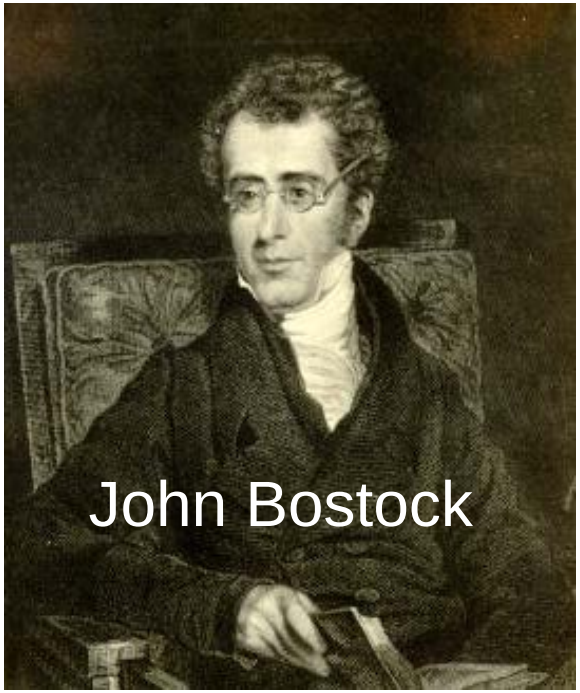
University Hospital
Zürich

Allergen-Specific Immunotherapy

Thomas M. Kündig
Head of Research
Dermatology

Prevalence of Allergies?



Prevalence of hay fever

Europa
20%

1971
4.4%

1981
8.4%

Catarrhus aestivus

28 Cases

1819

1829

1900
1%

2000
20%

Thorax 2000;**55**(Suppl 1):S2–S10

Family size, infection and atopy: the first decade of the "hygiene hypothesis"

David P Strachan

Department of Public Health Sciences, St George's Hospital Medical School, London SW17 0RE, UK

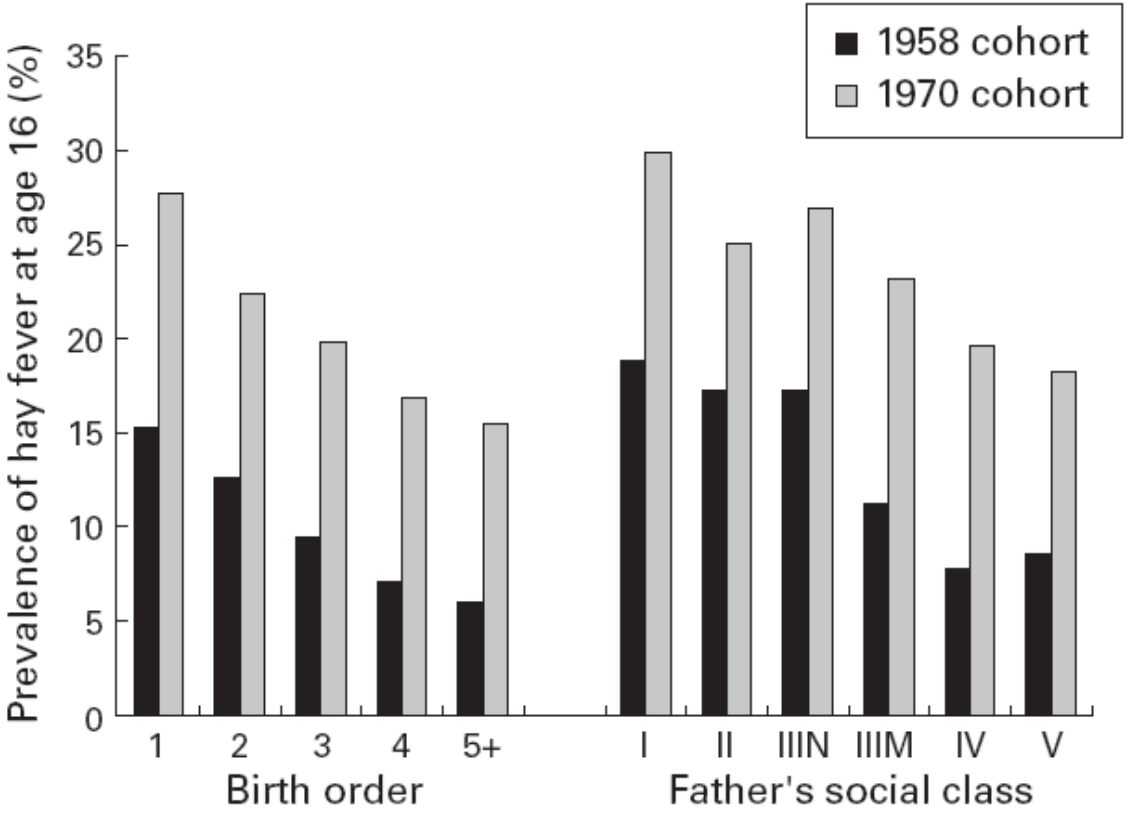
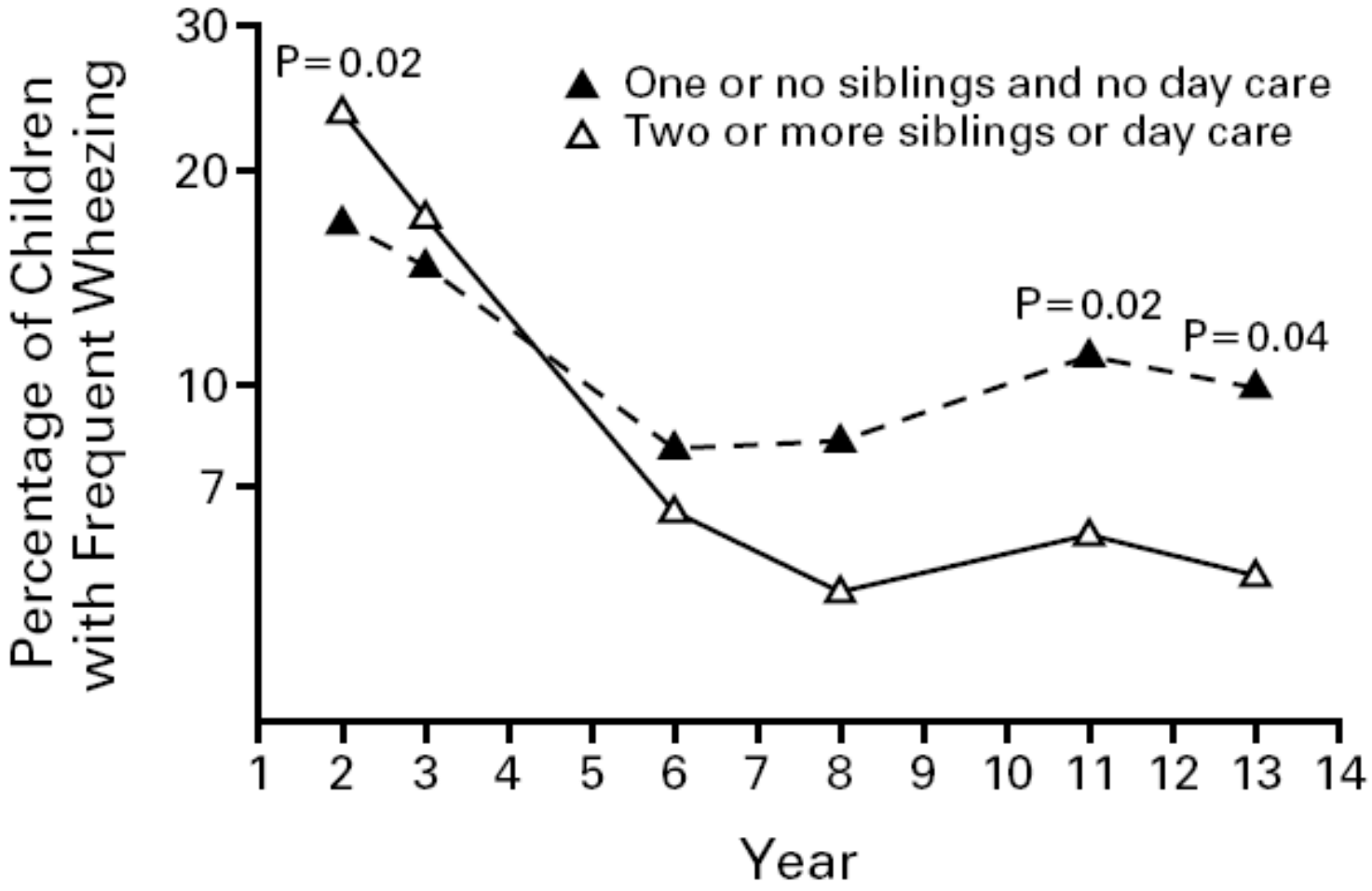


Figure 1 Prevalence of hay fever at the age of 16 in two national British birth cohorts born in 1958 and 1970, by birth order and father's social class.

SIBLINGS, DAY-CARE ATTENDANCE, AND THE RISK OF ASTHMA AND WHEEZING DURING CHILDHOOD

THOMAS M. BALL, M.D., M.P.H., JOSE A. CASTRO-RODRIGUEZ, M.D., KENT A. GRIFFITH, M.P.H., CATHARINE J. HOLBERG, PH.D., FERNANDO D. MARTINEZ, M.D., AND ANNE L. WRIGHT, PH.D.

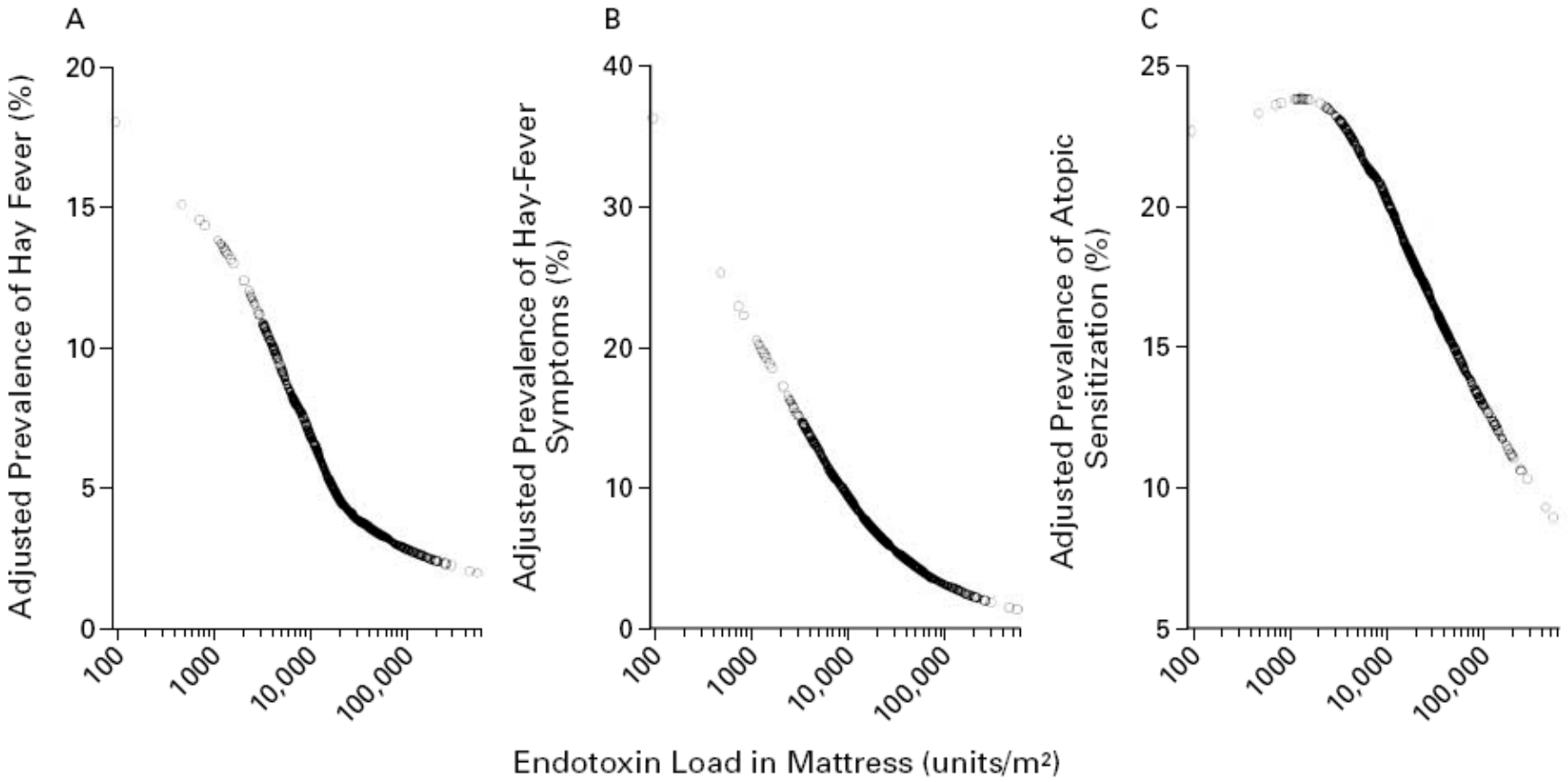


The New England
Journal of Medicine

VOLUME 347 SEPTEMBER 19, 2002 NUMBER 12

ENVIRONMENTAL EXPOSURE TO ENDOTOXIN AND ITS RELATION TO ASTHMA IN SCHOOL-AGE CHILDREN

CHARLOTTE BRAUN-FAHRLÄNDER, M.D., JOSEF RIEDLER, M.D., UDO HERZ, PH.D., WALTRAUD EDER, M.D., MARCO WASER, M.SC., LETICIA GRIZE, PH.D., SOYOUN MAISCH, M.D., DAVID CARR, B.SC., FLORIAN GERLACH, ALBRECHT BUFE, M.D., PH.D., ROGER P. LAUENER, M.D., RUDOLF SCHIERL, PH.D., HARALD RENZ, M.D., DENNIS NOWAK, M.D., AND ERIKA VON MUTIUS, M.D., FOR THE ALLERGY AND ENDOTOXIN STUDY TEAM



Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey

Lancet 2001; **358:** 1129–33

*Josef Riedler, Charlotte Braun-Fahrländer, Waltraud Eder, Mynda Schreuer, Marco Waser, Soyoun Maisch, David Carr, Rudi Schierl, Dennis Nowak, Erika von Mutius, and the ALEX Study Team**

	Stables and farm milk in the 1st year of life (n=218)	Stables, but no farm milk in the 1st year of life (n=48)	Farm milk, but no stables in the 1st year of life (n=189)	Farm milk, stables, or both after the 1st year of life (n=138)	Neither stables nor farm milk exposure (n=170)
Asthma diagnosis	1% (3) 0·14 (0·04–0·48)	6% (3) 0·51 (0·14–1·86)	6% (11) 0·48 (0·21–1·1)	11% (15) 0·88 (0·42–1·86)	12% (20) Reference
At least one wheeze attack in past 12 months	3% (6) 0·17 (0·07–0·45)	6% (3) 0·43 (0·12–1·52)	6% (12) 0·43 (0·20–0·92)	9% (12) 0·60 (0·28–1·28)	15% (25) Reference
Hay fever	3% (7) 0·20 (0·08–0·50)	4% (2) 0·25 (0·05–1·13)	4% (8) 0·24 (0·10–0·56)	13% (18) 0·88 (0·44–1.74)	16% (27) Reference
Runny nose and itchy eyes in past 12 months	5% (11) 0·27 (0·13–0·57)	8% (4) 0·44 (0·14–1·37)	7% (14) 0·42 (0·21–0·86)	12% (16) 0·65 (0·33–1·30)	20% (34) Reference
Atopic sensitisation†	12% (27) 0·32 (0.17–0·62)	21% (10) 0·56 (0·25–1·27)	15% (29) 0·43 (0·24–0·77)	29% (40) 0·99 (0·58–1·69)	33% (56) Reference

*Adjusted for age, sex, study area, parental education, family history of asthma and hay fever, number of older siblings and farming status. †Any reaction to inhalent allergens (house dust and storage mites, cat dander, grass and birch pollen, cow epithelium) of ⩾3·5 kU/L.

Table 2: **Frequency and risk (adjusted* odds ratio, 95% CI) of asthma, hay fever, and atopic sensitisation in relation to exposure to stables and farm milk in the 1st year of life**

Pets

Table 3. Relationship Between the Number of Dogs in the Home in the First Year of Life and the Prevalence of Allergic Sensitization at Age 6 to 7 Years*

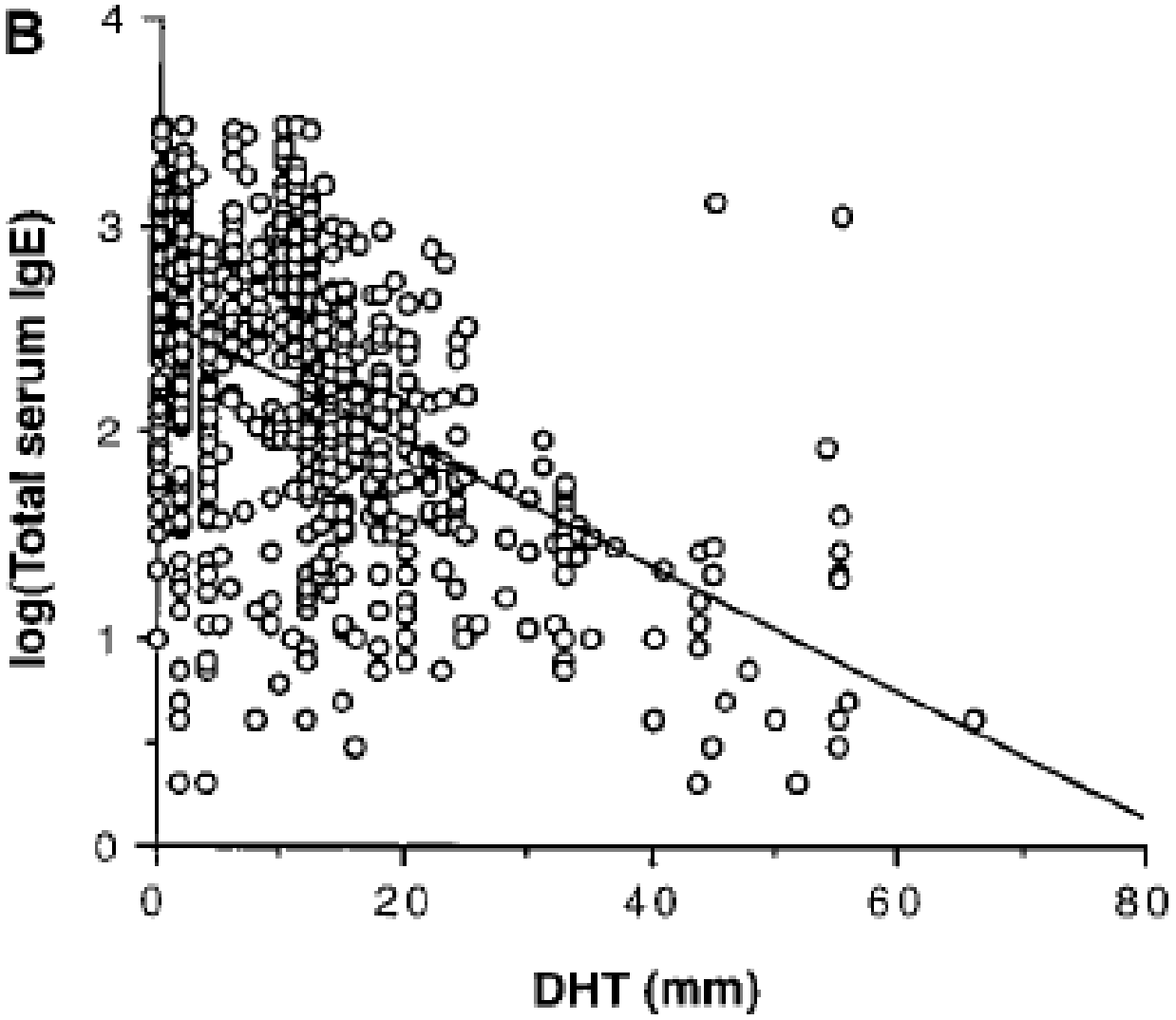
Variable	No./Total (%)			*P* Value†
	No Dog or Cat Exposure	No. of Dogs		
		1	≥2	
Skin prick test positivity				
Dog	19/220 (8.6)	6/148 (4.1)	0/36 (0)	.06
Cat	34/220 (15.5)	16/148 (10.8)	1/36 (2.8)	.07
Outdoor allergens‡	62/206 (30.1)	28/137 (20.4)	2/27 (7.4)	.01
Indoor allergens§	60/220 (27.3)	37/148 (25.0)	2/36 (5.6)	.02
Atopy‖	74/220 (33.6)	44/148 (29.7)	3/36 (8.3)	.009
Seroatopy¶	74/192 (38.5)	47/128 (36.7)	4/31 (12.9)	.02
Methacholine airway responsiveness	53/220 (24.1)	34/144 (23.6)	4/34 (11.8)	.27
Current asthma	17/223 (7.6)	9/147 (6.1)	2/36 (5.6)	.81

