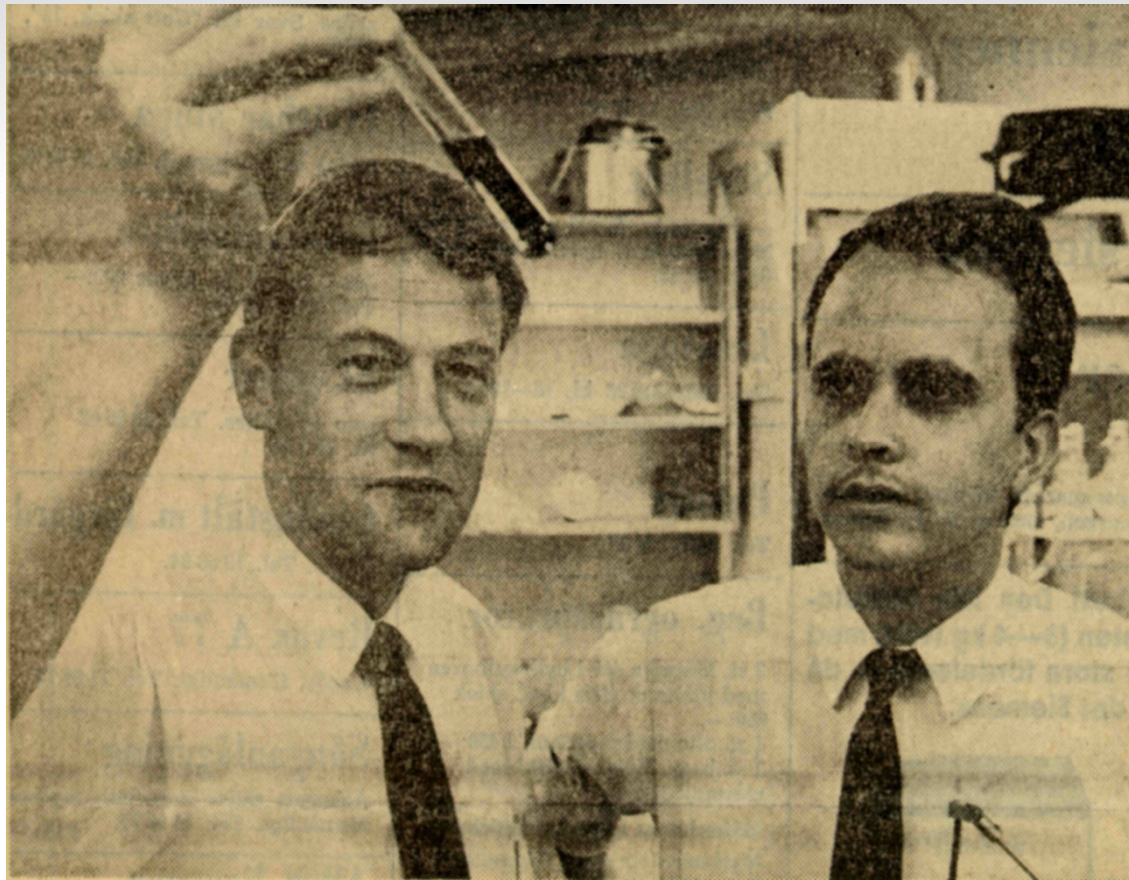
Anti-IgM



Gelfiltration, Sephadex G-200, av ett normalserum och ett utan IgA och IgD



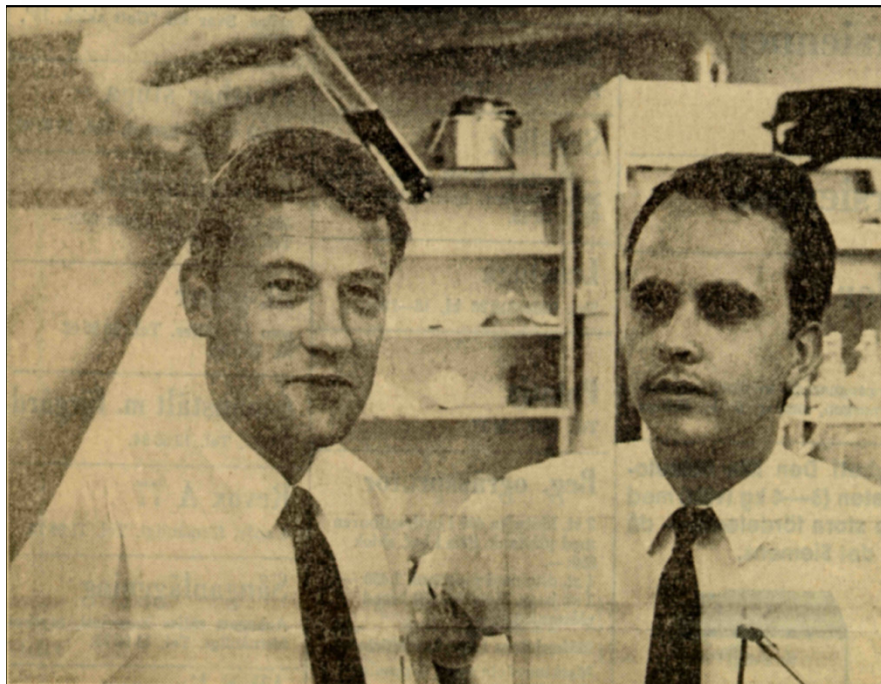
Look! We have discovered IgND!! Or is it IgE?



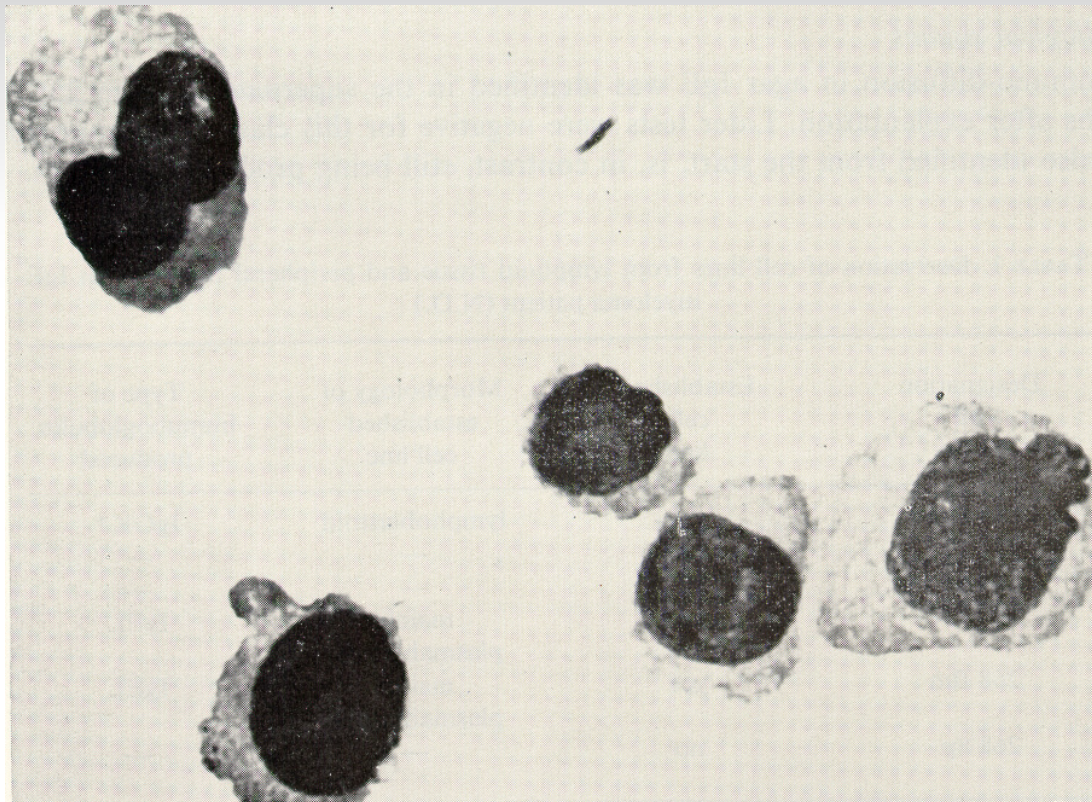
Look! We have discovered IgND!! Or is it IgE?

1967

2017



IgND producing plasma cell line



Nilsson, Bennich, Johansson, Pontén J Clin. Exp. Immunol 1970; 7:477

Några allergi-historiska höjdpunkter

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 γ A globulins

- Augustin R, Hayward BJ. *Immunology* 1960;3:45-73
- Heremans JF, Vaerman JP. *Nature* 1962;193:1091
- Fireman P, Vannier WE, Goodman HC. *J exp. Med* 1963;117:603
- Vaerman, JP, Epstein W, Fudenberg H, Ishizaka K. *Nature* 1964;203:1046

Blocking of Prausnitz-Küstner sensitization with reagin by ‘A chain’ of human $\gamma 1A$ -globulin

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

“Normal human $\gamma 1A$ -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 $\gamma 1A$ -globulin molecules”

Immunochemistry 1964;1:197-207.

