

The effect of antigen injections on skin reactivity to antigens

George A. Spreccace, M.D., Stanley G. Pomper, M.D., William B. Sherman, M.D., Arthur Lemlich, M.D., and Herman Ziffer, M.D., New York, N. Y.

A review was made of 100 patients with respiratory allergy treated an average of 11 years with some but not all the antigens to which they reacted. Skin tests were repeated annually. Statistical analysis with the aid of electronic data processing showed the following: Skin tests with antigens which were not included in the treatment showed no significant changes. Skin tests to antigens with which the patient was treated showed marked specific decreases, greater with treatment near the limit of tolerance of the individual patient than with less intensive treatment. Treatment with injections of house dust extract produced changes in skin tests less marked than those produced by pollen antigens. No statistically significant conclusions concerning the improvement in clinical symptoms could be reached.

Although desensitization treatment of allergic diseases has been used for decades, its efficacy is still the subject of controversy.^{1, 2, 3} In recent years physicians treating allergic disorders have endeavored to place their activities on a more scientific basis. This desire has led to the study of basic mechanisms, search for better defined antigens, wider use of quantitative methods, and re-evaluation of methods of treatment.

This presentation has few new ideas to offer. Rather, it is intended to supply statistical data relevant to ideas that have been reported in the past as clinical impressions.^{4, 5, 6}

The present work was intended to study the following questions:

1. Does prolonged allergy treatment effect a specific desensitization, reflected

From The Roosevelt Hospital, Robert A. Cooke Institute of Allergy.

Supported by Training Grant No. 5 T1 AI-201 from the National Institute of Allergy and Infectious Diseases of The National Institutes of Health, Bethesda, Md.

Presented in part at The Twentieth Annual Meeting of The American Academy of Allergy, San Francisco, Calif., February, 1964.

Received for publication July 22, 1965.

in reduction in the reaction to skin test, above and beyond any that might be expected to occur spontaneously?

2. Does the intensity of treatment affect these changes?
3. Can such changes be correlated with the clinical progress of the patient?
4. Does sensitivity to antigens not included in the treatment decrease spontaneously through the years in the natural course of the disease?
5. Do all antigens react similarly to treatment?

The study was furthermore designed to investigate the applicability of automatic data processing techniques in clinical allergy research.

MATERIALS AND METHODS

In selecting the case histories for the study, 708 charts in the practice of one of the authors (W. B. S.) were reviewed in alphabetical order until 100 were found that fulfilled the following criteria: (1) at least two years of adequate specific injection treatment; (2) respiratory allergy to pollens as one of the diagnoses; (3) yearly follow-up of the patients, including annual repetition of intracutaneous skin tests with pertinent antigens, whether or not included in the treatment.

The alphabetical method of selection used disregarded any real or presumed correlation between initials, racial origins, and hereditary traits.

All patients had been studied carefully before treatment was initiated. In addition to the records of skin tests and treatments, the charts contained paraphrases of the patient's reports of clinical results, as well as medication prescribed (antihistamines, steroids, bronchodilators, etc.). The charts had not been kept with the idea of such a study ever being performed and results of treatment were at times difficult to assess. For example, it was not always easy to tell whether the result in a given year was being compared to that in the preceding year, or in the original year of treatment, or to the condition before treatment.

Treatment consisted of subcutaneous injections of aqueous extracts of antigens. The intention was to give adequate doses of the antigens believed to be the most important causes of symptoms rather than small doses of all antigens to which positive skin test reactions were obtained. All except six patients received perennial rather than preseasonal treatment. Treatment, however, fell into a broad spectrum. Those receiving perennial injections which continuously produced local reactions lasting 24 hours or less were considered to be receiving maintenance dosage. Patients receiving preseasonal therapy or injections causing no local reactions were considered to be receiving less than maximum maintenance. Other combinations of therapy were considered intermediate in this scheme. The doses of antigen were high by the usual criteria, in the range of 50 to 500 mcg. of antigen protein nitrogen (5,000 to 50,000 PNU). The duration of the treatment of the patients studied ranged from two to forty-two years, with an average of eleven years. The fact that patients were not treated with all antigens to which they showed skin reactions permitted a comparison of changes in the skin test reactions to antigens with which they were treated to those with which they were not treated. Thus, the patients, in a sense, provided their own controls.

Several problems had to be considered in furthering the study. There was the fact that skin tests and treatment had been performed by more than twenty physicians over a span of four decades, beginning with Dr. Robert A. Cooke, with whom one of the authors (W. B. S.) was associated for many years. The other physicians comprised a third generation trained in the same methods.

The skin tests were usually performed with two or three dilutions of the same antigen each time, but not with the same dilutions each year. To facilitate the comparison of changes in the reactions to yearly skin tests, it was desirable to reduce the results produced by various strengths of antigen to a single equivalent. To accomplish this, in a preliminary study, twenty-two patients were tested with three tenfold dilutions of three different pollen extracts producing sixty-six triplets of reactions. A regression line calculated from these data, with a slope of 0.99, permitted the construction of a table relating degrees of reactions and strengths of solutions to single numbers (Table I).

Furthermore, two other experiments were designed as controls to study the merits of criticisms to which the main data might be open. On the one hand, Lowell⁷ has recently called attention to the fact that sites which have been injected subcutaneously with allergen extracts are less reactive to intradermal injections of the same and possibly other extracts. Since the patients studied were tested over the anterior aspect of the arm and given treatment injections over the posterior portions, it was not felt that the same sites were being used. However, 32 patients were each tested with identical antigens simultaneously on the anterior surfaces of both arms, the posterior aspects of which had been sites of previous treatment injections with the same antigens and no significant differences in skin tests results were noted.

