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Treatment of peanut allergy with rush immunotherapy

John J. Oppenheimer, MD, Harold S. Nelson, MD, S. Allan Bock, MD, Fran Christensen, BSN, MA, and Donald Y. M. Leung, MD, PhD
Denver, Colo.

Peanut and peanut products are a common food in the diet. Peanuts are also one of the most common foods responsible for food-induced anaphylaxis. Patients rarely lose sensitivity to peanuts. Although the ideal treatment is avoidance, this is often not possible because of hidden exposures; therefore, a more effective treatment is needed. Subjects with confirmed peanut allergy were treated in a double-blind, placebo-controlled study with peanut immunotherapy or placebo. Objective measures of efficacy included changes in symptom score during double-blind placebo-controlled peanut challenge (DBPCPC) and titrated end point prick skin tests (PST). Three subjects treated with peanut immunotherapy completed the study. These subjects displayed a 67% to 100% decrease in symptoms induced by DBPCPC. Subjects also had a 2- to 5-log reduction in end point PST reactivity to peanut extract. One placebo-treated subject completed the study. This subject had essentially no change in DBPCPC symptom scores or PST sensitivity to peanut. Two other placebo-treated subjects underwent a second PST session. These subjects had a 1- to 2-log increase in skin test sensitivity to peanut. All peanut-treated subjects were able to reach maintenance dose, and in no case did an anaphylactic reaction occur secondary to the peanut immunotherapy. The current study provides preliminary data demonstrating the efficacy of injection therapy with peanut extract and provides a future line of clinical investigation for the treatment of this potentially lethal disease. It should be noted, however, that the rate of systemic reactions with rush immunotherapy was 13.3%. Thus, at the present time, this therapy should only be considered investigational and done only in research settings with intensive care unit support immediately available. (J ALLERGY CLIN IMMUNOL 1992;90:256-62.)

Key words: Peanut allergy, rush immunotherapy, allergy immunotherapy, anaphylaxis

From the Departments of Medicine and Pediatrics, The National Jewish Center for Immunology and Respiratory Medicine, Denver, Colo.

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Reprint requests: Harold S. Nelson, MD, Department of Medicine, National Jewish Center for Immunology and Respiratory Medicine, 1400 Jackson St., Denver, CO 80206.

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Although peanuts and peanut products are common foods in the diet, they are also a frequent cause of food allergy. In a review of fatalities from food-induced anaphylaxis, four of seven cases were due to peanut.¹ Sensitivity to peanuts appears early in life and, once established, persists indefinitely. In a study performed at National Jewish Center, none of the 32 patients with peanut allergy followed for up to 16 years had lost their clinical sensitivity, and despite attempts to avoid this allergen, 75% of patients had accidentally ingested peanuts during the 5 years pre-

ceding reevaluation.² Currently, there are no curative therapies for peanut allergy or other food allergies. Treatment for such patients consists of strict avoidance of peanuts and supportive treatment when inadvertent exposure occurs.

Since peanut products are difficult to avoid, and peanut-sensitive patients rarely outgrow their allergy, we chose to investigate the use of immunotherapy for this potentially lethal condition. Previous studies have demonstrated that patients with bee venom-induced anaphylaxis can be protected by immunization.^{3, 4} Compelling anecdotes, as early as 1930, have suggested the efficacy of immunotherapy to foods.⁵ It was at this time that Freeman⁵ reported that, with the use of immunotherapy consisting of "rush inoculations," he induced a state of tolerance in a fish-allergic patient. This state of desensitization to fish could be maintained long term by daily ingestion of cod liver oil. We therefore undertook a prospective, double-blind, placebo-controlled evaluation of injection therapy for food allergy. Our preliminary data suggest that peanut-sensitive patients can be desensitized by rush injection immunotherapy.

METHODS

Subjects and study design

Eleven subjects, aged 14 to 43 years (mean age, 25.4 years), were enrolled in this study, which was approved by the National Jewish Center for Immunology and Respiratory Medicine Institutional Review Board.

