


History of Specific Immunotherapy and Allergen Standardization


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History of SIT and Allergen Standardization

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A Case of a periodical affection of the eyes and chest: 1819




John Bostock

SG Cohen & M Samter: Excerpts from Classis in Allergy 1992




Jonathan Bostock: (1819)

- "In about the beginning or middle of June of every year the following symptoms make their appearance."
 - "A sensation of heat and fullness in the eyes"
 - "A general fullness in the head"
 - "Sneezing"
 - "Tightness in the chest and difficulty breathing"
 - "Indisposition"
- "An idea has generally prevailed, that it is produced by the effluvia of new hay. Hence the popular name of hay fever"




"Experimental Researches on the Causes and Nature of Catarrhus Aestivus (Hay Fever or Hay Asthma)" (1873)




Charles H. Blackley

SG Cohen & M Samter: Excerpts from Classis in Allergy. 1992




Charles H. Blackley: (1873)


- He measured grass pollen in the air at various heights,
- Demonstrated an immediate and late skin reaction to grass pollen, and
- Showed that inhalation of grass pollen reproduced symptoms of hay fever



“Prophylactic Inoculation Against Hay fever (1911)
 SG Cohen & M Samter: Excerpts from *Classis in Allergy* 1992




Leonard Noon John Freeman



Leonard Noon and John Freeman (1911)


- “Hay fever is caused by a soluble toxin. The patients present the idiosyncrasy of being sensitive to this toxin.”
- Noon believed inoculations of timothy pollen extract to be producing anti-toxins.
- Noon used changes in conjunctival threshold to timothy to adjust therapy.
- Freeman reported clinical improvement persisting at least one season after a single year of treatment.



I Chandler Walker (1917)
 Peter Bent Brigham Hospital, Boston


Extended subcutaneous immunotherapy to treating patients with perennial asthma with injection of extracts of cat, dog and horse dander.

IC Walker. Jour Med Research 1917



John Freeman “Rush” Inoculation (1930)

- In 1928 Freeman began to give injections every hour and one-half or two throughout a 14-hour day in patients with rhinitis and/or asthma.
- Patients were hospitalized.
- “Thus a very satisfactory course can be put through in from two to four days”.
- Among the allergen extracts employed were:
 - Autogenous house dust
 - Cod fish
 - Horse dandruff
 - Grass pollen




A W Frankland & R Augustin: Controlled Trial of Grass Immunotherapy in Summer Hay Fever and Asthma (1954)

- **200 patients with grass allergy we re treated with one of four regimens:**
 - Two active grass extracts
 - Two presumed inactive treatments.
- **Assessment at end of pollen season:**

Results	Active	Inactive
Excellent/good	78	33
Moderate/poor	21	66


AW Frankland, R Augustin. Lancet 1954;I:1055-7



Double-Blind Studies of Effectiveness and Specificity of Injection Therapy in Ragweed Hay Fever

- Lowell & Franklin (1965 & 1967) observed patients on multiple allergen immunotherapy during one ragweed season.
- They matched pairs based on severity of symptoms.
- Ragweed extract was then reduced or removed from one of each pair’s extract and replaced with caramelized sugar solution.
- The patients’ symptoms were recorded during the subsequent ragweed pollen season.

NEJM 1965;273:675-9; JAMA 1967;201:915-7



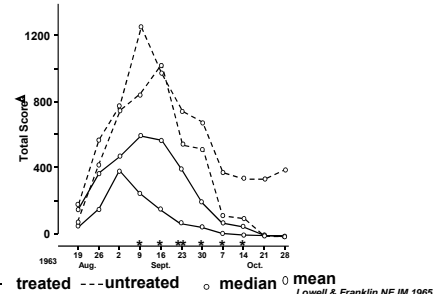
Double-Blind Studies of Effectiveness and Specificity of Injection Therapy in Ragweed Hay Fever

- In each study, subjects continued to receive the other components of their allergen extract mixture:
- “The untreated groups received injections of allergenic extracts other than ragweed -----tree, grass or plantain pollens”