Second, Tuft⁸ has presented work suggesting that there is a gradual decline in skin sensitivity with advancing age. Such a finding might obscure the changes in skin test reactions observed in this study. To investigate this factor another study was performed, the results of which will be presented in a separate report. No significant decrease in skin reactivity with age was found.

The 100 chosen charts were carefully reviewed for all information felt to be of possible usefulness. Based on the selected categories and subdivisions of information, two coding sheets were designed. The first included those categories pertinent to the initial evaluation of the patient (Table II). The second contained

Table I. *Skin test conversion table. Method by which skin reactions at various testing strengths are converted to a common numerical value*

<i>Conversion value</i>	<i>10,000 PNU</i>	<i>1,000 PNU</i>	<i>100 PNU</i>	<i>10 PNU</i>
1	0			
2	+	0		
3	++	+	0	
4	+++	++	+	0
5	++++	+++	++	+
6		++++	+++	++
7			++++	+++
8				++++

Table II. Coding sheet for initial over-all evaluation of the patient

Col. No.	Categories	1	2	3
1	Case No.			
2				
3				
4				
5	Card No.			
6				
7	Sex	Male	Female	
8	Age (yr.)	Less than 1	1-5	6-10
9	Original diagnosis (main + assoc.) No. 1	SVR	SVR-PVR	SVR-PA
10	Original diagnosis No. 2	SVR-PVR	SVR-PA	SA-PVR
11	Original diagnosis No. 3	AD-MKD	AD-MLD	U-MKD
12	Severity of main original diagnosis No. 1	Mild	Moderate	Severe
13	Severity of main original diagnosis No. 2	Mild	Moderate	Severe
14	Duration of symptoms before treatment No. 1	Less than 6 mo.	7-12 mo.	13-23 mo.
15	Duration of symptoms before treatment No. 2	Less than 6 mo.	7-12 mo.	13-23 mo.
16	Age of patient at onset of treatment (yr.)	Less than 1	1-5	6-10
17	Years of treatment	3-5	6-10	11-20
18	Intensity of treatment	Maximum maintenance	Less than maximum	Excess treatment
19	Location of treatment	Office	LMD	Mixed
20	Type of treatment	Preseasonal	Perennial	Intermediate
21	Original skin test—trees	1	2	3
22	Original skin test—grass	1	2	3
23	Original skin test—ragweed	1	2	3
24	Original skin test—dust	1	2	3
25	Later diagnosis	SVR-MLD	SVR-MKD	SA-MLD
26	Later diagnosis (year of treatment development)	1-3	4-6	7-10
27	Estimated degree of improvement	Excellent	Good	Fair

Abbreviations: S, Seasonal. V, Vasomotor. R, Rhinitis. P, Perennial. A, Asthma. AD, Atopic der-

Table III. Coding sheet for yearly follow-up

Col. No.	Categories	1	2
1	Case No.		
2			
3			
4			
5	Card No.		
6			
7	Intensity of treatment	Maximum maintenance	Less than maximum
8	Location of treatment	Office	LMD
9	Type of treatment	Preseasonal	Perennial
10	Steroid treatment	Used	Not used
11	Antihistamine treatment	Used	Not used
12	Trees—skin test	1	2
13	Trees—maximum dose (1,000 PNU)	Less than 1	1-2
14	Grass—skin test	1	2
15	Grass—maximum dose (1,000 PNU)	Less than 1	1-2
16	Ragweed—skin test	1	2
17	Ragweed—maximum dose (1,000 PNU)	Less than 1	1-2
18	Dust—skin test	1	2
19	Dust—treatment	Treatment	No treatment

4	5	6	7	8	9
11-19 SA SA-PA U-MLD No data No data 2-5 yr.	20-29 SA-PVR Other 6-10 yr.	30-39 SA-PA 11-20 yr.	40-49 21-30 yr.	50+ 30+ yr.	No data
2-5 yr.	6-10 yr.	11-20 yr.	21-30 yr.	30+ yr.	No data
11-19 21-30 No data	20-29 30+	30-39	40-49	50+	No data
4	5	6	7	8	
4	5	6	7	8	
4	5	6	7	8	
4	5	6			
SA-MKD 11-14	PVR-MLD 15-19	PVR-MKD 20-25	PA-MLD No data	PA-MKD	No data
Poor	None	No data			

matitis. U, Urticaria. MKD, Marked. MLD, Mild.

3	4	5	6	7	8
Excessive treat- ment Mixed Intermediate No data No data	No data				
3	4	5	6	7	8
3-5	6-10	11-20	21-30	30+	No treatment
3	4	5	6	7	8
3-5	6-10	11-20	21-30	30+	No treatment
3	4	5	6	7	8
3-5	6-10	11-20	21-30	30+	No treatment
3	4	5	6		

information relative to the yearly follow-up of the patient (Table III). Two mark sense cards were then designed following the coding sheet format (Figs. 1 and 2). Information was then transcribed from the patient's charts to the evaluation card and then to yearly detail cards, which were subsequently punched. These cards were run through an IBM 1401 computer to produce a printout of the clinical information for each patient in a proper time sequence that permitted initial time series analysis of pertinent factors (Table IV). These results were combined with basic data to produce one summary card for each patient (Table V). The summary cards were then subjected to cross-tabulation analysis on the IBM 1401 computer.