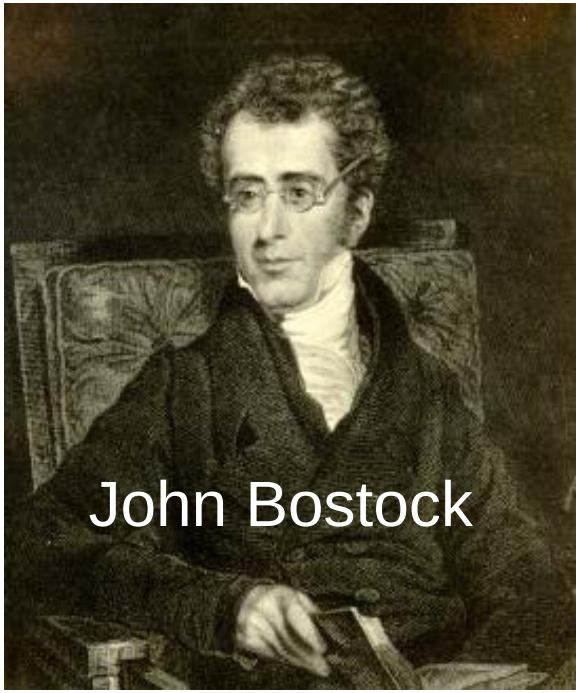
Ownby et al. JAMA 2002

The Inverse Association Between Tuberculin Responses and Atopic Disorder

Taro Shirakawa, Tadao Enomoto, Shin-ichiro Shimazu, Julian M. Hopkin*

SCIENCE • VOL. 275 • 3 JANUARY 1997





Prevalence of hay fever

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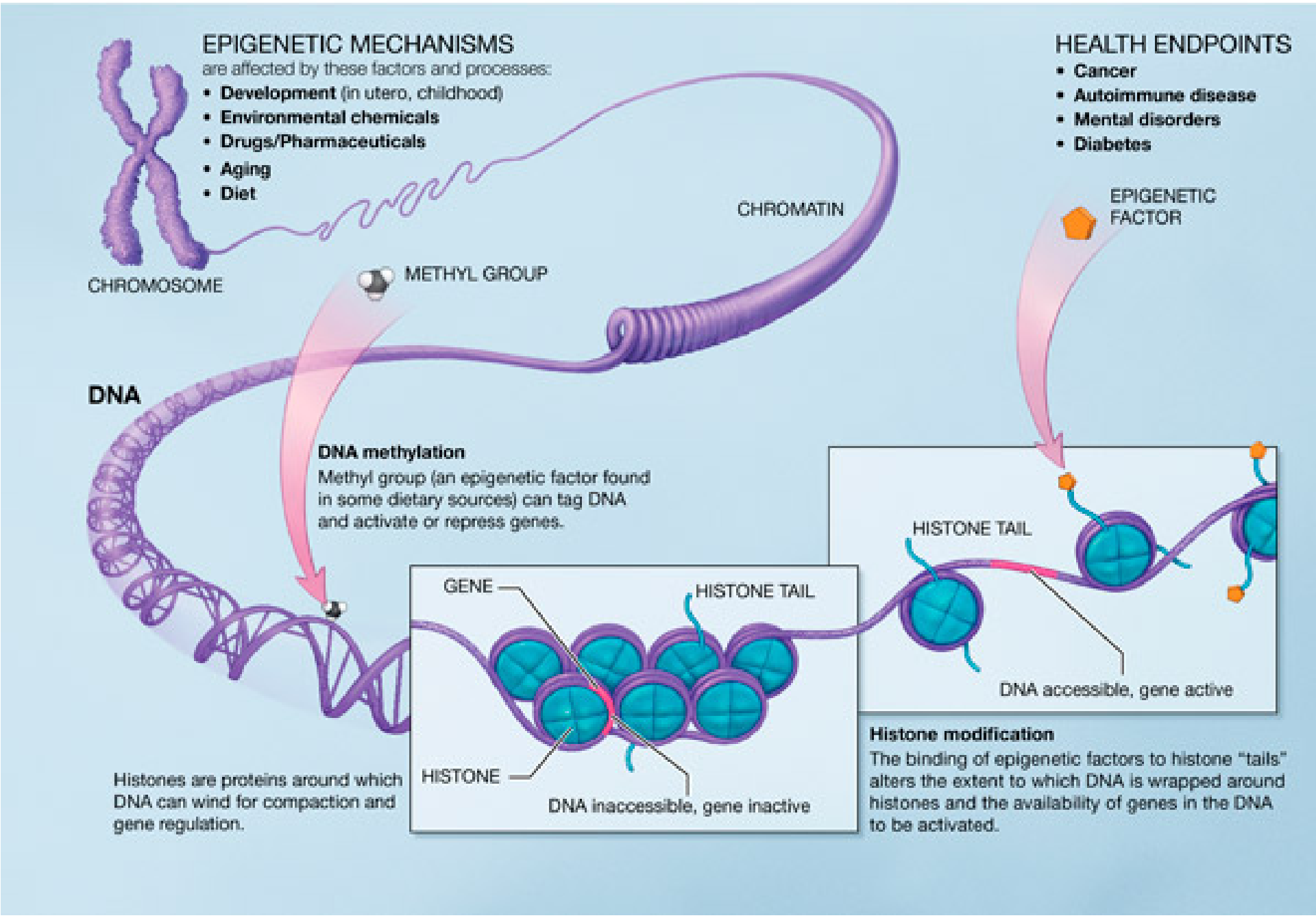
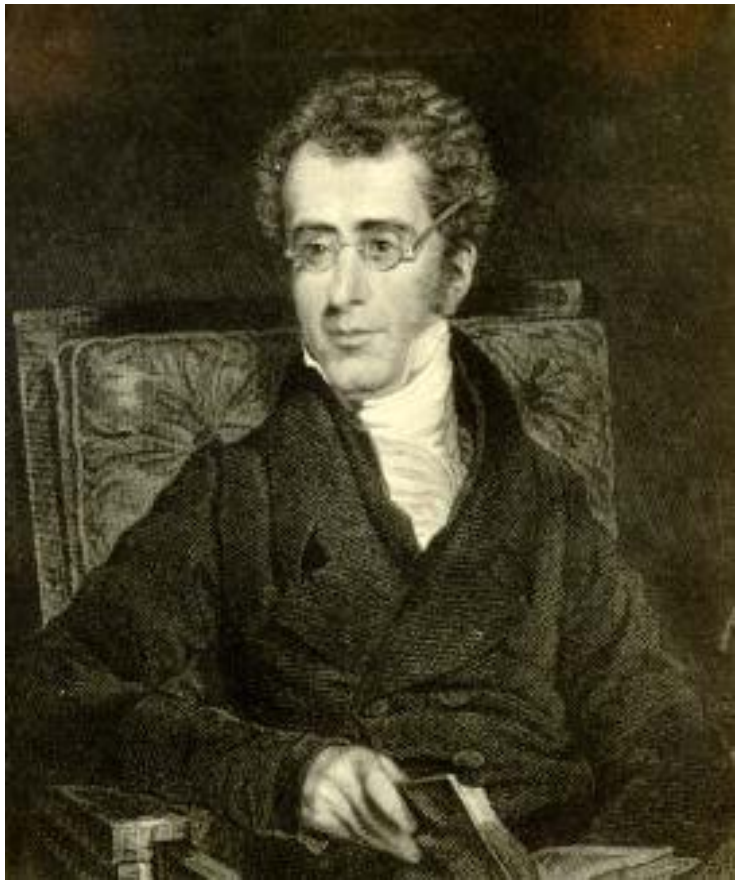

EPIGENETIC MECHANISMS
are affected by these factors and processes:
• Development (in utero, childhood)
• Environmental chemicals
• Drugs/Pharmaceuticals
• Aging
• Diet
HEALTH ENDPOINTS
• Cancer
• Autoimmune disease
• Mental disorders
• Diabetes
CHROMOSOME
CHROMATIN
METHYL GROUP
EPIGENETIC FACTOR
DNA
DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.
HISTONE TAIL
GENE
HISTONE TAIL
HISTONE
DNA inaccessible, gene inactive
DNA accessible, gene active
Histones are proteins around which DNA can wind for compaction and gene regulation.
Histone modification
The binding of epigenetic factors to histone "tails" alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.

Cause of Allergies?



John Bostock

1819 Catharrus aestivus

1829 Found 28 cases

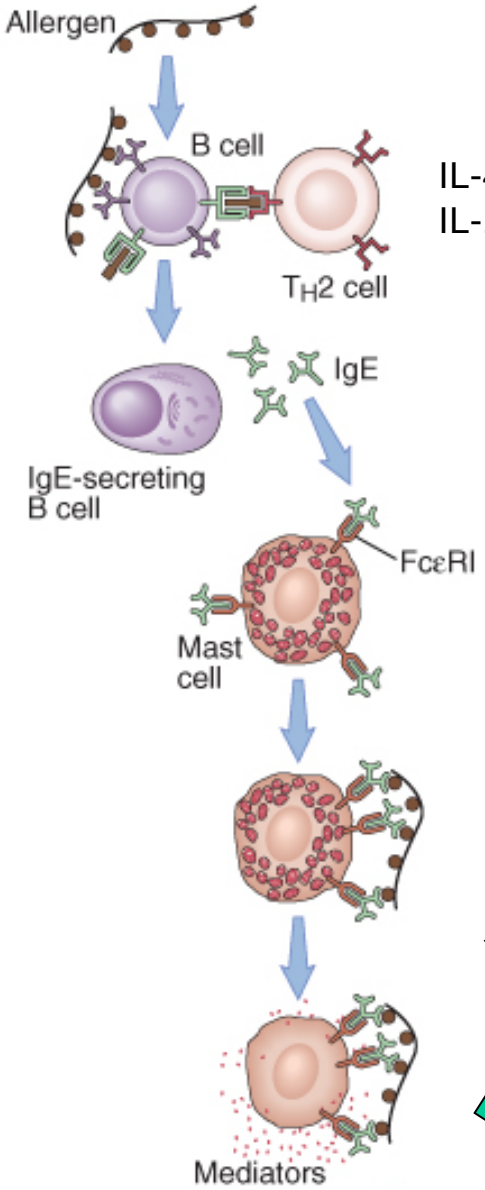
[1] John Bostock: Medical and Chirurgical Transactions, vol. x., 1819, p. 161.

Charles Blackley

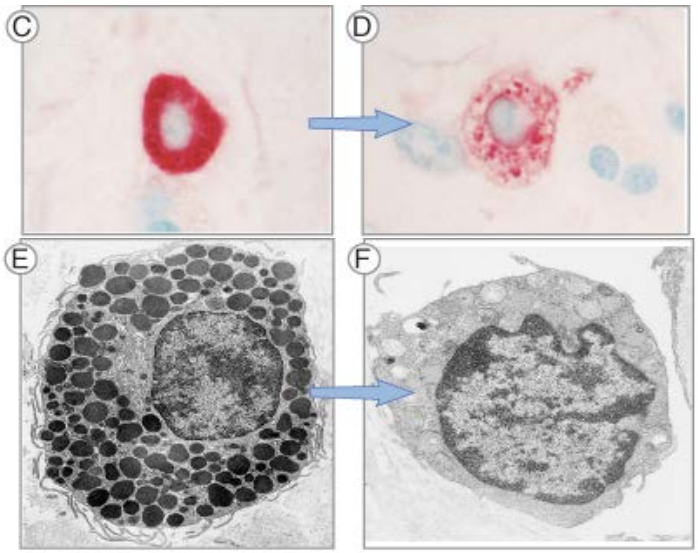
Catarrhus aestivus

caused by pollen

[2] C. H. Blackley: Experimental Researches on the Causes and Nature of Catarrhus Aestivus, London, 1873.



IL-4
IL-13



Vasoaktive Amine:
Histamin

Minuten

Sofort-Reaktion:
Vasodilatation
Bronchokonstriktion

Lipid-Mediatoren:
Prostaglandine
Leukotriene

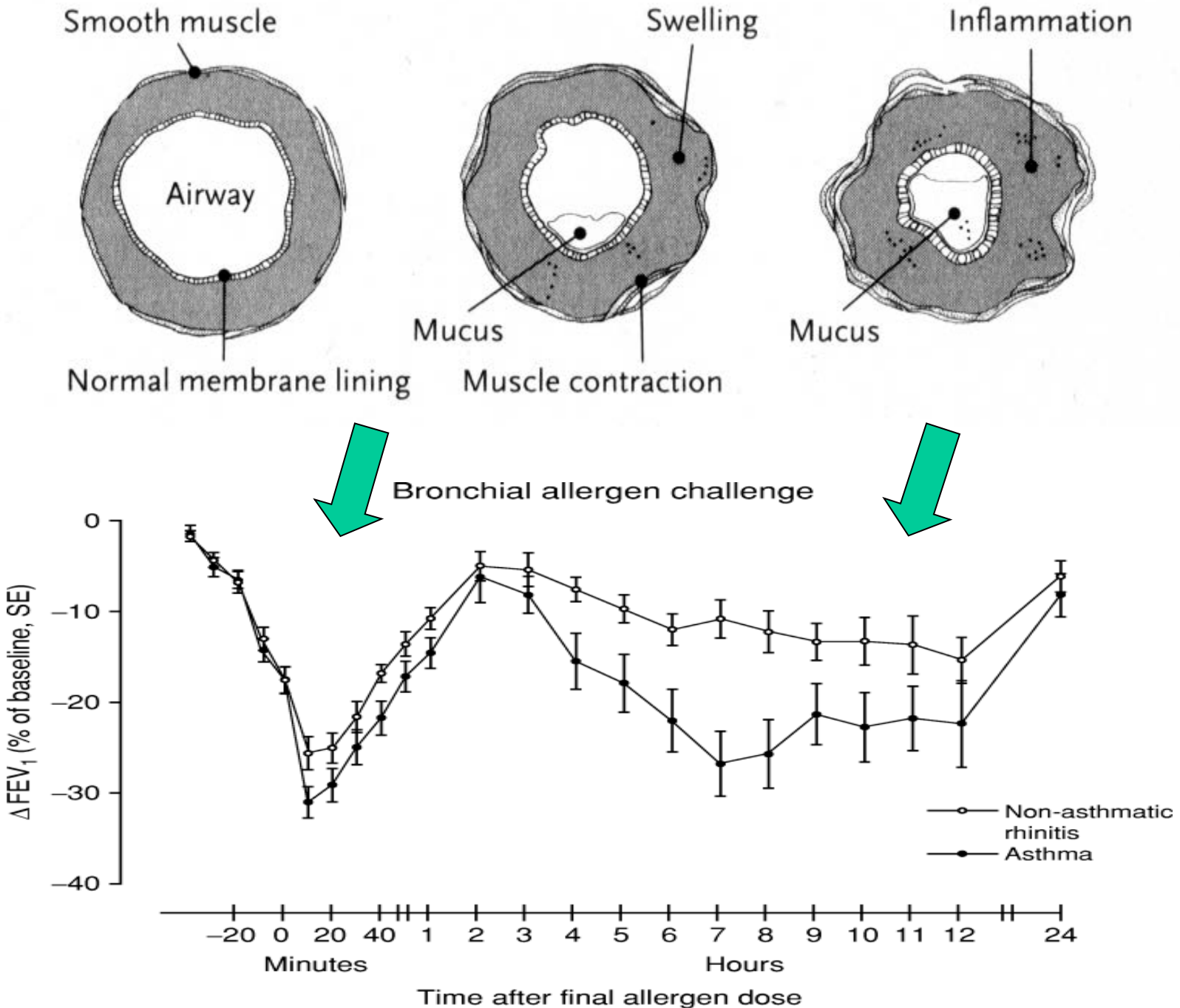
Stunden

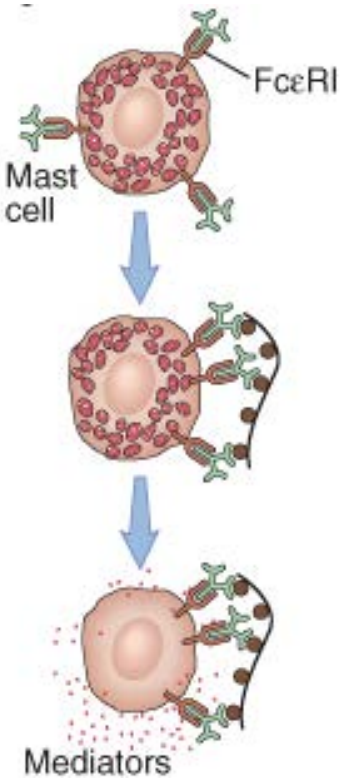
Anhaltende Bronchokonstriktion

Cytokine:
TNFα
IL-4

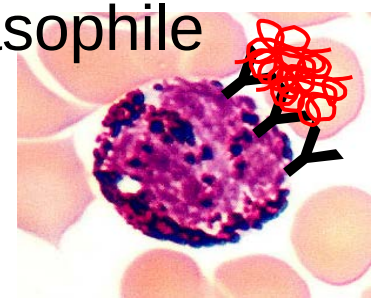
Tage

Spät-Reaktion:
Eosinophile
Neutrophile
Th2-Zellen


Smooth muscle
Airway
Normal membrane lining
Swelling
Mucus
Muscle contraction
Inflammation
Mucus
Bronchial allergen challenge
0
−10
−20
−30
−40
ΔFEV1 (% of baseline, SE)
Non-asthmatic rhinitis
Asthma
−20 0 20 40 1 2 3 4 5 6 7 8 9 10 11 12 24
Minutes
Hours
Time after final allergen dose



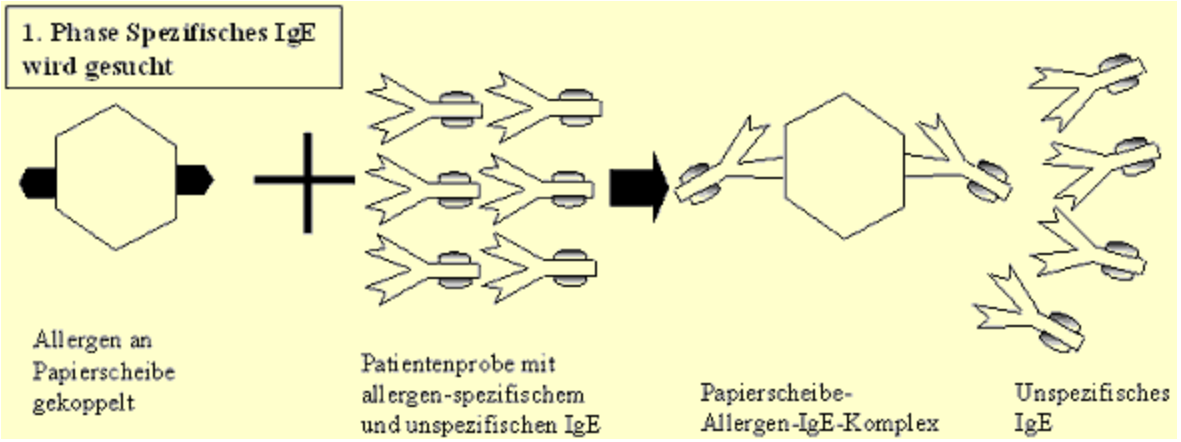
Basophile



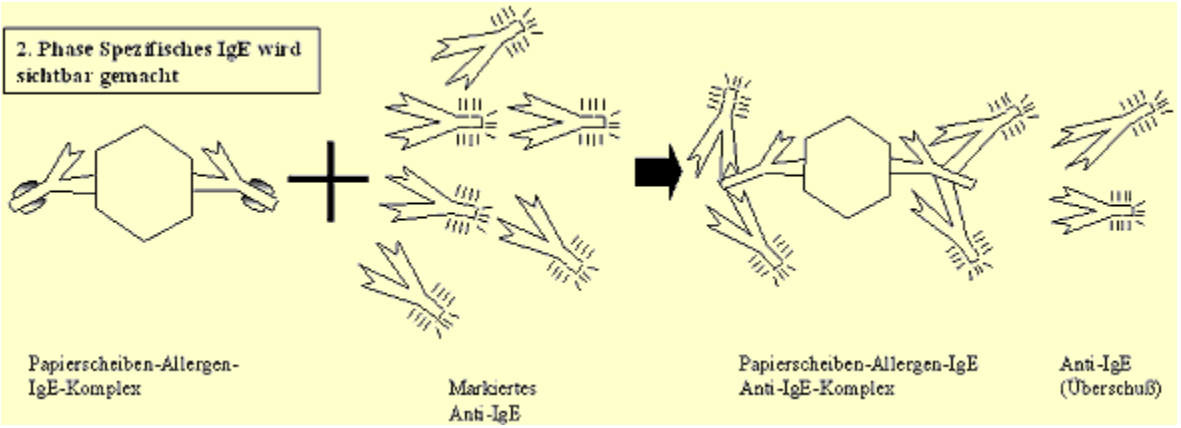
Dermis:	Urticaria
Subcutis:	Angioödem
Bronchien:	Asthma
GI-Trakt:	Koliken
Basophile:	Anaphylaxie

Ort der Allergenresorption = Ort der Symptome

Mit wenigen Ausnahmen.....


