

Small-dose emulsion treatment of ragweed pollinosis. A double-blind study continued for three seasons

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The use of emulsified pollen extract in the treatment of rhinitis due to allergy has been increasingly popular since its introduction by Loveless¹ and the extension of her original work by Brown.² Although the reports are too numerous to mention, there have been few well-controlled studies³⁻⁵ since Loveless⁶ published the results of a double-blind study in 1957. Only two such studies with aqueous therapy have been reported.^{7, 8}

Because all reports prior to the initiation of our study, and most of them since, have been primarily concerned with determination of the largest dose that could be given without producing a reaction, we became interested in evaluating the effects of very small doses, since reaction is one of the problems in emulsion therapy.

One purpose of our study was to determine the results of treatment with relatively small doses of emulsified pollen extract in rhinitis caused by allergy to ragweed pollen. A double-blind study was carried out through the allergy seasons of 1960, 1961, and 1962. We felt that an understanding of the difficulties in establishing proper experimental design was perhaps more important than the actual results themselves.

The study was initiated as a pilot study in 1960 in cooperation with the Committee on Specific Therapy of the American Academy of Allergy. Forty-five patients with ragweed allergic rhinitis were selected from The New York Hospital Allergy Clinic. These patients were grouped in pairs matched as closely as possible according to sex, duration of disease, previous aqueous hypo-

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sensitization treatment, dosage and response to such treatment, and presence of sensitivities other than ragweed. By use of a table of random numbers, one of each pair was selected for treatment and the other for placebo.⁹ Injections were given and evaluations made by one of us (N. I.) without knowledge of what the patients were receiving. Injections in the second and third years were given by Dr. Lloyd Barnes of our clinic staff. Those patients allergic to materials other than ragweed were given aqueous treatment with these perennially. Mold-sensitive patients were omitted from the study.

Of the forty-five patients who participated in the study from the beginning, twenty-nine had had previous treatment for 1 to 35 years with results which left room for improvement (Table I).

In 1960, a schedule (Table II) was established for deciding the dose to be given. All previously untreated new patients received four doses of aqueous extract beginning with 5 PNU, and the dose was doubled or tripled in two or three weekly injections until 100 PNU had been reached (for example, 5, 15, 40, 100 PNU). They then received 387 PNU of emulsified extract in the deltoid muscle. (The odd number of units was used because the American Academy of Allergy Committee on Specific Therapy was using pollen units as the measure, which we converted to protein nitrogen units.) In the second group of patients were those who had been treated with aqueous extract for less than 1 year. Those in whom the last aqueous dose was below 300 PNU received 387 PNU of emulsified extract. If the previous dose was over 300 but under 1,000 PNU, they received 967 PNU of emulsified extract. If the previous dose was over 1,000 PNU, they received 1,935 PNU of emulsified extract. In the last group were those who had been treated for over 1 year. These patients received 967 PNU of emulsified extract if the last aqueous injection had been below 900 PNU, while those whose previous injections of aqueous extract were more than 900 PNU received 1,935 PNU of emulsified extract.

Prior to the 1961 season, about two thirds of the patients returned and were treated in the same manner as they had been the year before, except that all were given 1,000 PNU of emulsified extract. In the 1962 season, twenty-one patients returned for treatment, and it was decided to treat all patients in both groups with placebo, although we continued to use the double-blind technique.

Emulsions were prepared with a Con-Scot emulsifier in 1960 and 1961, while in 1962, when all patients were receiving placebo, a simple mixture was achieved by drawing material in and out of the bottle through the intramuscular needle, until its appearance was grossly indistinguishable from that of a well-prepared emulsion.

The proportions of mineral oil, Arlacel, and aqueous material used were 45:5:50 in 1960, 60:7:33 in 1961, and 45:30:20 in 1962. The emulsions were given in a volume of 1.0 ml. the first season and 0.5 ml., for the most part, in subsequent seasons.