RESULTS

All criteria were carefully conceived and rigidly adhered to in order to deal with data as objective and "hard" as possible. The most important criteria concerned the tests of significant change in skin test reactions. Here two criteria were used and results were calculated separately according to each criterion. Criterion I compared the reactions to the initial skin tests with those to the

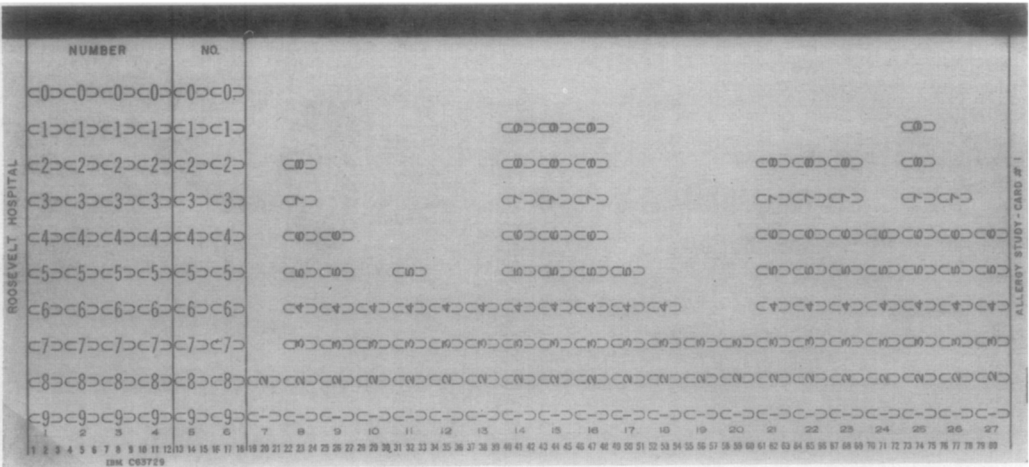


Fig. 1
Mark sense card associated with coding sheet (Table I).

Table IV. Typical "print out" for a patient. The initial evaluation is recorded across neath it.

Case No.	Sex	Age	Orig. Dx 1	Orig. Dx 2	Orig. Dx 3	Sev. Dx 1	Sev. Dx 2	Sx Rx 1	Sx Rx 2	Age Rx
0016	2	5	7	5	6	1	5	5	0	4
Years	Int. Rx	Loc. Rx	Type Rx	Ster. Rx	Ant. Rx	Trees test	Test diff.	Trees Rx	Rx diff.	Grass test
01/01	2	2	2	3	3	9	/-	1		5
02/01	2	2	2	3	3	5	/-1	1	0	5
03/01	2	2	2	3	3	6	1/-0	1	0	5

tests of the final two years of treatment. At least a hundredfold dilution change for each of the last two years was necessary to be considered significant. The last two years' skin reactions were used so that the likelihood of a random change would not influence the results. Criterion II was developed and used in an attempt to convert that group with equivocal changes according to Criterion I (a hundredfold dilution change for one of the last two years and a change of lesser degree for the other year) to definite results reflecting either significant or insignificant change. Using this criterion, skin tests in at least two of the three final years of treatment had to demonstrate a hundredfold dilution change in skin reaction to be considered significant. The results of this phase of the study are shown in Table VI, including the relative numbers in each category, the relative percentages, and the confidence limits at the 95 and the 99 per cent levels for both criteria used. Although 100 cases were reviewed, 153 antigens were studied since in some cases the changes with more than one antigen could be followed. On the basis of these results, the following statements can be made with adequate statistical support: (1) Skin test reactions to antigens with which the patient was not treated showed no significant change. (2) Skin test reactions

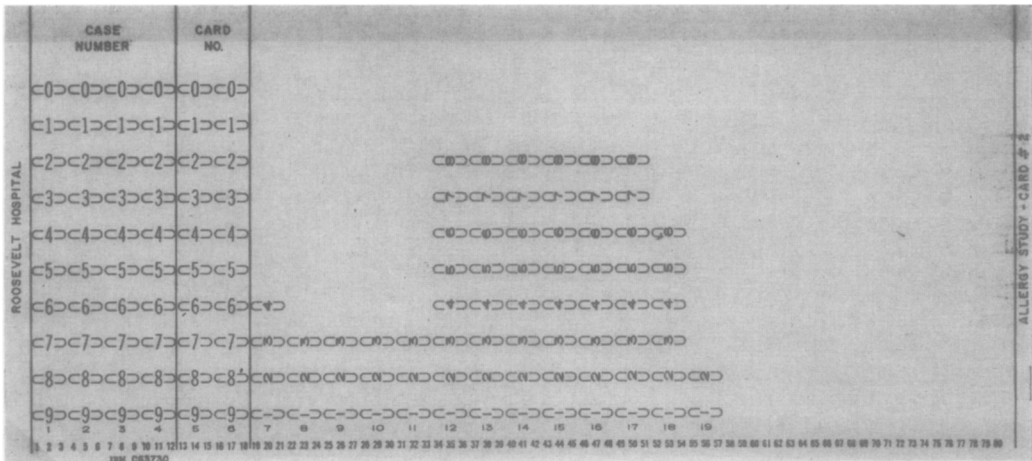


Fig. 2
Mark sense card associated with coding sheet (Table II).

the upper part of the sheet. The yearly follow-up data are listed in sequence be-

Yr. Rx	Int. Rx	Loc. Rx	Type Rx	Trees	Grass	Rag	Dust	Later Dx 1	Later Dx 2	Est. Imp.
1	2	2	2	6	6	7	3	9	8	3
Test diff.	Grass Rx	Rx diff.	Rag test	Test diff.	Rag Rx	Rx diff.	Dust test	Test diff.	Dust Rx	Rx diff.
/-1	1		6	/-1	1		6	/ 3	2	
0/-1	1	0	6	0/-1	1	0	3	-3/-0	2	
0/-1	1	0	7	1/-0	1	0	4	1/ 1	2	