1. Phase Spezifisches IgE wird gesucht
Allergen an Papierscheibe gekoppelt
Patientenprobe mit allergen-spezifischem und unspezifischen IgE
Papierscheibe-Allergen-IgE-Komplex
Unspezifisches IgE

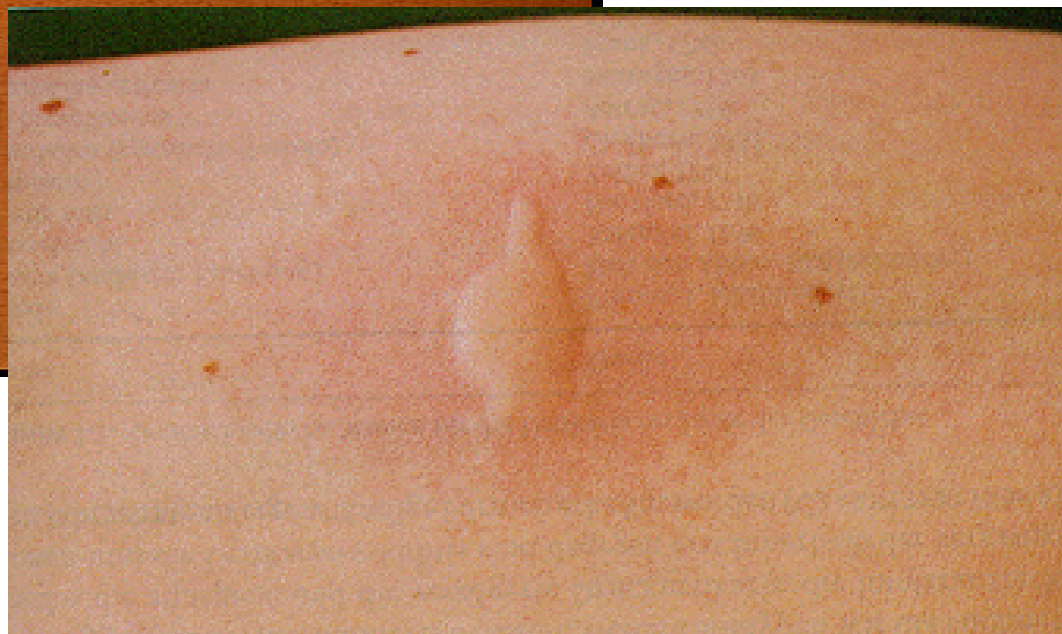
RAST


2. Phase Spezifisches IgE wird sichtbar gemacht
Papierscheiben-Allergen-IgE-Komplex
Markiertes Anti-IgE
Papierscheiben-Allergen-IgE Anti-IgE-Komplex
Anti-IgE (Überschuß)

CAP

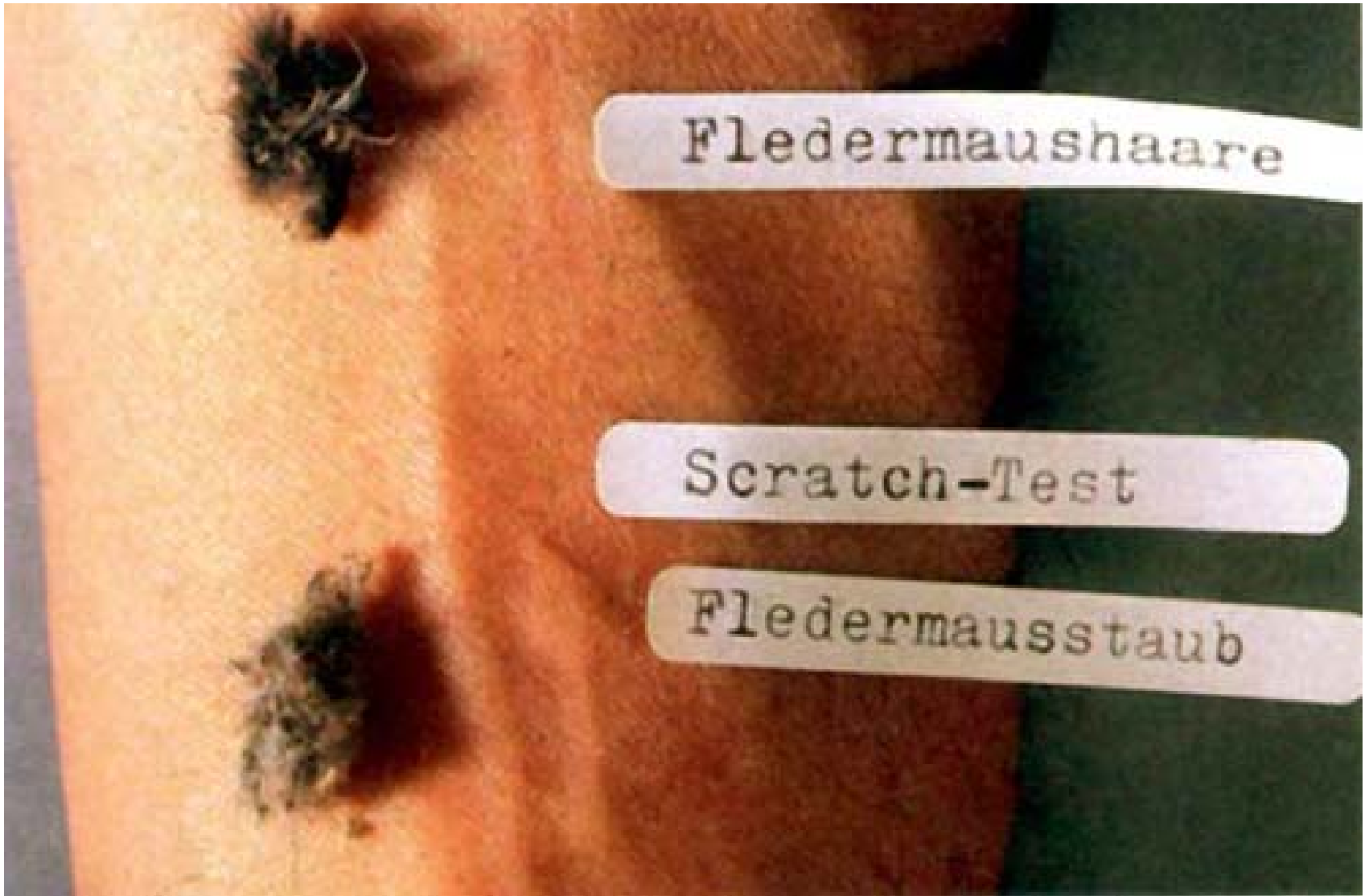

UniCAP®

Prick Test



Urtica = Quaddel

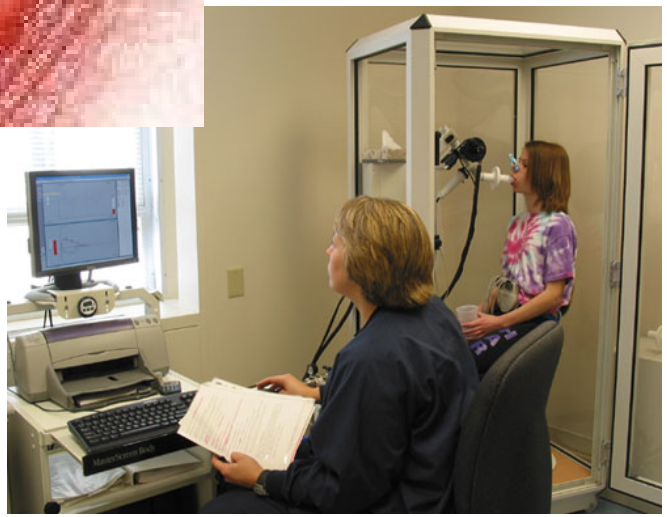
Sratch Test



NPT

CPT

BPT



Therapy of Allergies?

William Dunbar

Pollantin

[3] W. P. Dunbar: Zur Ursache und specifischen Heilung des Heufiebers, München, 1903.

Hay-Fever Treatment by Dunbar's Remedies (Pollantin).

John F. Barnhill

Since this article does not have an abstract, we have provided the first 150 words of the full text.

EXCERPT

INDIANAPOLIS, Aug. 6, 1906.

To the Editor: —I can heartily agree with all that Dr. Ingals has stated concerning pollantin. A year ago I reported two sets of hay-fever cases, one treated by pollantin and the other by the use of quinin locally in the form of a saturated solution sprayed into the nose and followed by an ointment of the same drug, as recommended by Helmholtz many years ago. My success with the simple quinin preparation was greater than with pollantin. I regard the literature accompanying the preparation very objectionable; it is impossible to prescribe pollantin for the patient without him learning all about the remedy he is using. ...

[3] W. P. Dunbar: Zur Ursache und specifischen Heilung des Heufiebers, München, 1903.

John Freeman

Leonard Noon

PROPHYLACTIC INOCULATION AGAINST HAY FEVER.

BY L. NOON, B.C. CANTAB., F.R.C.S. ENG.

(From the Laboratory of the Department for Therapeutic Inoculation, St. Mary's Hospital.)

HAY fever is a form of recurrent catarrh affecting certain individuals during the months of May, June, and July. It is caused by a soluble toxin found in the pollen of grasses.

Bostock (1819)[1] recognised the seasonal recurrence of hay fever as separating it from other forms of catarrh. Blackley (1873)[2] advanced much evidence in favour of the pollen theory of its causation, but we owe chiefly to Dunbar (1903)[3] the exhaustive scientific proof of this theory. Dunbar showed that

[1] John Bostock: Medical and Chirurgical Transactions, vol. x., 1819, p. 161.

[2] C. H. Blackley: Experimental Researches on the Causes and Nature of Catarrhus Aestivus, London, 1873.

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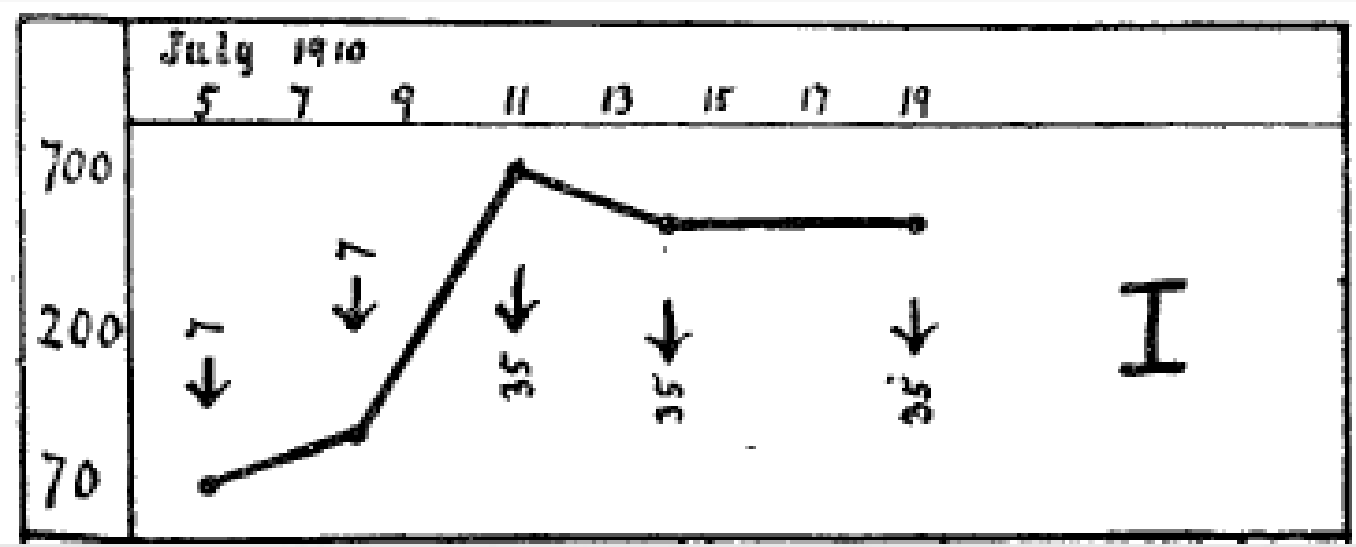
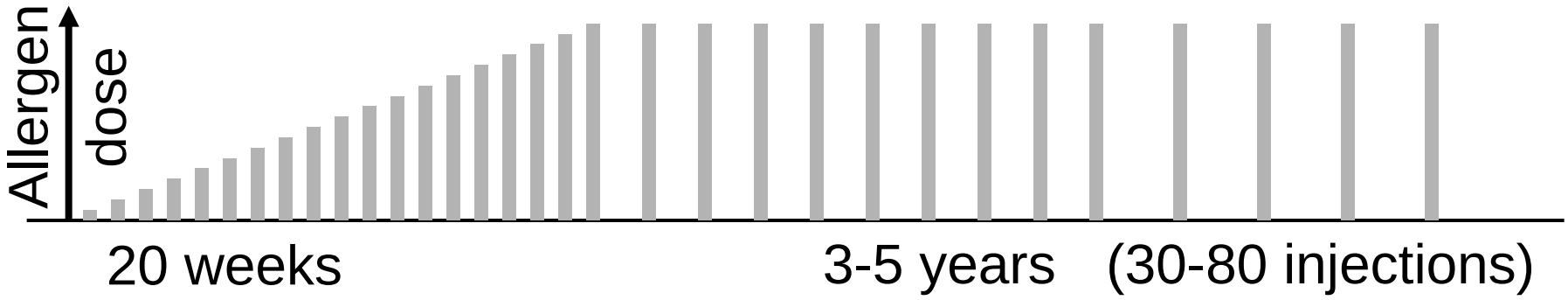


Subcutaneous Immunotherapy



Allergen Immunotherapy

High rate of success

Insect venoms	80-95%
Pollen	70-80%

Only causal treatment

Stops progression of disease

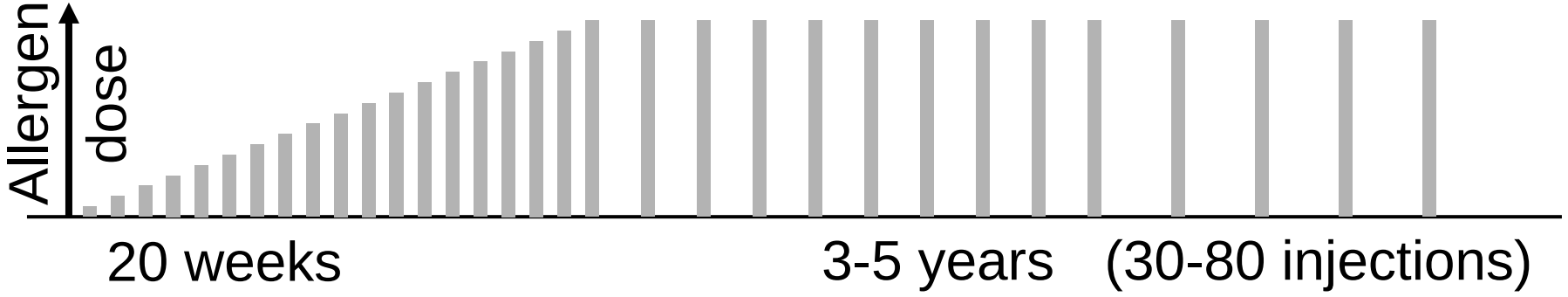
Long term effect

As effective as pharmacotherapy

Allergen Immunotherapy

Time consuming

Allergic side effects




POM
GRAZAX®
75 000 SQ-T
Standardised allergen extract of
Grass pollen from Timothy,
Phleum pratense.
30 oral lyophilisates


Staloral
Maintenance
FOR M SPECIMEN
FOR DEMONSTRATION
BY DR
688 EXTRACT OF 5 GR 100%
solution for sublingual administration
STALLERGENES
N° 00542011
02/03
Ref. N°
Exp.
08/2006
10 ml
Staloral
NOTICE PATIENT

Efficacy of sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: A systematic review and meta-analysis

Danilo Di Bona, MD, PhD,[a,e] Antonella Plaia, PhD,[b] Valeria Scafidi, PhD,[a,c] Maria Stefania Leto-Barone, MD,[d] and Gabriele Di Lorenzo, MD[d] *Palermo, Italy*

Conclusion: This meta-analysis found that SLIT with grass allergens is effective in patients with seasonal allergic rhinitis compared with placebo. The benefit is clinically modest, and criteria are needed to identify patients most likely to benefit from SLIT. (J Allergy Clin Immunol 2010;126:558-66.)

