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Effect of immunotherapy in chronic asthmatic children

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Ten children with chronic intractable asthma whose airway sensitivity had been established by means of inhalation challenges to specific antigens were hyposensitized over a period of 5 to 12 months. Five additional asthmatic children acted as "controls." Various aqueous antigens were used both for immunotherapy and for inhalational challenges. Therapy was given uninterruptedly. The total dose varied from 1,000 to 8,000 protein nitrogen units (PNU) in the controls and from 30,000 to 230,000 PNU in the subjects. Repeat challenges in the low-dose "control" group showed no changes in bronchial sensitivity. Ten children who received high total dosage all showed decreased bronchial sensitivity to specific antigens. Three children who were under study for 12 months could be evaluated clinically as well as physiologically since all four seasons were covered. There was no evidence of clinical, physiologic, or medication improvement in any of them, despite significant decreases in bronchial sensitivity. High-dose therapy appeared to decrease bronchial sensitivity significantly in all except two subjects. The effect was not related to the antigen dose but appeared to be an individual response of the subject.

Studies of the effectiveness of immunotherapy in the treatment of respiratory allergies have given conflicting results. Lowell and Franklin^{1, 2} found, in a carefully controlled double-blind study of ragweed hay fever patients, that those subjects who received therapy fared better than a control group. Fontana, Holt, and Mainland³ found no benefit from immunotherapy. Lichtenstein, Norman, and Winkenwerder,⁴ Sadan and associates,⁵ and Pruzansky and Patterson,⁶ studied ragweed hay fever patients who received high total dose immunotherapy. The latter three studies showed a diminished in vitro histamine release from leukocytes exposed to ragweed antigen in treated subjects, whereas the control (untreated) group showed no change. Furthermore, the blocking antibody

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TABLE I. Low total dose immunotherapy group (control group)

Subject and age (yr.)	Antigen	Duration of treatment (months)	Pre-therapy Br. Ch.* (PNU)	Total treatment dose† (PNU)	Post-therapy Br. Ch.‡ (PNU)
C. A. (12)	Timothy and June grasses	5	100	414	140
C. B. (13)	Timothy and June grasses	5	130	1,475	150
C. C. (16)	House dust	2	1,200	4,277	1,750
C. D. (14)	Alternaria and Hormodendrum	3	120	1,327	140
C. E. (14)	Alternaria	3	700	8,307	1,200

*Bronchial challenge prior to therapy: Amount of antigen in PNU required to produce a 25%

†Total amount of antigen administered in PNU.

‡Bronchial challenge after therapy: Amount of antigen in PNU required to produce a 25% drop

§The mean PEFR for base line month prior to therapy; PEFR's taken twice daily, 7 days a week,

||The mean of twice daily PEFR for the month after therapy, expressed as a percentage of pre

¶The bronchodilator medication score prior to therapy.††

#The bronchodilator medication score after therapy.††

**The steroids required in mg. of prednisone from the base-line month prior to therapy.

††The steroids required in mg. of prednisone for the month after therapy.

‡‡Medication scores are derived from a previously described formula.¹²

(IgG) levels of the treated group were increased. The subjects also had significant clinical improvement when compared to the control group.

Johnstone and Dutton⁷ conducted a controlled study on 210 children with perennial bronchial asthma in which one half of the children received placebo injections, while the other half received conventional hyposensitization therapy. At their sixteenth birthday, 22 per cent of the placebo-treated children were free of asthma compared to 72 per cent of the treated children. They further showed that the treated subjects who received the highest tolerated dose were clinically better than the subjects who received a lower dose of hyposensitization for maintenance. However, this study was evaluated clinically only, and no objective measurement was incorporated in its design.

Quantitative inhalation challenges have been used as an objective measure of the efficacy of hyposensitization therapy,⁸⁻¹⁰ but none of these studies reported on total dosage used in the therapy.

The purpose of this study was to measure the change in bronchial sensitivity to inhaled antigens in chronically asthmatic children after immunotherapy and to correlate this with the clinical response.

