

Repository therapy in ragweed hay fever

To the Editor:

The recently published paper by Norman, Winkenwerder, and D'Lugoff¹ entitled "Controlled Evaluations of Repository Therapy in Ragweed Hay Fever" reports negative findings with this procedure. They were discouraged to the point of abandoning further research with this modality. In perusing the paper, however, we find the data insufficient to justify their conclusions and decision. Unfortunately, errors in design and selection of patients mar this diligent study by excellent workers seriously engaged in resolving a difficult problem, the objective evaluation of hay fever therapy. Let us, therefore, elaborate on each of these errors.

The Design: One hundred and sixteen patients in groups varying from 17 to 43 were treated (including controls) in each of 4 years. The many variables affecting hay fever therapy (additional sensitivity to other allergens, infection, psychological factors, vasomotor effect owing to changes in temperature, air pollution, fluctuation in pollen, etc.) can so dilute the effect of treatment that it will make statistical analysis difficult or ineffective unless adequate numbers of patients are treated. In this respect, this study, along with most double-blind studies, has failed.

It is also apparent that the design of the experiment was not rigid and apparently not planned in advance but was improvised as it progressed. Patients were treated with a variety of emulsions and doses, and by single and multiple injections, varying from year to year. One cannot, therefore, make absolute comparisons from one year to another. Conclusions drawn can therefore be only on a yearly basis and not for a four-year period.

We also question whether the timing of the injections was sufficient to provide the maximum immunologic response. When single injections were given this was done two weeks before the onset of the season; where two injections were employed they were given two weeks apart, the last one also two weeks before the season. Our experience would suggest that two injections a month apart, the last one about a month before the season, is perhaps preferable. We base this procedure on the evidence presented by Davenport,² who showed that a better immunologic response was attained with longer periods between injections. Although his data relate to influenza vaccine, we believe it can be extrapolated to ragweed therapy.

Selection of Patients: Here we come to a serious defect in the paper. The patients selected for study had to give a positive reaction (what degree is not stated) to 0.1 PNU per milliliter by the intradermal test. This, in our opinion, is so selective as to be highly restrictive. Patients reacting to such a minimum of ragweed challenge do not represent the ragweed patients as a group, as encountered in practice. Many will not react to 1, 10, or even to 100 PNU. Others may not respond unless tested with concentrations as high as 2,000 to 5,000 PNU. All of these patients were eliminated from this study. In our experience less than 1 in 100 ragweed patients react to 0.1 PNU per milliliter. In our clinics as well as most clinics in New York, the first test done routinely is with 100 PNU. Rarely do we test with 10 or 1 PNU. (It would also be worthwhile knowing how many patients were tested by Norman and colleagues and the percentage of these selected for treatment by testing with 0.1 PNU.) This means then, that whatever conclusions drawn as to results of therapy, whether favorable or unfavorable, must apply *only to 1 per cent or less of the ragweed-sensitive population*. Logically, the conclusions cannot therefore be extended to the remaining 99 per cent of ragweed hay fever patients. For them, since they were excluded from the study, the evaluation still needs to be determined by their inclusion in another study.

Statistical Analysis:

1. Criteria of evaluation: The authors began by using per cent improvement as the criterion for evaluating the two treatments (repository and placebo). This method is extremely unsatisfactory and was finally dropped in the last two years of the study. Besides having a great deal of inaccuracy, percentage of improvement is not very sensitive to differences between patients.

2. Statistical testing of the data: In only one instance (1960) do the authors present the actual data and state the method of analysis.

For the 1963 study we are given neither the data nor the method of testing the data. This leaves no way of checking the results which are stated by the authors.

3. Review of the literature: The authors state that in the Dworetzky and Isaacs³ study, "Slightly more placebo-treated patients dropped out of this study because of dissatisfaction with results." Actually, the difference in drop-out rates was not slight at all, but statistically significant at the 5 per cent level.

They also reported the Friedlaender and Friedlaender⁴ study as "being significant at the 5 per cent level only." The authors actually reported that it was significant at the 2 per cent level.

In our review of the literature,⁷ it was observed that of 10 separate double-blind studies (counting each year of a multi-year study separately), 5 of them found that the treatment was significantly better than the placebo (at the 5 per cent level). Of the 5 remaining studies, 4 found the repository treatment better than the placebo, but not at a statistically significant level. Only one, limited to 13 patients, found the placebo to be better than the specific treatment.