Gianenrico Senna, MD[a]
Carlo Lombardi, MD[b]
Giorgio Walter Canonica, MD[c]
Giovanni Passalacqua, MD[c]

J ALLERGY CLIN IMMUNOL
SEPTEMBER 2010

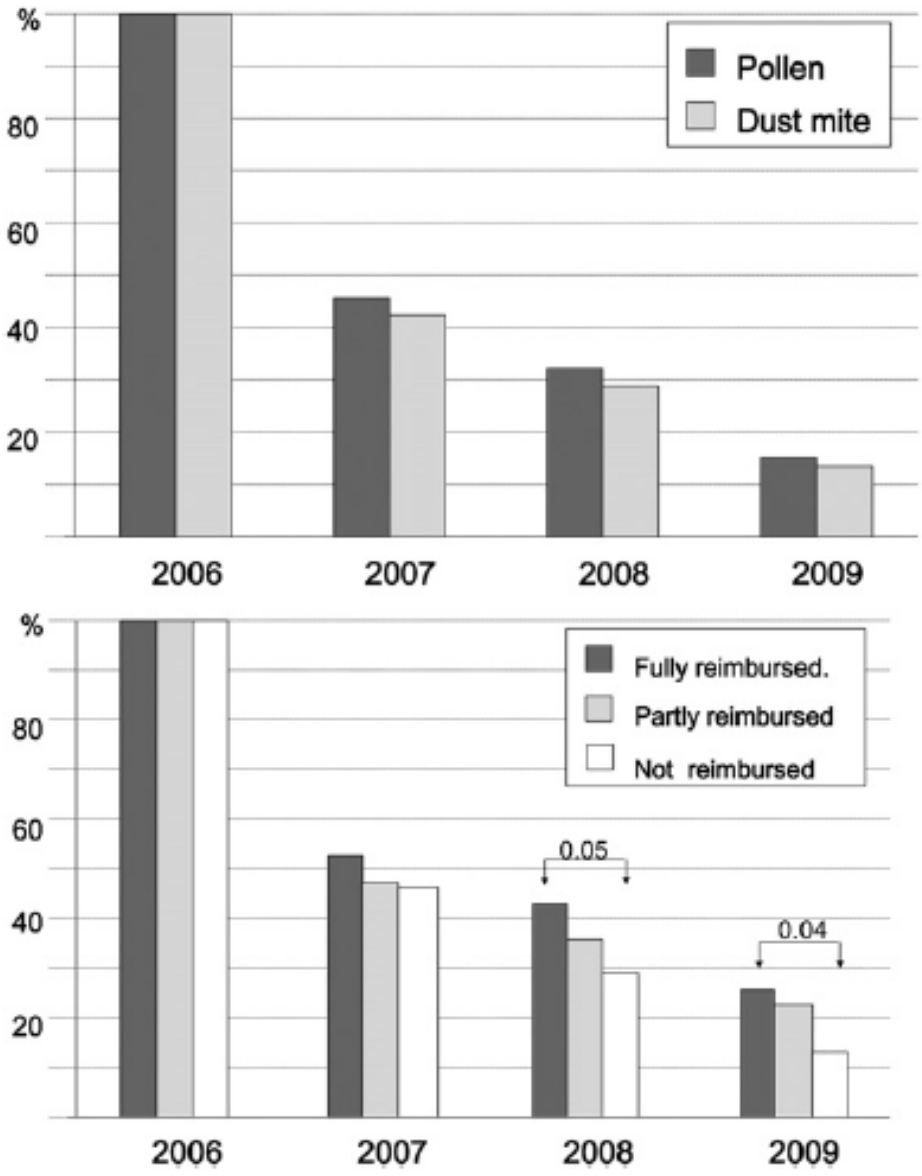
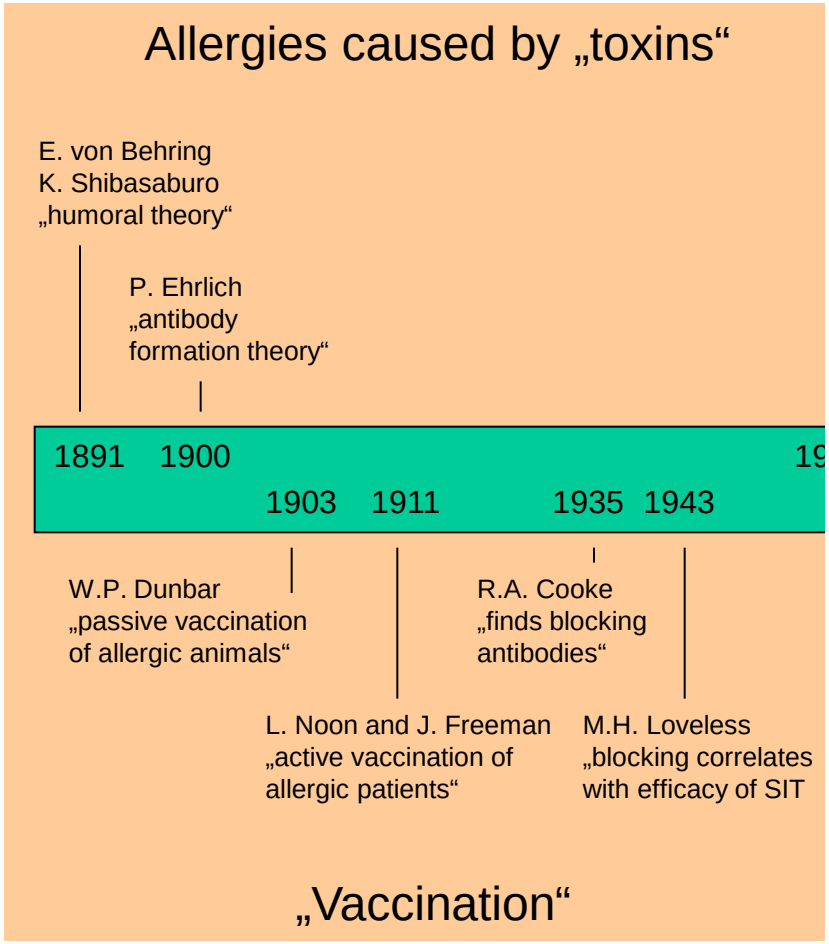


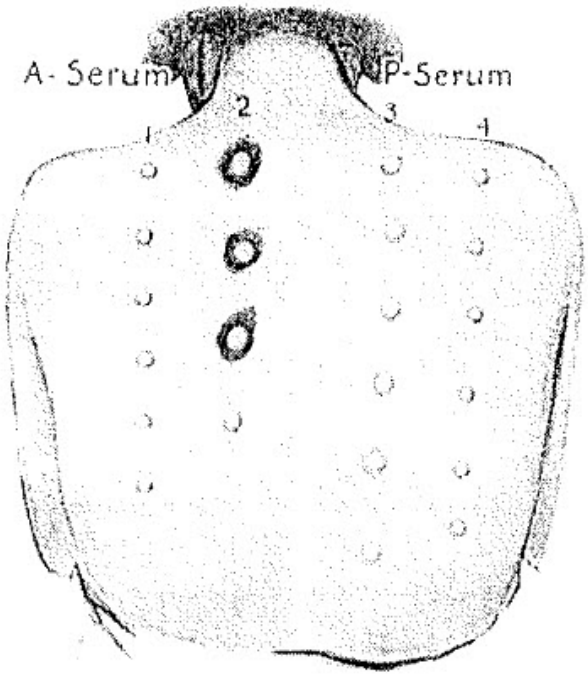
FIG 1. Percentages of SLIT treatments still ongoing at 1, 2, and 3 years after the initial prescription. *Upper panel,* Percentages for pollens and house dust mite SLITs. *Lower panel,* Percentages according to the reimbursement modality. Significant *P* values are indicated above the bars.

Mechanisms of Immunotherapy?

Understanding of Immunology

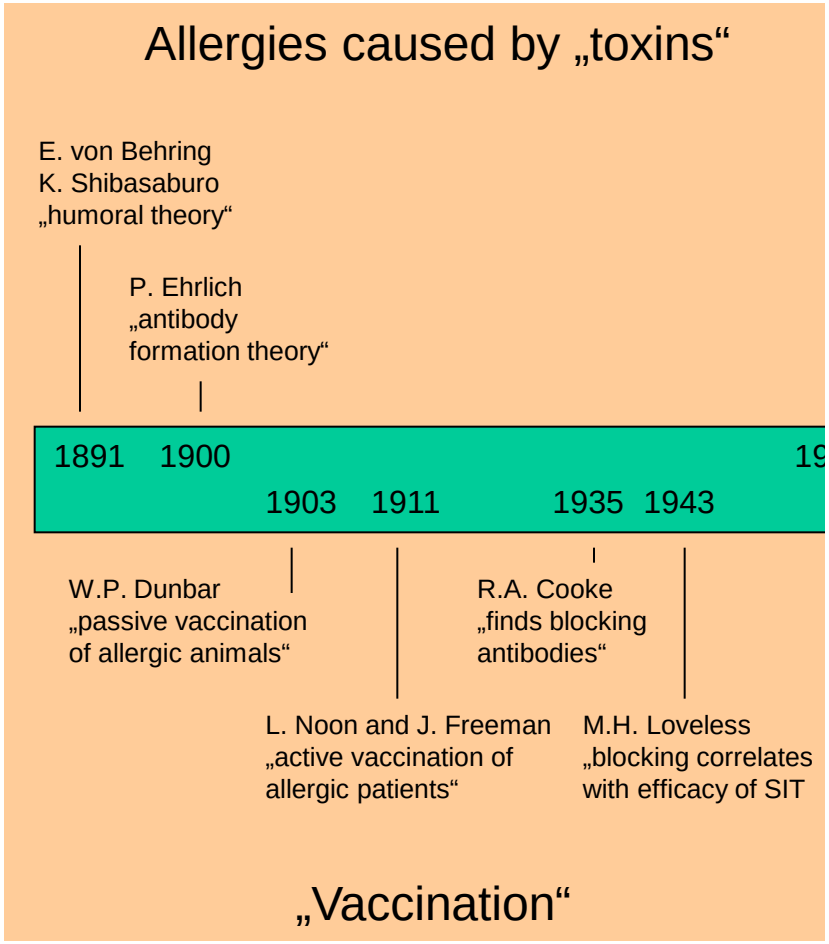


Interpretation of SIT



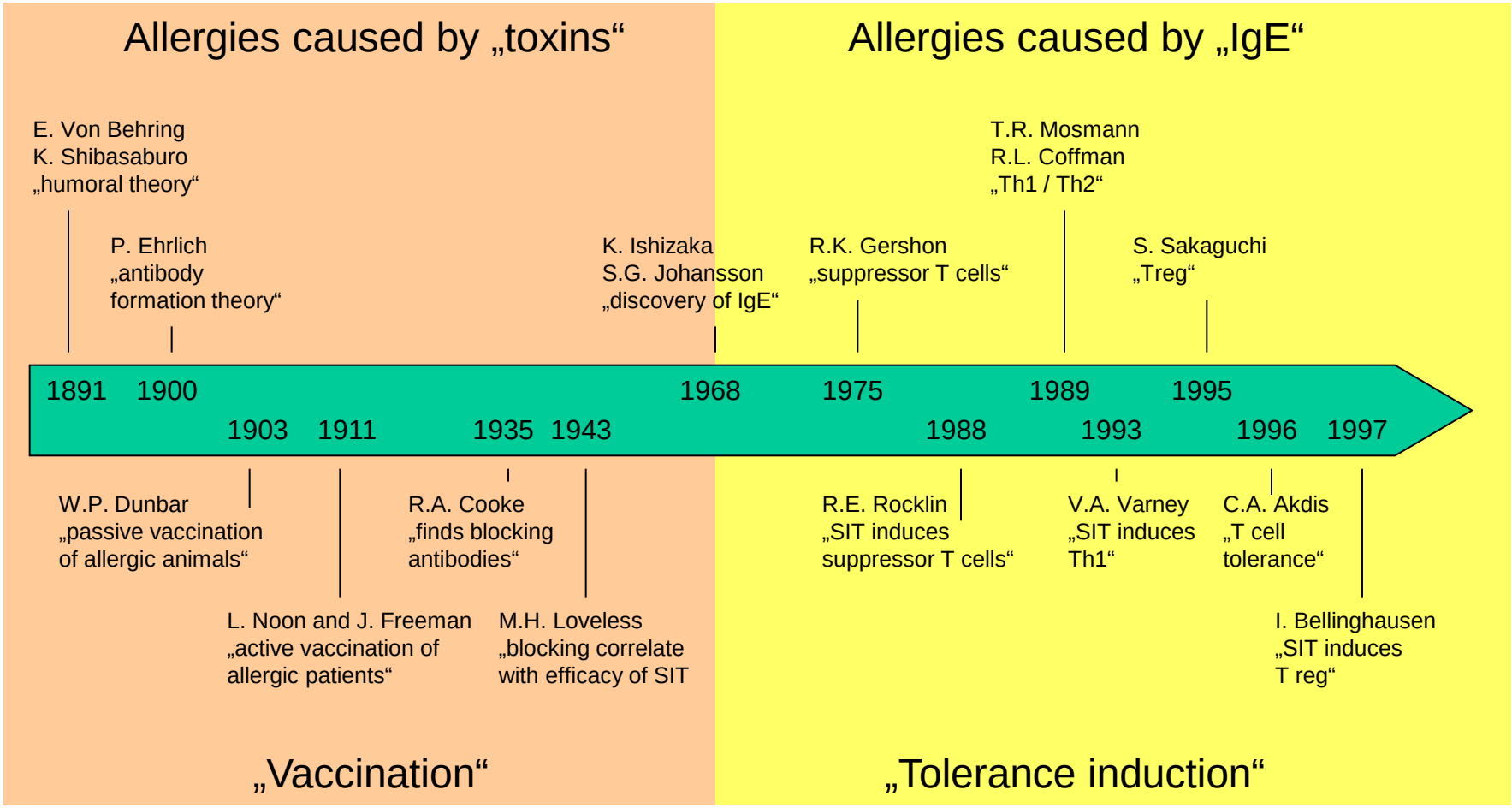
	A-serum				P-serum		
	1	2	Ragweed pollen extract units	Ragweed pollen extract units	3	4	
1:10	○	○	50	150	○	○	1:10
1:100	○	○	100	300	○	○	1:100
1:200	○	○	150	500	○	○	1:200
1:300	○	○	Saline control	700	○	○	1:300
1:400	○			1000	○	○	1:400
1:500	○			Saline control	○	○	1:500

Understanding of Immunology



Interpretation of SIT

Understanding of Immunology

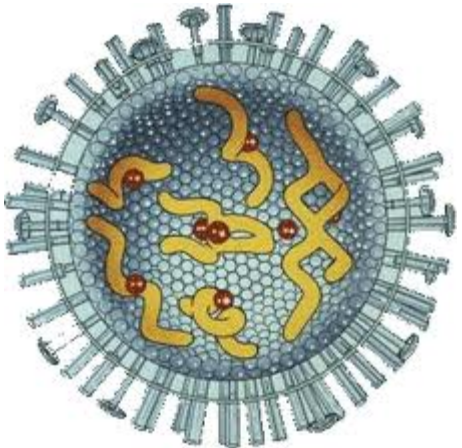


Interpretation of SIT

Tolerance or Vaccination?

Google images

influenza Search Images



Google images

hay fever Search Images

Flu:

Rhinitis
Conjunctivitis
Bronchitis

Hay fever:

Rhinitis
Conjunctivitis
Bronchitis

«Virus
macht Beschwerden»

«Immunsystem (IgE)
Macht Beschwerden»

Influenza A virus enhances IgE-mediated histamine release from human basophil leukocytes. Examination of the effect of viral neuraminidase and haemagglutinin

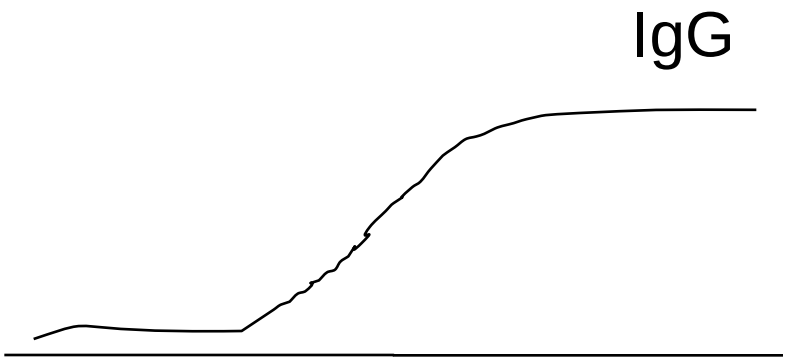
P. Clementsen, A. R. Douglas [1], J. J. Skehel [1], C. Hannoun [2], N. Bach-Mortensen [3] and S. Norn

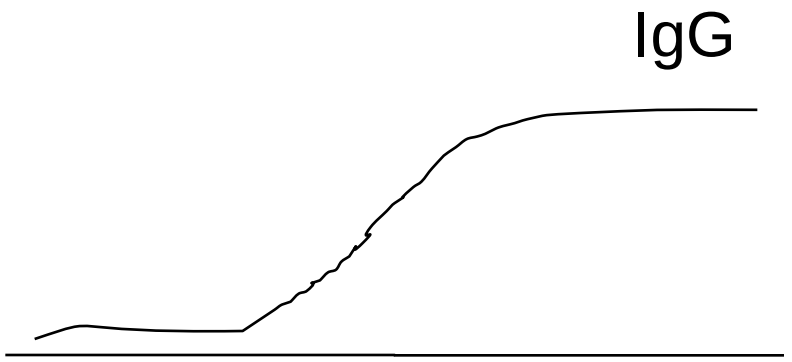
Dept. of Pharmacology, University of Copenhagen, Juliane Maries Vej 20, 2100 Copenhagen Ø, Denmark; [1] National Institute for Medical Research, Mill Hill, London NW7 1AA, UK; [2] Institut Pasteur, Unit of Viral Ecology, Paris, France; [3] Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark

IgE

Abstract

Histamine release caused by anti-IgE was examined in leukocyte suspensions from 10 healthy individuals. Influenza A virus was found to enhance the histamine release but did not release histamine *per se*. When monoclonal antibodies directed against the viral neuraminidase were included in the samples, the potentiating effect of the virus was completely abolished. The same occurred using a neuraminidase inhibitor. However, monoclonal antibodies directed against the viral haemagglutinin also abolished the potentiation. A binding of virus to the basophil cell surface by haemagglutinin therefore seems to be necessary for the viral neuraminidase to cause potentiation of mediator release.


IgG
T reg
Th1

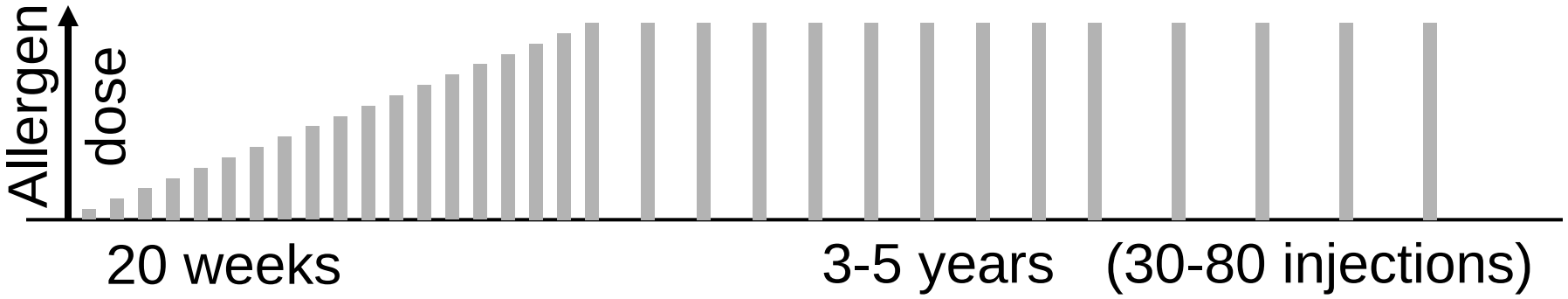

IgG
T reg
Th1

How can this be improved?

