Present Status of Subcutaneous Immunotherapy

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Present Status of Subcutaneous Immunotherapy (SCIT)

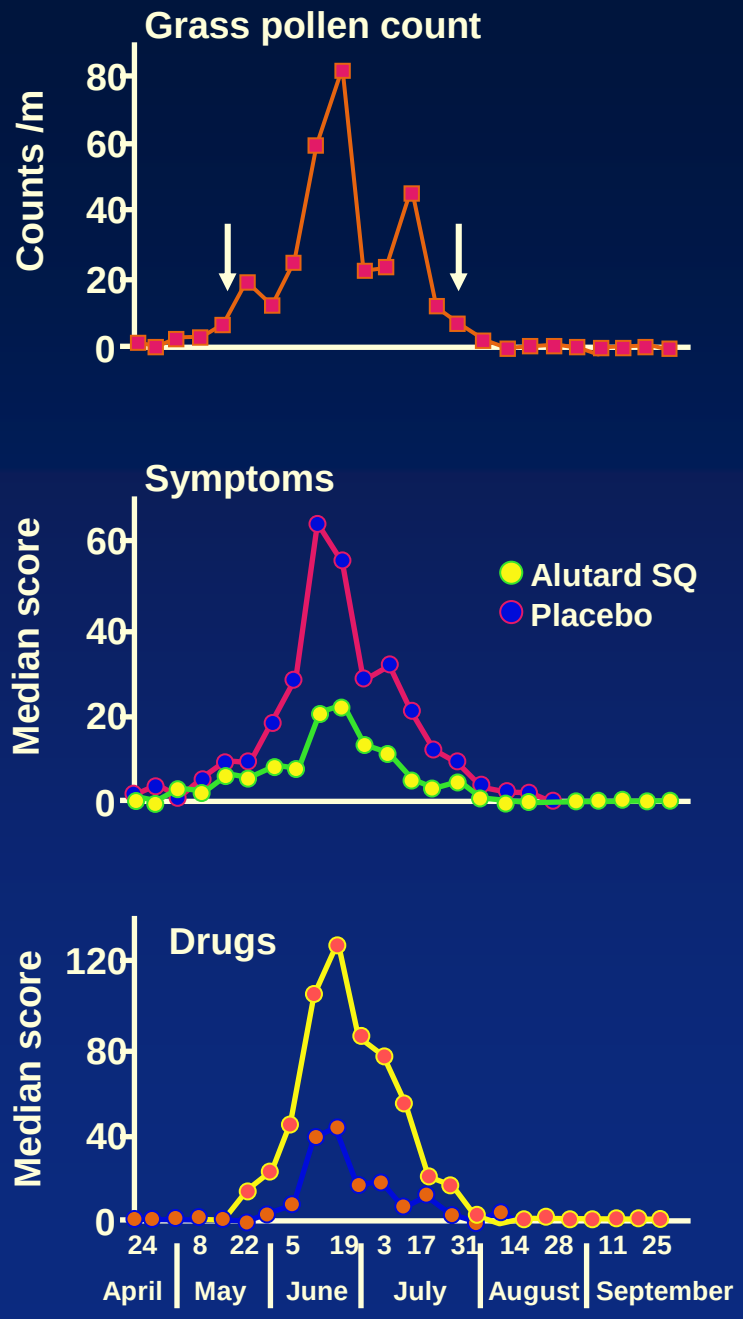
- Proven efficacy in allergic rhinitis and asthma.
- Identified effective doses
- Effective in multiallergen mixes
- Plausible mechanism
- Demonstrated prevention of:
  a. New sensitization
  b. Progression from rhinitis to asthma
- Established duration
- Persistence of efficacy after stopping

But:

- Inconvenient
- Occurrence of systemic reactions.

