

A NEW ORAL TREATMENT FOR RAGWEED HAY FEVER

Murray L. Maurer, M.D., and Margaret B. Strauss, M.S., New York, N. Y.

IN KEEPING with today's economy, newer modalities are sought for in the management of allergy, as, for example, the one-injection treatment in hay fever. But even this one, as well as a method of fewer injections for the treatment of hay fever, has distinct disadvantages, as for example in those individuals, especially children, who refuse to submit to the "needle." More important is the possibility of systemic reactions which can result from injections even when administered by the most experienced allergist.

A successful oral administration of pollen extracts under medical supervision would be a most desirable alternative method of treatment.

Touart²¹ in 1922 reported the relief of symptoms after the daily administration of tablets containing 0.1 mg. of the pollen protein. This one report seems to have stimulated interest in this form of therapy for, in the subsequent twenty years, there appeared numerous studies of this method of hay fever treatment. Many investigators reported good results in between 40 to 85 per cent of the patients treated while, on the other hand, other investigators reported less happy results and, in some cases, almost complete failures, even when the identical methods were employed.

It would appear, at least historically, that the cooperative study which Dr. Feinberg and his co-workers⁷ reported in the *Journal of the American Medical Association* in 1940 caused a loss of interest in oral ragweed hyposensitization. Their conclusion was that this oral method of treatment was definitely inferior to that obtained by parenteral administration of pollen extracts.

It is impossible to give a fair account of the average results of oral pollen treatment in the past because of the conflicting results in the published reports; because many different preparations of the pollen had been used and because there had been no apparent standardization of dosage.

Although previously published reports present conflicting conclusions as to the effectiveness of this oral treatment of hay fever, they are more or less unanimous on a number of points. These are: (1) that the oral ingestion of pollen is a safe procedure, (2) that gastrointestinal reactions are frequent and troublesome, sometimes severe, but never dangerous, (3) that only very rarely were seen focal symptoms of mild hay fever and asthma, or systemic reactions of dermatitis, pruritis, urticaria, malaise, headache, or feeling of exhaustion,

From The Allergy Clinic, University Hospital, New York University Medical Center.
Received for publication March 1, 1961.

(4) that severe constitutional reactions of anaphylactic character were almost unknown, and (5) that the pollen is absorbed enterally but that the rate and nature of this absorption is variable.

For four years a suspension of the alum-precipitated pyridine ragweed complex parenterally administered has been successfully used in the treatment of ragweed hay fever in the Allergy Clinic of the New York University Medical Center, University Hospital, and by associate physicians. This product solved many problems relative to parenteral prophylaxis because of its delayed absorption due to the complex formed in its preparation.

The successful use of this pyridine ragweed complex, as well as the results reported in the use of a chemically similar pyridine ivy complex in the oral treatment of poison ivy, prompted us to prepare the pyridine ragweed complex in tablet form for oral administration.

For convenience of administration, the pyridine ragweed complex was placed in tablets so that they contained 2,000 PNU per tablet. An empirical dosage schedule was established for the pre-seasonal treatment which was started in mid-May 1960. The initial dose was 1,000 PNU (one-half tablet) given every other day for two weeks. The dose was gradually increased, until four tablets (8,000 PNU) were given daily just before the onset of the season. It was expected that this dose, or a smaller dose, depending on the response of the patient, would be continued throughout the ragweed pollen season.

Thirty patients, ranging in age from 13 to 74, were studied. Eighteen patients were chosen who had had no treatment for at least two years, and twelve others who had objected in the past to the conventional multiple injection treatment because of poor results or the inconvenience associated with the therapy. These patients were unaware of their participation in this study. They visited the same clinic as did the hay fever patients, who were being treated by conventional methods, but received injections of buffered saline.

Eighteen of the thirty patients studied had no allergies other than ragweed hay fever. Four patients had a complicating pollen asthma. The intradermal method of skin testing was employed to classify the patients. Eleven patients were classified as Class A or AA, very sensitive; fourteen patients were classified as Class B, moderately sensitive. The remaining five patients were Class C or D, slightly sensitive.