NEJM 1965;273:675-9; JAMA 1967;201:915-7

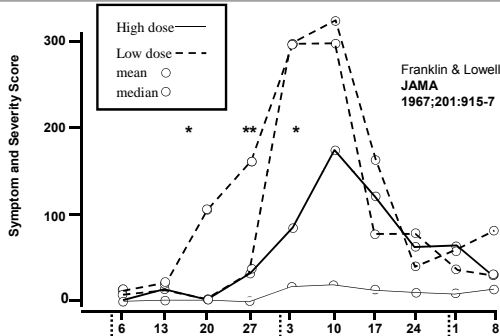


Effectiveness and Specificity of Ragweed Immunotherapy



— treated --- untreated ○ mean □ median
Lowell & Franklin NEJM 1965

95% Reduction in Ragweed Dose



Franklin & Lowell
JAMA
1967;201:915-7



Conclusions from the Studies of Lowell and Franklin

- Allergen immunotherapy is clinically effective in the treatment of allergic rhinitis.
- It is immunologically specific (all were receiving injections of other allergens).
- It is dose-dependent (a 95% reduction in dose resulted in loss of efficacy)
- It is effective administered as a multiple allergen mix to multiply sensitized patients.



The Value of Hyposensitization Therapy for Bronchial Asthma in Children -A 14-year Study

- Subjects: Every child with perennial bronchial asthma and positive skin tests referred to the pediatric allergy clinic of Strong Memorial Hospital (Rochester, New York) between August 1953 and January 1955.
- Randomly assigned to receive injections of saline, extract 10⁻⁷, 1/5,000 or 1/250 w/v concentration of each allergen to which they had a positive skin test.

DE Johnstone, A Dutton Pediatrics 1968;42:793-802



The Value of Hyposensitization Therapy for Bronchial Asthma in Children - A 14-year Study

- Parents did not know they were in a study, those evaluating the patients were unaware of which group the child was in.
- 230 enrolled, 173 still in study after 4 years and 130 completed the study on reaching age 16 years.
- Similar numbers dropped out of each treatment group.




DE Johnstone, A Dutton Pediatrics 1968,42:793-802



The Value of Hyposensitization Therapy for Bronchial Asthma in Children - A 14-year Study

- “Free of Asthma” After 4 years
 - placebo and lowest dose 18%
 - 1/5,000 w/v 58%
 - 1/250 w/v 81%
- “Free of Asthma” at end of study (age 16 years)
 - placebo and lowest dose 22%
 - 1/5,000 w/v 66%
 - 1/250 w/v 78%




DE Johnstone, A Dutton Pediatrics 1968;42:793-802

Conclusions from the Studies of Johnstone and Dutton

- Allergen immunotherapy is clinically effective the treatment of allergic bronchial asthma.
- It is dose-dependent.
- It is effective when administered as a multiple-allergen mix to multiply sensitized patients.
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DE Johnstone, A Dutton Pediatrics 1968;42:793-802

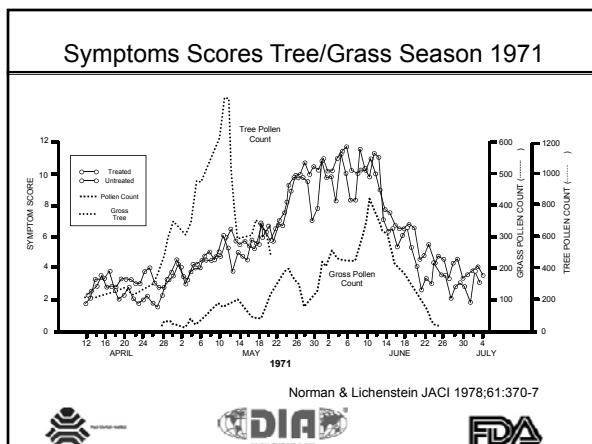
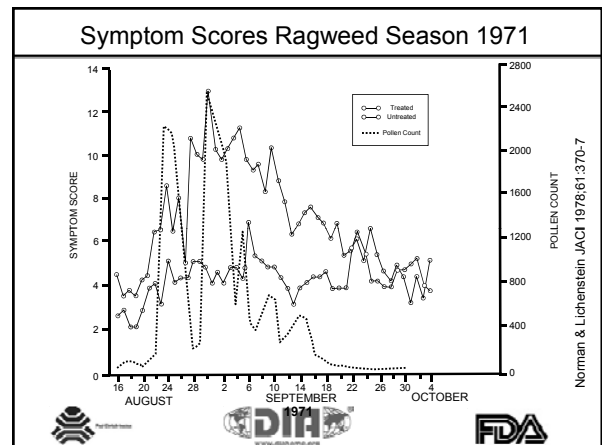




The Clinical and Immunologic Specificity of Immunotherapy




- 42 patients allergic to both grass and ragweed.
- Half received immunotherapy with ragweed for two seasons, neither group received grass immunotherapy.
- Treated patients did better during the ragweed season but there was no difference in symptoms during the grass pollen season.