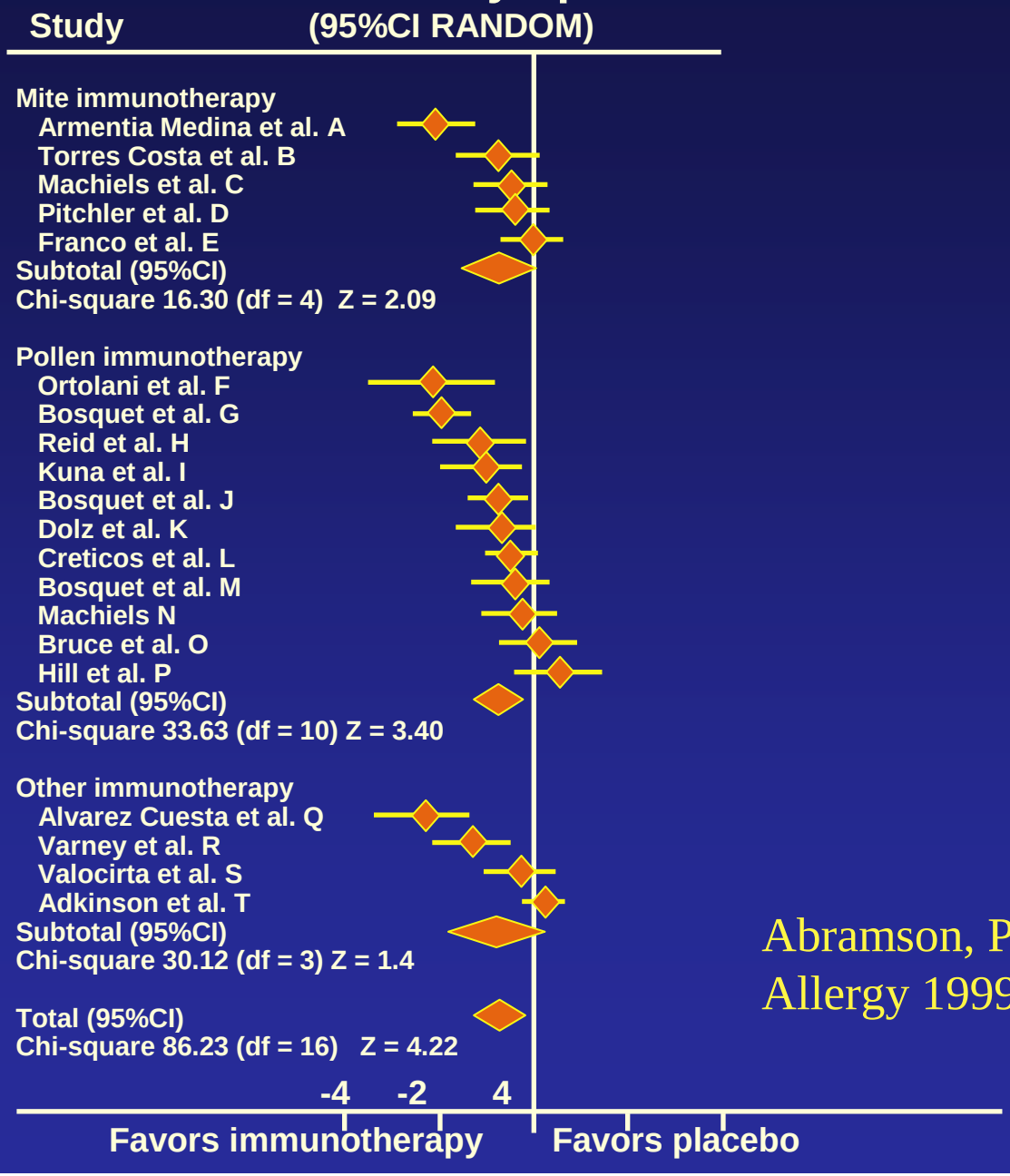
28 patients with severe hay fever uncontrolled by anti-allergic drugs.

Received a course of pre-seasonal grass immunotherapy or matching placebo.



VA Varney, et al
Br. Med. J
1991;302:265-9

Comparison: Allergen immunotherapy vs placebo
Outcome: Asthma symptom scores



Abramson, Puy, Weiner
Allergy 1999;54:1022-41

Efficacy and Safety of Specific Immunotherapy with SQ Allergen Extract in Treatment-resistant Seasonal allergic Rhinoconjunctivitis.

AJ Frew et al. J Allergy Clin Immunol 2006;117:319-25

- 347 adults with grass-pollen induced SAR inadequately controlled in previous year by antihistamines, topical steroids and eye drops.
- Randomized to preseasonal immunotherapy with timothy grass extract high dose (20 mg Phl p 5), low dose (2 mg Phl p 5) or placebo.