Results were based on the symptoms, graded from zero to 3 plus in intensity, and on the number of pills taken as recorded on the patients' daily logs, sometimes augmented by information obtained directly from the patients (Table III). These results were graded as *total relief* (no symptoms—no pills), *marked*

Table I

	<i>Age</i>		<i>Years of symptoms</i>		<i>Duration of treatment (Old patients)</i>
	<i>New patients</i>	<i>Old patients</i>	<i>New patients</i>	<i>Old patients</i>	
<i>Males</i>					
Range	23-54	14-79	3-30	3-58	1-30
Average	33.5	42.6	11.5	17.6	7.9
<i>Females</i>					
Range	13-45	13-71	1-23	2.5-36	2-35
Average	35.3	42.6	8	15	10.6

Table II. Dose schedule during 1960

<i>Previous aqueous</i>	<i>Last dose aqueous (PNU)</i>	<i>Emulsion (PNU)</i>
0	100	387
Less than 1 year	Less than 300	387
	300-1,000	967
	More than 1,000	1,935
1 year or more	Less than 900	967
	900 or more	1,935

Table III

<i>Relief</i>	<i>Symptoms</i>	<i>Pills</i>
Total	0	0
Marked	0-1+	0-1
Moderate	0-2+	0-2
Fair	2+	2-4
None	3+	3-4

Table IV. Moderate relief or better

<i>Patient classification</i>	<i>1960</i>	<i>1961</i>	<i>PRDO*</i> <i>1961</i>	<i>Corrected result</i> <i>1961</i>	<i>1962</i>	<i>PRDO*</i>		<i>Corrected result</i> <i>1962</i>
						<i>1962</i>	<i>Total</i>	
New, treated	3/9	8/9	(0/0)	8/9	3/5	(1/4)†	(1/4)	6/9 or less
New, placebo	2/7	2/3	(3/4)	3/7	0/2	(0/1)	(3/5)	2/7 or less
Old, treated	10/14	11/11	(1/3)	13/14	3/6	(1/5)	(2/8)	9/14
Old, placebo	11/15	11/11	(3/4)	12/15	7/8	(1/3)	(4/7)	10/15
Total, treated	13/23	19/20	(1/3)	21/23	6/11	(2/9)	(3/12)	15/23
Total, placebo	13/22	13/14	(6/8)	15/22	7/10	(1/4)	(7/12)	12/22

*The denominator represents the number of patients who dropped out prior to the 1961 season, and the numerator the number of these patients who gave as a reason the poor result of the treatment the preceding season.

†Dropped out because of constitutional reaction in 1961 despite good results.

relief (occasional mild symptoms—rare pill), *moderate relief* (occasional mild to moderate symptoms—occasional pill), *fair relief* (moderate symptoms much of the time—pills most of the time), and *no relief* (moderate to severe symptoms most of the time despite pills all of the time). Since it subsequently became apparent that the difference between moderate and fair relief was actually the difference between a good season and a bad one, and because our series was not large enough to justify finer discriminations, we grouped *total*, *marked*, or *moderate relief* together as good results, and *fair* or *no relief* as poor results.

Following each season, the patients were also asked to grade the season according to whether it was better than, worse than, or the same as the previous season. Initially, this was done with the thought of adding another method to evaluate the results, but it soon became apparent that it was a better indication of the fallibility of patients' memories than of the results of treatment.

RESULTS

The results for the three seasons during which the patients were studied are compiled in Table IV; the groupings were broken down into new (previously untreated) patients and old (previously treated) patients. As the study progressed, it was found that some patients for whom good results, according to our criteria, had been reported failed to return for treatment or requested a change back to aqueous treatment, because they were dissatisfied with these results. Therefore, it was recorded that these patients had had poor rather than good results the following year. The "poor-result dropouts" (PRDO) have been listed in separate columns in Table IV; the total number of such dropouts (denominator) and the number who gave as a reason the poor result of treatment during the previous season (numerator) are indicated. From these results a "corrected result" has been derived for that season. Thus, for example, in the previously untreated (new patient) group in 1960, three of nine treated patients and two of seven patients who received placebo reported good results. Following the 1961 season, eight of nine treated patients reported good results, compared to two of three of the placebo patients. However, there were no dropouts prior to the 1961 season among the treated group, while there were four in the placebo group, of whom three dropped out because of dissatisfaction with the previous results. Therefore, these three were added as poor results to the group treated in 1961, while the one patient who dropped out for other reasons was still considered as having had good results. This gave a corrected figure of three good results for the original seven patients in the placebo group, compared to eight out of nine patients with good results in the treated group.