Table V. *Coding sheet for individual patient summary*

Col. No.	Categories	X	0	1
1-25*	Evaluation card			
26	Actual years of		0	1
27	Treatment		0	1
28	Category of treatment†			Maximum maintenance
29	Steroids		No	Yes
30	Antihistamines		No	Yes
31	Trees treatment	No data	None	Complete
32	Average treatment last 3 yr. (1,000 PNU).	No data	None	Less than 1
33	Criterion I			Significant decrease
34	Criterion II			Significant decrease
35	Year of significant change	Not applicable	Over 15	1
36-40	Grass‡			
41-45	Ragweed‡			
46-50	Dust‡			
51	Untreated trees (Criterion I)			Significant decrease
52	Untreated trees (Criterion II)			Significant decrease
53	Year of significant change	Not applicable	Over 15	1
54-56	Untreated grass§			
57-59	Untreated ragweed§			
60-62	Untreated dust§			
63	Treated antigens			Better
64	Untreated antigens			Better

*The original evaluation card contained 27 columns but a column of "case number" and "card

†If more than 75 per cent of the treatment years were on maximum maintenance or less than 75 per cent of the treatment years were on maximum maintenance or less than maximum maintenance. One or more constitutional reactions for 25 per cent or more of the treatment years were

‡These columns are similar to columns 31-35 which summarize treatment of cases of tree al-

§These columns are similar to columns 51-53 which summarize changes in untreated tree aller-

to antigens included in treatment changed significantly in the great majority of instances, regardless of the intensity of treatment received. (3) Treatment with maximum maintenance dosage was associated with a much greater likelihood of change than was treatment with less than maximum maintenance dosage. (4) Treatment with ragweed antigen, a mixture of equal parts of giant and dwarf ragweed which are antigenically practically identical,^{9, 10, 11} was associated with a more significant skin test change than treatment with grass or trees. The grass antigen used was an equal mixture of timothy, orchard, and June grasses. These are antigenically similar.¹²⁻¹⁵ The tree extract is composed of a mixture of equal parts of extracts of pollens of ash, beech, birch, hickory, oak, poplar, and sycamore trees, all of which are different antigenically.^{16, 17} The greater change of the skin reaction of ragweed as compared with the other antigens might therefore be

2	3	4	5	6	7	8	9
2 2 Less than maximum	33 3 Excessive treatment	4 4 Pred. Maximum main- tenance	5 Pred. less than maximum	6	7	8	9
First half 1-2	Second half 3-5	6-10	11-20	21-30	30*		
Insignificant change	Questionable change	Increase					
Insignificant change	Questionable change	Increase					
2	3	4	5	6	7	8-10	11-15
Insignificant change	Questionable change	Increase					
Insignificant change	Questionable change	Increase					
2	3	4	5	6	7	8-10	11-15
No change	Worse						
No change	Worse						

number" were found to be superfluous.
maximum maintenance, this was so listed on the patient's record. If more than 50 per cent, but less
tenance, the classification was predominantly maximum or predominantly less than maximum main-
considered excessive treatment.
lergies.
gies.

due to its greater homogeneity. (5) In a small percentage of cases, skin reactions to antigens not included in treatment showed a significant increase; no antigens with which the patient was treated showed such a change.

Figs. 3, 4, and 5 represent year-by-year change in the average reactions to skin tests with various antigens. Changes in reaction to antigens with which the patients were treated and to those not included in treatment are shown in Fig. 3. Reaction to antigens not included in treatment showed no significant change in more than 25 years. Reactions to those with which the patients were treated showed a definite decrease. This decrease is noted to be significant (a two unit fall, Table I) after at least five years of treatment. This is in keeping with previous work of Tuft.⁵

When the changes in reaction to house dust were compared to those to pollens,

Table VI. Percentages of skin test reaction changes for different antigens with differ

Treatment categories	Criterion I		
	Patients reacting /total patients	%	95% confidence limits (%)
A. Significant decrease in skin test reactions			
1. All antigens, all types treatment	65/123	53	43-62
2. All antigens, maximum treatment	32/41	78	63-92
3. All antigens, less than maximum treatment	16/44	36	22-53
4. Ragweed, maximum treatment	24/29	83	66-93
5. Ragweed, less than maximum treatment	8/20	40	21-65
6. Mixed grasses, maximum treatment	7/9	78	44-96
7. Mixed grasses, less than maximum treatment	8/20	40	21-65
8. Mixed trees, maximum treatment	1/3	33	1.7-87
9. Mixed trees, less than maximum treatment	0/4	0	0-53
10. No treatment, all antigens	13/83	16	7-24
B. Significant increase in skin test reactions			
1. No treatment, all antigens	5/83	6	2.5-12.5

*Where patients react to, or are treated with, more than one antigen, each antigen is considered