Efficacy and Safety of Specific Immunotherapy with SQ Allergen Extract in Treatment-resistant Seasonal allergic Rhinoconjunctivitis: Results

Clinical results compared to placebo during peak pollen period:

	Symptoms	Medication
High-dose timothy	- 32% ($p < .0001$)	- 41% ($p < .0001$)
Low-dose timothy	- 19% ($p = .014$)	- 14% ($p = .16$ NS)

AJ Frew et al. J Allergy Clin Immunol 2006;117:319-25

Effective Doses in Double-Blind Studies (Major Allergen)

Allergen	Effective Doses	Less Effective Doses
Ragweed	4 to 24 µg Amb a 1	0.6 & 2.0 µg Amb a 1
D pt	3.25 to 12 µg Der p 1	0.7 µg Der p 1
D far	10 µg Der f 1	N.D
Timothy	15 & 20 µg Phl p 5	2.0 µg Phl p 5
Cat	11 to 17 µg Fel d 1	0.6 &3.0 µg Fel d 1
Dog	15 µg Can f 1	0.6 & 3.0 µg Can f 1
Birch	3.28 & 12 µg Bet v 1	N.D.
Alternaria	1.6 µg Alt a 1	N.D.

N.D. = Not determined

Major Allergen Content: U.S. Standardized Extracts

Extract	Conc	Major Allergen	Content
Ky blue	100k BAU/mL	Group 5	300 µg/mL
Orchard	100k BAU/mL	Group 5	918 µg/mL
Timothy	100k BAU/mL	Group 5	680 µg/mL
Bermuda	10k BAU/mL	Group 1	300 µg/mL
Sh ragweed	1:10 w/v	Amb a 1	420 µg/mL
D farinae	10k BAU/mL	Group 1	56 µg/mL
D ptery	10k BAU/mL	Group 1	76 µg/mL
Cat	10k BAU/mL	Fel d 1	43 µg/mL
Unstandardized:			
Dog AP (HS)	1:100 W/V	Can f 1	140 µg/mL

ALK-Abello' 2006

Major Allergen Content: U.S. Non-standardized Extracts

Extract	Conc	Major Allergen	Content
Birch	1:10 w/v	Bet v 1	390 mcg/mL
Olive	1:10 w/v	Ole e 1	430 mcg/mL
Sagebrush	1:10 w/v	Art v 1	1300 mcg/mL
Dog	1:10 w/v	Can f 1	5-10 mcg/mL
			ALK-Abello' 2006
Alternaria alternata	1:20 w/v	Alt a 1	<.01 to 6.1 mcg/mL
Aspergillus fumigatus	1:20 w/v	Asp f 1	<.01 to 64 mcg/mL
German Cockroach	1:20 w/v (Gly)	Bla g 2	8 to 66 mcg/ml

Effective Dosing with U.S. Standardized Extracts

Extract	Major Allergen Required	Added to 10 mL Vial (based on ALK values 2006)
Timothy	20 µg	0.6 mL 100,000 BAU/mL
S ragweed	12 µg	0.6 mL 1:10 w.v
D pt	7 µg	1.8 mL 10,000 AU/mL
D far	10 µg	3.6 mL 10,000 AU/mL
Cat	15 µg	7.0 mL 10,000 AU/mL
		(based on HS values)
Dog (AP)	15 µg	2.1 mL 1:100 w/v

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

DE Johnstone, A Dutton Pediatrics 1968l42:793-802

- Subjects: Every child with perennial bronchial asthma and positive skin tests referred to the pediatric allergy clinic of Strong Memorial Hospital 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.

