

Treatment of ragweed hay fever with Allpyral extracts

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The treatment of 144 ragweed hay fever patients with ragweed Allpyral extract during the 1963 season was found to have several advantages over treatment with aqueous ragweed extracts. Thus, it was possible to give fewer injections at longer intervals with a greatly reduced incidence of reactions, to give larger doses to highly reactive patients with more safety, to administer larger doses in the coseasonal type of treatment, and to give large doses at longer intervals to patients treated perennially.

Considerable interest has been evinced recently in the hyposensitization treatment of ragweed hay fever with an alum-precipitated pyridine extract of whole, undefatted ragweed pollen, designated as "Allpyral." The initial clinical report concerning its use was by Fuchs and Strauss¹ in 1959. They found, in a series of 78 adult patients highly sensitive to ragweed pollen, that the use of this extract produced equally good or even slightly better clinical results than in a control group given aqueous extracts. Fewer injections were required; also, they could be given safely at longer intervals, and there was a definitely lessened tendency to constitutional reactions. Since then, Gaillard and his co-workers² and Mamelok,³ in larger series of patients, have reported similarly favorable results. The possible advantages offered by this method of treatment prompted the authors to undertake further trial.

Accordingly, in 1961, a small series of ragweed hay fever patients was treated with ragweed Allpyral. The results of this study were reported in May, 1962.⁴ A larger series of patients was treated in the 1962 season, and the results

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reported in March, 1963.⁵ During the 1963 season, a still larger series was treated. Because of the increasing interest by allergists in this method of treatment, it was felt that a report of the authors' results during the 1963 season, as well as our general experience with this method of treatment after three years' trial, might prove helpful to those allergists contemplating its use. Although the authors have used other Allpyral extracts (grass, tree, dust, animal danders, etc.), we are limiting the present report of our results during the 1963 season solely to ragweed, feeling that it would lend itself to more standard and uniform clinical evaluation.

MATERIALS AND METHODS

A total of 144 patients were treated with the ragweed Allpyral extracts during the 1963 season. All patients were personally supervised by the authors. Eighty-three were seen in the private office of the senior author. Twenty-eight patients, mostly medical personnel, were seen in the outpatient clinic of Temple University Medical Center. Thirty-three patients were treated by one of us (P. T.) in the Allergy Department of the Bethesda Naval Hospital.

Of the 144 patients, 56 had had no previous ragweed hyposensitization therapy, and 30 had been treated the preceding season or seasons with aqueous ragweed extracts. Twenty-four patients, who formerly received aqueous ragweed extract on a perennial basis, were treated with ragweed Allpyral extract on a preseasonal basis in 1963. In 34 patients receiving treatment perennially, the aqueous ragweed extract was changed to Allpyral extract during the winter or early spring of 1962-1963 and treatment continued on a perennial basis. Five of the 144 patients reported just before the ragweed season (none earlier than July 28, 1963). They had to be given a "rush" treatment similar to that usually designated as "coseasonal" treatment.

The plan of treatment followed was similar to that employed by Fuchs and Strauss, with certain modifications. All patients included in the group had definite ragweed hay fever as verified by history, by skin test, and, in some instances, by ophthalmic tests with dry ragweed pollen. All patients had skin tests with different concentrations of the aqueous ragweed pollen extract for purposes of classification, according to the method suggested originally by Cooke.⁶ Those giving a marked positive reaction to ragweed 0.0001 N (10 PNU*) were classified as "AA"; those giving marked reaction to 0.001 N (100 PNU) were classified as class "A"; those giving positive reactions to stronger concentrations (R 0.01 N or 1,000 PNU or stronger) were designated as class "B" and "C." Upon the basis of this classification, Fuchs and Strauss suggested a dosage schedule for each class. But, since some of the initial doses seemed a little high, we modified their schedule somewhat, as a safety precaution.

The average dosage according to the skin test classification used in our patients is shown in Table I. Patients treated preseasonally received the injections at weekly intervals; however, in those patients previously treated preseasonally

*All aqueous extracts were standardized in milligrams of total nitrogen, whereas Allpyral extracts were standardized in protein nitrogen units (PNU).