The use of corrected results in the 1962 season admittedly makes the calculation artificial, since all patients in both groups received placebo that year, but for the purpose of consistency this corrected figure was used throughout the three years.

Statistical analysis

For each group, the percentage of good results based on the corrected figures for 1961 and 1962 has been plotted and 95 per cent confidence intervals on

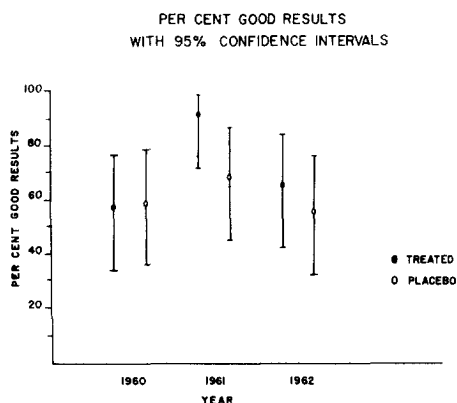


Fig. 1

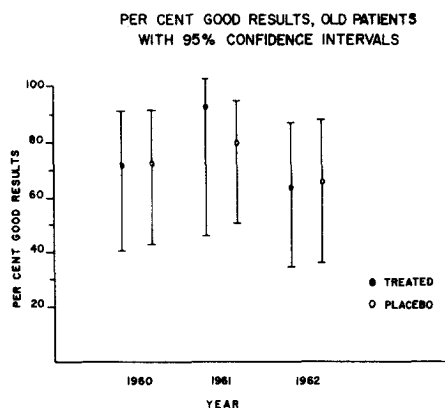


Fig. 2

either side of the means indicated.¹⁰ The significance is that there is less than a 5 per cent chance that the true percentage of good results will fall outside of the confidence intervals. Thus, if the intervals overlap, it is unlikely that the difference between the two percentages is significant. These figures therefore make it possible to compare one patient group with any other. Chi-square tests were also made as further confirmation of results.

It is clear without statistical evaluation that the results of treatment for all patients combined are no different from the results for patients who received placebo, except for a suggestive advantage in favor of the treated group in 1961 (Fig. 1). Further breakdown of data in terms of old patients (Fig. 2) and new patients (Fig. 3) reveals that the advantage in favor of treatment is limited to the latter group, although even here the difference between treated and placebo groups is suggestive but not significant. The results of treatment and placebo with the old patients were very similar for all three years, with more than two thirds of the patients doing well in both groups, despite the fact that the placebo-treated group had received placebo for three consecutive years, indicating the considerable degree of carry-over from previous treatment.

Adverse effects

Adverse effects were few and not alarming. In 1960, there were four treated patients with moderate local reactions, two of whom had mild systemic reactions. In 1961, there were three constitutional reactions, two of which, although not alarming, were of such severity that both patients dropped out of treatment in 1962 despite having had good results. There were no reactions, local or constitutional, in the placebo groups. No lumps or cysts were discovered.

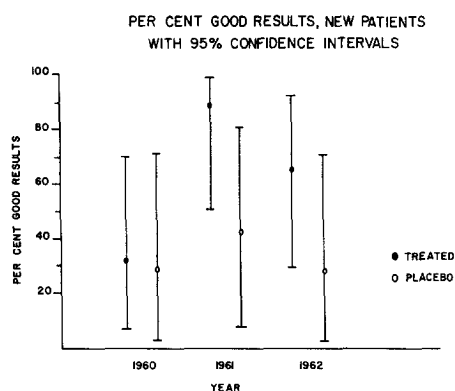


Fig. 3

DISCUSSION

As already stated, one of the major aims in this study was to learn something of the difficulties in establishing proper experimental design and evaluation of results. These difficulties proved to be a major obstacle. For example, an attempt was made to compare the patients' symptoms with those of the previous season, but we found this to be totally unsatisfactory. Since patients had very little ability to recall accurately the severity of the previous season, they were unable to state with any degree of accuracy whether they were better, worse, or the same during the current season. This experience has made us extremely doubtful that comparison of symptoms with those of previous years can be made by the patients' retrospective evaluation. The inaccuracies, except in the most extreme situations, such as a very severe season followed by one in which there were no symptoms whatever, are evident when one compares the patients' recollections with the recorded facts on the charts.