The concept of “reagin” 1965

..... “skin-sensitizing antibody is not a single, indivisible molecular species but is present in allergic sera in the form of labile complexes that...may dissociate...into smaller fragments with properties different from those of the intact skin-sensitizing antibody molecule”.

In *“Immunological Diseases”*,
eds. M. Samter & H.L. Alexander,
J. & A. Churchill Ltd, 1965, p. 521.

Blocking of the Prausnitz-Küstner test with IgND and IgG

Test solution	Blocking Ig	PK-weal size, sq mm at 10 min	Idem, at 26 min
1	Saline	64	115
2	IgND, 600 ug/ml	-	-
3	IgND, 60 ug/ml	-	-
4	IgND, 6 ug/ml	12	36
5	IgG, 600 ug/ml	44	113
6	IgG, 60 ug/ml	52	110

Stanworth D et al. The Lancet 1967;ii:330

**Detection of complete and incomplete
antibodies to egg albumins by means of a sheep
red cell-egg albumin antigen unit.**

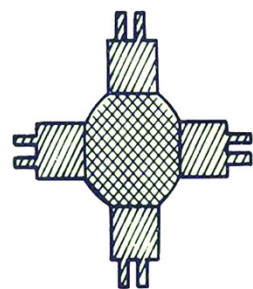
R.R.A. Coombs and Fiset M.L.

Br J Exp Pathol 1954;35:472-7

Radio Allergosorbent Test, RAST

Insoluble polymer-
allergen conjugate

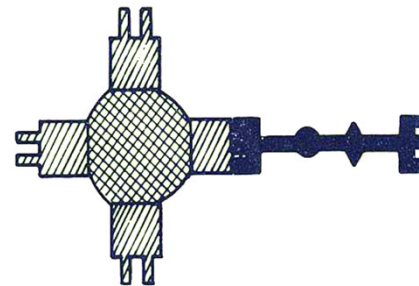
Allergen anti-
body of the
Ig E class
(reagin)



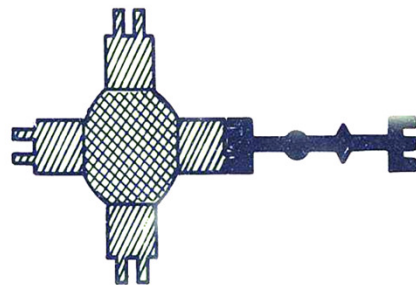
+



→



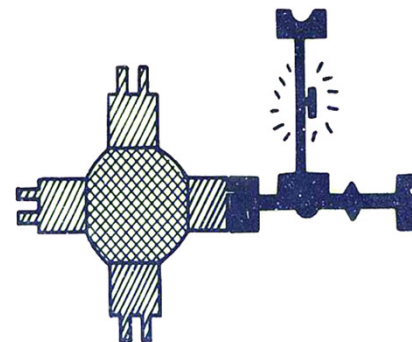
^{125}I -labelled
antibody to IgE



+



→



Wide, Bennich, Johansson, The Lancet 1967;ii:1105

Properties of IgND as of 1967

- **Mol. weight, sedimentation constant, unique antigens**
Johansson & Bennich, Immunology 13:381, 1967
- **Increased levels of IgND in atopic allergy**
Johansson, The Lancet ii:951, 1967
- **Dose-response blocking of PK-reaction**
Stanworth, Humphrey, Bennich & Johansson, The Lancet ii:330, 1967
- **Allergen-specific anti-IgND antibody by RAST**
Wide, Bennich & Johansson, The Lancet ii:1105, 1967

WHO Immunoglobulin Reference Centre, February, 1968



Photo taken by
SGO Johansson

W. Terry D. Rowe D. Stanworth K. Ishizaka H. Bennich

**Data on "reagin"
at the WHO Immunoglobulin Reference
Centre meeting, February, 1968**

	IgND	γE
Physico-chemical properties	++	-
Immunological characteristics	++	(+)
Biological activity	++	+



Karolinska
Institutet

Sverlge

Immunoglobulin E, a new class of human immunoglobulin*

**H.H. Bennich, K. Ishizaka, S.G.O. Johansson,
D.S. Rowe, D.R. Stanworth and W.D. Terry**

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.

Publications on IgE

55 203

**in peer-reviewed publications within
the field of allergy and clinical immunology**

**Web of Science
28 August, 2017**

Immunoglobulins

	IgG	IgM	IgA	IgD	IgE
Heavy chain	γ	μ	α	δ	ϵ
Sed. Constant (S)	7	19	7	7	8
Mol. weight ($\times 10^3$)	150	970	160	180	190
Half-life (days)	21	10	6	3	2
Carbohydrate (%)	2-3	12	7-11	9-14	12
Complement	++	+++	-	-	-
Placental transfer	+	-	-	-	-
Serum conc. (g/L)	10	1.5	2.5	0.03	0.000 05

The impact of IgE

- Acceptance of "allergy"
- Allergen characterization
- Allergy diagnosis
- Inflammation of "atopic allergy"
- Immunomodulation of allergy

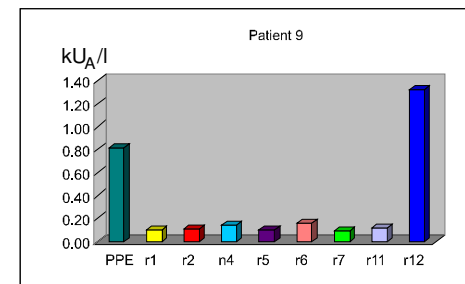
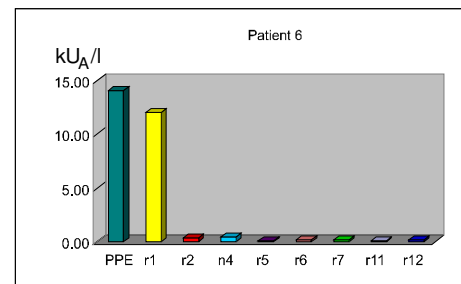
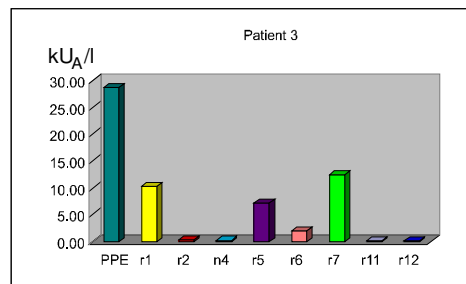
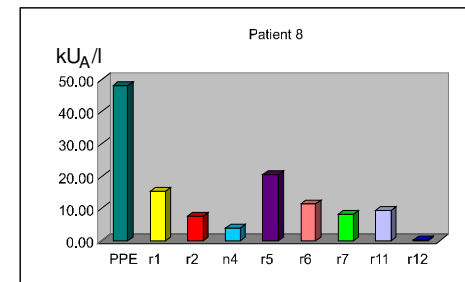
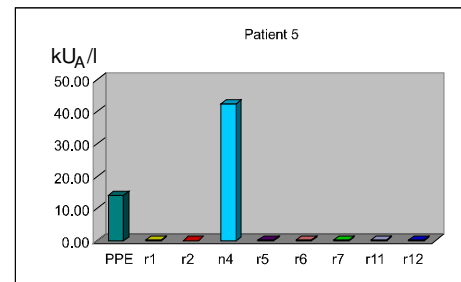
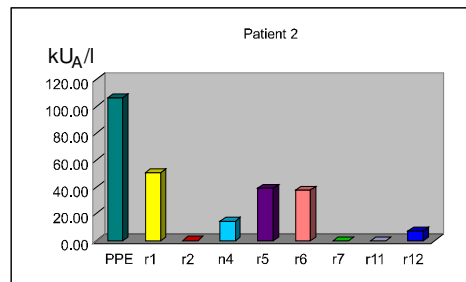
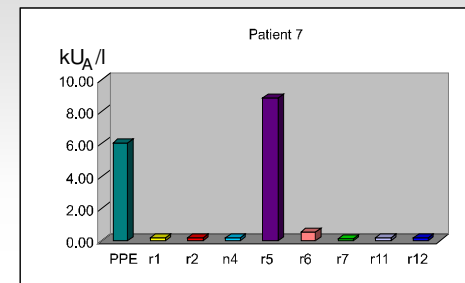
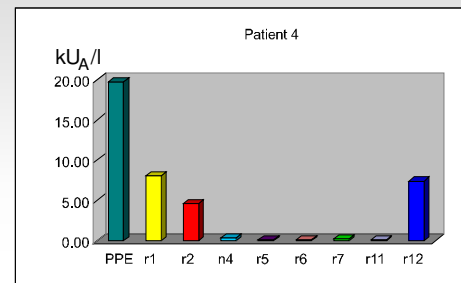
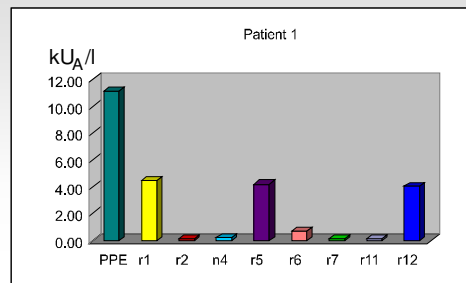




”Kroppen drabbas helt enkelt av en allergisk reaktion”.