Table I. *Average dosage schedule with ragweed Allpyral extract*

<i>Very sensitive AA or A</i>	<i>Mildly or moderately sensitive B or C</i>	<i>Previously treated High dosage</i>
10*	30	50
30	60	100
50	100	400
100	300	1,000
200	500	3,000
400	1,000	5,000
600	2,000	10,000
1,000	3,000	
2,000		

*Protein nitrogen units per cubic centimeter.

whose dosage tolerance was known, the injections were given weekly 3 or 4 times and then biweekly until the point of maximum tolerance was reached. Regardless of the skin test classification, the actual dosage of the Allpyral extract given to all patients was regulated by the degree of local reaction and the presence or absence of constitutional symptoms, as in treatment with aqueous extracts. More care was exercised with those patients treated for the first time, regardless of the skin test classification. But with patients who had been treated previously and whose maximum tolerated dosage in the previous season or seasons was known, the doses were increased slowly or rapidly depending on what they previously had tolerated. As will be pointed out later, this knowledge made it possible to reach the maximum tolerated dose more quickly in some patients so that fewer doses were required.

Those patients treated previously on a preseasonal basis began their treatment either in late March or early April. Patients receiving perennial ragweed treatment at intervals of 2 to 4 weeks throughout the year were converted to the Allpyral treatment usually in the late winter months of 1962-1963. In the perennial group, the dose of Allpyral extract was purposely made smaller during the conversion period, to avoid reaction. It was then increased fairly rapidly at 2 to 4 week intervals until the maximum tolerated dose was reached and continued at 2 to 4 week intervals. However, it was found out later that these precautions were unnecessary, since no reactions occurred during the conversion period. Patients reporting late for treatment were given the injections weekly until the maximum dose was reached.

Most of the patients were not informed that a different type of extract was being used. Therefore, to make certain that the clinical evaluation of the new treatment by the patient would not be influenced by the lengthened interval, the patient was given his regular dose one week and the Allpyral placebo (diluent without the ragweed) the succeeding week. In most patients, the injections were continued until the first week in August, which, in the Philadelphia area, is just before the beginning of the appearance of demonstrable pollen in the atmosphere. Most of the patients returned at weekly intervals throughout the season. Many did not receive further injections of ragweed Allpyral but,

instead, were given an injection of the Allpyral diluent at 1 or 2 week intervals, to determine whether the protection provided by their previous injections would persist throughout the season.

RESULTS

Number of injections

Of the total of 144 patients treated during the 1963 season, 105 received preseasonal treatment with ragweed Allpyral extract, 34 were converted from aqueous extracts given perennially to Allpyral extracts given perennially, and 5 were treated coseasonally with the Allpyral extract. The 105 patients treated preseasonally received a total of 1,261 injections, with an average of 12 injections. Fifty-four of the 105 patients received aqueous extract the preceding season, but satisfactory data as to their previous treatment with aqueous extracts could be obtained for only 25 patients. These 25 patients received 517 injections of the aqueous extracts during and throughout the preceding season, with an average of 21 injections; whereas, during 1963, the same patients received a total of 351 injections of Allpyral extract with an average of 14. These figures provide only a rough comparison of the number of injections needed with each type of extract, but show definitely that the maximum tolerated dosage could be reached with fewer injections of the Allpyral extract than with the aqueous form, even in patients treated for the first time. For example, five patients in the latter group required only 6 injections to reach their top dose, ten patients required only 7 injections, and six only 8 injections. As already indicated, patients previously treated either with the aqueous extract administered preseasonally or perennially, or with the Allpyral extract, were able to tolerate higher initial dosage and more rapid increases to reach their maximum than those treated for the first time. It also is of interest that many patients were able to take fairly large dosages of the Allpyral extract, even though, according to skin tests with the aqueous extracts, some were classified as AA grade patients. For example, eight class AA patients were able to tolerate an average of 2,750 PNU without reaction, reaching their top dose in an average of about 8 injections. These results emphasize the fact that the number of injections required by patients getting Allpyral extract was considerably less, almost by 50 per cent, than that previously required by patients getting aqueous extract. It must be remembered that, even though we had used the Allpyral extracts in the two preceding seasons, we still were trying to determine their safety and probably gave more injections than was necessary. However, after three years' experience with these extracts, we definitely believe that the maximum tolerated dose for most patients getting Allpyral extracts can be reached in from 6 to 8 injections, especially with those treated in previous seasons, rather than in the 12 to 15 injections required when aqueous extracts are employed.

