

The Journal of

Allergy

VOL. 33, NO. 6

NOVEMBER—DECEMBER, 1962

ORIGINAL ARTICLES

REPOSITORY EMULSION TREATMENT OF RAGWEED POLLINOSIS

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DURING the past few years, many allergists have sought to evaluate the efficacy of the repository method of treatment of ragweed hay fever. The adjuvant effect of mineral oil on antibody production was first demonstrated by Freund¹ and his co-workers in 1937. In 1947, Loveless² applied the principle of Freund's adjuvant to the treatment of ragweed pollinosis in an attempt to reduce the number of injections required by the conventional mode of therapy with aqueous ragweed antigen. Brown³ has reported on the use of repository therapy in several series of cases involving thousands of patients. Other studies have been carried out by a number of investigators.⁴⁻⁸

This paper will report on the results of emulsion therapy in 101 patients with ragweed hay fever treated in a double-blind study at The Roosevelt Hospital Allergy Clinic during 1960, also on a comparison (not double blind) with a group of 77 patients treated with aqueous ragweed extract.

MATERIALS AND METHODS

The methods of Brown were used with some modifications. The emulsion consisted of one part of emulsifier Arlacel A (mannide mono-oleate) and 9 parts Drakeol 6-VR mineral oil for the oil phase. The aqueous phase was regular ragweed pollen extract containing equal protein nitrogen content of the giant and short varieties, defatted and extracted with Coca's solution. Merthiolate was substituted for phenol as the preservative in order to maintain the stability of the water in oil emulsion.

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Presented before The American Academy of Allergy, Washington, D. C., Feb. 8, 1961.

Received for publication Jan. 8, 1962.

A Brown emulsor was used to prepare the emulsion which contained equal volumes of the oil and aqueous phase. Each patient received one cubic centimeter of emulsion injected with a 26 gauge, $\frac{5}{8}$ inch needle into the subcutaneous tissue overlying the triceps muscle of the arm.

SELECTION AND CLASSIFICATION OF PATIENTS

One hundred and one ragweed hay fever patients volunteered for the one injection treatment. All but 8 had been on routine injection therapy during the previous seasons. The latter were given a series of 4 weekly injections of aqueous extract before the injection of emulsion. The patients were classified as A, B, C, or D, chiefly by their skin tests reaction to intracutaneous aqueous ragweed antigen, but modified somewhat by the maximum tolerated subcutaneous dose during previous seasons. Class A patients received 1,000 protein nitrogen units of ragweed pollen extract in the emulsion; Class B, 2,500 protein nitrogen units; Class C, 5,000 protein nitrogen units, and Class D, 10,000 protein nitrogen units. The injections were given 6 to 10 weeks before the onset of the ragweed pollen season.

A given number of patients reported to the clinic on the afternoon of their appointment day. During the morning, a ragweed in oil emulsion and a saline in oil emulsion were prepared. The two emulsions were administered in a random manner as part of the double-blind controlled study, with only a technician, who had no part in their previous or subsequent treatment, aware of which patients received placebo injections. No medication was given before or after the injection. The patients were observed for approximately one hour and were told to telephone the allergy clinic if any large local or generalized systemic reaction occurred after leaving the hospital. A few antihistamine tablets were given to each patient for emergency use only.

INCIDENCE OF LOCAL REACTIONS

Of the 50 patients receiving the placebo injection, 28 experienced no local reaction at all. One had a local reaction lasting less than 24 hours; 6 had local reactions lasting 24 to 72 hours; 3 had local reactions lasting 72 hours to one week; one had a local reaction lasting 1 to 3 weeks; and 6 developed delayed local reactions which appeared at least 24 hours after the injection. The latter were characterized by areas of erythema and induration, usually lasting less than 7 days.

Of the 51 patients who received ragweed emulsion injections, 15 had no local reaction; 3 had local reactions lasting less than 24 hours; 8 had local reactions lasting 24 to 72 hours; 6 had local reactions lasting 72 hours to one week; 4 had local reactions lasting 1 to 3 weeks; and one developed a delayed local reaction.