**V. Toikkanen, Aftonbladet, 17 januari, 2005
i ett försök att förklara alkoholintoxikation,
s.k. ”baksmälla”.**

IgE sensitization to grass allergens



Allergi diagnos

Anamnes

Skin prick test (SPT)

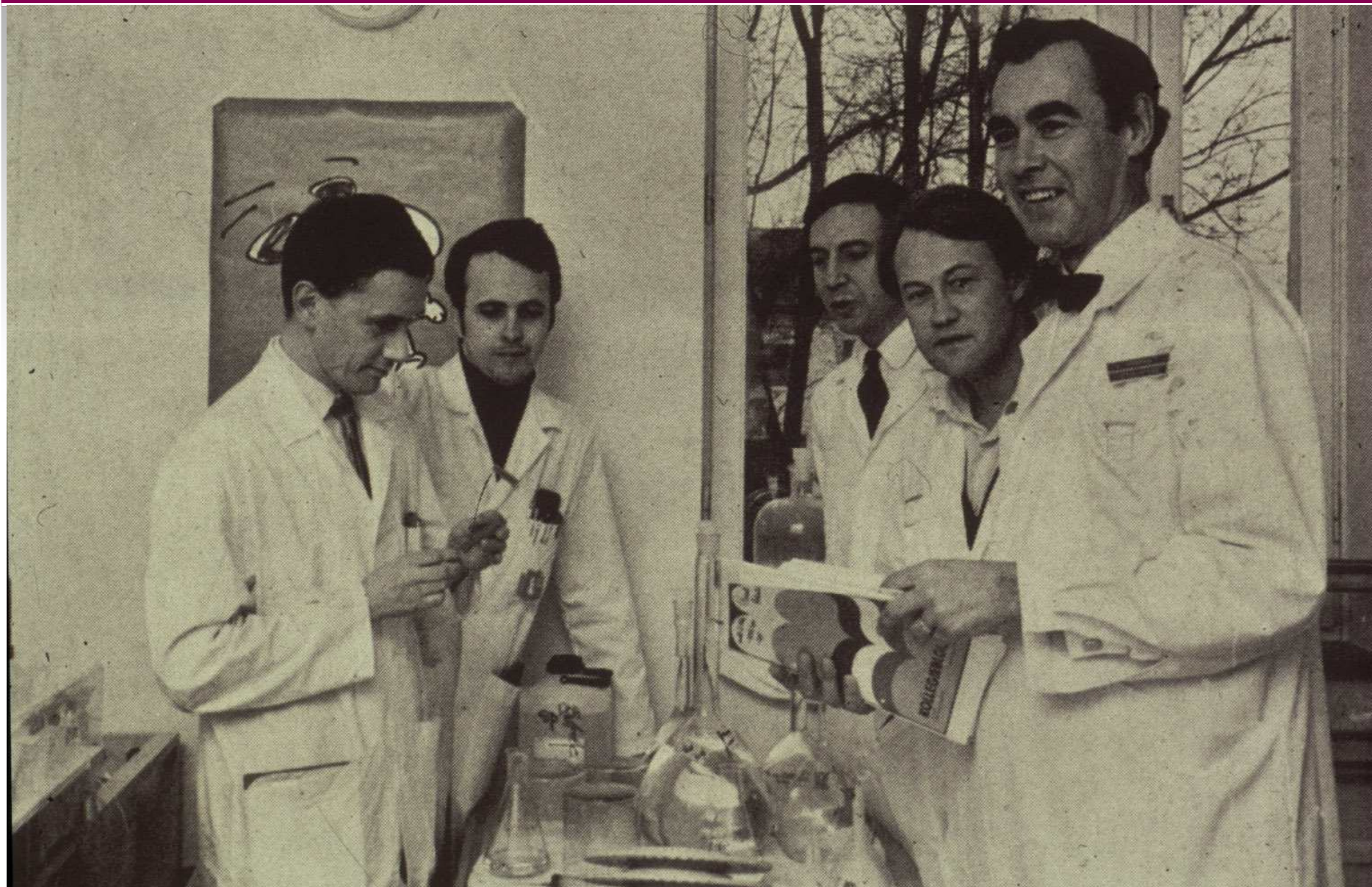
IgE antikropp testning

Allergen-provokation

Basophil allergen threshold sensitivity, CD-sens



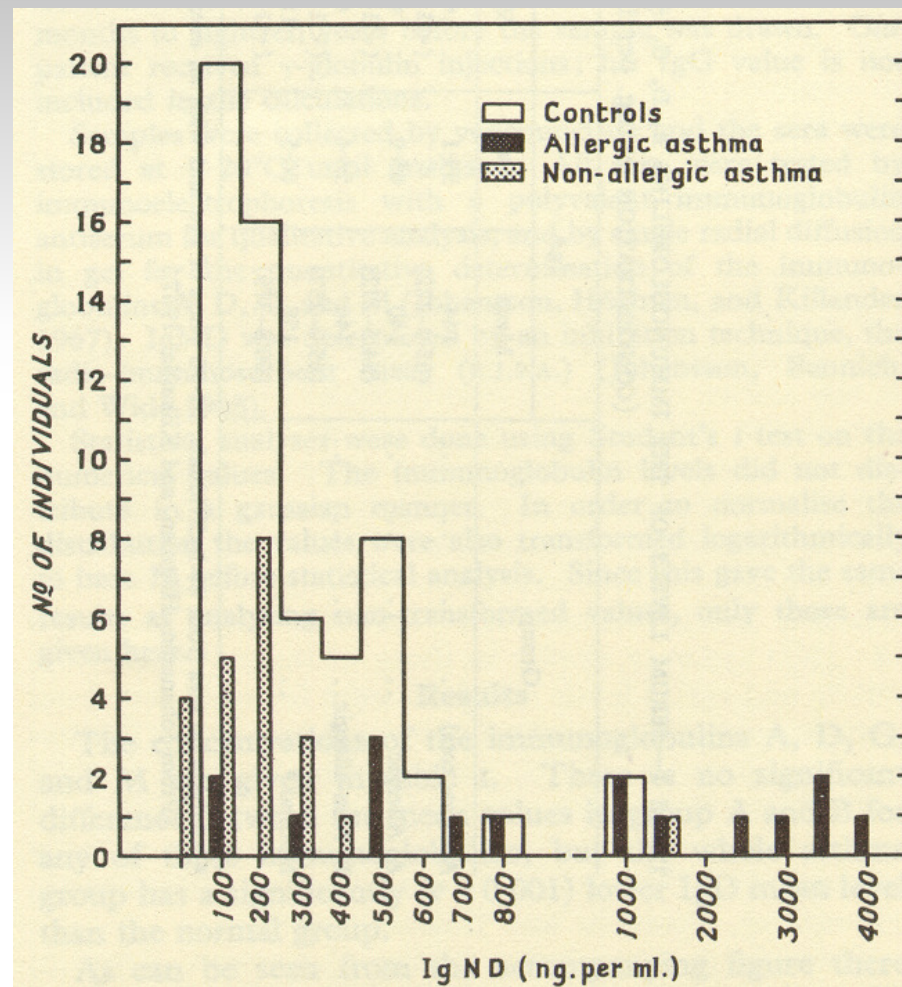
Karolinska
Institutet



Intradermal Skin Testing



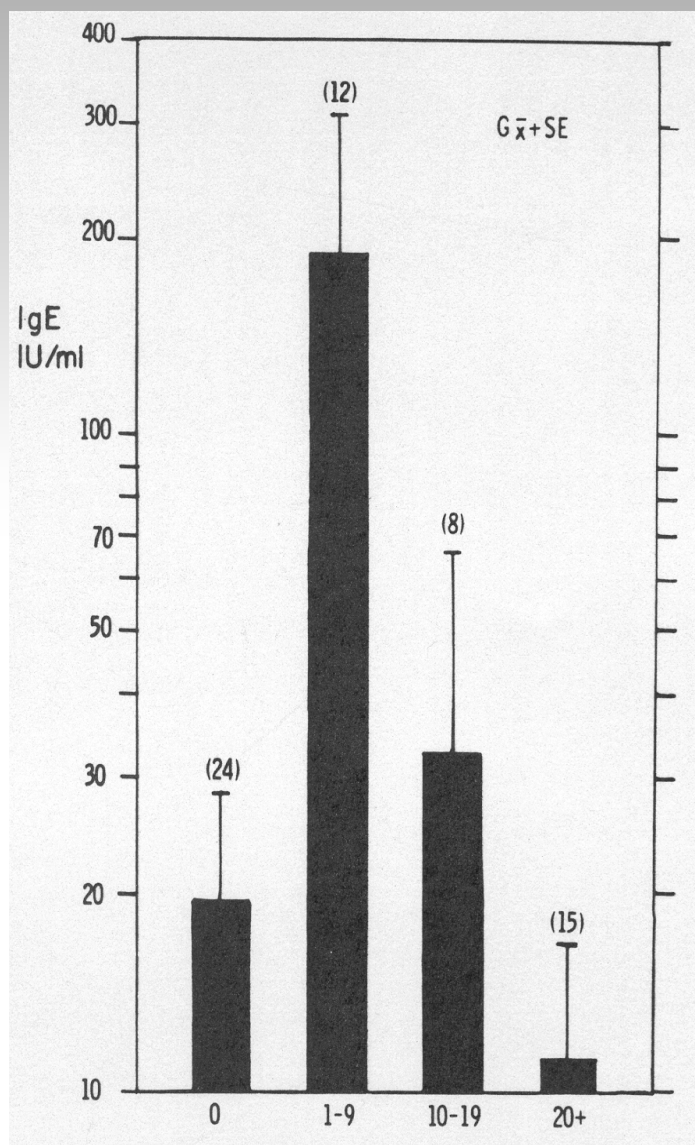
IgND nivåer i serum vid astma



Johansson, S.G.O., The Lancet 1967; ii:951.

Några icke-allergiska tillstånd med förhöjt serum-IgE