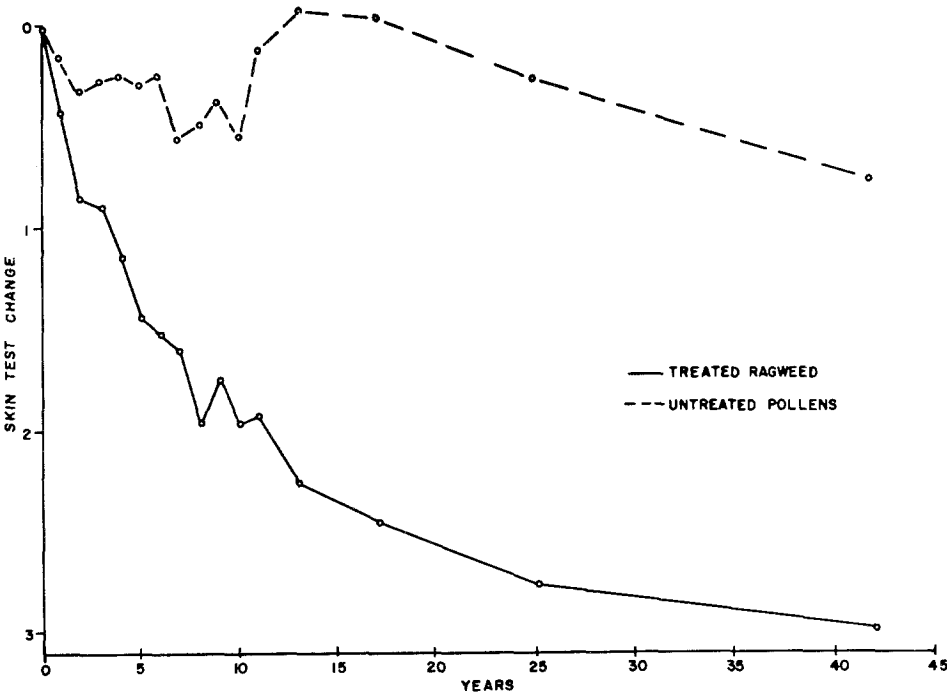


Fig. 3
Treated ragweed compared to untreated pollens.

ent modalities of treatment*

99% confidence limits (%)	Criterion II			
	Patients reacting/ total patients	%	95% confidence limits (%)	99% confidence limits (%)
37-62	73/153	48	42-58	37-62
57-92	37/61	61	46-73	43-77
17-57	13/46	28	16-46	13-48
60-95	28/38	74	7-87	55-90
16-71	9/25	36	19-57	16-65
34-98	8/18	44	24-68	18-77
16-71	4/17	24	9-49	5-59
0.3-94	1/5	20	1-66	0.2-78
0-68	0/4	0	0-53	0-68
6-27	21/92	23	13-33	13-37
2-17	7/92	8	3-16	3-18

separately. Therefore the total number of patients exceeds 100.

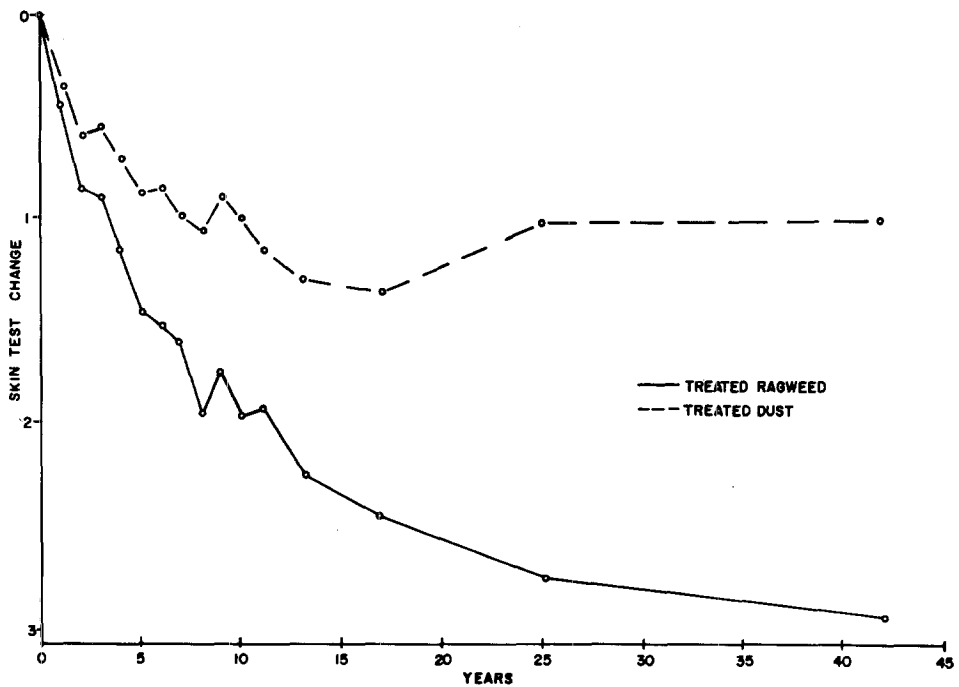


Fig. 4
Treated ragweed compared to treated dust.