All subjects had a history of SR (hypotension, acute bronchospasm, and/or generalized urticaria) after ingestion of peanuts, a positive prick skin reaction (wheal, >3 mm) to peanut extract (Hollister-Stier Laboratories, Spokane, Wash.), and a positive double-blind, placebo-controlled challenge to defatted peanuts. Subjects were then randomly assigned to receive either peanut immunotherapy or a placebo, which consisted of saline, carmalized sugar, and histamine. Investigators were blinded to the randomization code and group assignment. Subjects underwent peanut or placebo immunotherapy with a rush injection schedule. Subjects then received once-weekly maintenance injections for 4 weeks, after which they underwent a second DBPCPC. Titrated PSTs were performed with peanut extract and histamine at baseline after reaching the maintenance dose and after the fourth maintenance injection (Fig. 1).

Allergen extracts

The peanut extract was prepared from the same lot as the defatted peanut used for food challenge (Hollister-Stier Laboratories). This defatted peanut lot consisted of equal parts of Spanish, Virginia, and red skin peanuts. Full strength extract was 1:10 wt/vol.

Skin testing

End point titration prick skin testing was performed with concentrates and serial tenfold dilutions of peanut extract, 1:10 wt/vol. Controls included saline and histamine, 10 mg/ml. The end point was considered to be the last con-

Abbreviations used

PST:	Prick skin test
DBPCPC:	Double-blind placebo-controlled peanut challenge
ASCU:	Adult Special Care Unit
BP:	Blood pressure
SR:	Systemic reaction

centration of peanut extract to result in a wheal of 3 mm. Skin testing was performed by this method before immunotherapy on reaching maintenance dose and after 4 weeks of maintenance injections.

DBPCPC challenge

Subjects underwent DBPCPC during 2 separate days. On 1 day subjects received increasing doses of defatted peanut in capsules. Peanut challenges consisted of defatted peanut, which was the raw material used to make the peanut extract used for skin testing and immunotherapy. On another day, subjects underwent a placebo challenge with capsules containing lecithin. Challenges entailed increasing numbers of capsules ingested at 20-minute intervals. Subjects with a history of severe life-threatening reactions began their peanut challenges at 1 mg, whereas subjects suffering solely from cutaneous reactions began their peanut challenges at 100 mg of peanut. Doses were doubled approximately every 20 minutes (Table I). Just before each dose, subjective complaints and physical findings, including peak flow measurements (mini-Wright peak flow meter) and vital signs, were recorded. Challenges were stopped when subjects suffered from systemic symptoms, a >20% drop in peak flow reading or BP, or a single dose of 8 gm was ingested (total cumulative dose of 15.8 gm or 15.86 gm if challenges were started at 1 mg). These challenges took place in the National Jewish ASCU. All subjects were required to remain in the ASCU for 12 hours if they suffered from severe asthma or hypotension, and for 2 hours after total resolution of symptoms if they suffered from urticaria or gastrointestinal complaints.

Symptoms and signs (nausea, vomiting, urticaria, rhinitis, mucosal pruritus, asthma, and hypotension) were graded on a 0 to 3+ scale, with 3 being the most severe.

Rush immunotherapy

Four injections were administered each day in the ASCU. Subjects received subcutaneous injections of increasing doses of peanut extract or placebo at 60-minute intervals. The dose of the first injection was determined by both skin test reactivity to peanut and clinical history with regard to the severity of previous reactions (Table II).

Subjects' symptoms, vital signs, and peak flow measurements were obtained before immunotherapy and before each injection. Immunotherapy was stopped for the day if patients' peak flow readings decreased by >20% or if they experienced an SR or a local reaction of >30 mm. Subjects were required to remain in the ASCU for 1 hour after the final injection.

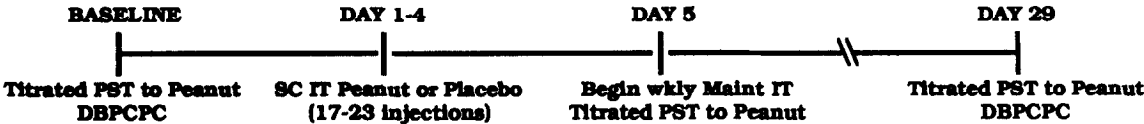


FIG. 1. Study design.