The validity of a study relates directly to the quality of the experimental design. The statistician should help to establish such an experimental design, rather than be called in afterward to make the best of a poorly conceived one.

It is clear from our findings that only previously untreated patients should be used in any study evaluating treatment. These patients must be seen frequently, the ideal being every day throughout the ragweed season. On each visit they should be closely questioned and examined. Symptom cards and daily logs have been found to be most unreliable. Very few patients have much motiva-

tion toward a project study and are mainly interested in getting the injections and doing well, if possible. They may like us and, if they do, be as guilty as we of selective perception, remembering only the good days and forgetting the bad; or, if they dislike us, they may do precisely the reverse. In one such example in the present study, a patient gave us symptom cards complete with zeros throughout the 1960 season and reported having needed only occasional pills; yet he stated that he felt "worse than the previous season." In 1960, the first year of the study, his result was reported as "marked relief, worse than the previous year." The following year his result was evaluated as "moderate relief and better than the previous season." In 1962, he requested a change back to the aqueous extract because of poor results. When asked how he could state that he had poor results when his symptom cards for the previous two years seemed to contradict this, he said, "I wanted so badly for this one-shot to work that I tried to talk myself into it, but I've been getting worse every year." He is now back on the aqueous extract which had served him so well in the past, leaving us with the problem of how to grade his results in 1960 and 1961. On the one hand, his symptom cards and the notes in his record must be used for the grading, since this is the procedure established before the study started. Yet the results were, in fact, poor. Perhaps if he had been seen at least once a week throughout the season by an unprejudiced—that is, an unknowing—observer, he might have been properly classified as having had poor results instead of improperly as having had good ones. Incidentally, he received placebo during the two years of emulsion therapy.

There has been much written and said about patient bias and physician bias, but too often it is assumed that the bias is positive. It is conceded that the patient may be biased against as well as toward a particular treatment, but it is equally important to realize that there may be negative as well as positive bias on the part of investigators. Perhaps this is not recognized to the extent that it should be. Too often a negative bias is regarded as somehow being more honest or more scientific than a positive one, and scepticism is thought more admirable than enthusiasm in a worker embarking on a project. Actually, neither attitude is ideal; both will affect evaluation of results, and it is to avoid both of these possibilities that the double-blind evaluation is essential.

It would serve both the project and the readers of a final report well if authors would evaluate their own positions regarding a study before work is begun and actually record what they expect to find, and, by all means, what they would like to find, in the results of their investigation. This recorded prediction should then appear in the introduction to the published paper.

Our own predictions were not recorded prior to embarking on the study, but it is recalled that we hoped and expected to find that the small doses of emulsion used in our study would give results equal to those with the larger doses used by others. Since we were not attempting to compare emulsion therapy with aqueous therapy, we gave no thought to the relative effectiveness of the two techniques.

CONCLUSION

When relatively small doses of emulsified extract were used in a double-blind study with matched pairs of patients, the treated group showed results identical to those of the group receiving placebo during the first year of treatment. During the second year of treatment, the emulsified extract gave somewhat better results than placebo, although the differences were not statistically significant. This difference between the two groups was entirely confined to patients who had been untreated prior to the initiation of the study.

With previously treated patients, there were no differences between the treated and placebo groups, since both groups showed equally good results, two thirds of the placebo-treated patients continuing to do well even after three years of placebo treatment. It is assumed that this is due to carry-over from previous aqueous treatment.

Thus, studies intended to show the effectiveness of this or any other type of treatment must be carried out exclusively with new and previously untreated patients.

Finally, these experiences have re-emphasized the necessity of carefully controlled double-blind studies and, conversely, the very limited value of those which depend upon subjective impressions of the patient and the "experience" of the practitioner.

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