PS Norman & LM Lichtenstein JACI 1978;61:370-7



The Immunologic Response to Immunotherapy

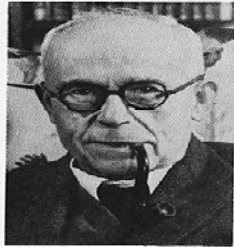

Increasing Conjunctival Tolerance with Injections of Timothy Grass

Noon demonstrated that increasing amounts of grass pollen extract were tolerated after injections of timothy extract

L Noon Lancet 1911

Demonstration of an antibody as the basis of sensitization by passive Transfer of Cutaneous Sensitivity to Fish (1921)

SG Cohen & M Samter: Excerpts from *Classis in Allergy*:

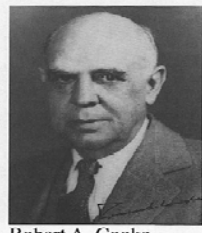
Carl Prausnitz Heinz Küstner

Carl Prausnitz and Heinz Küstner: (1921)

- Küstner was highly allergic to ingestion of fish or intracutaneous injection of fish extract.
- Küstner's serum was injected intradermally into Prausnitz.
- The site was challenged 24 hours later by intradermal injection of fish extract with a resulting positive cutaneous wheal and flare reaction.
- The technique was employed for the next half century to demonstrate the presence of "reaginic antibody"

Demonstration of "Blocking Antibody" (1935)

SG Cohen & M Samter: Excerpts from *Classis in Allergy* 1992year



Robert A. Cooke

Robert A Cooke (1935)

- "These studies have been interpreted by us as showing the development under treatment of a blocking or inhibiting type of antibody that prevented the action of the allergen on the sensitizing antibody."




Discovery of IgE

- Physicochemical Properties of Reaginic Antibody V. Correlation of Reaginic Activity with γ E-globulin Antibody.
Ishizaka K, Ishizaka T, Hornbrook MM. *J Immunol* 1966;97:840-53
- Immunological Studies of an Atypical (Myeloma) Immunoglobulin.
Johansson SGO, Bennich H. *Immunology* 1967;13:381-94.

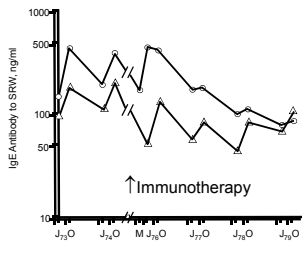
Gerald Gleich: Effect of 6 Years of Immunotherapy on IgE and IgG Antibodies to Ragweed (1982)

- Antibody levels were monitored 2 years before and 4 years following institution of ragweed immunotherapy.
- Before immunotherapy patients ragweed-specific IgE rose with each pollen season and declined off season.
- With immunotherapy there was an abrupt rise in specific IgE, but the seasonal increases were blocked, and IgE levels gradually declined.
- Specific IgG rose with immunotherapy and remained high.




G Gleich et al. J Allergy Clin Immunol 1982;70:261-71

Effect of Ragweed Immunotherapy on Specific IgE Levels






G Gleich et al. J Allergy Clin Immunol 1982;70:261-71

Ross Rocklin: The Generation of Antigen-Specific Suppressor Cells during Allergy Desensitization (1980)

- Mononuclear cells from ragweed allergic subjects were stimulated with ragweed Amb a 1.
- Prior to immunotherapy they did not suppress ragweed induced lymphocyte proliferation.
- Following 6 and 12 months of immunotherapy they suppressed lymphocyte proliferation by 31% and 48%.