TABLE I. Peanut-challenge schedule

Dose No.	Amount of defatted peanut
Schedule for doses starting at 1 mg (dosing at 20-minute intervals)	
1	1 mg
2	5 mg
3	10 mg
4	20 mg
5	50 mg
6	100 mg
7	200 mg
8	500 mg
9	1 gm
10	2 gm
11	4 gm
12	8 gm
Schedule for doses starting at 100 mg (dosing at 20-minute intervals)	
1	100 mg
2	200 mg
3	500 mg
4	1 gm
5	2 gm
6	4 gm
7	8 gm

Statistics

Because of the small number of subjects who completed the protocol and underwent a second DBPCPC, statistical analysis could not be performed.

RESULTS

Patients' characteristics

A total of 11 patients were randomized for inclusion in this study. Subjects were aged 14 to 43 years with a mean of 25.4 years. All subjects had a positive skin test to peanut extract. Initial end point PST reactivity to peanut varied from 1:10,000,000 wt/vol to 1:1000 wt/vol with a mean of approximately 1:10,000 wt/vol. All subjects had a positive DBPCPC. Positive reactions at baseline (before immunotherapy) occurred at doses from 30 mg to 8 gm of peanut with a mean dose of approximately 4 gm. Peanut-challenge scores at baseline varied from 3 to 11, with a mean symptom score of 5.

TABLE II. Representative schedule for rush immunotherapy to peanut

Day	AM	ml
1	8	1:10,000 wt/vol* 0.05
	9	0.1
	10	0.2
	11	0.4
2	8	1:1,000 wt/vol 0.05
	9	0.1
	10	0.15
	11	0.2
3	8	0.3
	9	0.4
	10	0.5
	11	1:100 wt/vol 0.07
4	8	0.1
	9	0.15
	10	0.2
	11	0.3
5	8	0.4
	10	0.5

*Used for dilutions >1:10,000 wt/vol.

The study was terminated and the randomization scheme was unblinded when a formulation error in the pharmacy resulted in the accidental administration of a maintenance dose of peanut extract to a placebo-treated subject. The subject died of anaphylaxis. At the time of the incident, eight subjects had reached a maintenance dose of peanut or placebo immunotherapy, six had completed a second titrated skin test session, and four subjects had undergone a second DBPCPC. Despite the early termination of the study, we believe that these clinical data collected during this trial strongly suggest that the treatment was effective, and we will present these data obtained up to the time of termination of this study.

Changes in DBPCPC after immunotherapy

In the three peanut-treated subjects, there was marked reduction in symptom scores during the second challenge. As illustrated in Fig. 2 and Table III, the mean symptom score for the three subjects in the peanut-treated immunotherapy group was 8.7 before immunotherapy. After peanut immunotherapy, the

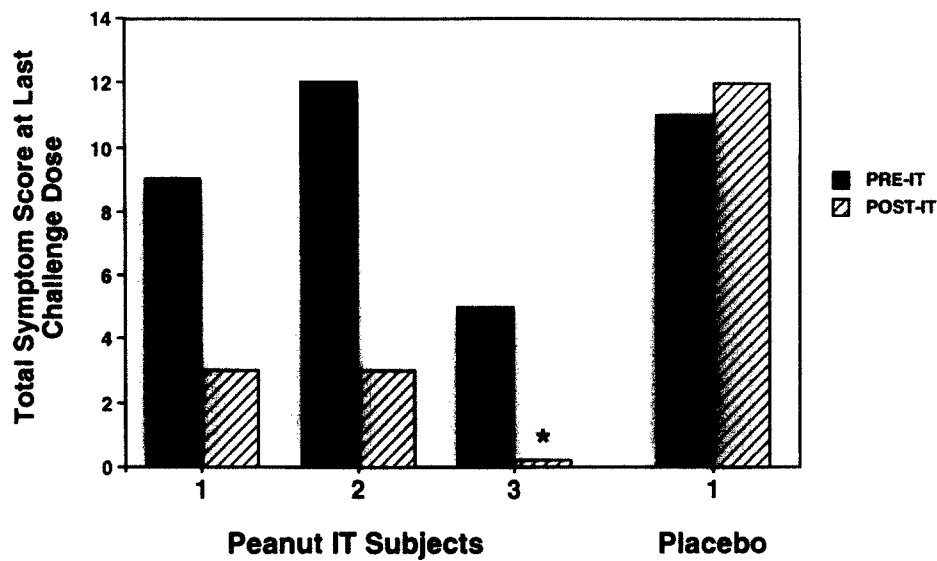


FIG. 2. Symptom scores of DBPCPC before and after immunotherapy. After peanut immunotherapy, but not placebo therapy, there was a 67% to 100% reduction in total clinical symptoms triggered by DBPCPC. Subject C (*) had no symptoms after immunotherapy challenge; *Pre-IT*, before immunotherapy; *Post-IT*, after immunotherapy.