SUBJECTS AND METHODS

Fifteen children, 14 boys and 1 girl between the ages of 9 and 16 years, from the resident population at the Children's Asthma Research Institute and Hospital (CARIH), Denver, were studied. The subjects were selected on the basis of (1) positive skin tests, (2) positive inhalation tests to the same antigens, and (3) history in keeping with skin tests and challenges. Ten children received high total dosage immunotherapy (designated as "treated" group), and 5 other children receiving low total dosage immunotherapy served as a control group.

The inhalational challenge was done when the patient had no asthma, and oral or inhaled bronchodilators were omitted for at least 12 hours before testing. Prior to testing the children

Pre-therapy PEFR§	Post-therapy PEFR	Pre-therapy medication score¶	Post-therapy medication score#	Pre-therapy steroid**	Post-therapy steroid††
22	56	62	96.5	135	110
39	55	14	55.5	0	0
69	81	111.5	88.5	595	835
63	53	77.5	94	900	905
47	44	111.5	145	0	160

drop in peak expiratory flow rate (PEFR), which is sustained.

in PEFR, which is sustained.
expressed as a percentage of predicted.
dicted.

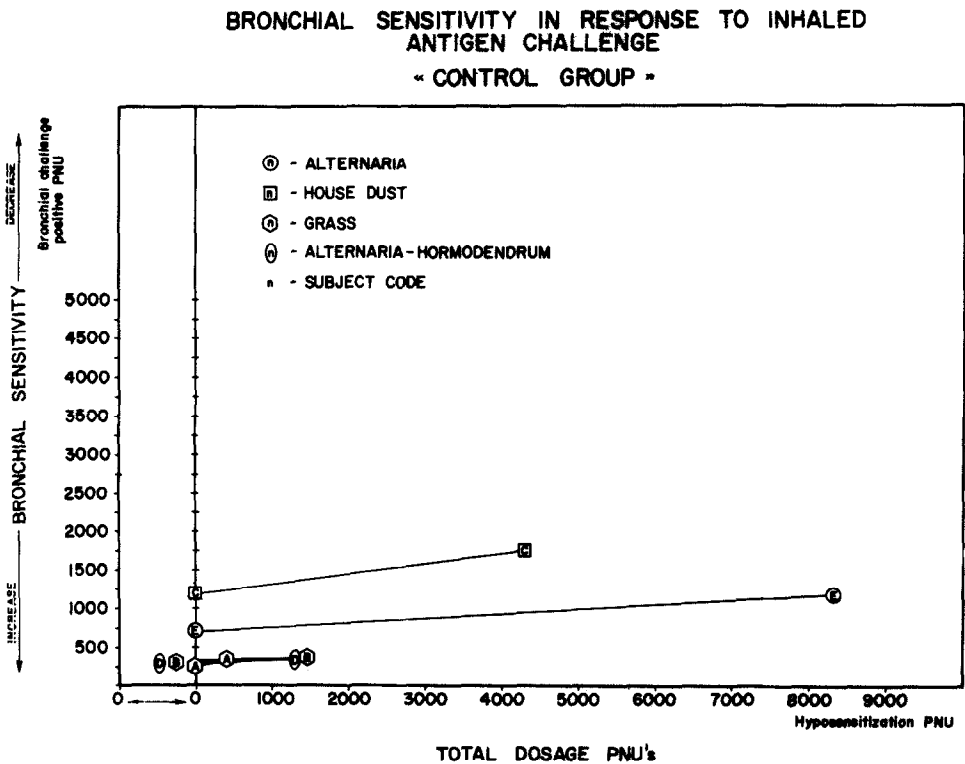


FIG. 1. The vertical axis indicates the amount of antigen required to obtain a positive challenge. The horizontal axis indicates the cumulative total amount of antigen that had been administered.