Allergen Immunotherapy

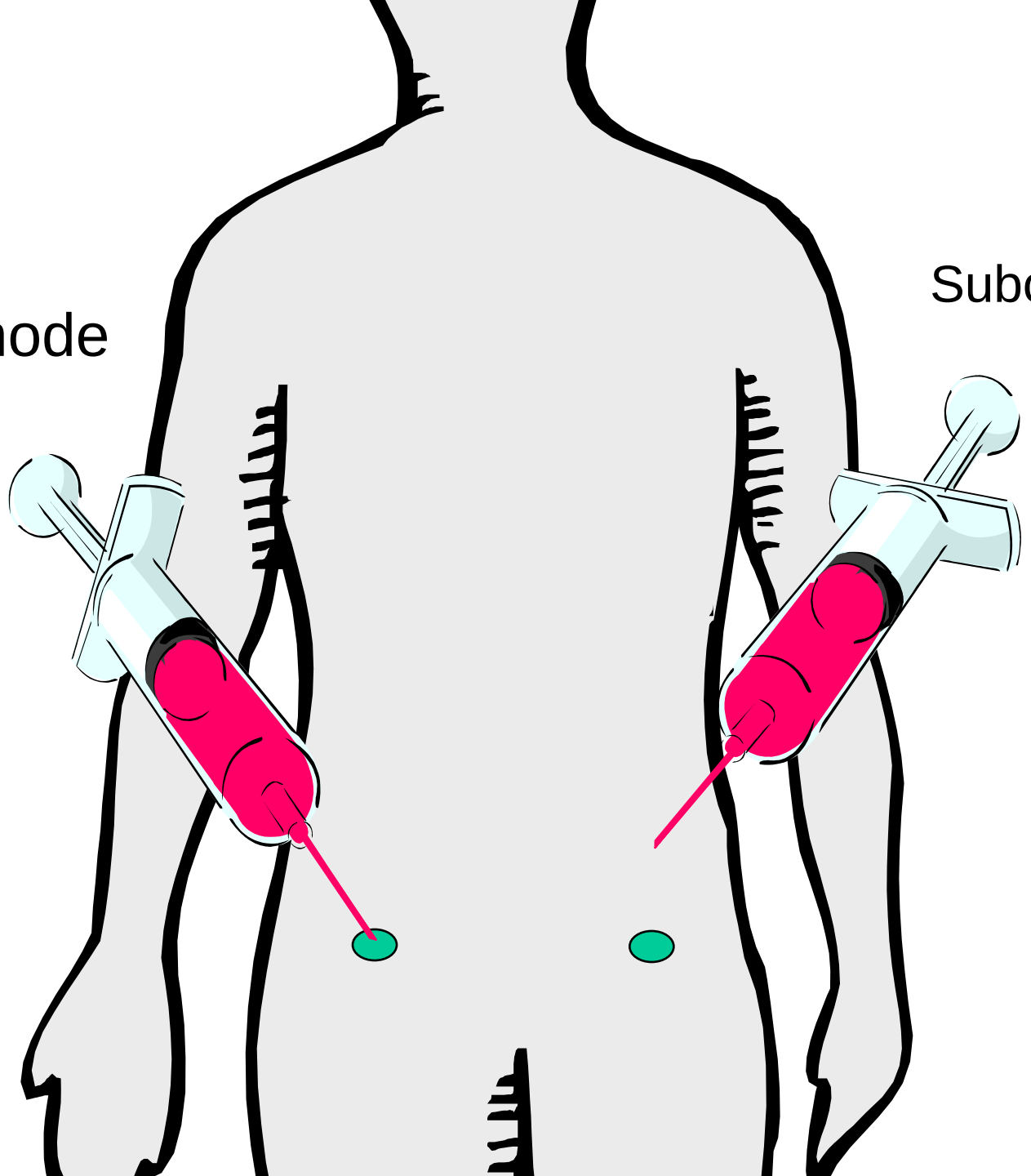
Time consuming

Allergic side effects

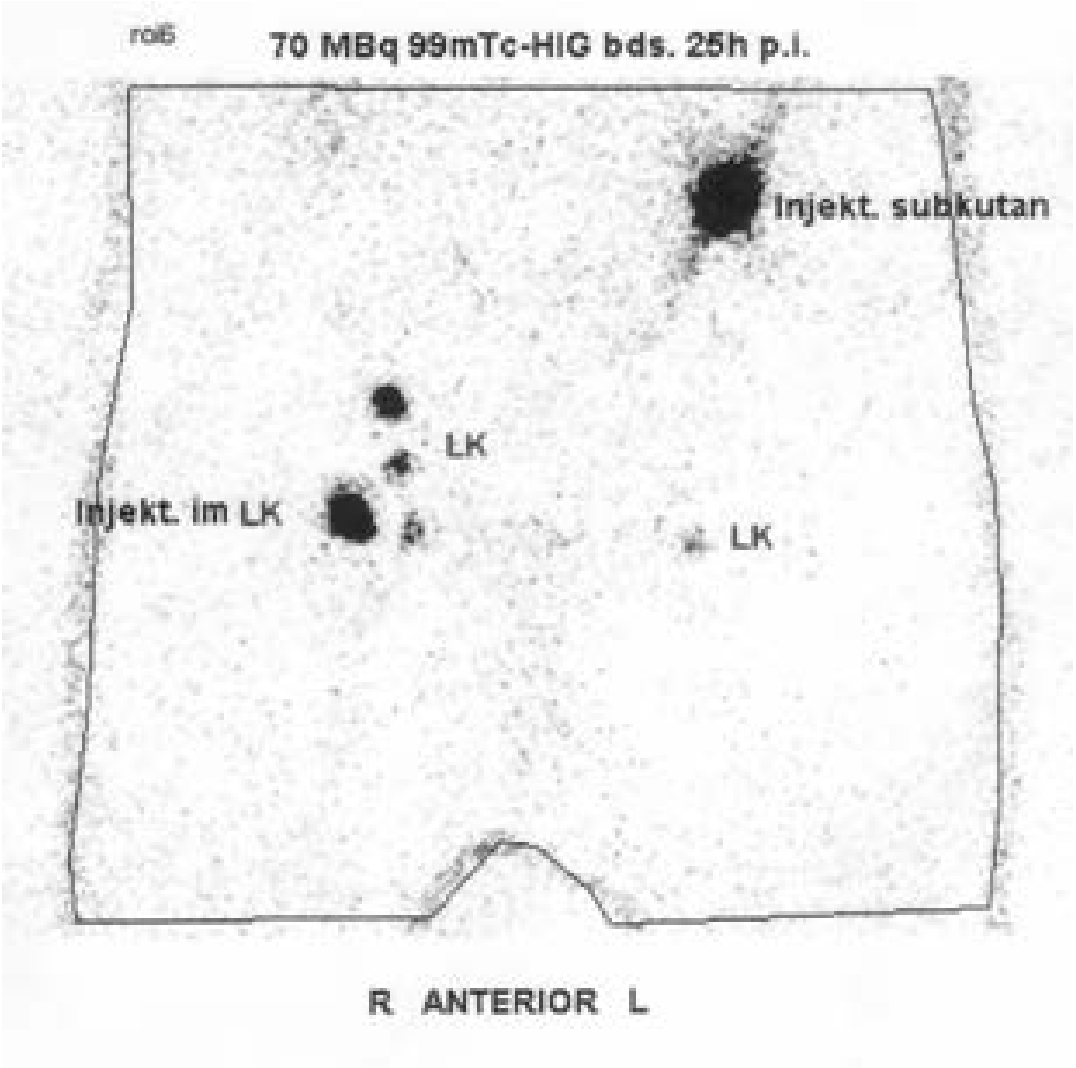


into
lymph node

Subcutaneous

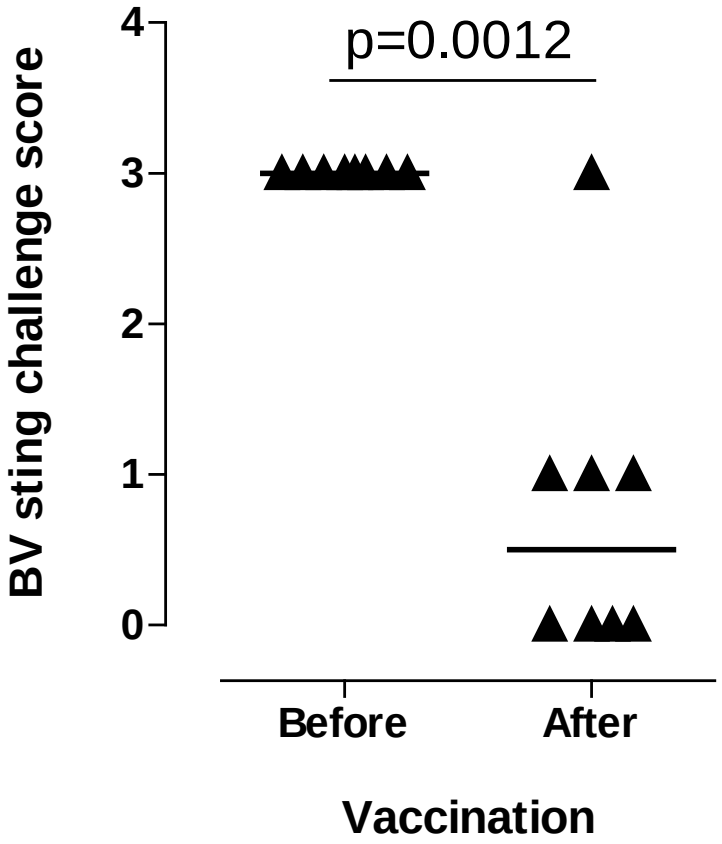


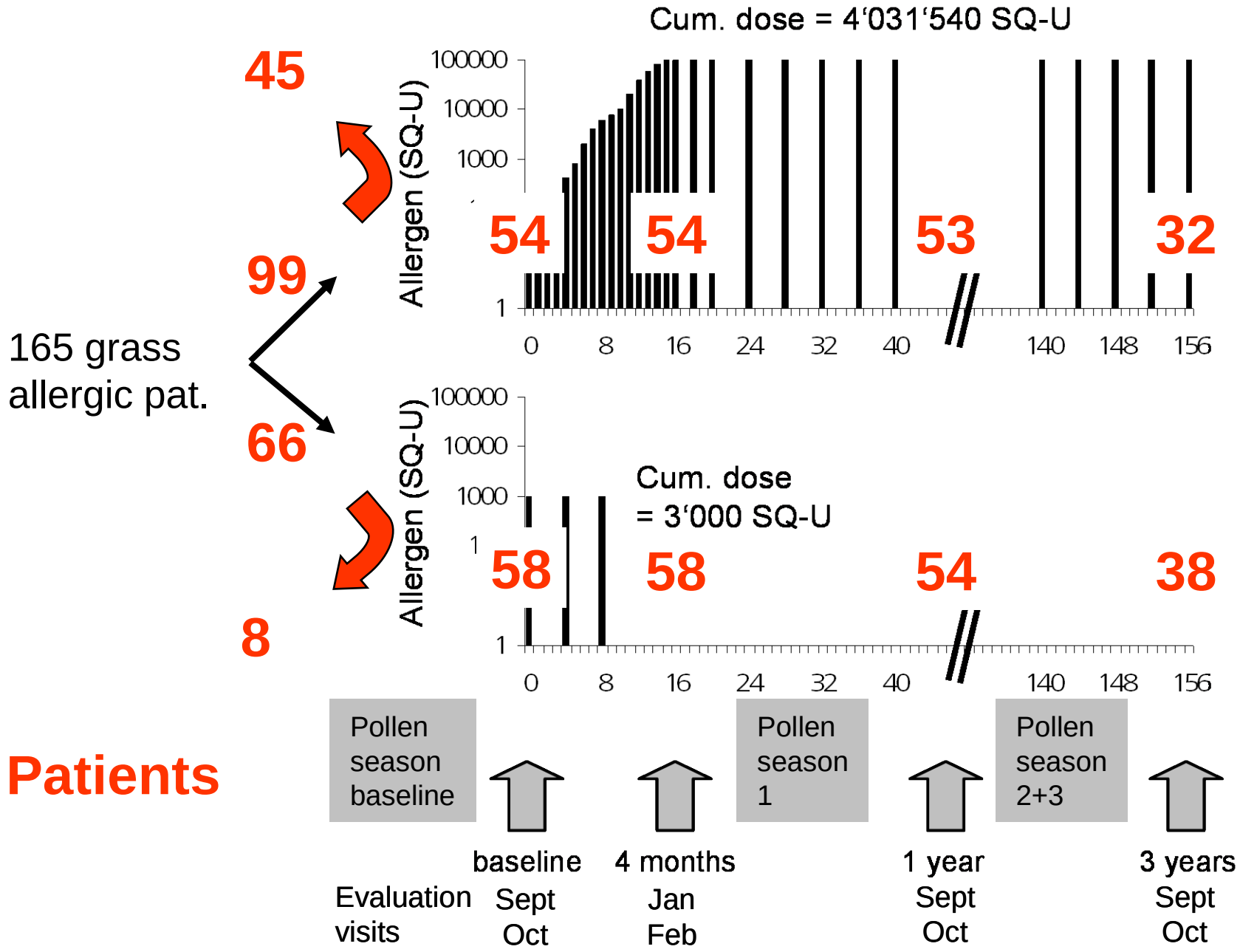
25 h


roi6
70 MBq 99mTc-HIG bds. 25h p.i.
Injekt. subkutan
LK
Injekt. im LK
LK
R ANTERIOR L


Dräger

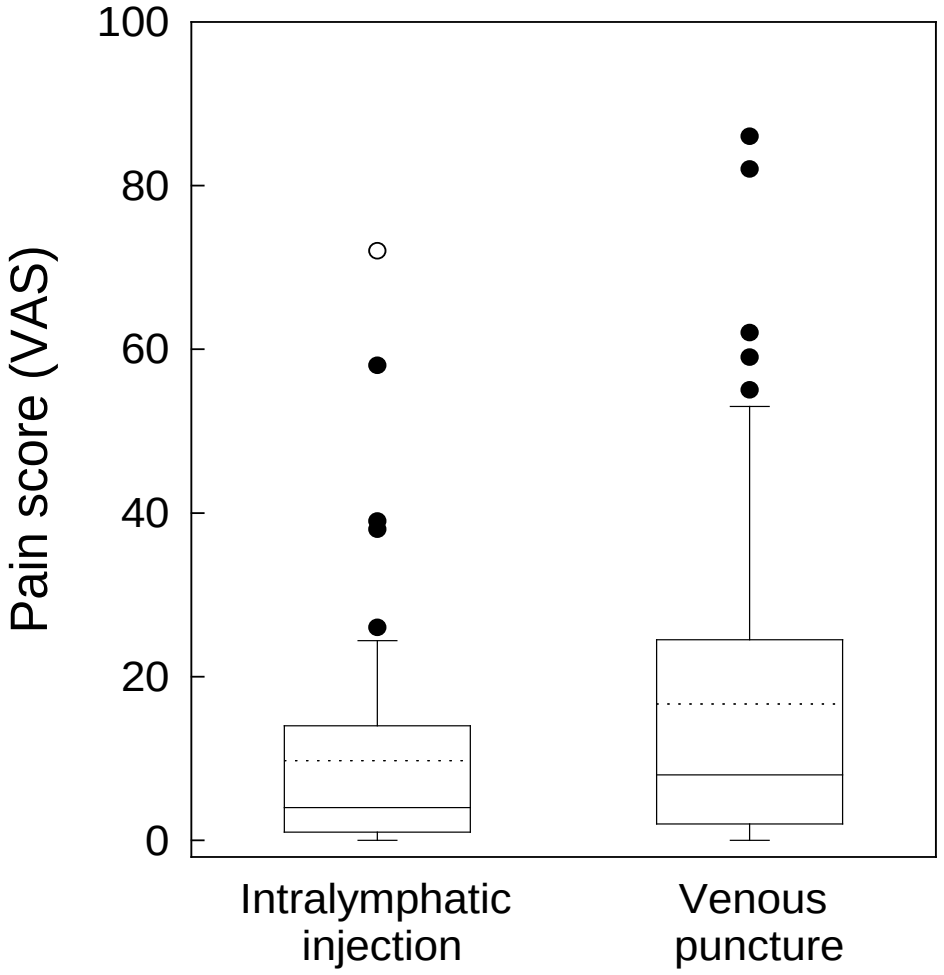
Sting Provocation





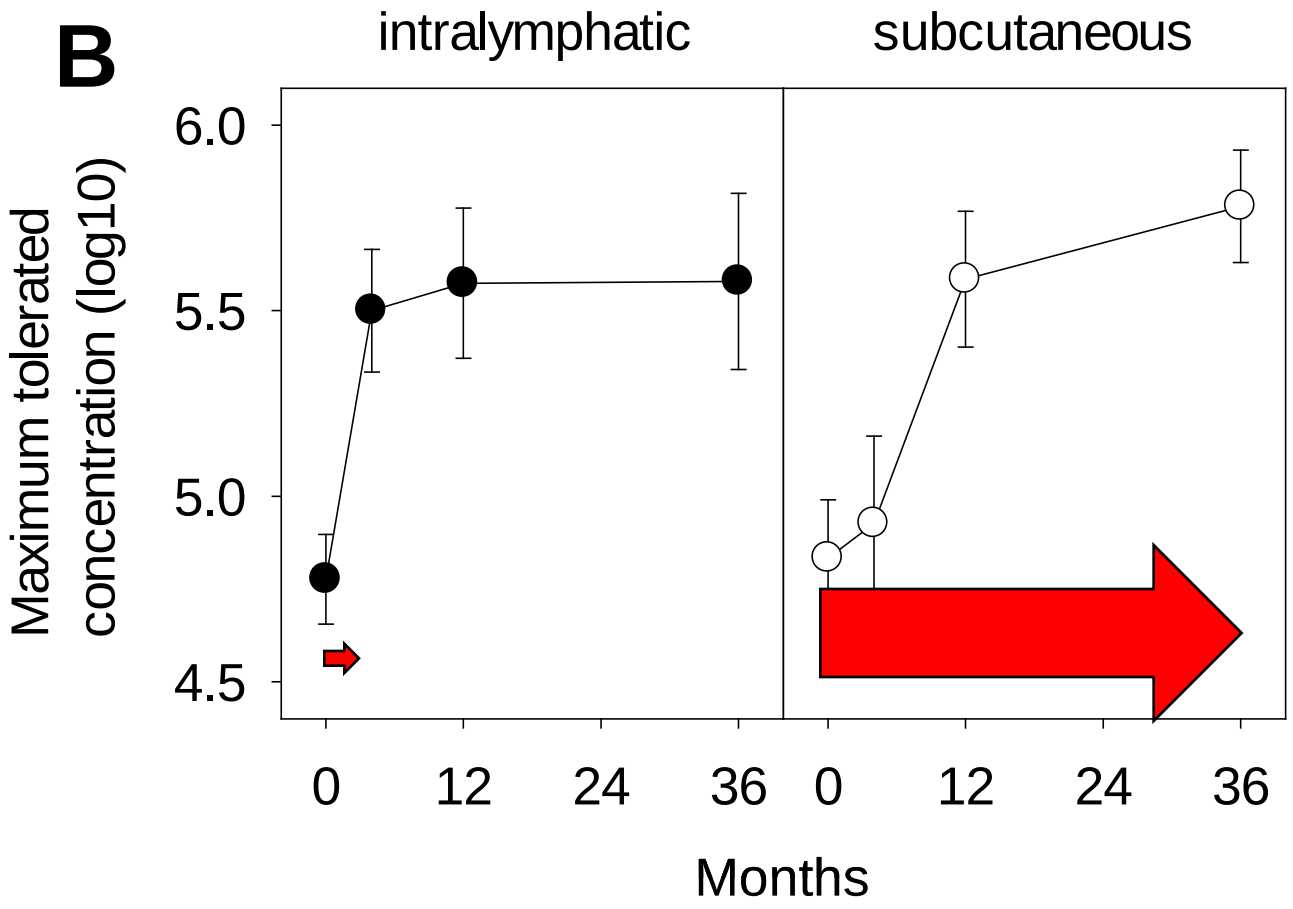
Senti et al. PNAS 2008

Pain?