- **Helminth infestation, t.ex. Ascaris, Schistosoma**
- **Bakteriella infektioner, t.ex. Staphylococcal stammar som har enterotoxiner, så kallade “super-antigen”, pertussis**
- **Virus infektioner, t.ex. cytomegal virus (CMV)**
- **Exposition för luftföroreningar, t.ex. tobaksrök**
- **Hög konsumption av alkohol**
- **Hostsirap som innehåller folkodin**
- **GVHD, Graft Versus Host Disease**

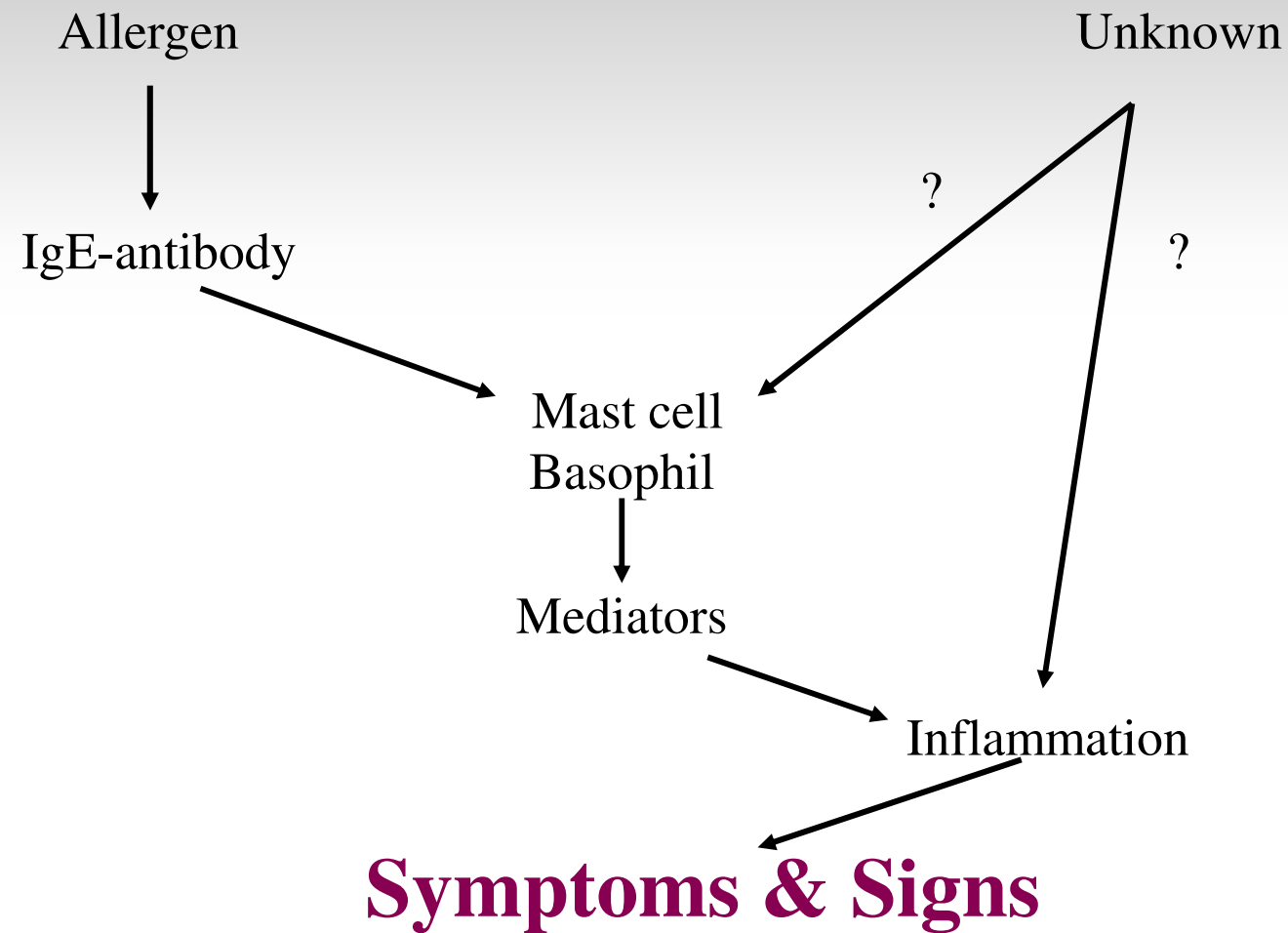


Cigaretter per dag

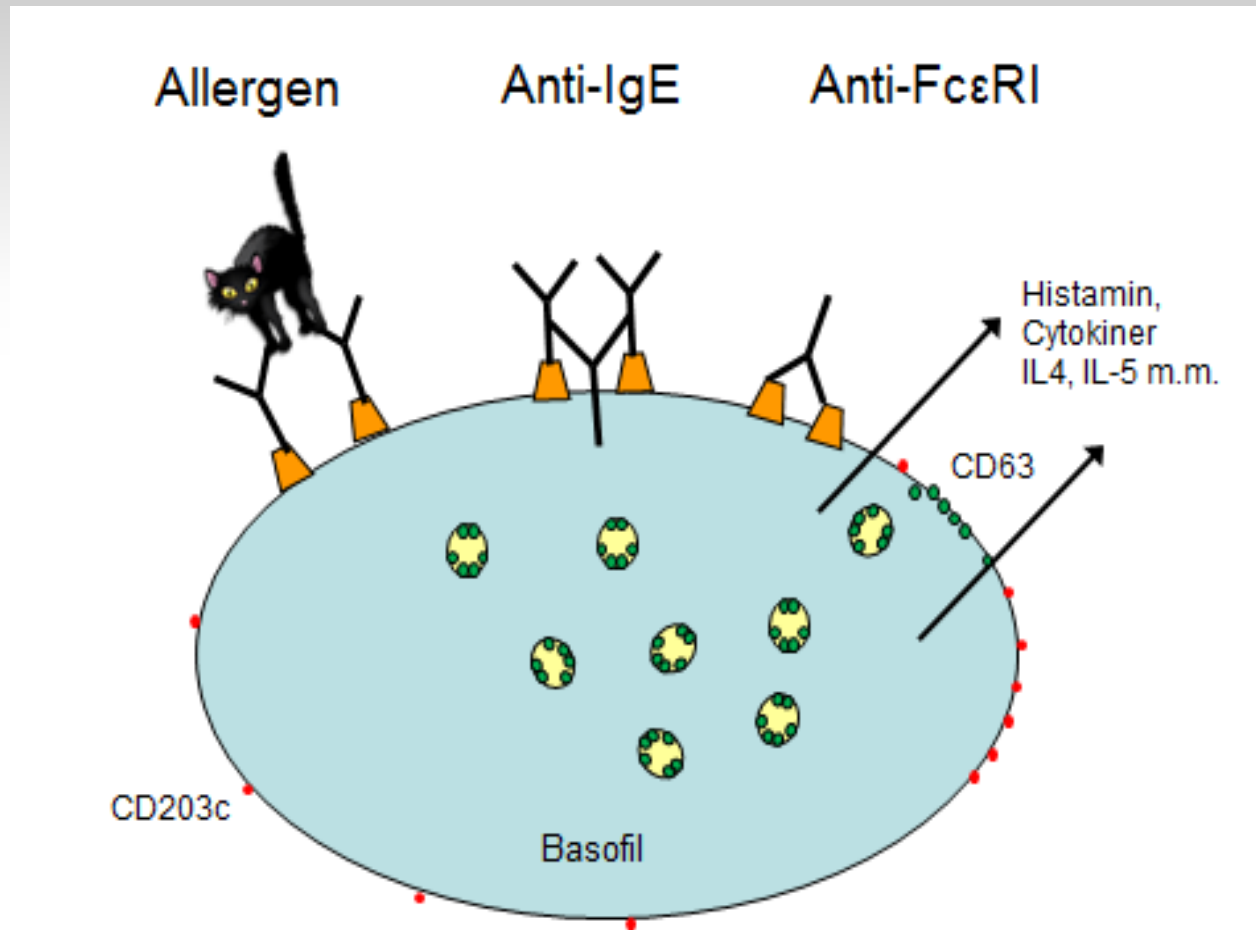
**Rökning ger förhöjda
serumnivåer av IgE
men inte IgE-antikroppar
mot tobak**