R Rocklin et al. N Engl J Med 1980;302:1213-9

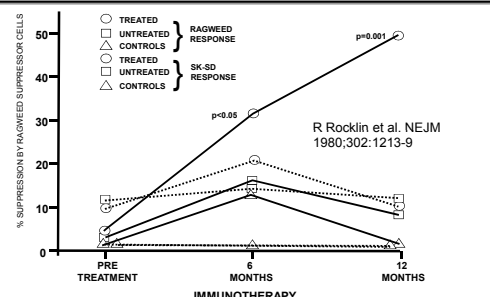
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Allergen-Specific Suppressor Cells with Ragweed Immunotherapy






R Rocklin et al. NEJM 1980;302:1213-9

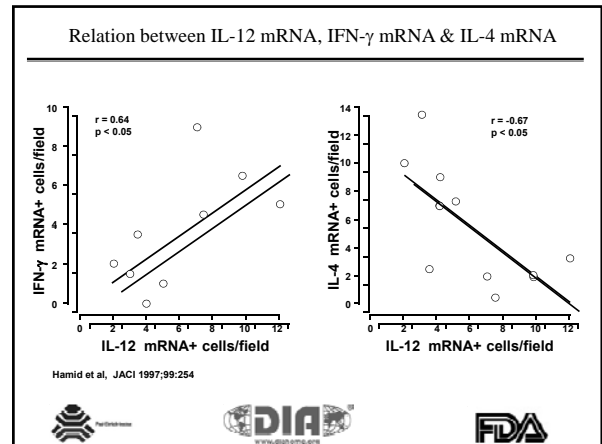
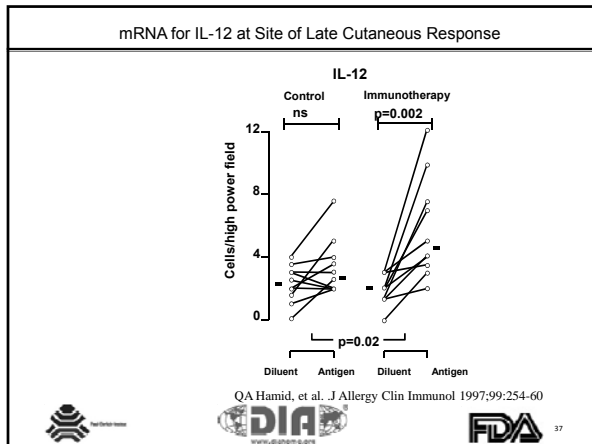




Increases in IL-12 mRNA⁺ Accompany Inhibition of Allergen Late Skin Test Responses after Successful Grass Pollen Immunotherapy

- 10 subjects who had received 4 years of grass pollen immunotherapy and 10 allergic controls had skin biopsies 24 hours after injection of grass pollen extract.

QA Hamid, et al. J Allergy Clin Immunol 1997;99:254-60

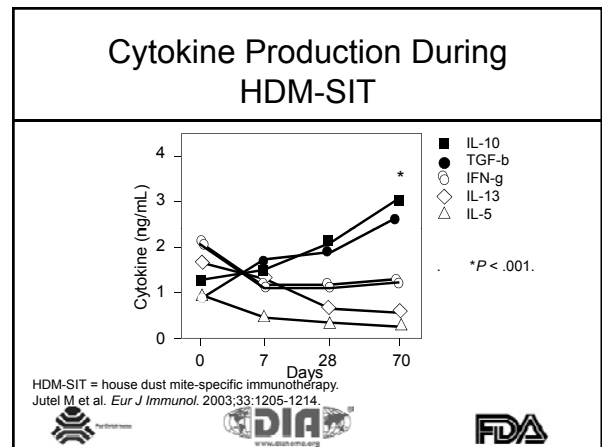






IL-10 and TGF- β Cooperate in the Regulatory T Cell Response to Mucosal Allergens in Normal Immunity and Specific Immunotherapy

- Immunotherapy to house dust mite extract induced antigen-specific suppressive activity in CD4+CD25+ T cells in allergic subjects.
- The regulatory/suppressor T cells secreted IL-10 and TGF- β
- These cytokines induce IgG4 and IgA and suppress IgE production by B cells.
- Mimics the healthy immune response to environmental allergens.