TABLE II. High total dose immunotherapy group (treated group)

Subject and age (yr.)	Antigen	Duration of treatment (months)	Pre-therapy Br. Ch.* (PNU)	Total doset (PNU)	Post-therapy Br. Ch.† (PNU)
A.	Alternaria	5	700	31,665	8,200
(13)	House dust	5	3,700	75,665	10,000 (neg.)
	Grass	6	5,200	92,665	10,000 (neg.)
B.	House dust	7	2,700	33,765	6,250
(9)					
C.	Grass	7	1,700	75,257	5,000
(14)	Alternaria	7	1,450	40,051	8,000
D.	Alternaria	12	700	121,025	4,000
(12)					
E.	Alternaria	7	80	48,681	3,200
(10)					
F.	Grass	12	1,500	230,555	5,000
(11)					
G.	Grass	12	2,700	161,417	10,000 (neg.)
(13)	Alternaria	8	1,700	47,177	3,250
H.	House dust	8	1,700	135,777	4,000
(13)					
I.	House dust	9	2,200	137,607	3,500
(10)					
J.	Alternaria	9	120	119,714	3,000
(14)	Ragweed, mixed (short and tall)	5	3,200	104,714	4,000

*Bronchial challenge prior to therapy: Amount of antigen in PNU required to produce a 25%

†Total amount of antigen administered in PNU.

‡Bronchial challenge after therapy: Amount of antigen in PNU required to produce a 25% drop

§The mean PEFR for base-line month prior to therapy; PEFR's taken twice daily, 7 days a

||The mean of twice daily PEFR for the month after therapy, expressed as a percentage of pre

¶The bronchodilator medication score prior to therapy††

#The bronchodilator medication score after therapy.††

**The steroids required in mg. of prednisone from the base line month prior to therapy.

††The steroids required in mg. of prednisone for the month after therapy.

‡‡Medication scores are derived from a previously described formula.¹²

were examined to exclude clinical evidence of asthma, and base line peak expiratory flow rates (PEFR), measured on a Wright Peakflow Meter, were recorded to confirm that they were approximately the predicted value for each child. The patient inhaled a solution of the antigen, diluted in buffered saline, aerosolized by a No. 40 DeVilbiss nebulizer and delivered by a compressor through an open system. The chest examination and PEFR were monitored every few inhalations. If the first solution of antigen, containing 200 protein nitrogen units (PNU) in 1 ml. of buffered diluent, produced no effect, the subjects were challenged with concentrations of 5,000 PNU per milliliter and 10,000 PNU per milliliter. The maximum level of challenge in this study was 10,000 PNU. A sustained drop in PEFR of 25 per cent from base line levels or clinical evidence of asthma was considered as the end point. Open bronchial challenges are semiquantitative at best. There is no way of ascertaining the amount that actually reaches the bronchi because much remains in the mouth and pharynx or is dissipated into the air. Hence, changes in sensitivity are required to be large to be significant.

When a positive response was obtained, the amount of antigen remaining in the nebulizer was measured, and by subtraction the amount delivered was determined. The final dosage administered up to the point of a positive response was obtained by adding the amount used at various concentrations (e.g., response at 8,200 PNU = 200 PNU + 5,000 PNU + 3,000 PNU of the 10,000 PNU per milliliter dilution). Challenges for different antigens were never performed less than 7 days apart in the same subjects.

The sensitivity was expressed as the amount of antigen, in PNU, that had been administered. A control challenge with buffered saline preceded each antigen test to exclude nonspecific responses.

Pre-therapy PEFR§	Post-therapy PEFR	Pre-therapy medication score ¶	Post-therapy medication score #	Pre-therapy steroid**	Post-therapy steroid††
99	111	2	1	0	0
63	48	0	3	0	0
59	91	79.5	0	0	0
77	67	181	144	510	840
54	66	88	104	0	0
82	68	50.1	141	0	0
76	38	78.5	103	175	0
82	74	77.5	8	550	0
81	85	67	7	0	0
45	59	23	81	0	0

drop in PEFR, which is sustained.

in PEFR, which is sustained.

week, expressed as a percentage of predicted.
dicted.