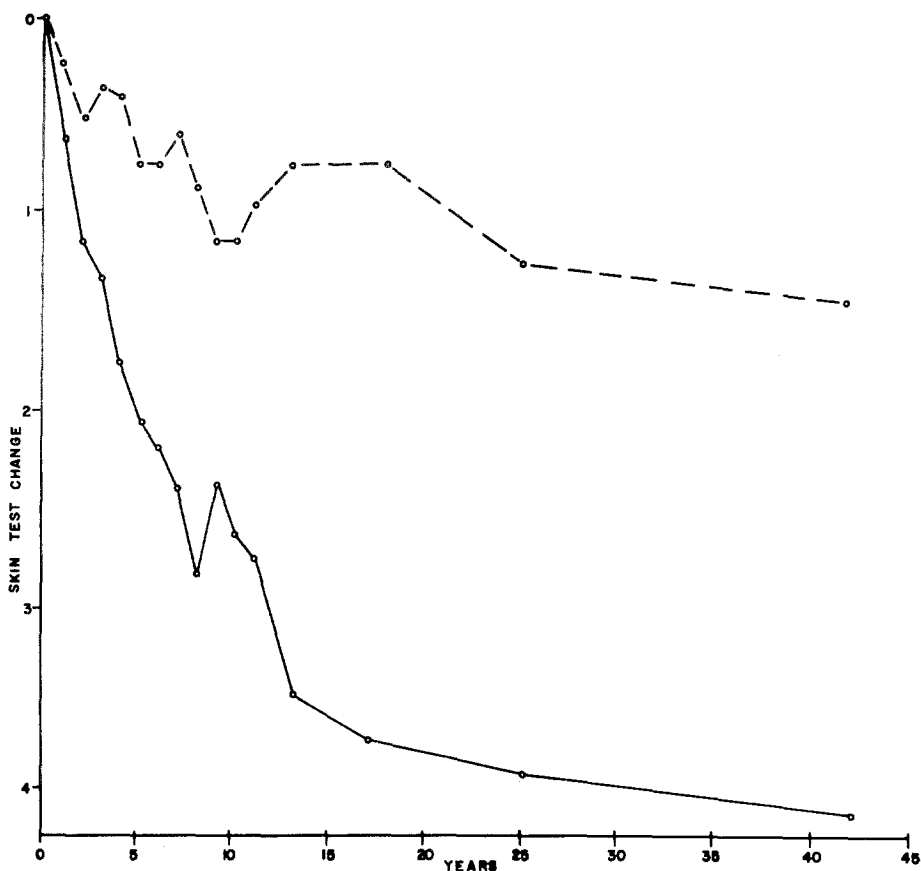


Fig. 5

Treated ragweed: "maximum maintenance" (solid line) compared to "less than maximum maintenance" (broken line).

the reactions to pollens showed a strikingly greater change (Fig. 4). This reflects the nature of the house dust extract, a complex mixture of antigens, none of which are present in concentrations comparable to the pollen antigens available. On the other hand, it suggests that injections of house dust extract, which have sometimes been scorned by immunologists, are not entirely without effect in treatment.

Fig. 5 compares the results of treatment of ragweed allergy with "maximum maintenance" treatment and with lower but still reasonable doses. It is apparent that the more intensive treatment produced greater changes in the skin tests. We did not have a comparable group of patients treated with doses that would be considered low by usual standards.

The final summary cards developed for each of the 100 cases studied contained all information derived from the charts assembled under 64 items (Table V). Each of these items was cross-tabulated against each of the other items by means of the IBM 1401 computer. Pertinent correlations were then subjected to analysis to determine statistical significance. The following is a listing of significant correlations as well as interesting noncorrelations:

1. a. In patients treated with ragweed pollen, the likelihood of a significant reduction in the skin test reaction was directly related to the activity of the reaction to the original skin test ($p < 0.01$). When all the pollens included in treatment (trees, grass, and ragweed) were studied, this correlation was significant at the 5 per cent level.

b. The rate with which significant reduction occurred was also directly related to the original skin test strength, when ragweed was considered ($p < 0.01$).

c. This reduction was directly related to intensity of treatment, when ragweed and the grouped pollens were studied ($p < 0.05$).

d. In the age group studied (predominantly adults), the reduction was directly related to age, when tree and grass pollen antigens were considered ($p < 0.05$).

e. It was directly related to dosage in the last three years of treatment ($p < 0.01$).

2. There was no apparent correlation between the strength of the original skin tests and dosage in the last three years of treatment. It will be recalled here that the average duration of treatment was 11 years.

3. There was a direct correlation between age of patient at beginning of treatment, duration of symptoms before treatment, original skin test strength, and duration of treatment ($p < 0.01$), regardless of skin reaction change.

4. There was no correlation between the use of adrenal steroids and the change in skin test reactions of antigens, whether or not included in the treatment.

5. There was no correlation found between the degree of clinical improvement as judged from the records and skin test change with treatment.

DISCUSSION

The data presented show clearly that a definite decrease in the reaction to skin tests accompanies specific treatment by injection of antigens and is more marked with high dosage, perennial treatment than with lower dosage and/or preseasonal treatment. However, only six patients were studied who received preseasonal treatment. No one had received coseasonal injection therapy. That such change is not due to a normal aging process, testing error, or local desensitization is attested by the absence of significant changes in the reactions to antigens not included in the treatment, control studies with histamine and codeine, and the injection-site study. The shortcomings of serial skin test readings of numerous observers throughout the last forty years are felt to be offset by three considerations. First, the complement of physicians collectively responsible for the skin test data centered about a nucleus of three constant members during most of the observation period. Second, all other physicians were trained in skin testing and interpretation according to the same criteria. Third, the performance of tests in multiple dilutions and their use as described above in assigning a value for each recording increased the reliability of the procedure. Thus, the results presented give strong support to the concept that actual reduction of sensitization accompanies specific injection treatment.

The question of relative benefits of coseasonal, preseasonal, and perennial treatment has been the subject of numerous reports and opposing conclusions.¹⁸⁻²² This reflects the nature of the data supporting these conclusions, in most cases subjective evaluation of symptoms. The data presented herein relate rather to much more objective criteria of change.

The question of possible change in skin reactivity with advancing age has likewise been considered in the past. Tuft⁸ reported decreasing reactions to food antigens in allergic persons as well as skin reactivity to histamine in nonatopic individuals in the later decades. We found no correlation between skin reactivity to histamine and age. This will be reported separately. The fact that a nonspecific, temporary local desensitization will result from repeated antigen injections has been reported in the past.^{7, 23, 24} The control patients studied with this in mind failed to reflect any variation in skin test reaction dependent on site of extract treatment. Skin tests were done on the anterior surface of the arm, injections given on the posterior aspect. The importance of uniformity of technique in obtaining reproducible results in skin testing has been amply stressed in the literature. It is felt that the technique used in the present study was suitable.

The question of whether extract injection treatment is associated with desensitization demonstrable by skin tests has been the subject of many studies since the early observations of Noon and Freeman on conjunctival reactivity.^{5, 25-35} Notable among these for the similarity of approach and conclusions reached is the work of Tuft.⁵ A review of these studies reveals basic agreement with the results reported above. The contribution of the present work is felt to rest upon statistical analysis, facilitated by the use of automatic data collection and processing techniques.