M Jutel, et al. Eur J Immunol 2003;33:1205-14



Immunotherapy: The First Hundred Years

- The original description by Leonard Noon in 1911 was followed by:
 - Demonstration of efficacy with a wide range of allergens in both allergic rhinitis and asthma.
 - Appreciation of the complex immune response including: blocking antibody, suppression of IgE, generation of allergen-specific suppressor cells (Treg) and immune deviation from a Th2 to a Th1 cytokine profile.

The Unfulfilled Need for Allergen Extract Standardization

Noon units, weight/volume, and protein nitrogen units failed to accurately reflect allergenic potency.

Purpose of Standardization of Allergen Extracts

To produce reference preparations with known and reproducible composition and potency for calibration of extracts for diagnostic and therapeutic use.

S Dreborg, R Einarsson. Allergy 1991;47:418-23



Standardization: the Beginning Scandinavian Society of Allergology (1972)(1972)

- Objective:
 - Safety
 - Precision in diagnosis and therapy
- Method:
 - Titrated prick skin tests in 10-20 allergic subjects
 - Concentration giving wheal equal to 1 mg histamine Hcl termed 1 HEP or 1,000 Biological units
 - In vitro testing with pooled serum for subsequent batch-to-batch control.

K Ass, A Backman, L Belin, B Weeke Allergy 1978;33:130-7



Improvements in Biological Standardization

- Guidelines for quantitative skin prick tests.

(H-J Malling. Allergy 1987;42:391-4)

- Content of major allergens standardized against reference extract by quantitative immunoelectrophoresis (QIF) and other allergens controlled by crossed radio immunoelectrophoresis (CRIE)

(L Ingemann, D Venov. 3rd Paul Ehrlich Seminar 1983).



World Health Organization/International Union of Immunological Societies (WHO/IUIS) Initiative (1980-9)

- The Allergen-standardization Subcommittee developed International Reference Preparations of several allergen extracts.
- The initiative failed because the references were not adopted by industry or by regulatory authorities.

R van Ree, et al. Allergy 2008;63:310-26



Use of Major Allergen Content for Standardization

- Major allergen content was found to correlate with biological activity.
- Effective immunotherapy was found to be associated with major allergen dosing of 5-20 micrograms. But:
- Measurements of major allergen, however, is dependent on technique, reference, and antibody (ability to recognize isotypes of the allergen).

R van Ree. J Allergy Clin Immunol 2007;119:270-7



The CREATE Project (2001-2005)

- A project of 28 organizations within the 9 EU countries.
- Purpose was to evaluate:
 - The potential of recombinant allergens to serve as reference materials.
 - The potential of available ELISAs to accurately measure these allergens.

R van Ree, et al. Allergy 2008;63:310-26



The CREATE Project: Results

- Nine recombinant molecules representing 8 major allergens were compared with purified natural allergens for physico-chemical and immunological characteristics.
- Three (rBet v 1, rPhl p 5a, and rDer p 2) showed sufficient similarity to be selected.
- For each protein, 1 or 2 ELISAs were identified which gave similar dose-response curves for the recombinant and natural allergens.

R van Ree, et al. Allergy 2008;63:310-26



The Current Status of Standardization



Standardization of Allergen Extracts in the United States

- Under the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Agency (FDA).
- Grass and house dust mite allergens initially standardized by intradermal skin testing (BAU and AU).
- Short ragweed and cat initially standardized by major allergen content (FDA units).
- Hymenoptera venoms by proteins plus major allergen content (hyaluronidase, phospholipase A1 and A2).
- Manufacturers' extracts compared to CBER standard by in vitro testing.



Determination of the Biological Equivalent Unit: The ID₅₀EAL

- Select 15 subjects highly allergic to the extract undergoing assessment.
- Inject intradermally serial 3-fold dilutions of the extract.
- Calculate the dilution resulting in sum of two transverse diameters of the flare of 50 mm.
- Assign potency in Biological Equivalent Units.



Current Standardization Practices in Europe

- In house standardized extracts are established by each manufacturer:
 - 15-30 allergic subjects are prick skin tested
 - Dose determined with wheal equivalent to histamine or codeine standard.
 - Potency expressed in a variety of units: BU, IR, AU, HEP, SQ.
- No external reference to ensure consistency among manufacturers.



Optimal Standardization

- Determine allergen composition to insure all relevant allergens present.
- Quantify major allergens
- Quantify total allergenic activity using a panel of patients or patients' sera.