When the patient showed positive skin tests, a positive inhalation challenge to one or more antigen(s), and a compatible history, then immunotherapy to the antigen(s) was considered to be indicated. Each antigen was injected subcutaneously and separately. The initial dose of antigen was 0.05 ml. of 10 PNU per milliliter. If previous injections caused no significant reaction, the antigens were administered as follows: 0.1, 0.2, 0.3, 0.4, and 0.5 ml. Then 0.05 to 0.5 ml. of 100 PNU per milliliter, 1,000 PNU per milliliter, and 10,000 PNU per milliliter extract concentrations were given. Following this injections of 20,000 PNU per milliliter extract were started at 0.25 ml. and were maintained between 0.25 and 0.5 ml. Injections were given twice weekly initially until the dose of the particular antigen reached 0.1 ml. of 10,000 PNU; then weekly injections were employed until the dose of 0.5 ml. of 10,000 PNU had been attained. Thereafter, extract was given every 2 weeks.

Inhalation challenges were repeated after therapy. The amount of antigen required to induce a positive inhalational challenge was measured and recorded. A significant increase in PNU of antigen required to induce a positive challenge indicated decreased bronchial sensitivity, while a decrease in amount of antigen indicated an increase in reactivity.

RESULTS

In the low-dose group ("control"), 8,300 PNU of antigen was the largest amount administered by the end of the study. The dose varied from 414 to 8,037 PNU (Table I). There was no appreciable change in bronchial sensitivity in any subject, but it is of some interest to note that Subject C. A. was so sensitive

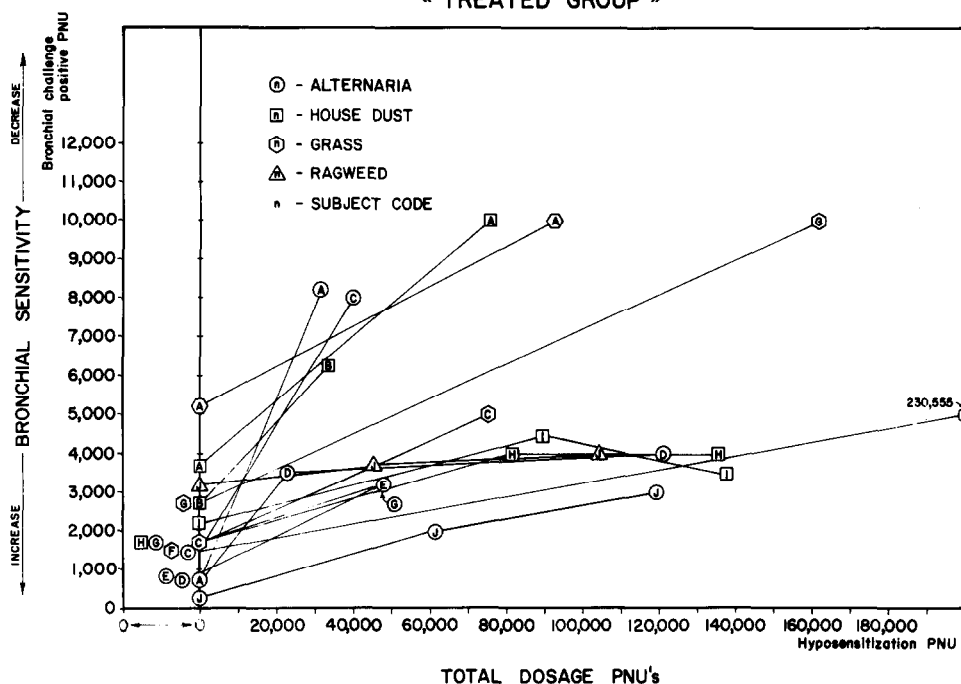
BRONCHIAL SENSITIVITY IN RESPONSE TO INHALED
ANTIGEN CHALLENGE
" TREATED GROUP "

FIG. 2. The vertical axis indicates the amount of antigen required to obtain a positive challenge. The three challenges noted at the 10,000 PNU level were negative at this cutoff point. All others were positive at the indicated level. The horizontal axis indicates the cumulative total amount of antigen that had been administered.

that a total dose of 414 PNU was the maximum that could be achieved in 5 months compared to over 8,000 for Subject C. E., indicating the variable nature of individual sensitivity to immunotherapy.

In the high-dose group ("subjects"), the dose reached varied from 31,665 PNU (Subject A., Table II) to 230,555 PNU (Subject F.). Three challenges reached experimental negativity, i.e., 10,000 PNU. Two of these were in the same subject (A.), and one was in Subject G. Furthermore, Subjects A. and G. both were positive to another antigen, but both had received a much smaller total dosage of the antigens to which they were still positive.