Zetterström et al, Br. Med. J. 1981, 283:1215

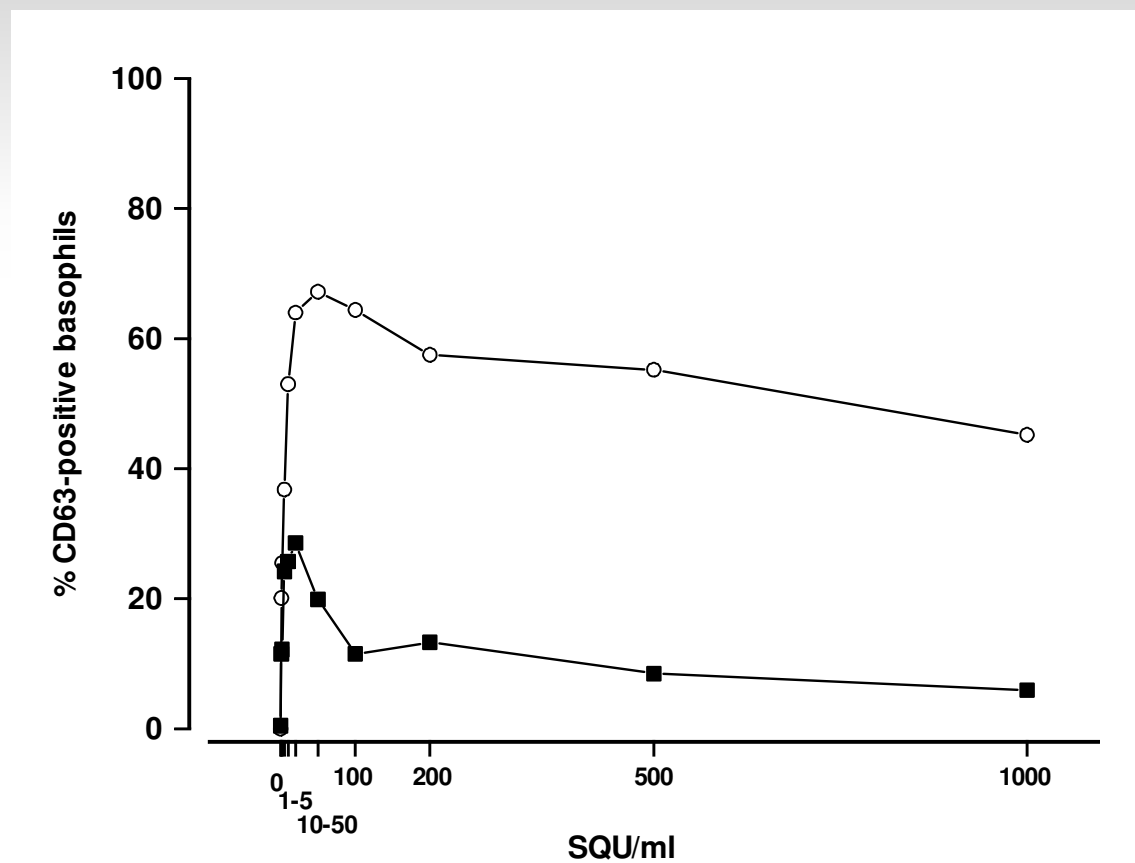
The hypersensitivity sequence



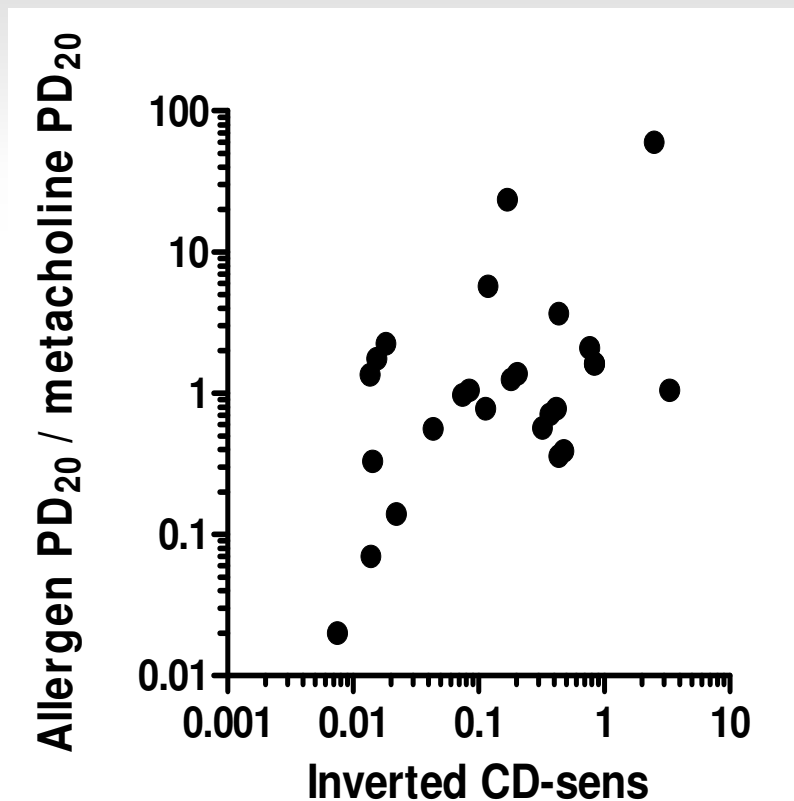
Mast cell / Basophil triggering



Basophil allergen threshold sensitivity, CD-sens

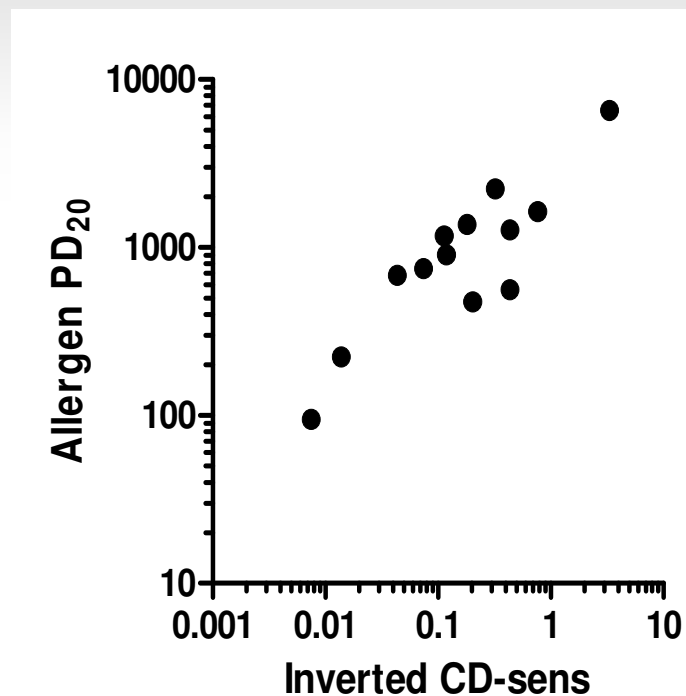


Bronchial Allergen Provocation (BAP) titration compared to CD-sens

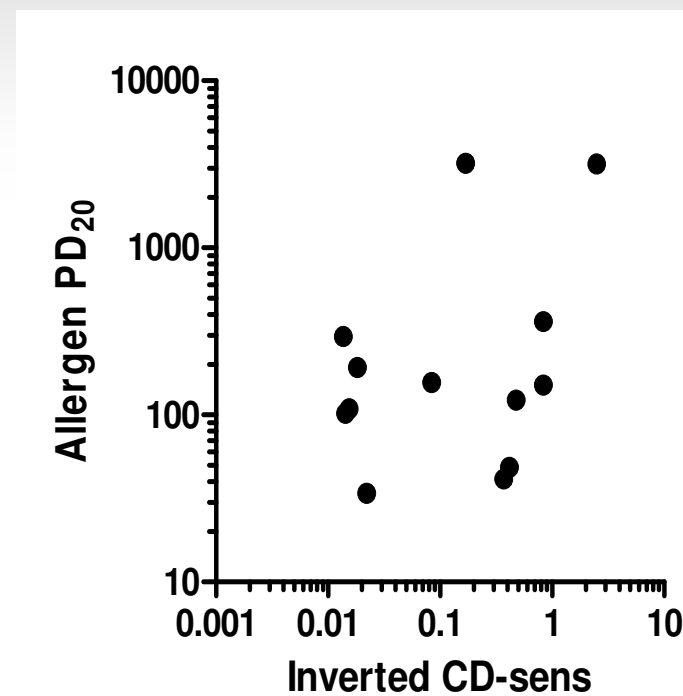


Dahlén, Nopp, Johansson et al, CEA 2011;41:1091

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

Allergi diagnos

Anamnes

Skin prick test (SPT)