The findings reported assume greater interest as well as a more speculative nature when an attempt is made to relate them to demonstrated antibody changes. Sherman, Stull, and Cooke⁴ reported in 1940 a decline in skin-sensitizing antibody following several years of injection treatment. This was more recently corroborated by Connell and Sherman,³⁷ who concluded that prolonged treatment produces a decrease in skin-sensitizing antibody not explained by advancing age or duration of symptoms. It was also found that 65 per cent of skin test results were consistent with the corresponding SSA titer, whereas 35 per cent were significantly at variance. Whether or not the divergence between skin test and corresponding SSA titer is in part related to level of thermostable or blocking antibody awaits further study. In the report cited, the inherent error of intracutaneous skin testing was felt to be plus or minus one tenfold dilution of antigen. The similarity of changes suggests that prolonged intensive treatment with antigen injections produces desensitization by any objective measure (Fig. 6).

In a report by Van Arsdel and Middleton³⁸ the effect of extract treatment on the release of histamine *in vitro* by specific antigen was studied. Treatment and clinical remission were associated with a great suppression of histamine release that was only partly explained by the neutralizing of blocking antibody. The authors suggested that true desensitization might occur with treatment through the destruction of antibody-forming clones. This intriguing concept was discussed recently by Crowle,³⁹ who demonstrated "exhaustion and extinction" of antibody-producing clones by persistent antigen stimulation.

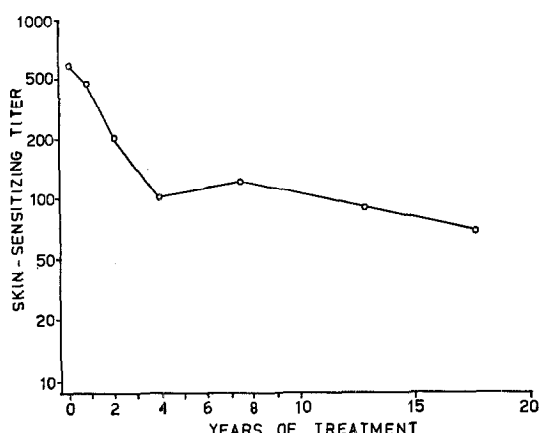


Fig. 6

Skin-sensitizing titer after various periods of aqueous injection therapy. Each circle represents the geometric average titer of fourteen to sixty-three patients treated for the specified time. (From Connell and Sherman, *J. ALLERGY* 35: 169, 1964.)

It will be apparent that very little discussion has been devoted to the question of clinical improvement. It is felt that skin tests give more objective immunologic evidence of desensitization. The efficacy of specific treatment has long been recognized by practicing allergists and their patients, and has recently been documented by appropriate double-blind studies.⁴⁰ The absence of correlation between degrees of clinical improvement and skin test change in the present study reflects the need for more accurate methods of evaluating clinical symptoms.

The experience of the authors with automatic data collection and processing techniques revealed it to be very acceptable in the interpretation of objective or "hard" data but shortcomings were evident when subjective or "soft" data were presented.

CONCLUSIONS

1. Skin tests with antigens to which the patient showed skin reactions but which were not included in the treatment showed only slight changes.
2. Skin tests to antigens with which the allergic patient was treated showed marked specific decreases in reaction. These changes generally occurred after at least five years of injection treatment, and were most evident with homogenous antigens.
3. These changes were greater with treatment near the limit of tolerance of the individual patient than with less intensive treatment.
4. Treatment with injections of house dust extract produced changes in skin tests similar to but less marked than those produced by pollen antigens.
5. With the data utilized, no statistically significant conclusions concerning the improvement in clinical symptoms could be reached.
6. Objective data concerning allergic diseases are suitable for electronic data processing.

The authors wish to thank Harvey S. Cohen of General Dynamics, Electric Boat Division, Groton, Connecticut, for assistance in statistical and mathematical analysis.