Two subjects showed little change in inhalation challenge test results after therapy. Subject I., who showed an increase of about 1,300 PNU (2,200 initial to 3,500 at the end) appeared to be less sensitive, but this was not very striking considering that a total dose of 137,607 PNU had been injected in 9 months. A change in only 800 PNU in one of the antigens used for Subject J. (3,200 to 4,000) can be considered as no change considering the variability inherent in the method.

All the remainder showed marked differences in antigen sensitivity (Fig. 2, Table II), but it was apparent that the degree of change did not depend on

TABLE III. Individual results

Group	Number of patients		
	Improved*	No change†	Worse‡
High-dose group (10 patients)	3	6	1
Low-dose group (5 patients)	0	3	2

*Significant improvement in PEFR; decreased bronchodilator and/or steroid requirement.

†Significant improvement in only one of the above parameters.

‡Significant worsening of all the parameters.

the amount of antigen administered, the response appearing to depend on the individual. For example, Subject A. was negative to 2 antigens at 10,000 PNU when 92,665 and 75,665 PNU, respectively, had been administered and were very nearly negative (8,200 PNU) at a total dose of 31,665 PNU of another antigen. At the same time, after receiving 230,555 PNU of antigen, Subject F. responded on inhalation challenge at 5,000 PNU (though this showed much less sensitivity than the initial level of 1,500 PNU). Of the 4 subjects (D., H., I., and J.) whose bronchial sensitivity was monitored during therapy, maximum reduction in bronchial sensitivity was achieved at a higher dosage than that administered to the control group, but beyond a certain dosage no further decrease in bronchial sensitivity was evident (Fig. 2).

Examination of the type of antigen given shows no indication that this was a significant factor in the response.

DISCUSSION

It appears from these data that (1) high-dose immunotherapy decreases airway sensitivity as measured by bronchial challenge to the same antigen; (2) the response is highly variable and appears to depend on the individual response of each subject; (3) in all instances bronchial sensitivity decreased, although in one case the change was a little significance. Others have also noted individual variability in response to this form of immunotherapy¹¹ (Table III).

The three subjects that could be evaluated clinically because of a complete "4 season" follow-up were of some interest, although generalizations cannot be drawn with so few individuals. One (D.) showed a moderate decrease in bronchial sensitivity, no real change in average PEFR performed twice daily 7 times a week, and a decided increase in medication requirements, especially steroids. The only conclusion that can be drawn is that sensitivity to *Alternaria* was not the only factor involved. Subject F. presented a similar picture except that no steroids were employed at any time. Subject G. who became negative to one antigen (grass at 10,000 PNU), showed a moderate increase in bronchodilator medication requirements but a very marked drop in steroids. This change in steroid therapy would be more impressive if the antigen involved was of a perennial nature rather than seasonal.

There were 3 subjects who showed an improvement in all parameters. Subjects A., C., and I. showed better PEFR averages in the face of decreased medication.

Each of these did not have a full 12 months of therapy, however, and the changes may well have been unrelated to the immunotherapy.

The remainder showed no improvement in PEFr average scores, medication (bronchodilator) requirements, or steroid intake. None of the control group showed any significant changes in any parameter.

All the subjects in this study were so-called "mixed" type asthmatics. There were, without doubt, aspects of their asthmatic process that were reagin-mediated (skin tests, seasonal history, positive immediate bronchial challenges), but, other precipitant elements that could not be elucidated (intrinsic, idiopathic) were patently present as well. In fact, it is likely that the second elements were playing a dominant role.

It is, therefore, not really surprising to find that, despite very significant decreases in bronchial sensitivity to high-dose antigen therapy, a concomitant improvement in PEFr and a reduction in medication requirements did not occur. The clinical and physiologic results might have been more impressive had these children been purely "seasonal" asthmatics without a background of much more refractory unknown factors.

Physiologic measures of delayed reactions were not performed, but none of these subjects returned to the hospital unit within an 8 hour period for relief of asthma following challenge, indicating the absence of significant delayed clinical response.

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