IgE antikropp testning

Allergen-provokation

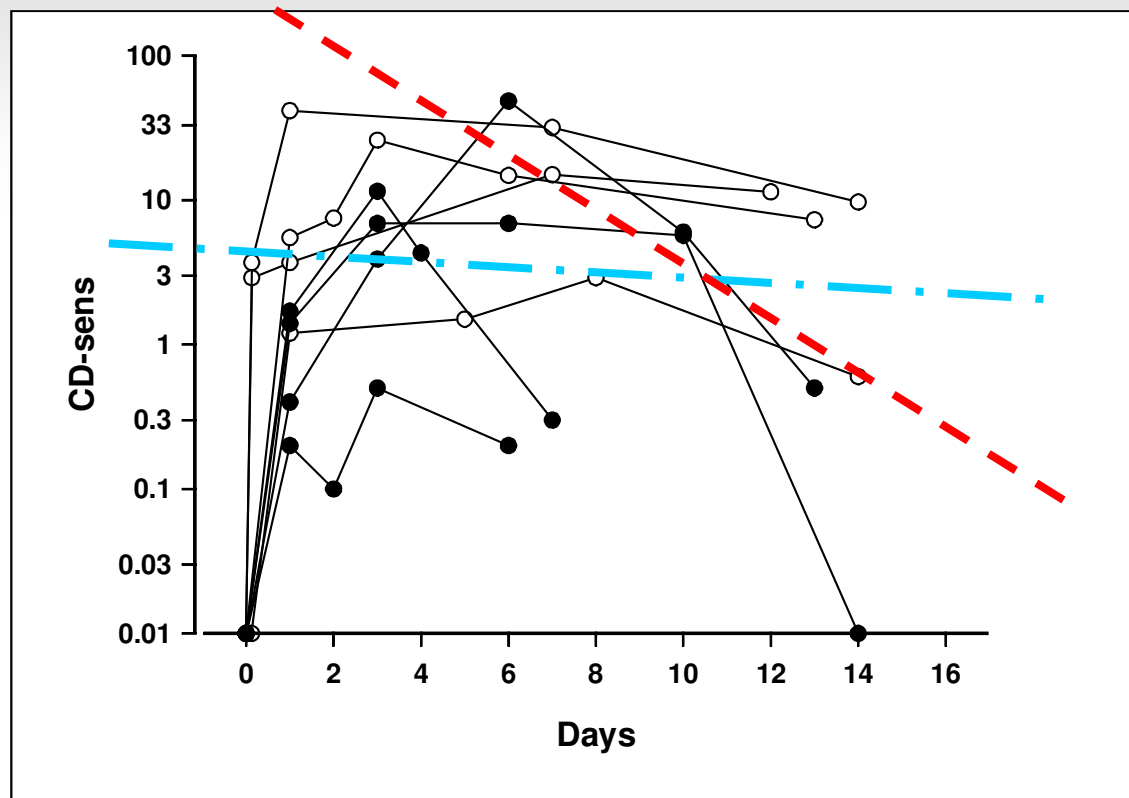
Basophil allergen threshold sensitivity, CD-sens

Passive IgE-sensitization by blood transfusion

S.G.O. Johansson, A. Nopp, M. van Hage,
N. Olofsson, J. Lundahl, L. Wehlin, L. Söderström,
V. Stiller, H. Öman

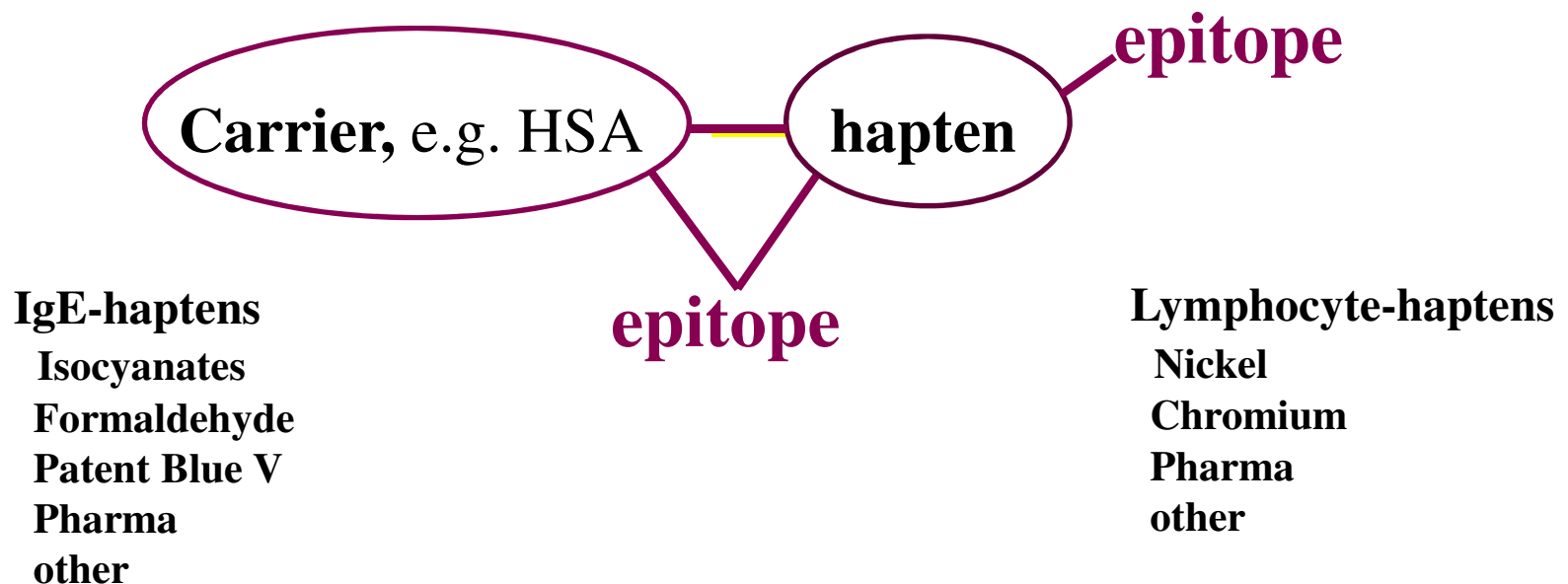
Allergy 2005; 60:1192-1199

CD-sens efter plasmatransfusion.
“Fast group”(röd) $T^{1/2}$ appr. 4 dagar
“Slow group” (blå) $T^{1/2}$ appr. 10 dagar



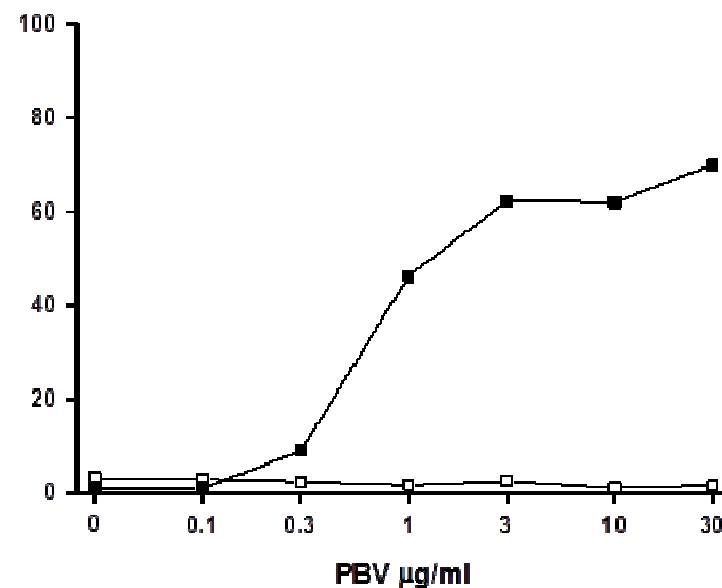
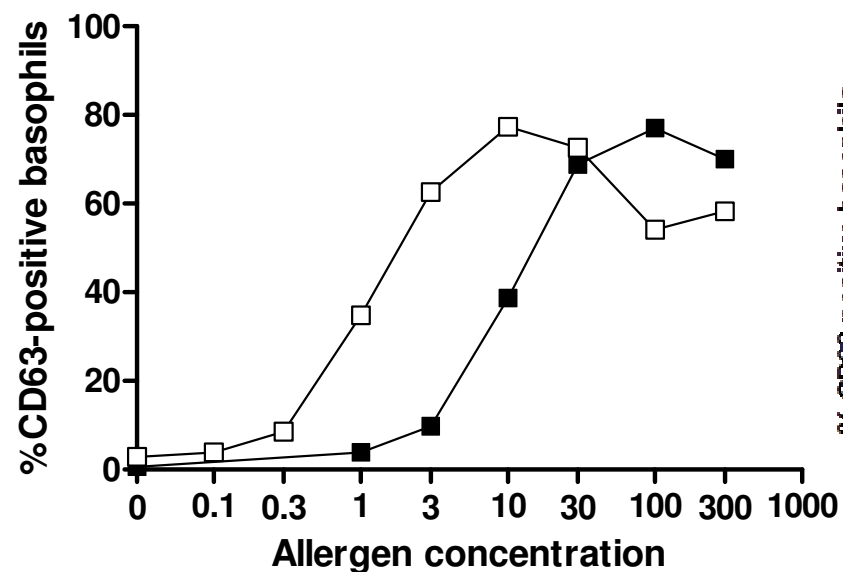
Allergen, hapten