TABLE III. Symptom scores during DBPCPC before and after immunotherapy

Treatment group	Peanut IT-treated subject 1		Peanut IT-treated subject 2		Peanut IT-treated subject 3		Placebo-treated subject	
Study day	Pre-IT	Post-IT	Pre-IT	Post-IT	Pre-IT	Post-IT	Pre-IT	Post-IT
Last tolerated dose	1.0 gm	8.0 gm	8.0 gm	8.0 gm	8.0 gm	8.0 gm	8.0 gm	8.0 gm
Nausea	3+	1+	3+	1+	0	0	2+	3+
Vomiting	3+	0	0	0	0	0	2+	2+
Urticaria	0	1+	3+	1+	2+	0	3+	3+
Rhinitis	0	0	0	0	0	0	2+	0
Mucosal pruritus	3+	1+	0	1+	0	0	2+	1+
Asthma	0	0	3+	0	3+	0	0	3+
Hypotension	0	0	3+	0	0	0	0	0
Treatment	SQ EPI	SQ EPI	SQ EPI	No RX	SQ EPI	No RX	SQ EPI	SQ EPI
			IV steroids					
			Hespan					
			ASCU adm					

Pre-IT, Before immunotherapy; *Post-IT*, after 4 weeks of maintenance immunotherapy; *SQ EPI*, subcutaneous epinephrine; *No RX*, no treatment; *IV*, intravenous; *adm*, admission.
Clinical symptoms were graded on a scale of 0 to 3+ with 3+ being the most severe.
After peanut immunotherapy, but not placebo therapy, patients demonstrated reduced clinical symptoms elicited by DBPCPC.

mean symptom score decreased to 2.0. In contrast, the placebo-treated subject's symptom score was 11 at baseline and 12 after placebo immunotherapy. The individual symptom scores for each subject are described in Table III.

The dramatic reduction in clinical symptoms after peanut immunotherapy is best illustrated by describing the DBPCPC of active-peanut-treated subject B before and after peanut immunotherapy. The subject was a

23-year-old white woman with a history of mild asthma requiring only occasional β_2 -agonist therapy. Before immunotherapy, the patient developed generalized urticaria approximately 1 hour after receiving 8 gm (cumulative dose, 15.86 gm) of peanut. Several minutes later, she complained of shortness of breath. Peak flow meter readings dropped from a baseline of 470 to 150 ml. Auscultation revealed decreased breath sounds, wheezing, and a prolonged expiratory phase.

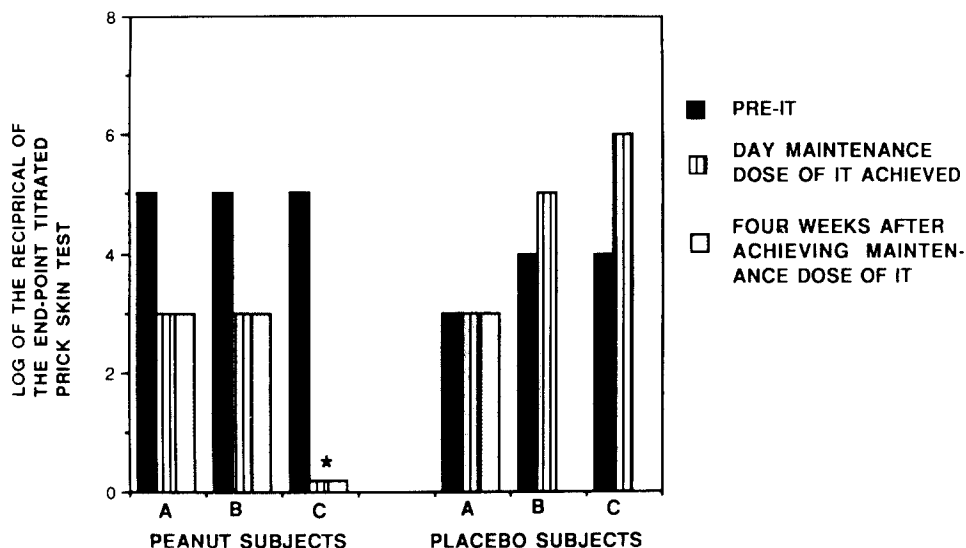


FIG. 3. End point titrated PST reactivity to peanut extract before and after immunotherapy. After peanut immunotherapy, but not placebo therapy, there was a 2- to 5-log reduction in end point skin test reactivity to peanut extract. Peanut-treated subject C (*) had no wheal noted to peanut extract at 1:10 wt/vol with unchanged positive control; *Pre-IT*, before immunotherapy; *IT*, immunotherapy.