No correlation could be drawn between the effectiveness or tolerance to this oral preparation and the skin sensitivity of the patient. There was also no uniformity of results obtained when compared to the results of past conventional multiple injection therapy, either with aqueous ragweed extracts or with pyridine ragweed complex extracts. With but one exception, the patients concerned in this study were considered to have had about the same exposure to the ragweed pollen during the 1960 season. Also considered in compiling the following results of treatment with this oral preparation was the fact that, in spite of the detailed daily log of symptoms kept by the patient and the results of careful questioning of the patient at the time of his weekly visits, the appraisal of symptoms was subjective.

Excellent results were reported by four patients, good results by fourteen, fair results by three, and poor results by nine. This satisfactory result of relief of symptoms in 60 per cent of the patients treated is considerably less than that which can be expected in the conventional multiple injection treatment of hay fever. A more careful study of the results of treatment with this oral preparation, however, produces some interesting observations.

Of the thirty patients studied, nineteen had had previous treatment by the multiple injection method. Of these nineteen patients, only five or 23 per cent had derived satisfactory results with their last course of conventional treatment. The incidence of satisfactory results was increased to 63 per cent (twelve patients) after oral therapy in this group.

Another very interesting observation was that eight of the nine patients who reported poor results observed that their hay fever symptoms began with the very onset of the presence of pollen in the air. Indeed, these patients complained of symptoms at least one week before the first patients receiving conventional treatment reported any symptoms. Six of these patients were asked to discontinue their oral treatment just prior to the traditional season's peak period at the very beginning of September in the New York area. Of these, four reported some lessening of their symptoms and two reported no change after the cessation of therapy. One patient, who had omitted to take any pills during the first eight days of August because of an intercurrent illness, was asked to increase the dose when she developed severe hay fever on August 15. She reported that she felt quite well after September 5, the period of highest pollen incidence and in which the most severe symptoms were reported. Two patients were continued through the peak of the season on their pre-season dosage level with a persistence of severe hay fever.

Four patients had a history of asthma complicating their ragweed hay fever. On oral treatment, one patient, considered a poor result, was unchanged. Two patients, who were markedly benefited by this form of treatment, also had far fewer symptoms referable to their lower respiratory system. The fourth patient reported that he had only fair relief of hay fever, but that the complicating asthma was also less than in previous years.

There were no serious side reactions observed during the course of this study. In only one patient was gastrointestinal distress of any severity reported. This patient complained that a dose greater than one-half tablet daily caused nausea and abdominal cramps. This patient finally tolerated one tablet daily. The results of her treatment were only fair. These results were comparable to those obtained with conventional treatment, the injections of which she also tolerated poorly.

Two other patients complained of very mild gastrointestinal symptoms of a fleeting nature. And last, one patient complained of an increase of hay fever symptoms of approximately two hours' duration following each tablet taken during the pollen season.

It is interesting that one patient who had a demonstrable duodenal ulcer prior to onset of treatment did not complain of any gastrointestinal distress.

Two of the patients studied had an associated atopic dermatitis. This skin eruption was not influenced by this oral pyridine ragweed complex.

A complete blood count and urine analysis was performed on each patient prior to the onset of treatment and prior to the end of treatment. In no instance was there any change which was a result of the treatment.

We were unable to produce consistently positive reactions in previously sensitized skin sites of nonallergenic individuals after feeding this preparation in large doses. This, we believe, is due to the fact that the rate of absorption from the gastrointestinal tract is much too slow to produce sufficient antigen concentration in the blood to react locally at the sensitized sites.

Our studies to determine serologic changes in pre- and post-treatment sera are not yet completed. They will be reported later if they fail to confirm the reports of other investigators.

We conclude that, although in this pilot study the results obtained were inferior to those expected with conventional therapy, the oral administration of the pyridine ragweed complex deserves additional investigation because of the following findings:

1. The oral ingestion of the pyridine ragweed complex in tablet form was a completely safe procedure.

2. In the nineteen patients who had had past treatment, the results with oral therapy were superior.

3. Three of four patients, who reported asthma as a complication of hay fever in the past, had considerably less asthma on oral therapy.

4. The early appearance of hay fever symptoms, particularly in those patients in whom the results of oral treatment were considered to be poor, suggests that these patients were overdosed. A more adequate dosage schedule is still to be established.