4. Experimental design: The technique used in 1963, while it introduced a more objective symptom score, also introduced a new difficulty: Patients previously treated in 1961 and 1962 were used, and these were years of poor results of treatment. The patients treated in 1960, when good results were obtained, were not included in the 1963 study. This may have introduced a bias in favor of patients not responding to treatment.

Assuming that no errors were made and that the conclusion of the authors that the repository procedure was ineffective was correct, there would then be some important questions to answer:

1. Why should "desensitization which has been adequately demonstrated for house dust, bee venom, animal danders, penicillin and streptomycin sensitivity, etc.,"⁵ fail in the case of ragweed sensitivity? If it works for this diverse group of allergens, why shouldn't it work for ragweed pollinosis? And if it doesn't work, what is the explanation? It would seem better to look for such an explanation for this than to drop experimentation after four years of effort.
2. Since ragweed pollinosis is an immunologic disease and since it has been shown that multiple aqueous injections are effective in double-blind studies,⁶ why should they not be effective when given in repository form? If anything, they should be more effective, since antigens injected in adjuvants have been repeatedly shown to be superior immunologically to injected aqueous antigens.
3. Newer techniques, including antibody response, histamine release from white blood cells of patients, and Rebuck's skin window technique, have shown favorable response following aqueous injection therapy. These tests are completely objective. Perhaps with the use of adjuvants the same positive effects may be noted with these parameters. But since this has not been done, can it really be said that the repository technique has failed?

In summary, we believe that since the number of patients treated was small and highly selective, no firm conclusions can be drawn about the effectiveness or ineffectiveness of the repository method of treatment of ragweed pollinosis. It is hoped that in the future, with the use of adequate sample size, giving standardized emulsions, adequately spaced to insure maximum anamnestic response and properly controlled, that the question of the efficacy of the repository procedure will be finally settled. The present findings of Norman and colleagues,¹ are inadequate and inconclusive, as are most of the studies reported to date.⁷

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Reply

To the Editor:

The letter of Prigal and Miller deplores our statement that we have become discouraged from further investigation of repository therapy. As stated in our report, this viewpoint applies only to currently employed mineral oil and Arlacel adjuvants. If the results of desensitization depend on the development of blocking antibody, and if the appropriate type of repository becomes available, and the optimum time for administration in relation to pollen exposure is determined, this method could be a useful advance in treatment. Why presently available mineral oil repositories failed to relieve hay fever symptoms in our hands is not clear. In studies employing the same methods of observation and a similar study design, however, intranasal steroid sprays, preseasonal injections of whole extract, and similar injections of Antigen E showed significant therapeutic effect. (Reports on the latter two methods are in preparation.)

While one may criticize the design of our study of repositories as lacking sufficient numbers of patients, our plan was based on the concept that a small number of patients thoroughly studied will give more reliable results than a larger number less thoroughly studied. Our favorable results with other methods of treatment confirm the usefulness of this concept.

Without going into detail about the various points raised by Prigal and Miller, several items may be noted:

1. We made no attempt to compare one year with another, although four years of results were available.

2. The timing of injections was based on the best clinical experience available to us at the time. It is doubtful that the development of antibody depends so rigorously on the spacing of injections. We do not consider it very useful to try to extrapolate the data of Davenport obtained with viral antigens to the employment of ragweed antigens in patients already sensitized by previous exposure. Suitable studies of antibody production from repositories containing ragweed extract in hay fever patients are needed. The methods for obtaining such data had not been developed at the time of our study.

3. Although the requirement that patients react to 0.1 PNU per milliliter of ragweed in an intradermal test may seem restrictive, out of the many patients who volunteered for study and had clinically acceptable histories of ragweed hay fever, only two were rejected for lack of a positive skin test, and these patients did not react to 1,000 PNU per milliliter. In any event, highly sensitive patients are more appropriate for this kind of study, as any differences due to therapy stand out more clearly in such patients.

4. A statistical test of the data is possible only when one wishes to ask whether a seemingly positive result could be due to chance. When one has a negative result (as we have) this question cannot be asked. There is no way of proving or testing the reliability of a