The subject received a total of three subcutaneous injections of 0.3 ml of epinephrine, 1:1000. Her peak flow readings improved only to 190 ml. Approximately 90 minutes after the onset of wheezing, the subject complained of nausea and lightheadedness. Physical examination revealed a pulse of 102 and a BP of 76/0. Before DBPCPC, the patient's baseline BP had been 110/70. The patient started receiving hetastarch (Hespan [a volume expander]; DuPont Critical Care, Wilmington, Del.) and was hospitalized in the ASCU. She was maintained with frequent β_2 -agonist-nebulizer treatments and was administered 60 mg of intravenous methylprednisolone (Solu-Medrol; The Upjohn Co., Kalamazoo, Mich.). Approximately 30 minutes after this therapy, the patient's BP rose to 96/60. Her bronchospasm subsided within several hours with resolution of asthma symptoms and normalization of peak flow measurements. By the following morning, the patient was back to baseline with regard to symptoms, vital signs, and peak flow measurements.

After peanut immunotherapy, the subject ingested all doses of the peanut challenge. Approximately 50 minutes after the last challenge dose, the subject complained of minimal (1+) pruritus of her left conjunctiva. Approximately 90 minutes after the last challenge dose, she complained of minimal (1+) nausea. After 120 minutes, a single 7 by 9 mm hive was noted on the subject's left forearm. No therapeutic intervention was required. These symptoms all resolved within 3 hours of her last food-challenge dose.

Changes in end point titrated skin testing to peanut after immunotherapy

Six subjects (three treated with peanut extract and three with placebo) underwent titrated prick skin testing before and after rush immunotherapy. As illustrated in Fig. 3 and Table IV, all three subjects who underwent immunotherapy to peanut demonstrated a marked decrease in skin test sensitivity (mean reduction, 33,400-fold). In contrast, the three subjects treated with placebo demonstrated a slight increase in skin test sensitivity to peanut (mean increase, 36.7-fold). There was no change in reactivity to histamine in any of these subjects.

SRs to rush peanut immunotherapy

Overall, there was a 13.3% incidence of SRs with peanut immunotherapy (16 reactions in a total of 120 injections). Urticaria occurred with 62.5% (10 reactions) of SRs, whereas conjunctival injection and asthma each occurred in 25% (four reactions each) of SRs (Table V). All these asthma attacks responded to inhaled β_2 -agonist therapy plus, in three cases, one dose of subcutaneous epinephrine. There were no episodes of hypotension, and no subjects required hospitalization for their adverse reactions.

DISCUSSION

This study was undertaken to establish the safety and efficacy of peanut immunotherapy by injection. The results suggest that this is an effective form of therapy. To qualify for this study, subjects were re-

TABLE IV. Changes in PST after peanut immunotherapy

	Pre-IT	Day maint dose of IT achieved	4 Weeks after achieving maint dose
Peanut-treated subject			
A	1:100,000	1:1,000	1:1000
B	1:100,000	1:1,000	1:1000
C	1:100,000	No PST reaction	No PST reaction
Placebo-treated subject			
A	1:1,000	1:1,000	1:1000
B	1:10,000	1:1,000,000	4 Weeks maint dose not reached
C	1:10,000	1:100,000	4 Weeks maint dose not reached

Maint. Maintenance; IT, immunotherapy.