REFERENCES

1. Alexander, H. L., Johnson, M. C., and Alexander, J. H.: Measurement of Circulating Ragweed Antibodies and Antigen, *J. ALLERGY* 17: 349, 1946.
2. Alperstein, B. B.: Oral vs. Parenteral Pollen Therapy, *J. ALLERGY* 11: 498, 1940.
3. Bernstein, T. B., and Feinberg, S. M.: Oral Ragweed Pollen Therapy. Clinical Results of Experiments on Gastro-Intestinal Absorption, *Arch. Int. Med.* 62: 297, 1938.
4. Black, J. H.: The Oral Administration of Pollen, *J. ALLERGY* 10: 156, 1938.
5. Brown, E. A., Holden, E. M., and Nobill, C.: The Skin Test Blocking Antibody Response to Oral Pollen Therapy and the Criteria for Its Use, *Ann. Allergy* 5: 402, 1947.
6. Egeberg, R. O., and Painter, J. M.: Oral Pollen Therapy: A Comparative Study, *Ann. Allergy* 5: 415, 1947.
7. Feinberg, S. M., Foran, F. L., Lichtenstein, M. R., Padnos, E., Rappaport, B. Z., Sheldon, J., and Zeller, M.: Oral Pollen Therapy in Ragweed Pollenosis, *J. A. M. A.* 115: 23, 1940.
8. Fuchs, A. M., and Strauss, M. D.: The Clinical Evaluation and the Preparation of Suspensions of New Water Insoluble Whole Ragweed Pollen Complex, *J. ALLERGY* 30: 66, 1959.
9. Hecht, R., Mosko, M. M., Lubin, J., Sulzberger, M. B., and Baer, R. L.: The Absorption of Whole Ragweed Pollen From the Gastrointestinal Tract, *J. ALLERGY* 15: 9-13, 1944.
10. Hiff, E. H., and Gay, L. N.: Oral Treatment of Hay Fever With Ragweed Pollen, *Bull. Johns Hopkins Hosp.* 70: 378, 1942.
11. Langs, R. J., and Strauss, M. B.: Oral Prophylaxis Against Poison Ivy Dermatitis With Aqua Ivy Tablets, *J. ALLERGY* 30: 130, 1959.
12. Levin, S. J., and Shulsky, L.: Serologic Changes After Oral Ragweed Pollen Therapy in Children, *J. ALLERGY* 13: 1-17, 1941.

13. Rockwell, G. E.: Clinical Results in the Prevention and Treatment of Hay Fever by Oral Administration of Pollens of the Grass and Ragweed Types, *Ohio State M. J.* 34: 784, 1938.
14. Rockwell, G. E.: Enteral Absorption of Pollen Antigen, *J. Lab. & Clin. Med.* 27: 328, 1942.
15. Schwartz, S. C.: Oral Pollen Therapy, *J. Lab. & Clin. Med.* 25: 566, 1940.
16. Sherman, W. B., Stull, A., and Cooke, R. A.: Serologic Changes in Hay Fever Cases Treated Over a Period of Years, *J. ALLERGY* 2: 225, 1940.
17. Stier, R. F. E., and Hollister, G.: Desensitization by Oral Administration of Pollen Extracts, *Northwest Med.* 36: 166, 1937.
18. Strauss, M. B., and Spain, W. C.: Studies on Poison Ivy and Other Dermatitis Producing Plant Parts Wherein Active Resinous Principals Are Suspended in Aqueous Solution, *J. ALLERGY* 17: 1, 1946.
19. Thiberge, N. F.: Is Oral Pollen Treatment Dependable? *South. M. J.* 38: 523, 1945.
20. Thonmen, A. A.: Asthma and Hay Fever in Theory and Practice, Springfield, Ill., 1931, Charles C Thomas, publisher, p. 764.
21. Touart, M. D.: Hay Fever: Desensitization by Ingestion of Pollen Proteins, *New York M. J.* 116: 199, 1922.
22. Zeller, M.: Oral Ragweed Pollen Therapy, *J. ALLERGY* 10: 579, 1939.