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

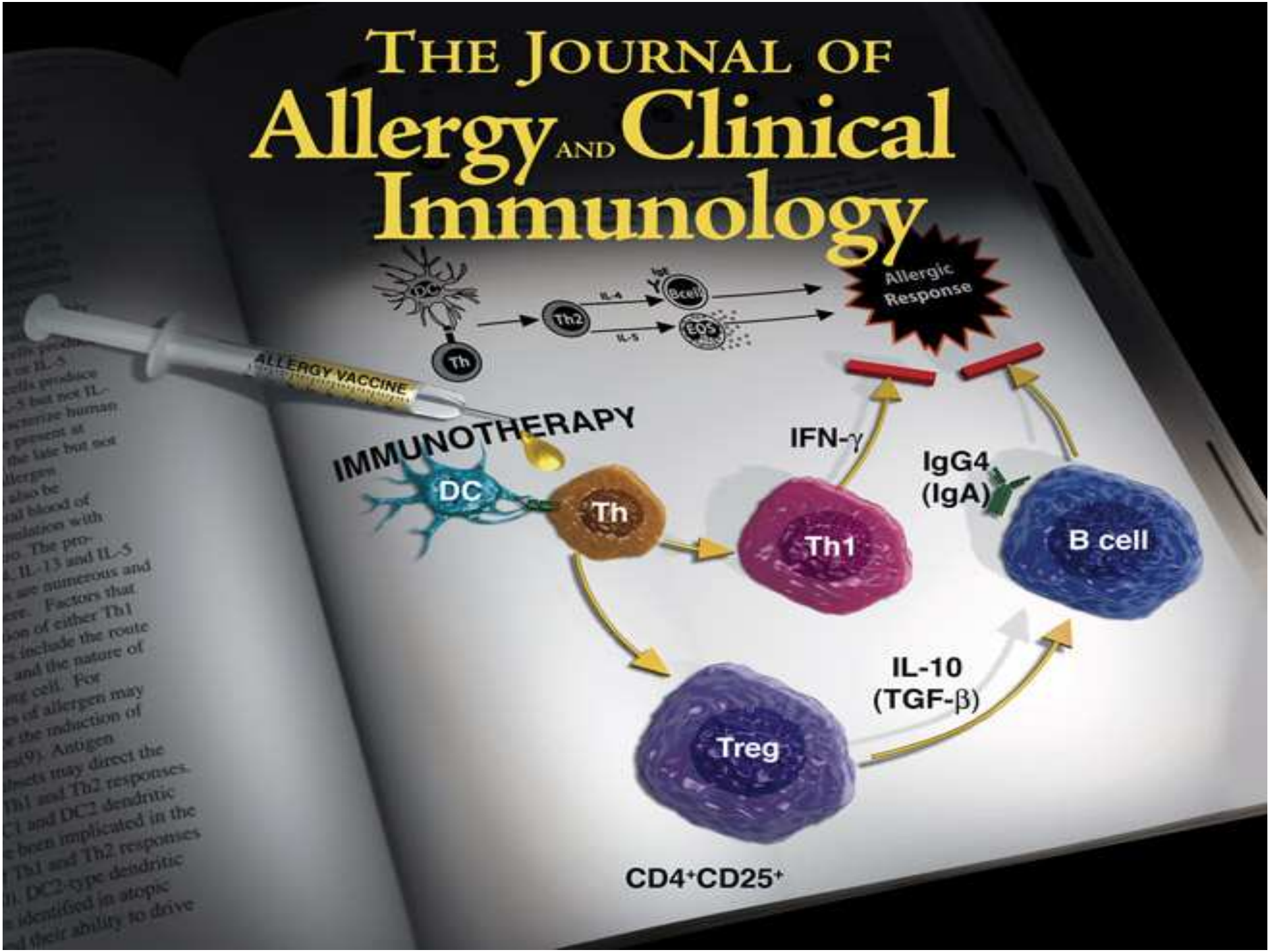
- Parents did not know they were in a study, those evaluating the patients were unaware of which group the child was in.
- 230 enrolled,173 still in study after 4 years and 130 competed the study on reaching age 16 years.
- Similar numbers dropped out of each treatment group.

DE Johnstone, A Dutton Pediatrics 1968l42:793-802

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 yr)
  - placebo and lowest dose 22%
  - 1/5,000 w/v 66%
  - 1/250 w/v 78%

DE Johnstone, A Dutton Pediatrics 1968l42:793-802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Th1
IgG4
(IgA)
B cell
IL-10
(TGF-β)
Treg
CD4+CD25+

Allergen Immunotherapy: Disease Modification

- Prevents new sensitizations in monosensitized subjects
- Prevents progression to asthma in subjects who only have allergic rhinitis
- Persistence of improvement for ears after discontinuation of treatment.

Prevention of New Sensitizations in Asthmatic Children Monosensitized to House Dust Mite by Specific Immunotherapy. A Six-year Follow-Up Study

GB Pajno et al. Clin Exp Allergy 2001;31:1392-7

134 children, ages 5 to 8 years, with intermittent asthma with or without rhinitis, and single sensitization to house dust mite.

- Parents of 75 children accepted immunotherapy
- Parents of 63 children rejected immunotherapy.