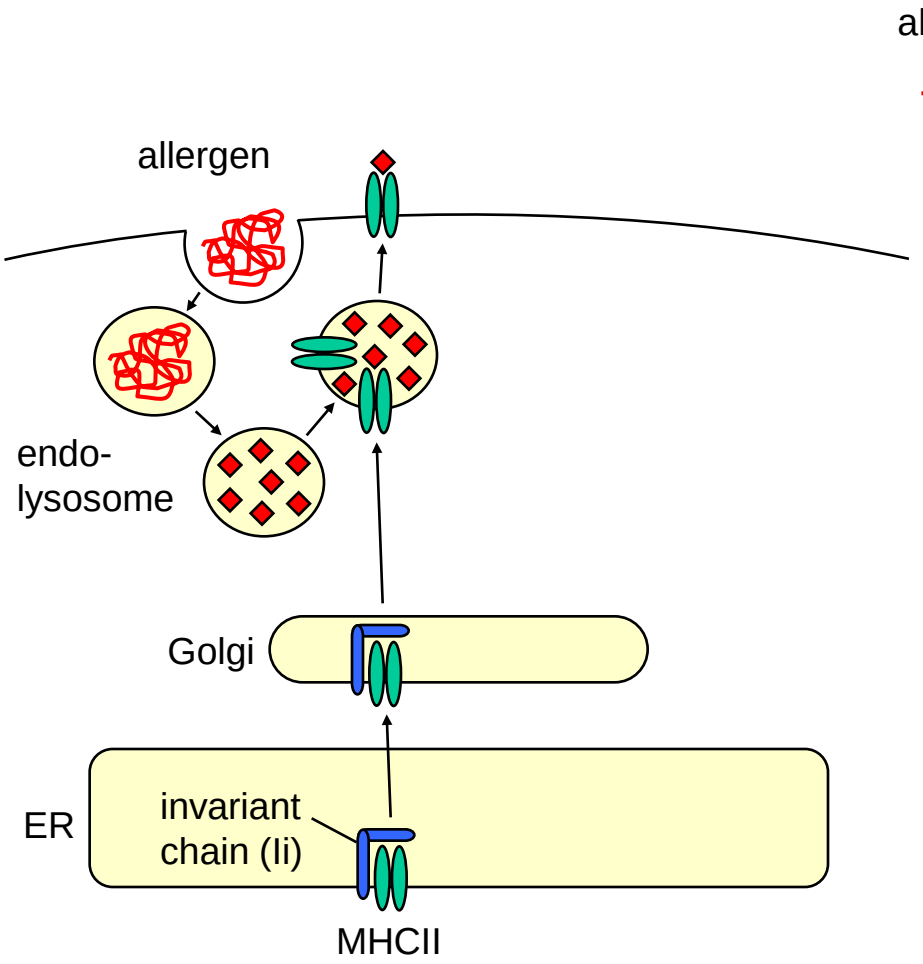
Senti et al. PNAS 2008

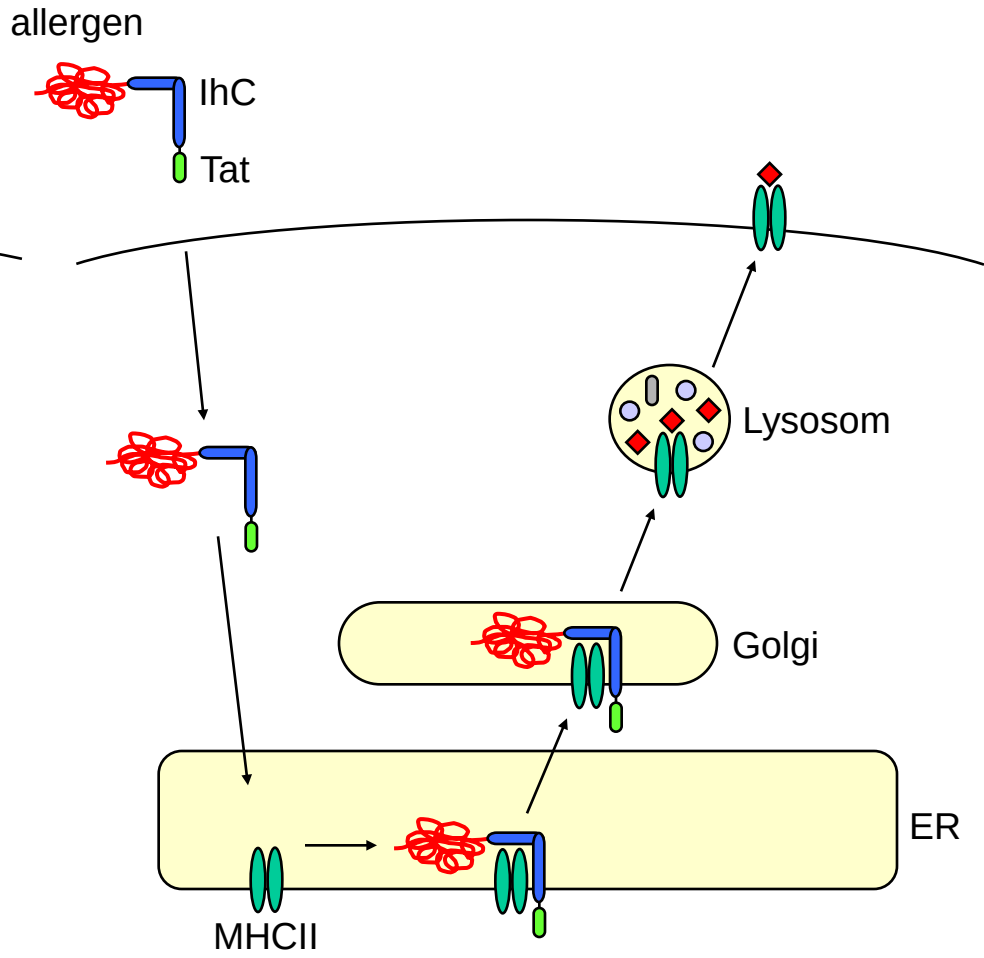
Nasal Provocation Test



Senti et al. PNAS 2008

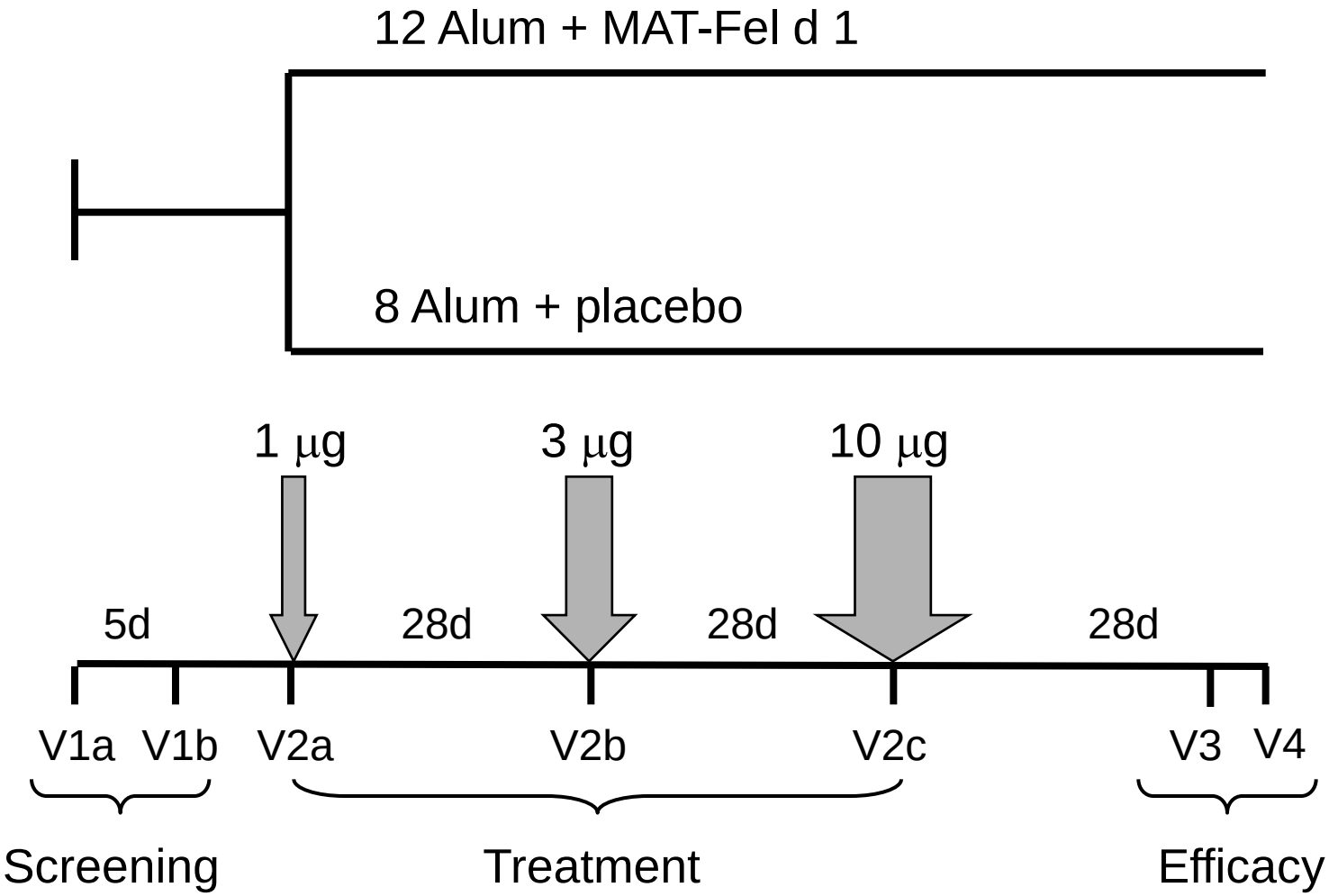
Antigen Presentation



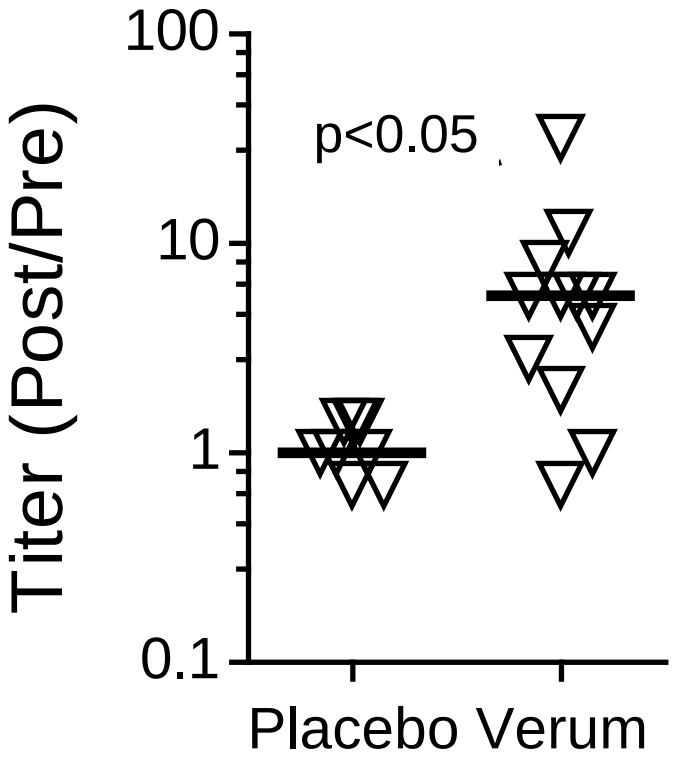


Matinez-Gómez et al. Allergy 2009

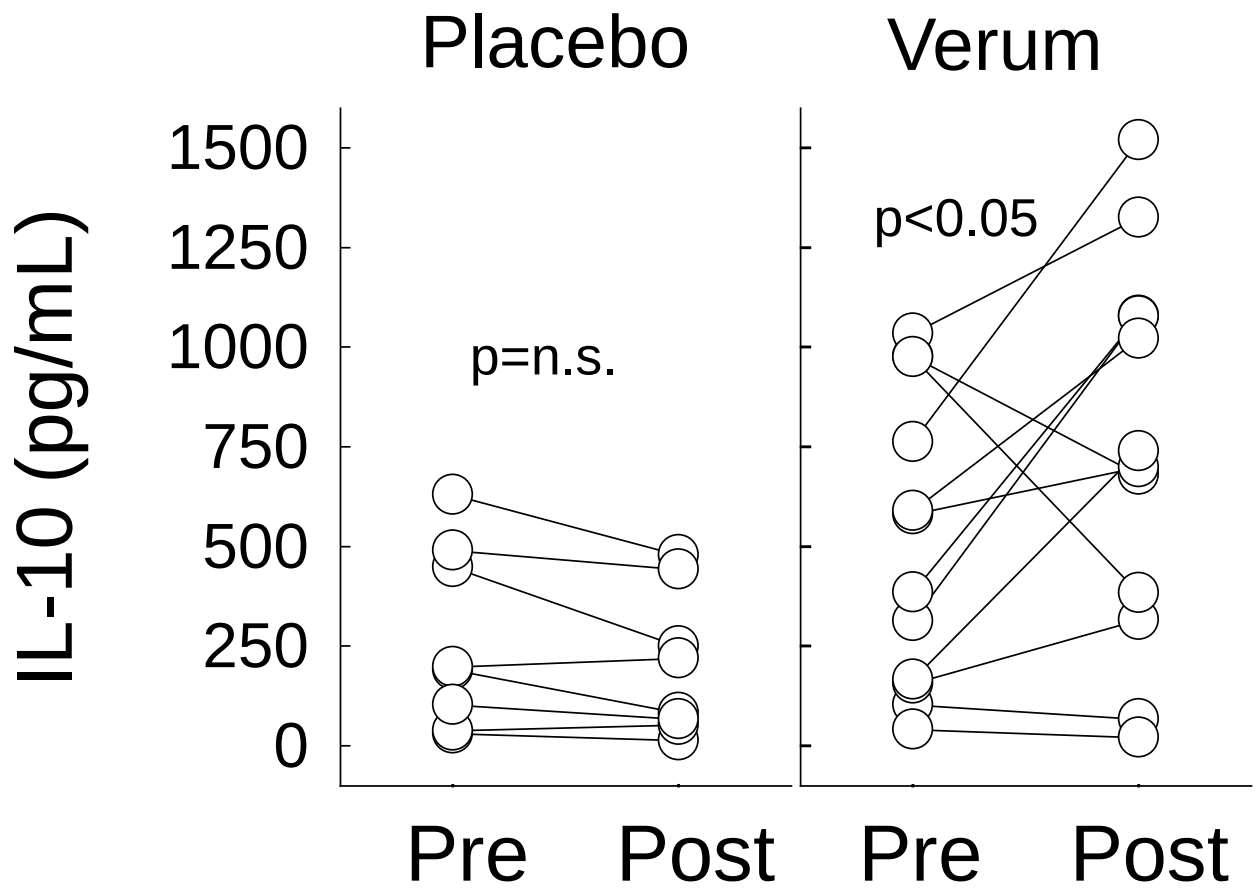
IVN-CAT-001b


12 Alum + MAT-Fel d 1
8 Alum + placebo
1 μg
3 μg
10 μg
5d
28d
28d
28d
V1a
V1b
V2a
V2b
V2c
V3
V4
Screening
Treatment
Efficacy

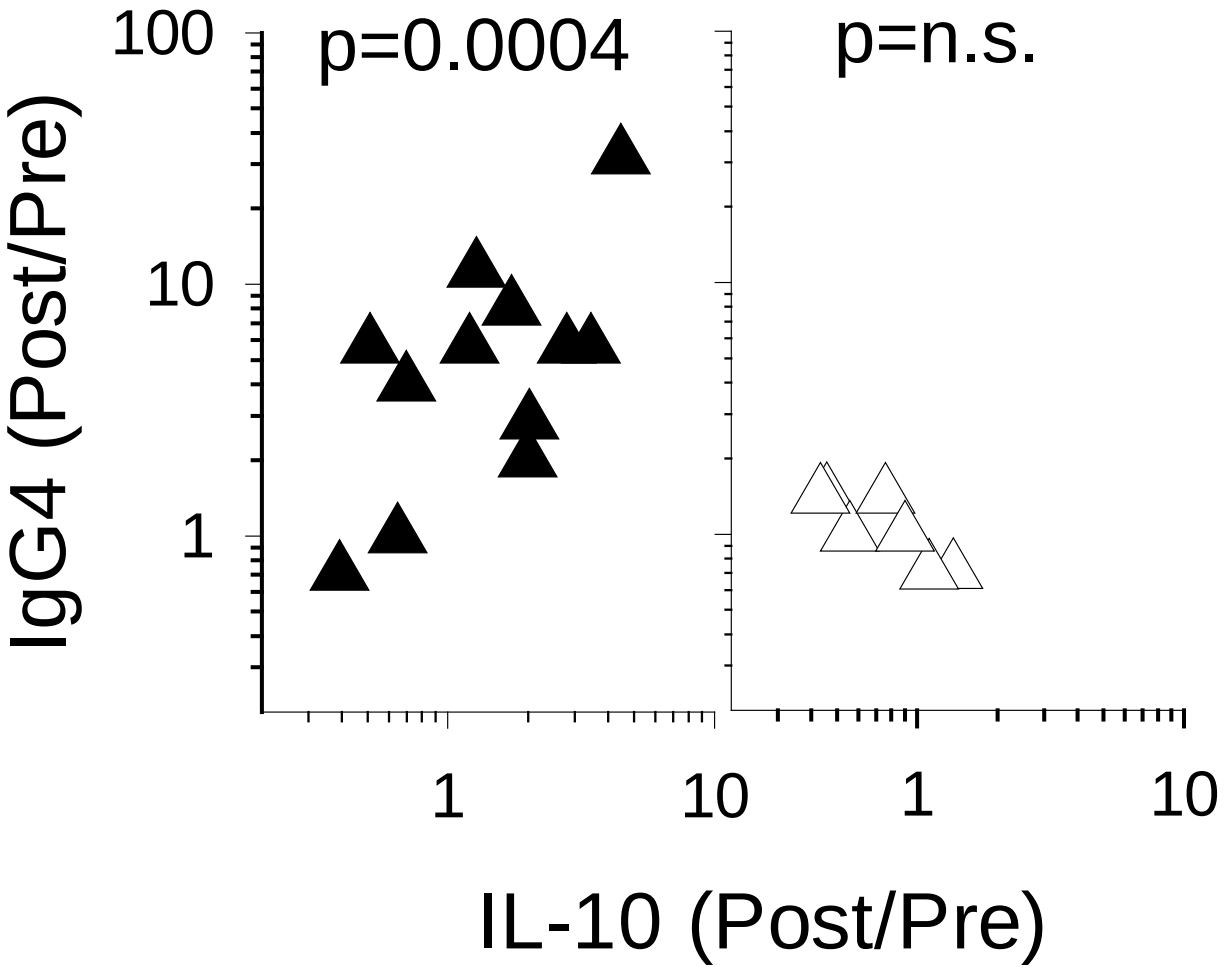
IgG4



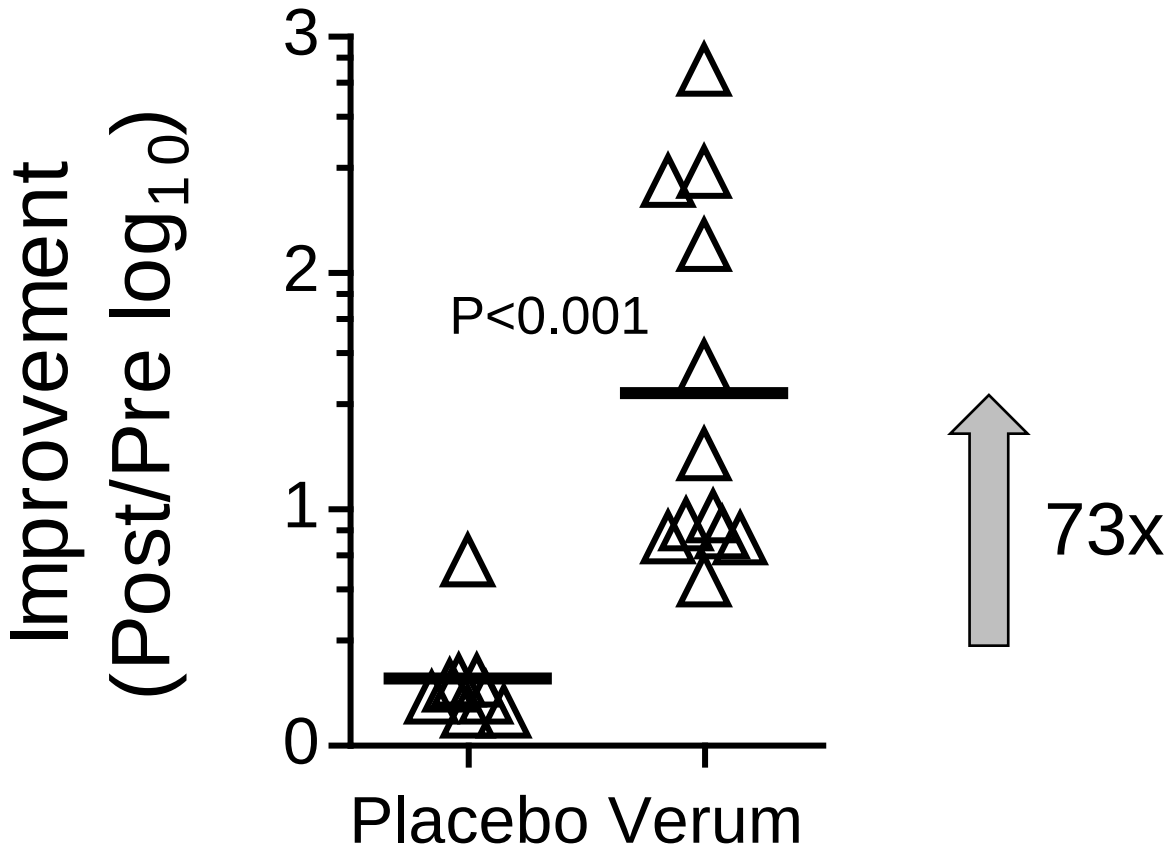
IL-10


Placebo
Verum
IL-10 (pg/mL)
1500
1250
1000
750
500
250
0
p=n.s.
p<0.05
Pre
Post
Pre
Post