Highly sensitive patients

The results in this group of patients are of special interest because one of the supposed advantages of Allpyral extract is that reactions are less frequent with the latter than with the aqueous form. Twenty-nine patients are included

in this group. In previous years, none of the 29 was able to tolerate what would be considered average doses of the aqueous extracts (1,000 PNU or more) without reaction; in fact, more than half of the group were unable to tolerate dosages in excess of 50 PNU. Yet, in 1963, of 24 patients treated by the senior author, 22 tolerated much larger doses of Allpyral extract without reaction; for example, 13 patients reached a maximum dose between 1,000 and 10,000 PNU. Two patients in the group, who formerly developed reactions from very small doses of the aqueous extract, likewise could not tolerate larger doses of the Allpyral extract. One patient developed a marked local reaction from 50 units and a second one from 10 units. The remaining five patients treated by the junior author (P. T.) are of particular interest in relation to reactions. All five patients had received injections of aqueous ragweed extract in 1962, but developed constitutional reactions on repeated occasions, following injections of the aqueous extracts in the following relatively low dosage (listed in PNU units)—10, 60, 100, 100, and 200 units. All five were able to tolerate fairly large doses of the Allpyral extract (three, 3,000 PNU, another, 4,000, and the fifth, 5,000) with no constitutional reactions, and with only slight local reactions in two of the five patients.

Our experience with these low-dosage patients substantiates a professed advantage of the Allpyral extracts over the aqueous form, namely, that it provides a means of giving the extracts to reactive patients in larger dosage than was possible with the aqueous form.

Coseasonal type of treatment

In previous years, when a patient would present himself for hyposensitization treatment either just before or at the onset of the ragweed season, "rush" or coseasonal treatment was given. This consisted of administering small doses of the aqueous extract at 24 or 48 hour intervals and increasing the dose slowly, often by not more than 10 or 20 units, to avoid either a possible reaction or an increase in symptoms; also, at times, the extract was given in small doses intracutaneously. Therefore, the results obtained in five patients (Table II)

Table II. *Coseasonal treatment with ragweed Allpyral extract*

<i>Patient</i>	<i>Age</i>	<i>Skin test classification</i>	<i>First dose</i>		<i>Maximum dose</i>		<i>Treatment during season</i>		<i>Total No.</i>		<i>Clinical result</i>
			<i>Date</i>	<i>PNU</i>	<i>Date</i>	<i>PNU</i>	<i>Date</i>	<i>PNU</i>	<i>Doses</i>	<i>PNU</i>	
J. B.	26	B	8/1	20	8/12	1,200	8/28 9/14	10 10	7	2,390	Good
A. B.	30	B	7/28	50	8/9	3,000	0	0	7	6,050	Good
A. F.	36	A	7/28	20	8/7	600	8/30 9/11	10 10	6	1,370	Fair
J. F.	36	AA	7/31	10	8/12	2,000	9/7	10	8	3,990	Good
R. P.	19	C	8/6	50	8/12	4,000	8/21 9/11	10 10	7	7,850	Fair

treated in the coseasonal manner with Allpyral extracts are of special interest. All five patients had positive clinical histories of ragweed hay fever and positive skin and eye tests to ragweed pollen. None had had previous hyposensitization therapy. All five patients received treatment no earlier than July 28, 1964, with initial doses of 10 to 50 units, depending upon skin test classification. The dosage usually was doubled and given daily or every 48 hours in order to reach a maximum just before the onset of the season. It can be seen from the table that doses of 2,000, 3,000, and 4,000 were given to three patients without reaction. Once the season had begun, very small doses (10 units) were given when deemed necessary, along with whatever symptomatic therapy (usually antihistamines) was required. There were no significant reactions, and the clinical results in three patients were good and only fair in the other two. If similar results could be obtained in a larger series of patients, this method of treatment might find wider application in patients coming in late for treatment or even in the form of booster doses given to patients previously treated with Allpyral extracts.

Perennial group

As previously indicated, 34 patients who had been getting injections of the aqueous extracts on a perennial basis were converted to the Allpyral extract during the winter of 1962-1963. The conversion usually was made by giving small doses of Allpyral extract at first and then increasing to the equivalent dosage or even to a larger one as quickly as possible. In all instances, this conversion was completed before the end of July. No difficulty was experienced in making the conversion; in fact, after our initial experiences with the extracts, we gave some patients a dose of Allpyral extract equivalent to the amount of aqueous extract which the patient previously received, without inducing a reaction. Furthermore, in at least three patients, the interval between injections was lengthened to 6 weeks, and in three patients to 8 weeks, without reaction. From our experience with this group of patients, we believe that patients getting aqueous ragweed extract on a perennial basis safely could be given the equivalent dose of the Allpyral extract without fear of reaction and even at intervals up to 6 or 8 weeks.