TABLE V. Adverse reactions to peanut immunotherapy

	Active A	Active B	Active C	Active D	Active E
Total no. rush injects	22	23	17	19	14
Total no. maint injects	9	10	5	1	0
Adverse rxn	3	4	1	4	4
Urticaria	3 (1)	0	0	3	2
Conj injection	0	3 (1)*	0	0	0
Asthma	0	1	0	1	2
Asthma and urticaria	0	0	1	0	0
% Adverse rxn/inject	9.7 (11)*	12 (10)*	4.5 (0)*	20 (0)*	28.6 (maint not reached)
Large local rxn†	2	4	0	1	2
Grade					
1	1	0 (2)*	0	1	1
2	1	0	0	0	1
3	0	0 (2)*	0	0	0

Injects, Injections; rxn, reactions; maint inject, maintenance injections; conj, conjunctival.

*Number in parentheses signifies number of reactions during maintenance injections.

†Large local reactions: grade 1, >30 mm but <50 mm; grade 2, >50 mm but <70 mm; grade 3, >70 mm.

quired to have a history of SRs to peanuts, a positive DBPCPC, and positive PSTs to peanut. Eleven patients began this protocol of rush peanut immunotherapy, eight patients achieved maintenance immunotherapy (four received peanut- and four received placebo-injection therapy), six patients underwent a second set of titrated PSTs (three received peanut- and three received placebo-injection therapy), and four patients underwent a second DBPCPC after 4 weekly maintenance injections. Three of four patients who completed the protocol had received peanut immunotherapy, whereas one patient had received placebo. The three subjects who received immunotherapy to peanut had a marked decrease in symptoms with DBPCPC, varying from a 67% reduction to complete loss of clinical symptoms (Fig. 2). These subjects also had a marked decrease in end point titrated PSTs to peanut. This change in skin test reactivity varied from a 1000-fold reduction to total loss of skin test reactivity to peanut (Fig. 3). In contrast, the one pla-

cebo-treated subject who underwent a second DBPCPC demonstrated no reduction in symptom score or skin test sensitivity to peanut (Figs. 2 and 3). Two other placebo-treated subjects, who did not undergo a second DBPCPC, demonstrated a slight increase in skin test sensitivity to peanut (Fig. 2). This increase in sensitivity may be due to sensitization from the previous peanut challenge. Previous studies at National Jewish Center and other centers have demonstrated that patients with peanut allergy do not outgrow this food sensitivity.^{2, 6} The fact that three of three patients receiving active immunotherapy had marked reduction in clinical symptoms strongly suggests that this is not a chance observation.

We also performed peanut-specific IgE and IgG by ELISA. IgE and IgG levels to peanut rose in all subjects (Giclas P, Oppenheimer JJ, Nelson HS, Leung DYM. Unpublished data). The rise in these immunoglobulin levels did not correlate with active or placebo immunotherapy, and the rise in the peanut-spe-

cific IgE and IgG of the placebo-treated group presumably occurred as a result of stimulation by oral peanut challenge.

Peanut anaphylaxis is a potentially fatal disease complicated by the fact that peanuts are commonly used as an adulterant in the preparation of foods. This finding is best exemplified in the case of a Brown University student who died of peanut anaphylaxis after ingesting only "two bites" of chili that was adulterated with peanut butter.¹ Although there are supportive measures that can be instituted in the event of an accidental exposure, such as epinephrine and intravenous fluid volume expansion, such measures occasionally fail. For this reason, we chose to examine the efficacy of immunotherapy with peanut extract in the treatment of patients with confirmed peanut anaphylaxis. This study demonstrates that peanut-injection immunotherapy, after a rush protocol, can be accomplished with what is probably an acceptable risk, considering the serious nature of the condition being treated. The overall adverse SR rate was 13.3%. This may be compared to rush immunotherapy with pollen extracts in which SR rates as high as 3.8% have been reported.⁷ In our study, all the SRs were mild to moderate. No patient suffered from a fall in BP or required hospitalization for an SR.

In summary, the current study provides preliminary data demonstrating the efficacy of this therapy in the treatment of a potentially lethal disease; a disease for which, at the present time, there is no adequate therapy. The consistent diminution in clinical signs/symptoms and skin test reactivity after peanut immunotherapy attest to a clinical and immunologic response.

These results provide compelling evidence that additional controlled studies with immunotherapy for peanut allergy are indicated. The potential for serious and even fatal reactions during peanut immunotherapy must, however, not be underestimated. Thus, until additional experience has been acquired, studies should be conducted only in specialized centers in which highly trained intensive care unit staff are available.

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This publication is dedicated to the memory of Jess Stephenson.

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