Four of the placebo patients and 9 of the patients treated with ragweed emulsion developed subcutaneous nodules palpable 3 months after injection. The nodules were usually less than 2 cm. in diameter. No draining abscesses or painful nodules were noted.

INCIDENCE OF CONSTITUTIONAL REACTIONS

One patient treated with placebo reported having itching of the eyes for 2 hours after injection. Five of the patients treated with ragweed emulsion said they had systemic reactions, one of which (Patient 1) was actually observed and treated in the clinic. This patient developed a moderate constitutional reaction approximately 2 hours after repository therapy characterized by generalized urticaria and hay fever symptoms. Treatment with epinephrine and antihistamines afforded prompt relief. This patient had received 5,000 protein nitrogen units of ragweed emulsion and had received no conventional treatment during the previous 4 years. She was Class A by intracutaneous skin test but had reached a dose of 10,000 protein nitrogen units of aqueous ragweed extract in 1956.

The other patients treated with ragweed emulsion who were said to have had systemic reactions were not observed in the clinic but reported the symptoms when seen for follow-up study at the onset of the ragweed pollen season. Patient 2 received 5,000 units of ragweed emulsion and said that he sneezed for one week after the injection. Patient 3 stated her entire arm remained swollen and indurated for 3 days. Two hours after the injection she became drowsy, coughed, sneezed, and did not feel well for 5 days. Patient 4, developed sneezing, lacrimation, and rhinorrhea 3 days after the injection. Patient 5, had a temperature elevation of 101° F. the evening of the injection. She developed a local reaction involving the entire arm which persisted for 10 days.

RESULTS

During the ragweed pollinating season all the patients who had received repository therapy were instructed to report to the clinic each week and to keep a daily record of symptoms, classified as severe, moderate, mild, or no hay fever, on the basis of duration of symptoms during each 24 hour period.

A comparable group of 77 patients, with a similar distribution of classifications A, B, C, and D, was selected at random from the patients receiving conventional aqueous ragweed extract injection therapy. These patients kept similar records of symptoms.

The record cards represented the uninfluenced reports of the patients. They were reviewed by physicians who were not aware of the treatment of the patients. The double-blind nature of the comparison of the ragweed and placebo emulsions was strictly maintained. The comparison of treatment with the emulsions and with aqueous ragweed extract could not be considered double-blind since the patients knew which had been used. However, the evaluation was made by physicians who did not know the patients or their previous treatment.

The score cards of the 3 groups of patients (placebo repository, ragweed repository, and conventional aqueous therapy) were statistically evaluated. The patient days during the season on which no symptoms, slight, moderate or severe were reported, were tabulated. It was found that the patient days of slight or moderated symptoms did not contribute materially to the evaluation of results. Therefore, in the final analysis, only patient days on which no

symptoms (Fig. 1) or severe symptoms (Fig. 2) were reported were considered. On this basis the group receiving the ragweed emulsion reported for the entire season 50.5 per cent of days with no symptoms and 5.6 per cent with severe symptoms. The placebo-treated patients reported 37.8 per cent of days with no symptoms and 13.3 per cent of severe symptoms. The conventionally treated group reported 59.6 per cent of days with no symptoms and 5.1 per cent of severe symptoms (Table I).

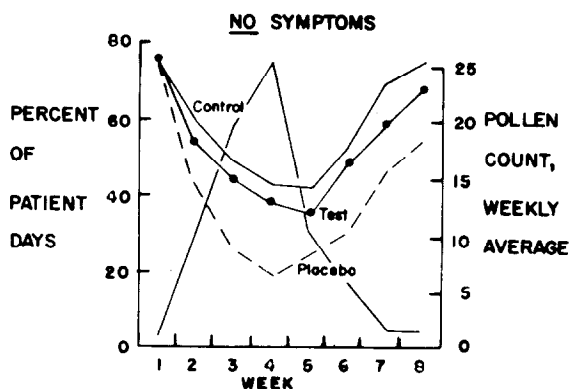


Fig. 1.—Days of no symptoms in test (emulsion-treated group), control (aqueous extract-treated group), and placebo group. The curve of pollen counts is superimposed.