Reactions

Of the 1,261 injections given to 105 patients as part of their preseasonal treatment with the Allpyral extract, reactions considered *constitutional* followed the injections on only three occasions. In one patient, the injection was followed within ten to fifteen minutes by slight sneezing and slight local reaction; in a second, by a slight increase in the atopic dermatitis eruption of the hands; and in a third, by some generalized hives appearing 24 hours later. The reaction in the latter patient was rather mild and responded quickly to antihistamine therapy. Even though this patient had been given the same dose of extract at the preceding visit without reaction, and, also, had eaten certain foods which could have been responsible for the hives, we classified it as a constitutional reaction, since we could not exclude the injection as a possible cause. On the whole, how-

ever, the tendency to constitutional reactions in patients getting Allpyral extract was considerably less than that seen after therapy with aqueous extracts. None of the patients had angioedema, asthma, or constriction of the chest, which often are part of the constitutional reactions following aqueous therapy.

Local reactions

These were also much less frequent after injections of the Allpyral extract than after injection of aqueous extract. Thus, of the total of 1,261 injections given, immediate slight local reactions occurred 36 times in 14 patients, and a delayed local reaction (two days later) in one patient. It seldom was necessary to lower the dose upon subsequent visits; usually, the dose was repeated and, in some instances, even increased in regular fashion, especially if the local reaction was slight. When a local reaction occurred, it consisted of swelling, redness, and itching, similar to that seen after injections of aqueous extracts. In no instance did we observe any persistent induration or nodule such as has been reported after repository pollen injections.

As previously indicated, many patients who previously could not tolerate large doses of aqueous extract received the Allpyral extract in larger dosage without undue reaction. This also was true of those patients treated by the "rush" or coseasonal method and of those who formerly received aqueous extract perennially but who were given injections of the Allpyral extract in 1963.

On the whole, it would seem from our experience that a distinct advantage of the Allpyral extracts over aqueous ones is the greatly lessened tendency to reactions and, therefore, comparatively greater safety.

Clinical effect

The final test of a new method of treatment of hay fever is its clinical effectiveness. This is always difficult to estimate accurately, even when patients keep a daily record of their symptoms and of the drugs required for relief in relation to the pollen concentrations of their area. No attempt was made to obtain an accurate estimate of our patients' symptoms by means of diaries. However, all patients were seen at regular intervals throughout the hay fever season, and, at each visit, efforts were made to get detailed information concerning their symptoms and the drugs being taken for relief. At the end of the season, the patients were asked specifically to compare their clinical results in 1963: (1) with that of untreated seasons and also (2) with that of their symptoms in 1962 when treated (a) with aqueous extracts and (b) with Allpyral extracts. We arbitrarily classified the relief obtained according to the number of days of bad hay fever as: poor, or less than 50 per cent (7 days); fair, 50 to 70 per cent (5 days); good, 70 to 90 per cent (3 days); and excellent, 90 to 100 per cent (less than 1 day). Even though the total pollen count in the Philadelphia area in 1963 was $2\frac{1}{2}$ to 3 times as high as in 1962, the clinical results of treatment in all of the 144 patients were quite satisfactory. Only 8 patients had poor results (less than 50 per cent relief), 12 had fair results, 84 had good results, and the remaining 40 had excellent results. Data as to the comparative results between aqueous and Allpyral treatment was obtained in

81 patients. Of those, 33 noted no change, 40 felt they were improved, and 8 thought they were worse.

On the whole, the clinical results in patients treated with ragweed Allpyral extracts were as good as and perhaps even better than in patients previously treated with aqueous ragweed extracts. The Allpyral extracts, in our experience, possess the added advantage of fewer injections (by 50 per cent) required, the ability of reactive patients to take larger doses than when treated with the aqueous extract, and many fewer reactions, both local and constitutional. The good results obtained in the five patients treated by the "rush" coseasonal method suggest a wider application of this method in patients reporting late for treatment. Finally, the fact that patients getting perennial treatment could safely tolerate doses given at intervals of up to 6 or 8 weeks suggests the possibility that many hay fever patients could get along on fewer injections of the Allpyral extract (6 or 8) given perennially than previously was possible with the aqueous extract.

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