Prevention of New Sensitizations

- **Immunotherapy was administered for 3 years, with 3 years follow-up**
- **Maintenance dose 1/2 customary adult.**
- **At the end of the 6 years new sensitization had occurred in:**

- Immunotherapy	**17/69 (24.6 %)**
- Medication control	**36/54 (66.7 %)**

GB Pajno, et al . Clin Exp Allergy 2001;31:1392-7

Prevention of Asthma by Specific Immunotherapy (PAT)

L Jacobsen, et al. Allergy 2007;62:943-8

- **Children ages 7-13 years with allergic rhinitis and no diagnosed asthma**
- **Immunotherapy for three years with Birch (13μg Bet v 1) and/or Timothy (20μg Phl p 5)**
- **Follow-up 2 and 7 years after stopping immunotherapy**

Prevention of Asthma by Specific Immunotherapy

L Jacobsen, et al. Allergy 2007;62:943-8

Results on follow-up: No Asthma / Asthma:

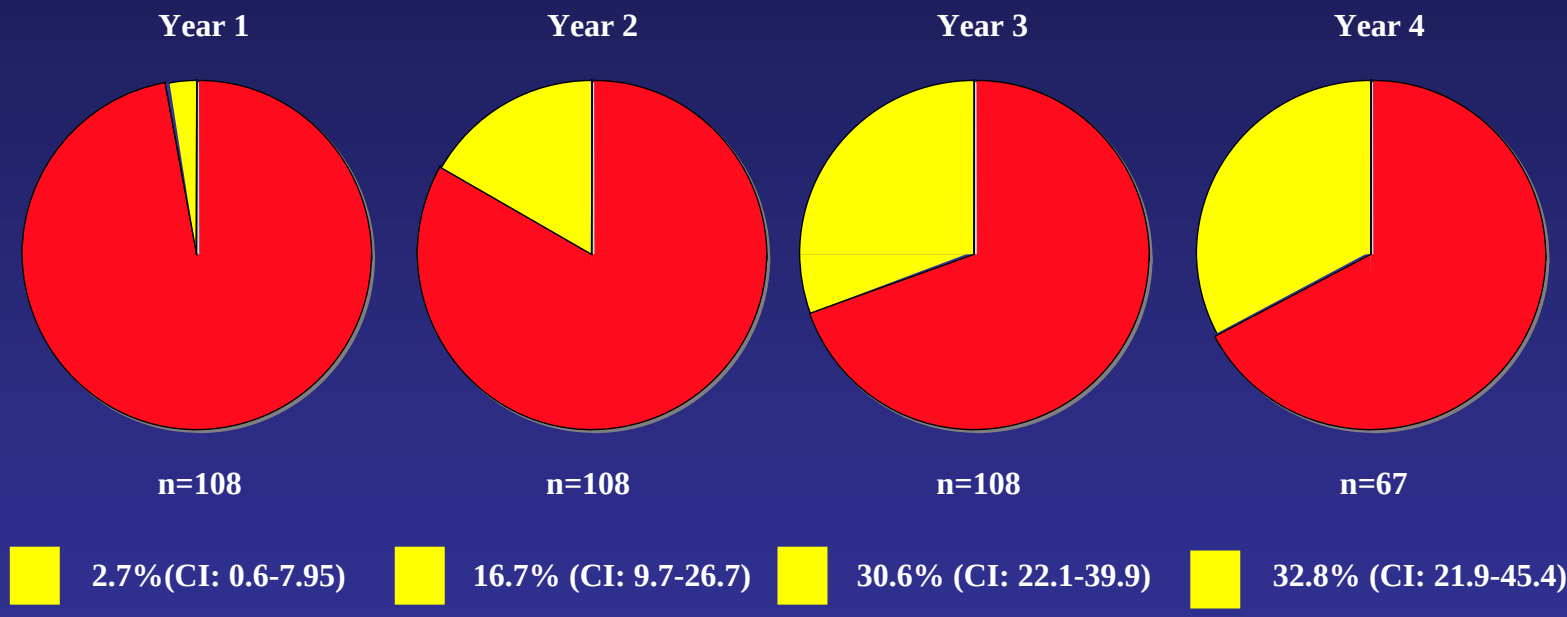
	SCIT	Control	Odds Ratio
3 years	60/19	40/32	2.52
5 years	60/15	38/29	2.68
10 years	48/16	29/24	2.48