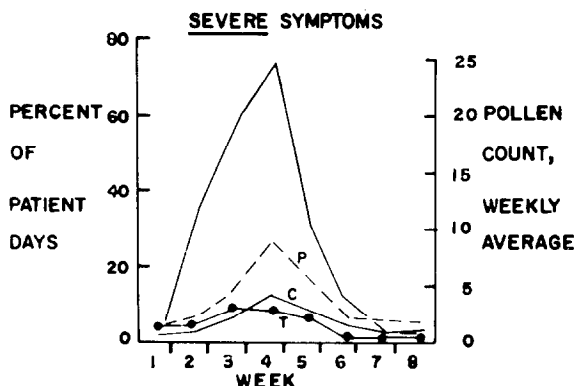


Fig. 2.—Day of severe symptoms. The various groups and the pollen counts correspond to those in Fig. 1.

When the results of the placebo group of patients were evaluated by classification, the "A" patients had the most severe symptoms, the "B" less severe than "A," the "C" less severe than the "B," and the "D" the least severe season. The patients receiving ragweed emulsion and classified as "D" had the best season, whereas the "A," "B," and "C" patients had similar seasons.

TABLE I. CLINICAL RESULTS IN EMULSION-TREATED, CONVENTIONALLY TREATED, AND PLACEBO-TREATED PATIENTS

	RAGWEED REPOSITORY PATIENTS	CONVENTIONALLY TREATED PATIENTS	PLACEBO REPOSITORY PATIENTS
Days of no symptoms	50.5%	59.6%	37.8%
Days of severe symptoms	5.6%	5.1%	13.3%

After the ragweed pollinating season was over, questionnaires were sent to the placebo-treated and ragweed emulsion-treated patients asking for a comparison of the 1959 and 1960 seasons. Of the 45 patients treated with ragweed emulsion who replied, 20 found their hay fever symptoms to be much improved, and 2 found their symptoms to be much worse than the previous year. Of the 38 patients who had received placebo who replied, 12 found their hay fever better, but 12 found it much worse than the previous year. The remainder found the season to be either the same, slightly better, or slightly worse. It was our feeling that the comparison of the different group of patients during the same season gave more valuable information than the patients' estimate of the previous season.

Blocking Antibody Titers.—Blocking antibody titers were determined by the passive transfer method of Prausnitz-Küstner using the serum of patients before and after repository emulsion therapy. None of the 4 placebo-treated patients who were studied developed any blocking antibody. Eighteen of the 21 ragweed repository-treated patients who were studied developed blocking antibodies, but, of the 3 ragweed repository-treated patients who failed to develop any blocking antibodies, all had excellent ragweed hay fever seasons. Thus a definite correlation between high blocking antibody titers and a good ragweed season was not established. However, the development of blocking antibody in 18 of the 21 patients studied who had been treated with ragweed emulsion appears to warrant further investigation. These studies are now being carried out.

CONCLUSIONS

Fifty patients with ragweed hay fever were treated with a ragweed emulsion and 51 with a placebo emulsion in a double-blind study. The results were definitely superior in the group treated with the ragweed emulsion.

A group of 77 patients of comparable ragweed sensitivity as judged by skin tests, treated with aqueous ragweed extract, was also compared with the groups treated with ragweed and placebo emulsions. This comparison was not double blind, since the patients were aware whether they received an emulsion or aqueous extract. The results of treatment with the ragweed emulsion and with aqueous extract were similar, both being better than those of the placebo group.

It was found most reliable to compare the groups of patients on the basis of days of no symptoms and days of severe symptoms, since the greatest discrepancies occurred when patients were asked to evaluate slight and moderate symptom days.

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