IL-10 Correlates with IgG4



Nasal Tolerance



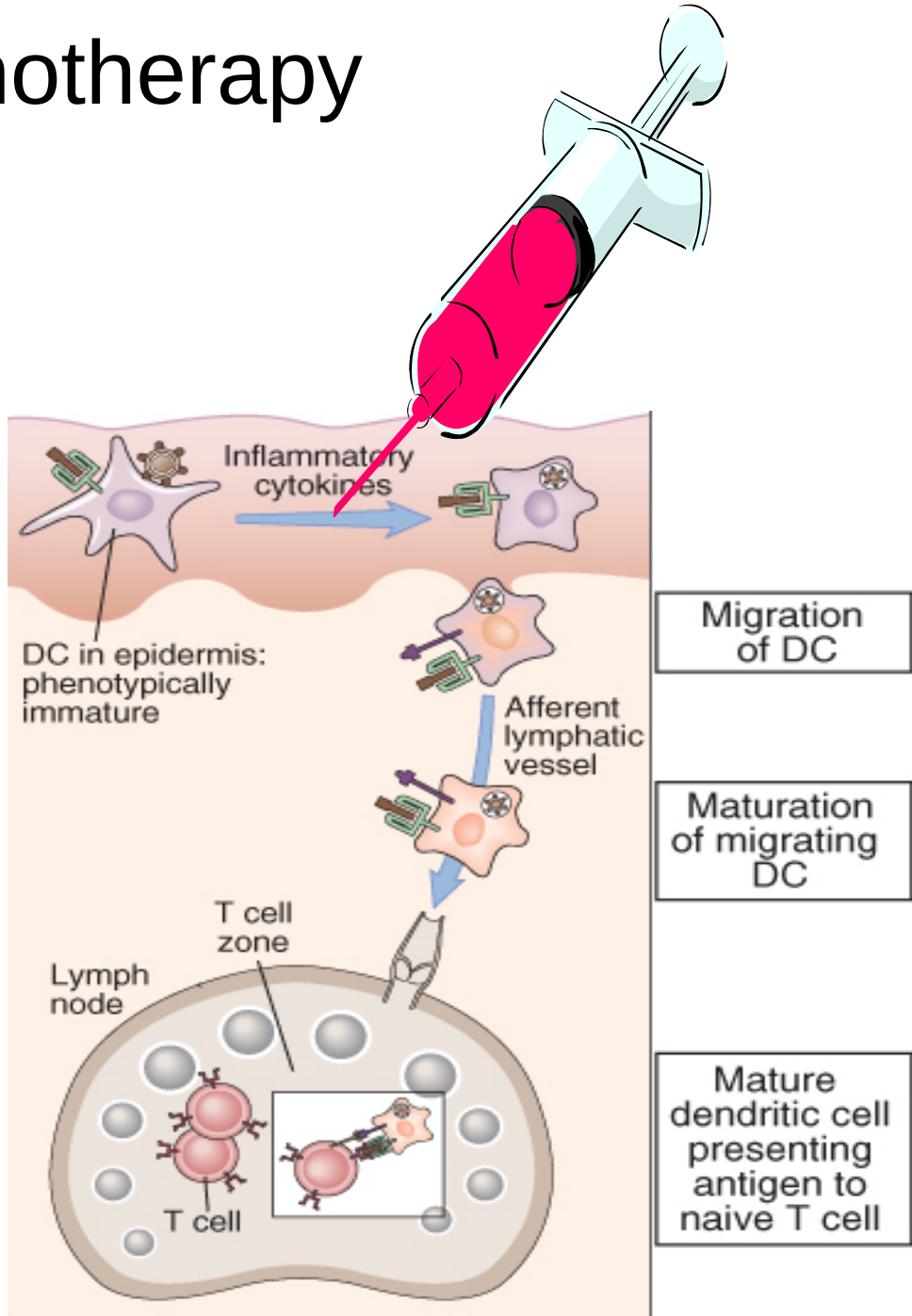
DISCOVER®
MAGAZINE

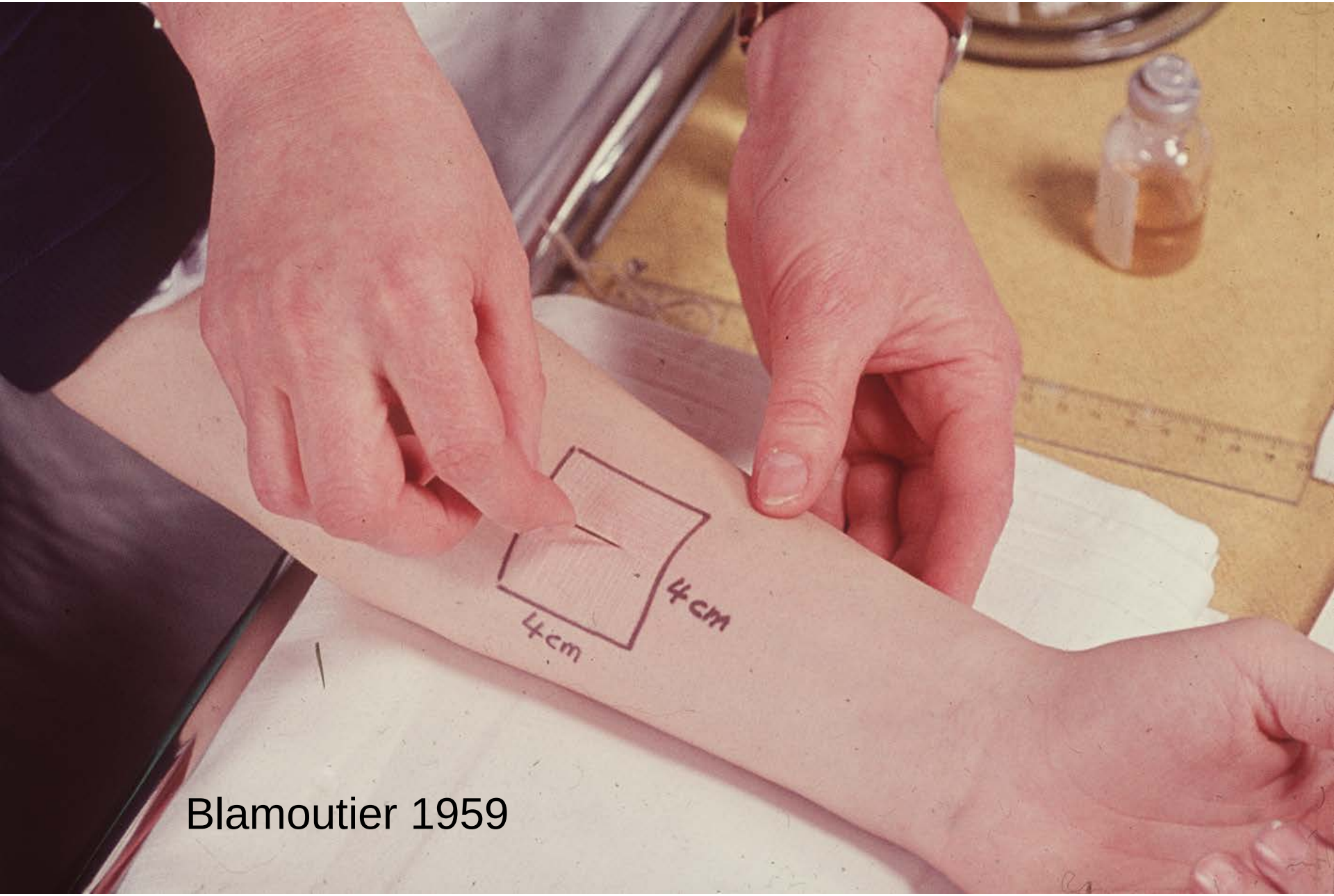
Not Exactly Rocket Science

Lymph node injections provide safer, faster and easier relief against hay fever

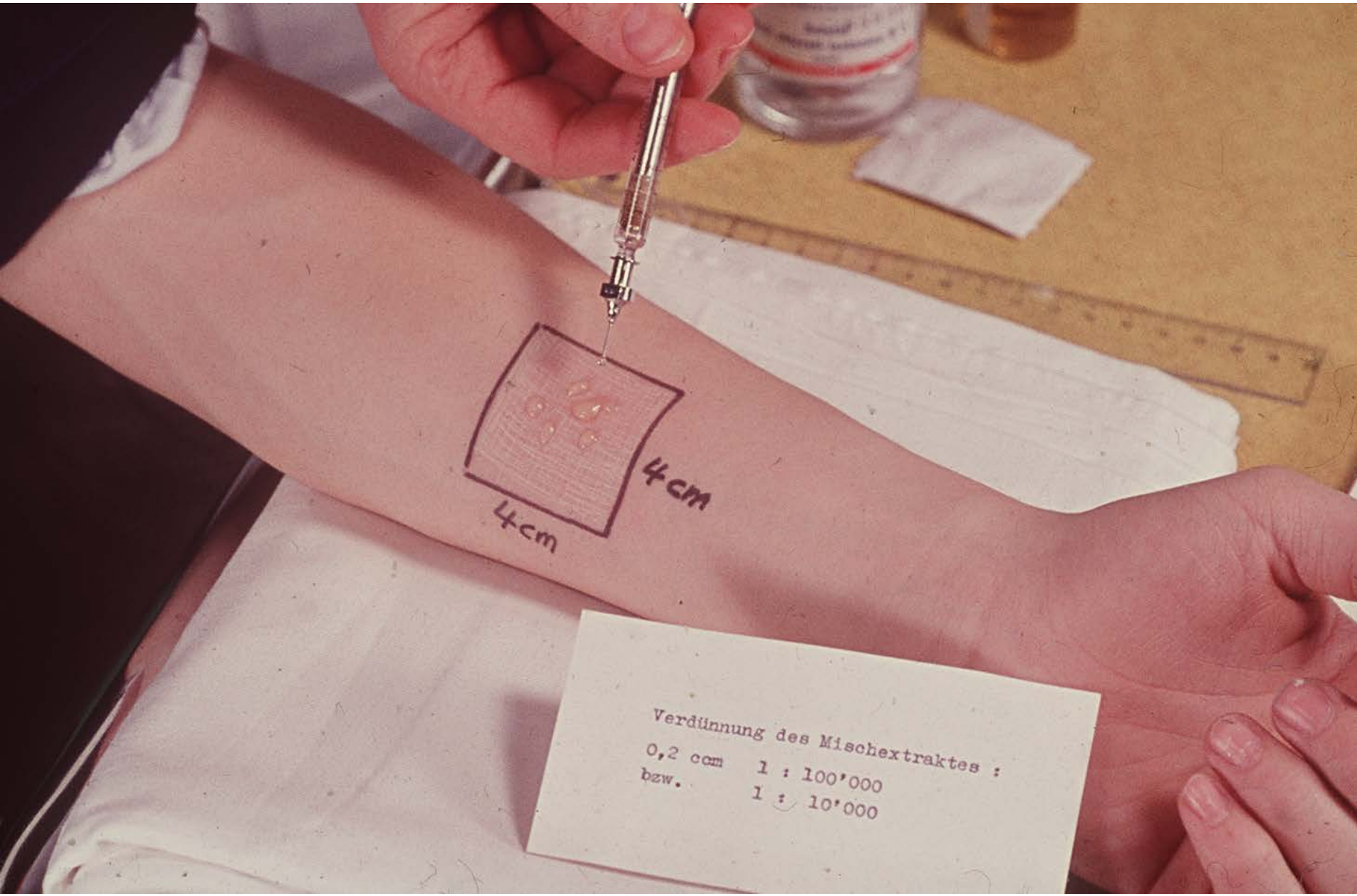
Epicutaneous Immunotherapy

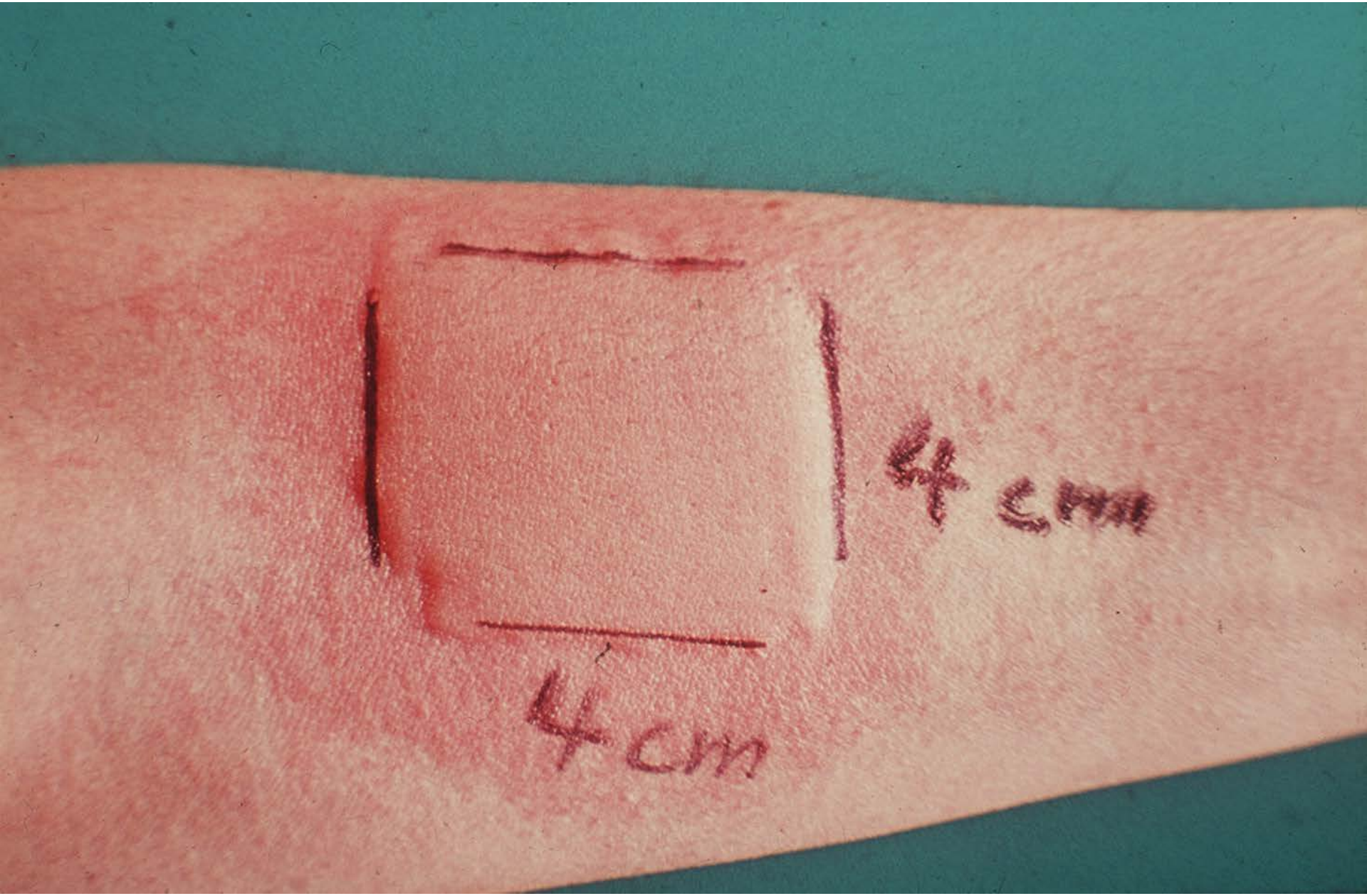
(EPIT)



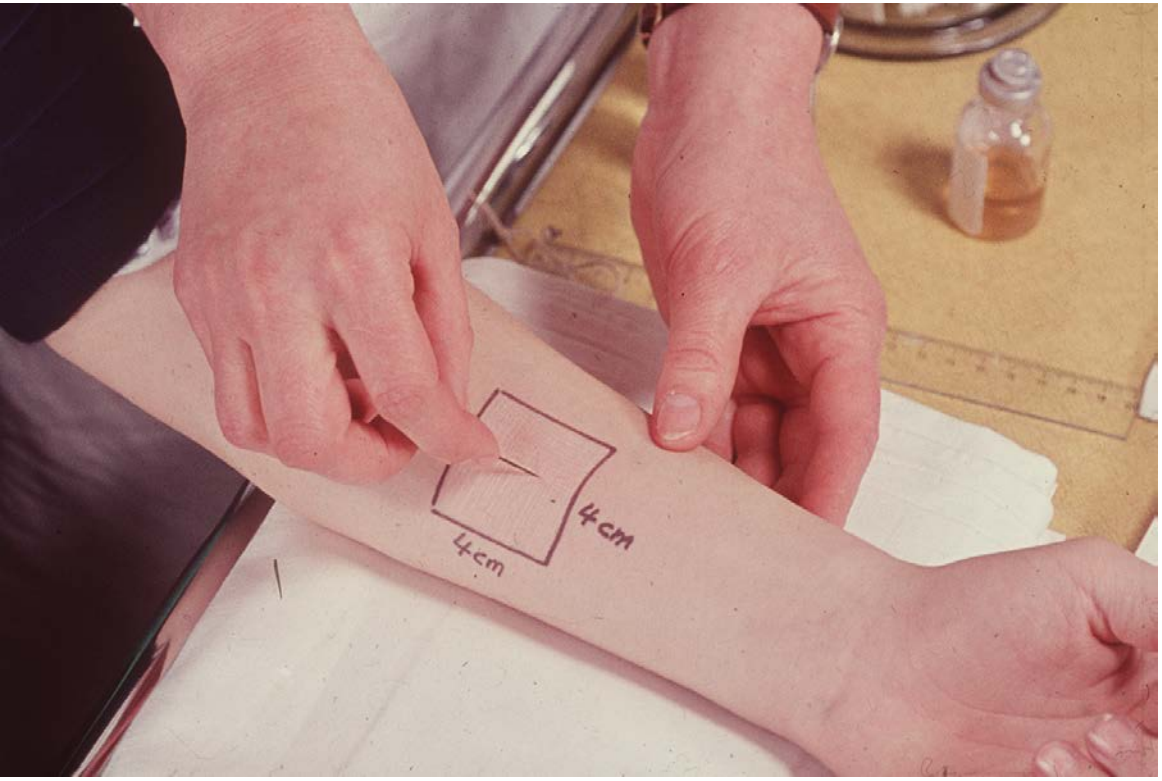


Blamoutier 1959


4cm
4cm
Verdünnung des Mischextraktes :
0,2 ccm 1 : 100'000
bzw. 1 : 10'000


4 cm
4 cm

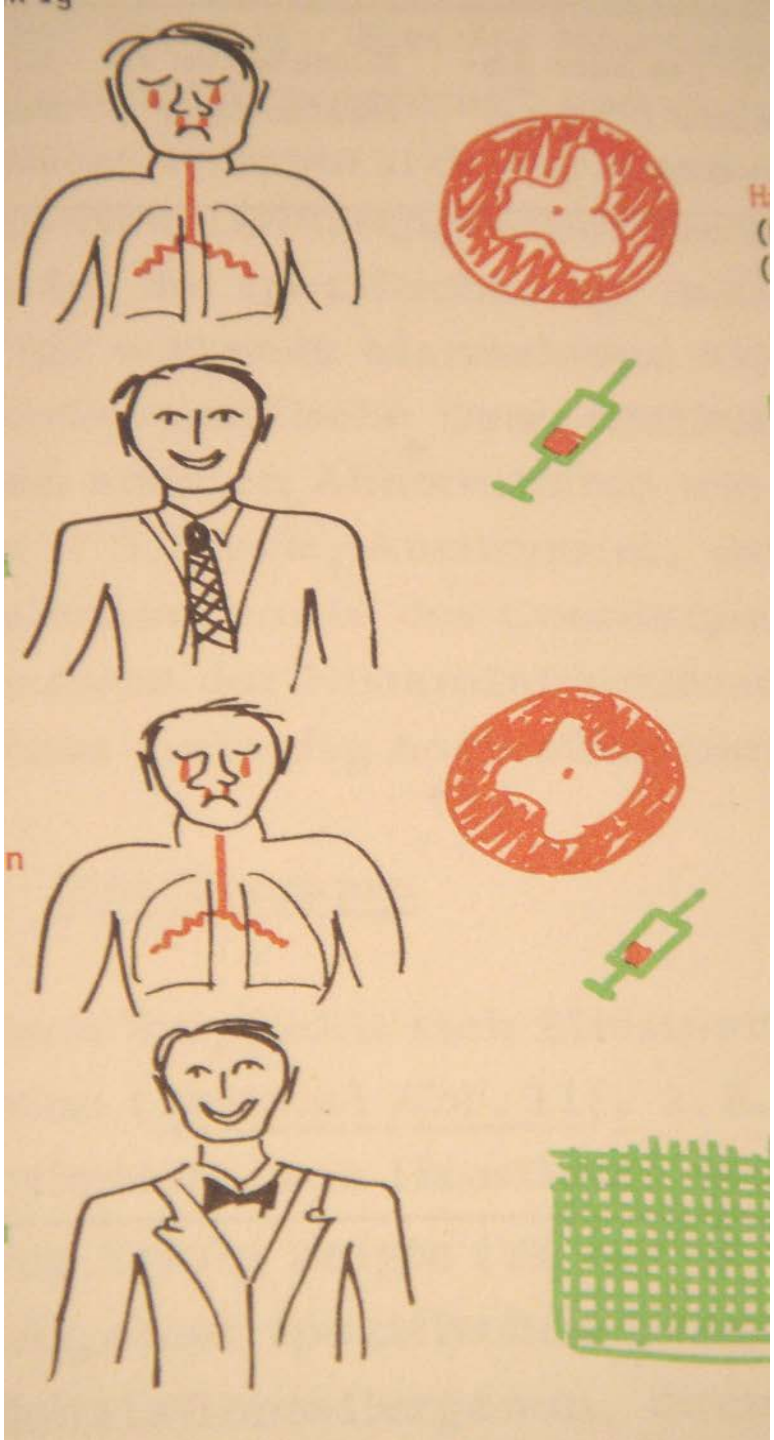
Scarification (Blamoutier 1959)



Eichenberger, H. and Storck, H.
Co-seasonal desensitization of pollinosis with the scarification method of Blamoutier.
Acta Allergologica, *XXI:* 261-267, 1965.