Persisting Efficacy After Discontinuing Immunotherapy

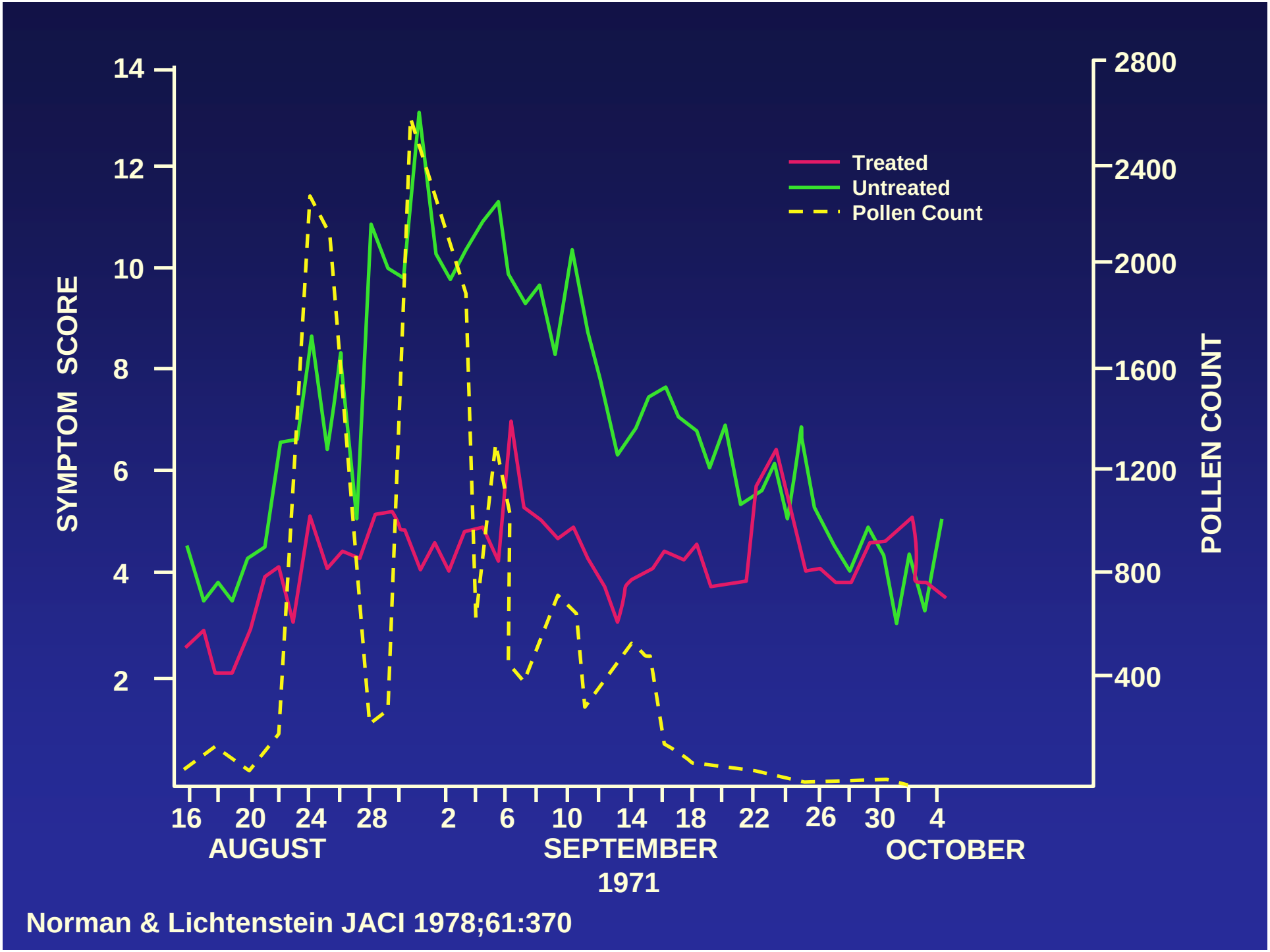
- 108 patients stopped treatment after they had received grass pollen immunotherapy for 3-4 years for allergic rhinitis with good symptomatic response.
- Maintenance dose contained approximately 12 mcg group 5 allergen.
- Questionnaire annually determined recurrence of symptoms.

C Ebner, et al. Allergy 1994;49:38-42.

Relapse Rate Following Discontinuation of Immunotherapy



C Ebner, et al. Allergy 1994;49:38-42.



Norman & Lichtenstein JACI 1978;61:370

Categories of Symptom Relief In Allergic Rhinitis (Compared to Placebo)

Very Modest (usually < 10%)
- Leukotriene receptor antagonists

Modest (usually <20 %)
- Antihistamines
- Anticholinergics (rhinorrhea only)
- Decongestants (obstruction only)
- Nasal steroids (begun when symptomatic)

Moderate (usually 20-40 %)
- Cromolyn (6 times per day)
- Antihistamine/decongestant combinations

Appreciable (usually > 40%)
- Nasal corticosteroids (begun before the season)
- Subcutaneous Allergen Immunotherapy