**Low mol. weight "chemical"
immunogenic when linked to carrier**

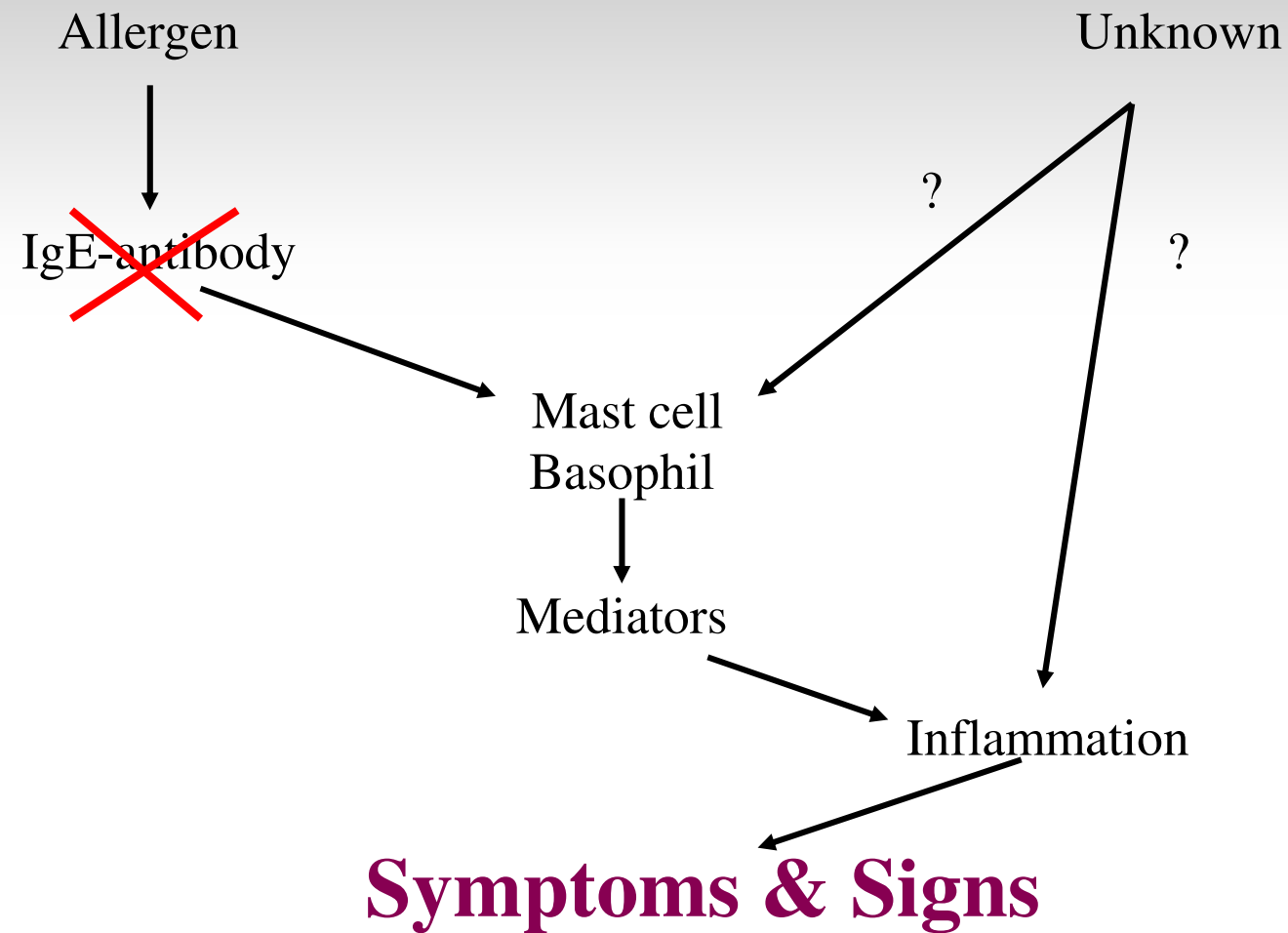


Basophil allergen threshold sensitivity, CD-sens, before (■--■) and after (□--□) washing.

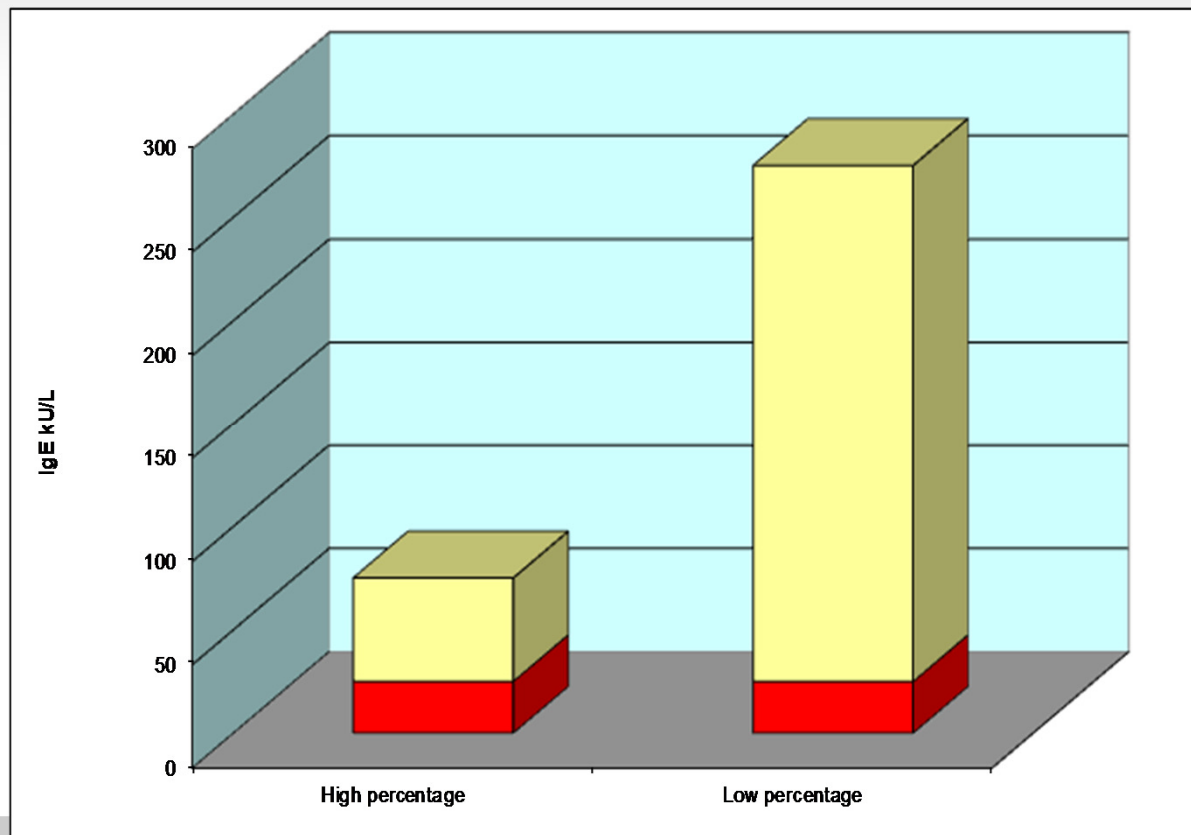
Left conventional allergen and right Patent Blue