1961 “improvement or complete relief”	found in 35 of 42 patients
1962 “amelioration”	found in 57 of 72 patients
1963 “amelioration”	found in 52 of 60 patients
1964 “amelioration”	found in 118 of 141 patients

Reviewed in Senti et al. Allergy 2001



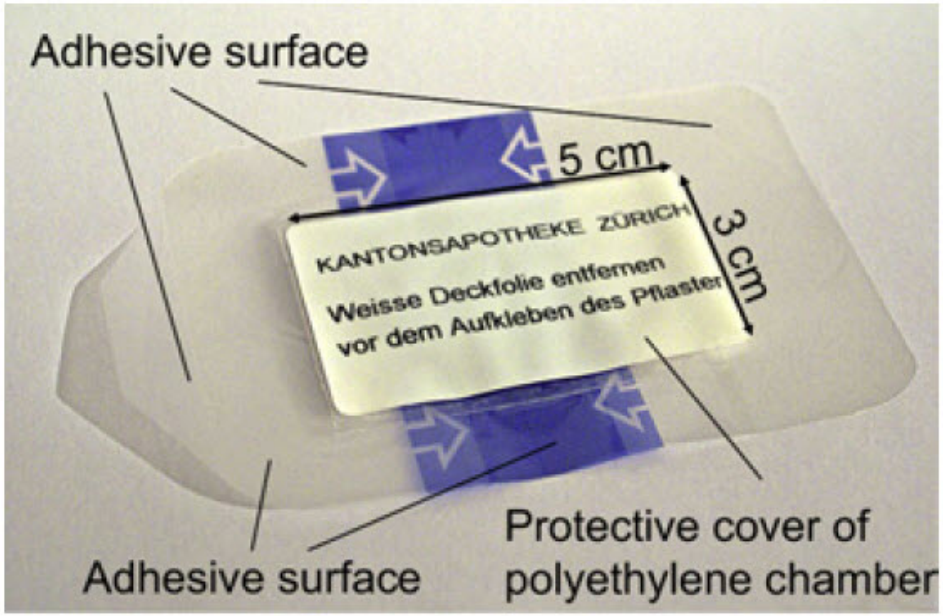
Storck H.

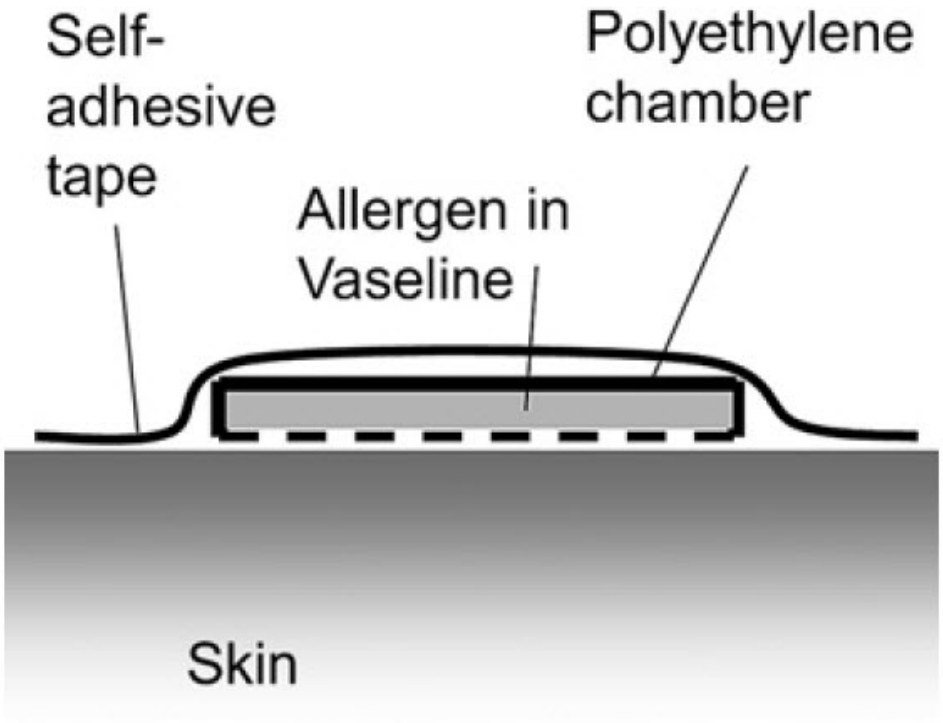
Allergie - Allergie und Praxis

Huber Verlag

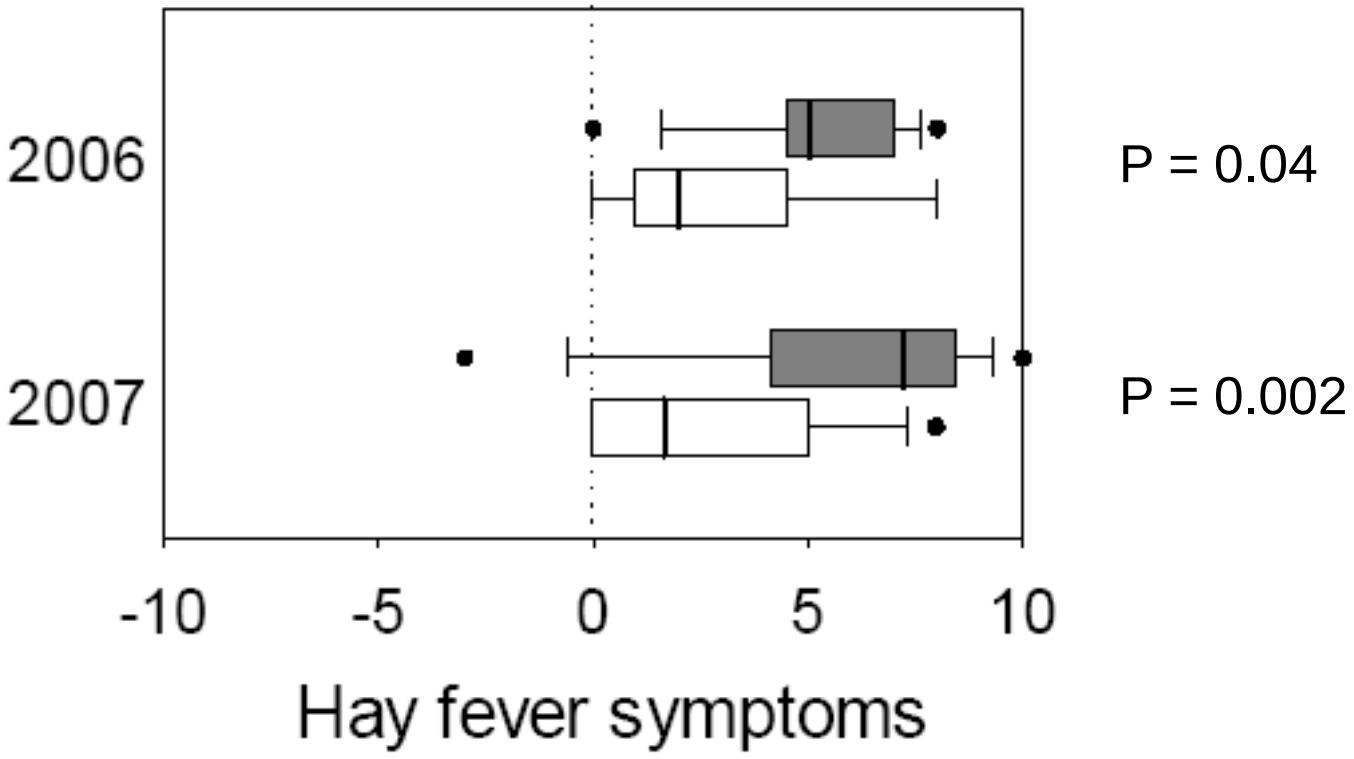

Scotch
Transparent Tape
1/2 in x 500 in
127mm x 127m
(13.8 yd)
3M

6x

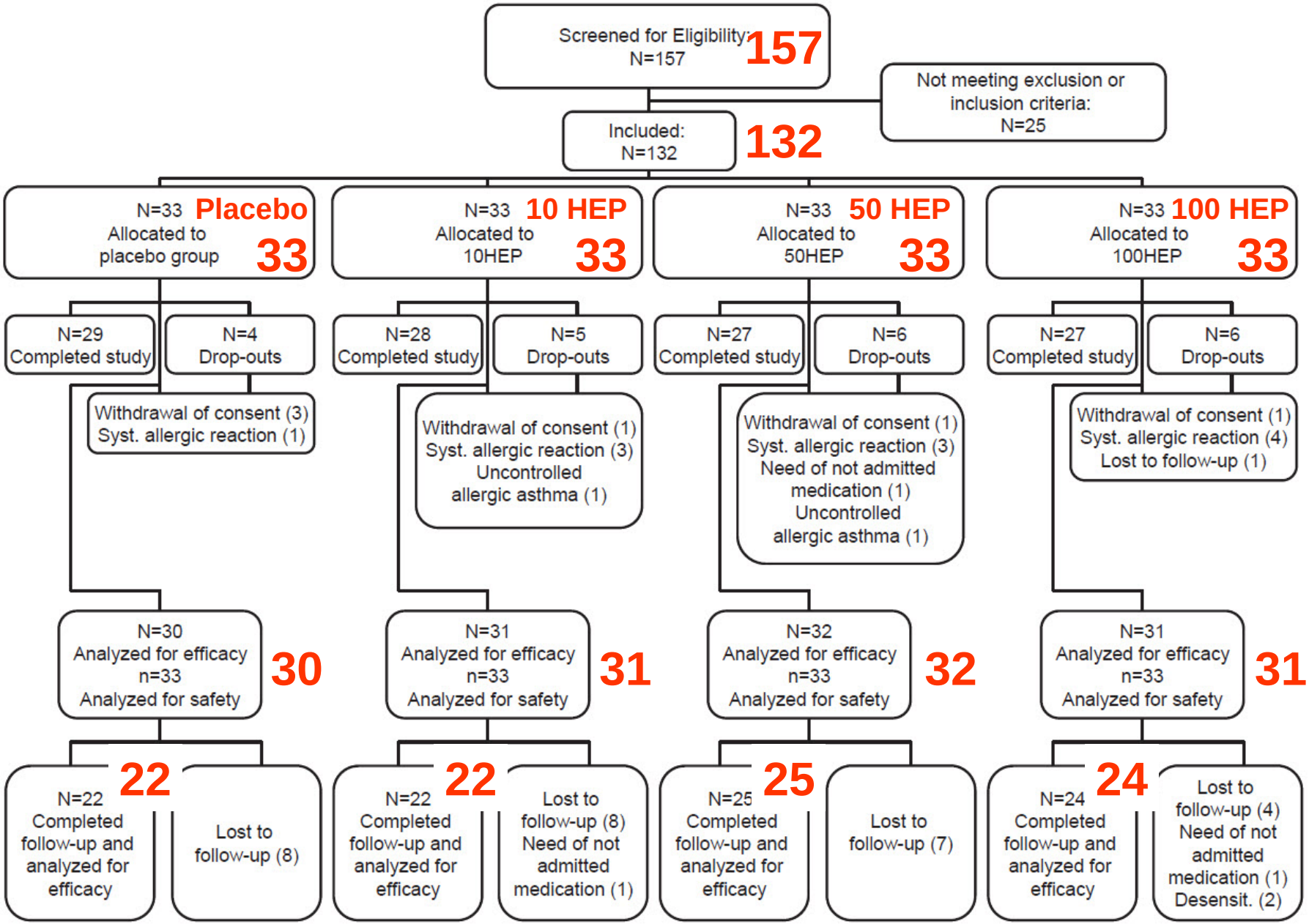

Adhesive surface
5 cm
3 cm
KANTONSAPOTHEKE ZÜRICH
Weisse Deckfolie entfernen
vor dem Aufkleben des Pflaster
Adhesive surface
Protective cover of
polyethylene chamber


Self-
adhesive
tape
Polyethylene
chamber
Allergen in
Vaseline
Skin

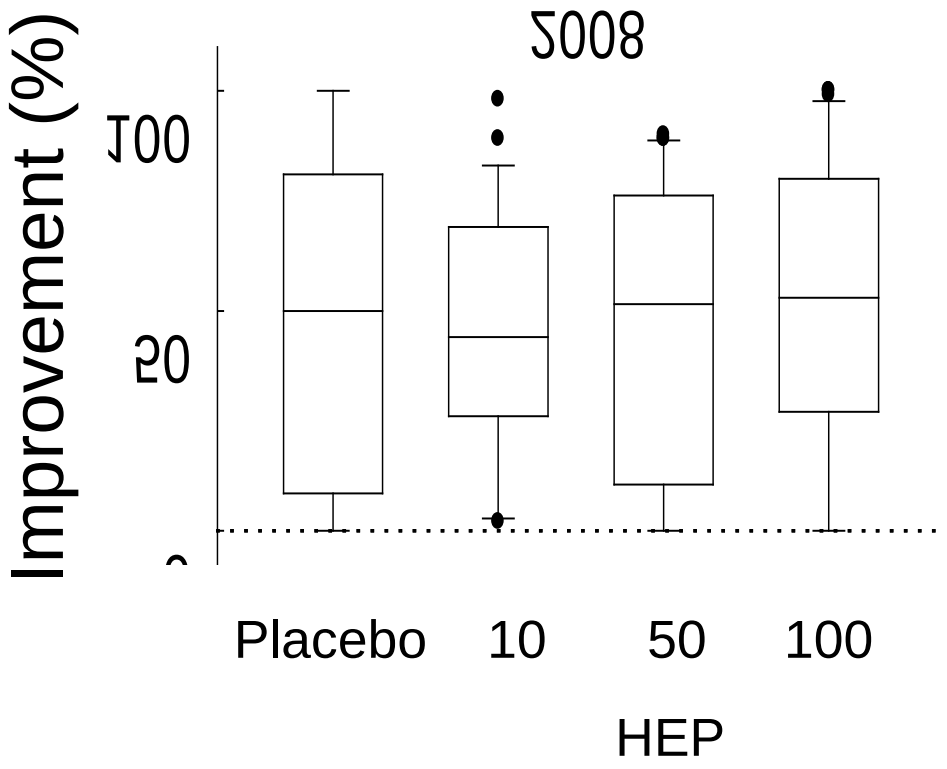
Symptoms



Senti et al. JACI 2009

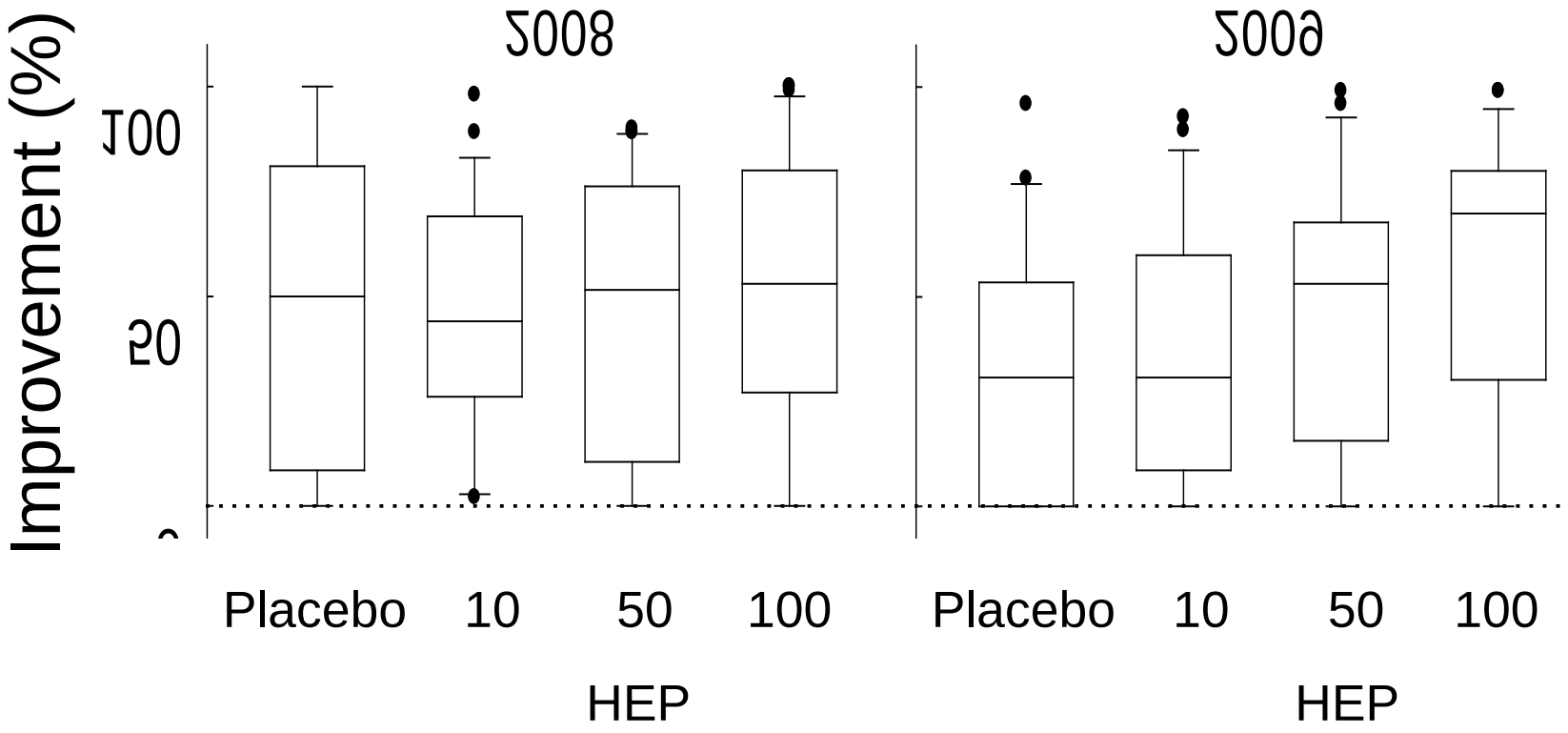

Screened for Eligibility:
N=157
157
Not meeting exclusion or inclusion criteria:
N=25
Included:
N=132
132
N=33 Placebo
Allocated to placebo group
33
N=33 10 HEP
Allocated to 10HEP
33
N=33 50 HEP
Allocated to 50HEP
33
N=33 100 HEP
Allocated to 100HEP
33
N=29 Completed study
N=4 Drop-outs
N=28 Completed study
N=5 Drop-outs
N=27 Completed study
N=6 Drop-outs
N=27 Completed study
N=6 Drop-outs
Withdrawal of consent (3)
Syst. allergic reaction (1)
Withdrawal of consent (1)
Syst. allergic reaction (3)
Uncontrolled allergic asthma (1)
Withdrawal of consent (1)
Syst. allergic reaction (3)
Need of not admitted medication (1)
Uncontrolled allergic asthma (1)
Withdrawal of consent (1)
Syst. allergic reaction (4)
Lost to follow-up (1)
N=30
Analyzed for efficacy
n=33
Analyzed for safety
30
N=31
Analyzed for efficacy
n=33
Analyzed for safety
31
N=32
Analyzed for efficacy
n=33
Analyzed for safety
32
N=31
Analyzed for efficacy
n=33
Analyzed for safety
31
22
N=22 Completed follow-up and analyzed for efficacy
Lost to follow-up (8)
22
N=22 Completed follow-up and analyzed for efficacy
Lost to follow-up (8)
Need of not admitted medication (1)
25
N=25 Completed follow-up and analyzed for efficacy
Lost to follow-up (7)
24
N=24 Completed follow-up and analyzed for efficacy
Lost to follow-up (4)
Need of not admitted medication (1)
Desensit. (2)

Symptoms



Senti et al. JACI 2012

Symptoms



Senti et al. JACI 2012

The Cow-Pock — or — *the Wonderful Effects of the New Inoculation!* — Vide. the Publications of y^e^ Anti-Vaccine Society.