REFERENCES

1. Vaughan, W. T., and Black, J. H.: Practice of Allergy, ed. 3, St. Louis, 1954, The C. V. Mosby Company.
2. Gould, M. M.: Treatment of Hay Fever Patients With Alum Precipitated Pyridine Pollen Extracts and Evaluation of Therapy by Means of the Intracutaneous Threshold Test, *Excerpta Med.*, October, 1961, Internat. Congress Series, No. 42, p. 101.
3. Markow, H., and Spain, W. C.: Further Observations Concerning the Effect of Pollen Therapy Upon Cutaneous Sensitiveness in Late Hay Fever, *J. ALLERGY* 6: 227, 1934.
4. Sherman, W. B., Stull, A., and Cooke, R. A.: Serologic Changes in Hay Fever Cases Treated Over a Period of Years, *J. ALLERGY* 11: 225, 1940.
5. Tuft, L., and Heck, V. M.: Ragweed Pollen Desensitization in Hay Fever, Relationship to Skin Test Reaction, Dosage and Clinical Results, *J. ALLERGY* 28: 124, 1957.
6. Loveless, M. H.: Immunologic Studies of Pollinosis. IV. The Relationship Between Thermolabile Antibody in the Circulation and Clinical Immunity, *J. Immunol.* 47: 165, 1943.
7. Lowell, F. C.: Effect of Subcutaneous Injections of Allergenic Extract on the Local Reactivity to Intracutaneously Injected Extract, *J. ALLERGY* 34: 35, 1963.
8. Tuft, L., Heck, V. M., and Gregory, D. C.: Studies in Sensitization as Applied to Skin Test Reactions. III. Influence of Age Upon Skin Reactivity, *J. ALLERGY* 26: 359, 1955.
9. Coca, A. F., and Grove, E. F.: Studies in Hypersensitiveness. XIII. A Study of the Atopic Reagents, *J. Immunol.* 10: 445, 1925.
10. Walzer, M., and Grove, E. F.: Studies in Hypersensitiveness. XVI. On Antigens, a Comparative Study of the Antigenic Properties of Pollens, Egg-White, and Glue, in Guinea Pigs, as Determined by the Intravenous and Dale Methods of Testing in Anaphylaxis, *J. Immunol.* 10: 483, 1925.
11. Brown, A.: Studies in Hypersensitiveness. XXIV. On the Question of the Identity of the Atopens of the Pollens of High Ragweed and Low Ragweed, *J. Immunol.* 13: 73, 1927.
12. Scheppegegrell, W.: The Immunological Classification of Common Hay Fever Plants and Trees, *M. J. & Rec.* 117: 721, 1923.
13. Chobot, R.: Studies in Specific Hypersensitiveness. XXVIII. The Relationship of the Atopens of Bermuda Grass (*Cynodon dactylon*) and Timothy Grass (*Phleum Pratense*), *J. Immunol.* 16: 281, 1929.
14. Coca, A. F., Walzer, M., and Thommen, A. A.: Asthma and Hay Fever in Theory and Practice, Springfield, Ill., 1931, Charles C Thomas.
15. Stull, A., Cooke, R. A., and Barnard, J. H.: The Biologic Identity of Certain Grass Pollens Causing Hay Fever, *J. ALLERGY* 3: 352, 1932.
16. Kahn, I. S., and Grothaus, E. M.: Tree Pollen Hay Fever and Asthma in the South, *South. M. J.* 23: 658, 1930.
17. Tuft, L., and Blumstein, G.: Incidence and Importance of Tree Pollen Hay Fever With Particular Reference to Philadelphia and Vicinity, *J. ALLERGY* 8: 464, 1937.
18. Markow, H., and Rosen, E. A.: Results in the Treatment of Hay Fever. A Comparison of the Results of Preseasonal and Perennial Methods of Treatment of Ragweed Hay Fever, *M. Rec.* 155: 203, 1942.
19. Peshkin, M.: Critique of the Perennial Treatment of Pollen Allergy, *J. ALLERGY* 7: 477, 1936.
20. Vander Veer, A.: The Relative Merits of Seasonal and Perennial Treatment of Hay Fever, *J. ALLERGY* 7: 578, 1936.
21. Unger, L.: Perennial vs. Preseasonal Hay Fever Treatment, *J. ALLERGY* 3: 318, 1932.
22. Vaughan, W. T.: An Improved Coseasonal Therapy, *J. ALLERGY* 3: 542, 1932.
23. Storm van Leeuwen, W.: Ueber den Mechanismus der Desensibilisierung der allergischen Haut, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* 69: 1, 1930.
24. Wagner, H. C., and Rackemann, F. M.: Studies in Hay Fever: Specific Desensitization of Skin Sites in Actively Sensitive Persons, *J. ALLERGY* 7: 543, 1936.
25. Noon, L.: Prophylactic Inoculation Against Hay Fever, *Lancet* 1: 1572, 1911.
26. Freeman, J.: Further Observations on the Treatment of Hay Fever by Hypodermic Inoculations of Pollen Vaccine, *Lancet* 2: 814, 1911.
27. Levin, S. J.: The Effect of Massive Pollen Therapy on Skin Test Sensitivity, *J. ALLERGY* 8: 26, 1936.
28. Ogilvie, A. G.: Changes in Skin Response in Asthma: A Skin Test Follow-Up of Asthmatics, *Brit. M. J.* 1: 370, 1954.
29. Bruce Pearson, R. S.: Observations on the Effect of Injection of Pollen Extracts on the Skin Sensitivity of Hay Fever Subjects, *Guy's Hosp. Rep.* 20: 55, 1940.
30. Vander Veer, A., and Clarke, S. A., Jr.: Permanent Results Following Treatment for Late Hay Fever, *J. ALLERGY* 6: 551, 1935.

31. Colmes, A., and Rackemann, F. M.: Further Observations on the Changes in Skin Tests Following Specific Pollen Therapy, *J. ALLERGY* 4: 473, 1933.
32. Markow, H., and Spain, W. C.: The Effect of Consecutive Years of Treatment Upon Cutaneous Sensitiveness in Late Hay Fever, *J. ALLERGY* 4: 363, 1933.
33. Brown, G. T.: Maximum Dosage in Pollen Therapy, *J. ALLERGY* 3: 180, 1931.
34. Colmes, A.: Serial Skin Tests as a Guide in the Treatment of Hay Fever, Preliminary Report, *J. ALLERGY* 3: 449, 1932.
35. Lamson, R. W., Piness, G., and Miller, H.: Pollen Allergy. IV. With Special Reference to Skin Reactions Before and After Treatment With Fall Pollens, *Am. J. M. Sc.* 175: 799, 1928.
36. Lamson, R. W., Piness, G., and Miller, H.: Pollen Allergy. Skin Reactions of Patient Before and After Treatment With Spring (Grass) Pollens, *Am. J. M. Sc.* 175: 791, 1928.
37. Connell, J. T., and Sherman, W. B.: Skin Sensitizing Antibody Titer. III. Relationship of the Skin-Sensitizing Antibody Titer to the Intracutaneous Skin Test, to the Tolerance of Injections of Antigens, and to the Effects of Prolonged Treatment with Antigen, *J. ALLERGY* 35: 169, 1964.
38. Van Arsdell, P. P., Jr., and Middleton, E., Jr.: The Effects of Hyposensitization on the in Vitro Histamine Release of Specific Antigen, *J. ALLERGY* 32: 348, 1961.
39. Crowle, A. J.: Immunologic Unresponsiveness to Protein Antigens Induced in Adult Hypersensitive Mice, *J. ALLERGY* 34: 504, 1963.
40. Lowell, F. C., and Franklin, W.: A "Double Blind" Study of Treatment With Aqueous Allergenic Extracts in Cases of Allergic Rhinitis, *J. ALLERGY* 34: 165, 1963.