The hypersensitivity sequence



Sera with high and low percentage of IgE antibodies. Before omalizumab, Xolair



Uppföljning avomalizumab, Xolair, behandling endast möjlig med CD-sens

Anafylaxi vid narkos relaterad till Neuro Muscular Blocking Agents, NMBA

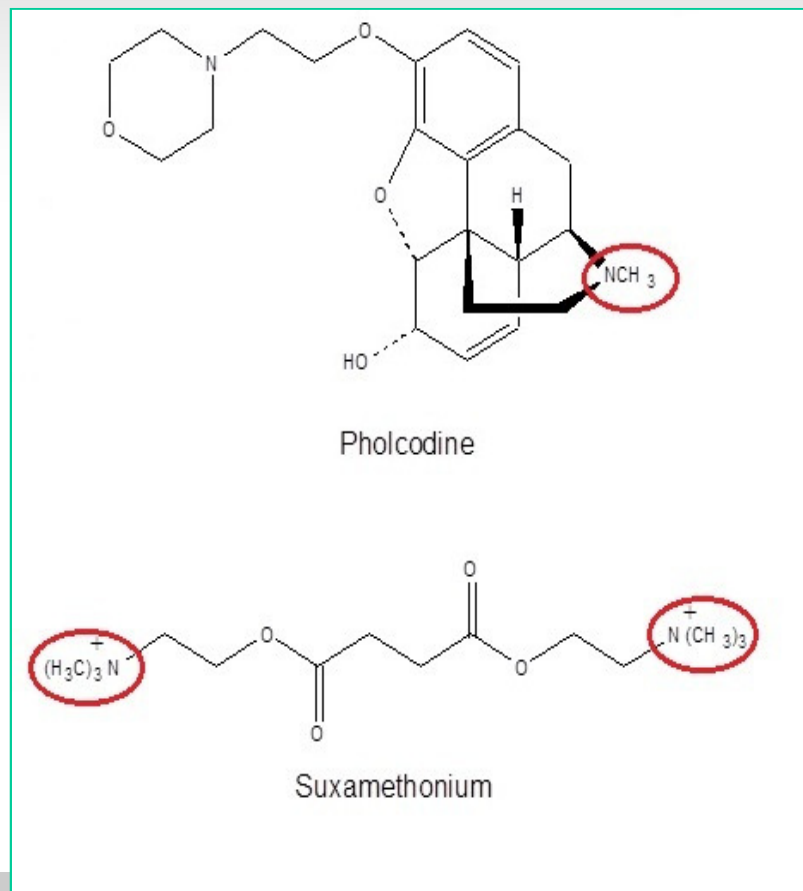
France	>1: 6 500
Norway	~1: 5 000
Sweden	~1: 83 000
Denmark	~1:180 000
USA	~1:500 000

Quantities (mg/inhabitant/year) sold of some cough syrups containing “opiates”

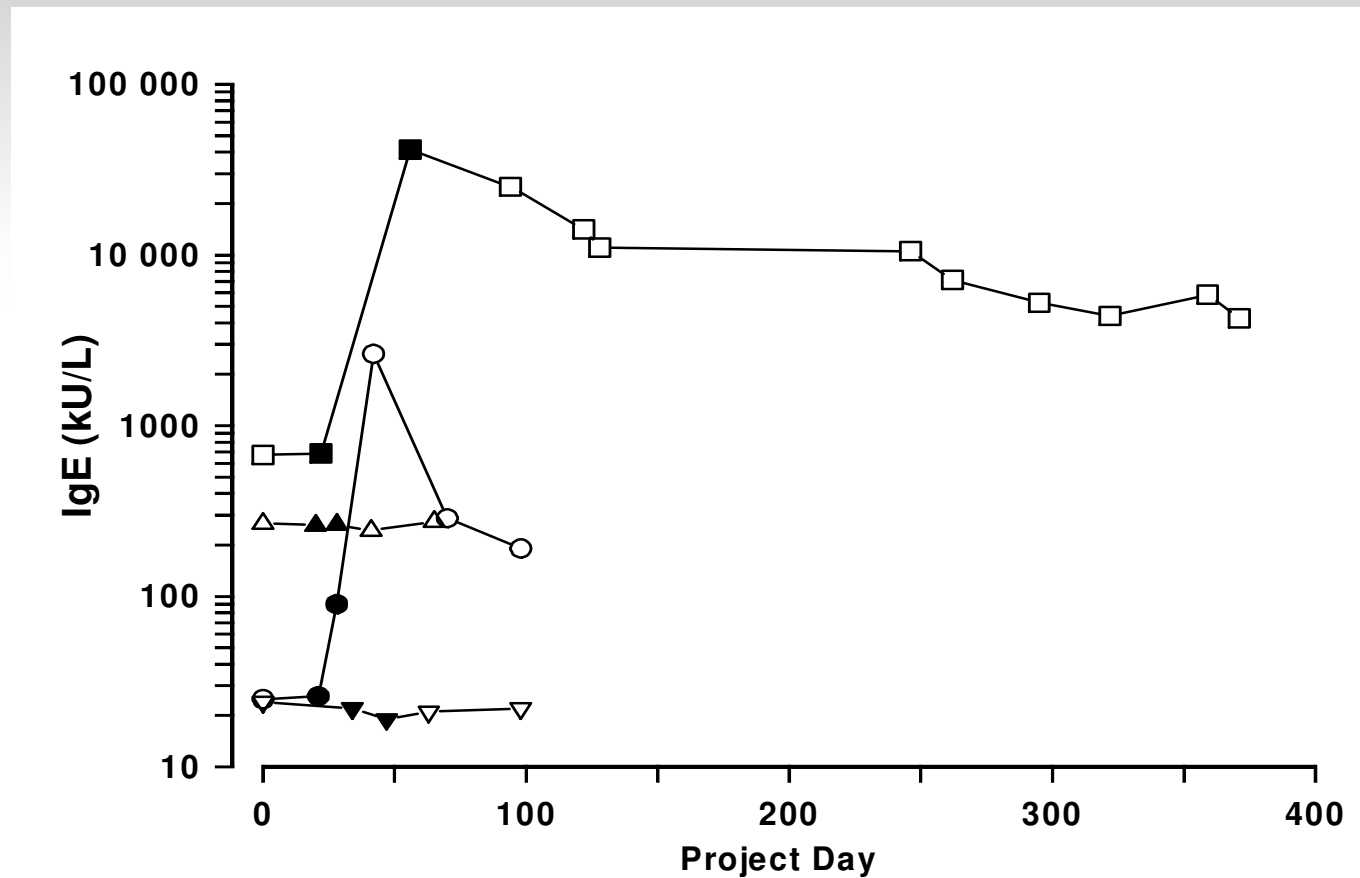
	Norway	Sweden
Morphine	43	35
Ethylmorphine	30	63
Codeine	552	244
Noscapine	69*	67*
Pholcodine	42*	not available

* OTC

**Pholcodine (PHO) is monovalent
for the allergen epitope, QAI,
while NMBA, i.e. suxamethonium, are bivalent**



PHO intake stimulates IgE synthesis



Florvaag et al., Allergy 2006;61:49

Norwegian cough syrup containing pholcodine



26 March, 2007

European Medicine Agency, 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.**



Annual profit > 50 000 000 USD

IgE:s roll i immunförsvaret?

- **”Rensar”** luftvägar och mag-tarm kanal med en ”allergisk reaktion”
- **”Portvakt”**, upptäcker tidigt främmande ämnen och aktiverar immunförsvaret
- **Basala immunförsvaret** mot tarmparasiter
- **Förstärker immunsvaret** genom att stimulera produktionen av antikroppar



Karolinska
Institutet



EAACI
EUROPEAN ACADEMY OF ALLERGY
AND CLINICAL IMMUNOLOGY



IgE 50 years

Past, Present and Future

From Bench to Bedside

6 October 2017

Stockholm, Sweden

SFFA

SVENSKA FÖRENINGEN FÖR ALLERGOLOGI
SWEDISH ASSOCIATION FOR ALLERGOLOGY

www.sffa.nu

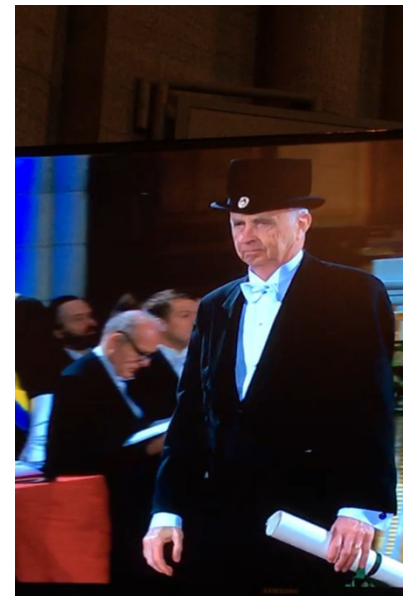
**Venue: Aula Medica, Karolinska Institutet, Stockholm,
Sweden**

Tack

SGO Johansson



Doc hon causa
Universidad San Pablo
Madrid, Spain



Doc hon causa
Uppsala University
Uppsala, Sweden