Hay Fever

A Comparative Clinical Evaluation of Treatment with Aqueous Pollen Extracts, Alum-Precipitated Pyridine Pollen Extracts and Aqueous Pollen in Oil Emulsions

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• **Three different types of pollen extracts are currently being used in the prophylactic treatment of hay fever. A comparative clinical study of their efficacy reveals that all are about equally efficacious. The alum-precipitated pyridine pollen extracts may be slightly better. Since only 14 to 16 injections are required for prophylactic treatment, they may well replace the older aqueous pollen extracts, 20 to 35 injections of which are usually necessary to provide relief.**

The aqueous pollen in oil repository method of treatment needs only one to four injections for comparable results, but this so-called "one-shot" treatment can only be administered by one who is trained in emulsion therapy and has come to know by experience the proper maximum dose.

CURRENTLY there are three kinds of preparations used in injection therapy of seasonal allergic rhinitis due to pollen—aqueous pollen extracts, alum-precipitated pyridine pollen extracts, and the aqueous pollen in oil emulsions employed in the so-called "respository" treatment.

Aqueous Pollen Extracts

Subcutaneous injection treatment with the aqueous pollen extracts for the relief of hay fever is the oldest and most widely used. It is considered efficacious and, except for a constitutional reaction which may occur if an improper dose is given, is without danger in administration. Aqueous pollen extracts can be easily made in one's own office laboratory or can be obtained from commercial sources. Treatment is usually prophylactic or preseasonal, although sometimes these preparations are used during the height of the hay fever season for amelioration of symptoms.

Hyposensitization is brought about by a series of subcutaneous injections of increasing amounts of the specific pollen allergens to which the patient is clinically sensitive. However, exactly how hyposensitization is accomplished by this means has never been adequately explained. One theory is that the injection of potent specific allergens calls forth the production of blocking, neutralizing or immune antibodies. The antibodies are relatively heat stable and do not have the property of sensitizing the skin of a normal individual. They compete with the skin-sensitizing antibodies in uniting with the antigen without releasing the noxious chemicals that produce the allergic reaction. Since it has never been unequivocally proved that there is a correlation between clinical improvement in the patient and the titer of the immune blocking antibodies in the serum, it is probable that some other mechanism is at work either in place of, or in addition to, that of blocking antibody formation.

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Alum-Precipitated Pyridine Pollen Extracts

Treatment with alum-precipitated pyridine pollen extracts is being used by a limited number of allergists, mostly experimentally. As with the aqueous pollen solutions, the injections are administered subcutaneously in a series of gradually increased doses. The treatment is primarily prophylactic. These extracts are not simple to prepare and are not currently commercially available. A laboratory with adequate ventilation is necessary to get rid of the especially noxious odor which arises from the pyridine used in preparing them. The alum-precipitated pyridine pollen extracts used in the present study were prepared by Margaret Strauss of the New York University Hospital Allergy Laboratory, as follows: The extracting fluid consisted of one part pyridine and one part 0.3 per cent sodium carbonate solution. Non-defatted pollen was thoroughly mixed with a specified amount of this fluid and the mixture was allowed to stand for three days in a cool room, after which the liquid was filtered from the solids and then was Seitz-filtered for sterilization. Next, under sterile conditions, one part of sterile distilled water was added to one part of the pyridine-bicarbonate pollen extract, the mixture being stirred constantly as this addition was going on. Then one part of sterile 2.0 per cent potassium aluminum sulphate in one-fourth normal sulphuric acid was added. This formed a

precipitate. After standing overnight, the mixture was centrifuged and the supernatent solution discarded. The residue was washed four times with large quantities of sterile saline solution, sterile glass beads being used to separate the particles of the precipitate and to facilitate washing. The final volume of the suspension was then made up to the initial volume with sterile saline solution. A protein nitrogen determination was run on this final sterile product.

Advantages claimed for these extracts are:

1. All of the original fractions in the pollen grains are incorporated in the extract. This includes the oil fraction which some investigators insist contains an allergically active constituent.

2. The suspension is slowly absorbed, as has been shown by passive transfer studies. Thus, local irritation and swelling at the sites of the injections are avoided and there is less likelihood of constitutional reaction.

3. Because of slow absorption, fewer injections are required to maintain the patient's optimum dose. An obvious and recognized disadvantage of these extracts is that they cannot be used for testing purposes.

Aqueous Pollen in Oil Emulsions

Repository injection treatment of hay fever with an aqueous pollen in oil emulsion has received considerable attention in the lay as well as the scientific press. The fact that only a very limited number of injections are said to be necessary for hay fever protection has made this form of treatment desirable, especially in the opinion of the patient. Although the method is currently being used by an increasing number of allergists throughout the United States, the emulsions must be made with care.

The object is to produce a water in oil emulsion in which the water phase is aqueous pollen extract. The tiny droplets of aqueous pollen extract are contained within an external phase of mineral oil, kept in suspension by electrical charges set up during the process of emulsification and discharged slowly into the general circulation at intervals which have been determined by laboratory experiment.

The preparations are made by using a non-ionic emulsifier to aid the emulsion of aqueous pollen extracts with a specially prepared very light mineral oil. Since the introduction of this form of treatment, several different proportions of the oil and emulsifier have been suggested, as well as varying the amounts of the aqueous pollen extract. These variables, as well as those having to do with the means of producing the emulsion, pose difficulties for physicians wishing to use this method of therapy.

Many of the arguments that were initially advanced against the use of aqueous pollen in oil emulsions have been answered, but many objections remain: There is no standardized method of preparing the emulsion; the formula has been repeatedly changed and modified; the technique of examining the emulsion after preparation to determine if it is a good emulsion requires training in microscopy; there is no fully accepted method of determining the patient's optimum dose; care must be taken in administering emulsion deep subcutaneously, lest the emulsion escape to the dermis; there is suspicion that the inadvertent injection of emulsified extracts containing allergens to which the patient is not sensitive may result in the production of new immediate or delayed sensitivities. The question of carcinogenicity of mineral oil is an academic one and there is no certain answer. Millions of emulsion injections have been administered in a period of 20 years with no reports of carcinoma having been produced. Mineral oil has been used orally and rectally, obviously absorbed by lacteal vessels, for a long time with no carcinogenicity reported. However, should a case be reported tomorrow, the problem would then cease to be academic.

In preparing 100 cc. of the oil phase of the emulsion in this study, 35 ml. of Arlacel® A* which is a non-ionic emulsifier, and 65 ml. of Drakeol® 6VR† which is a mineral oil, were used. To this was added 0.02 ml. of Tween 80*. A hemoglobin pipette was used to measure this small amount. Tween 80 is a surfactant which was added to ease the work of emulsification and to lessen the milling and homogenization which frequently occurs with water in oil emulsions.

Equal amounts of the water phase, which was an aqueous pollen extract, and the oil phase were employed in preparing the emulsion. No more than 4.0 ml. was prepared at any one time—2.0 ml. of the oil phase (the Arlacel-Drakeol mixture) and 2.0 ml. of the aqueous phase (the aqueous pollen extract). Emulsification was carried out by means of the Conscot Emulsifier‡ for a period of at least 25 minutes, as advised by the manufacturer.

The Conscot Emulsifier is a power-driven machine providing 12 strokes per minute and delivering alternate thrusts to the plungers of two interchangeable 10 cc. Luer Lock syringes. The syringes are connected to each other by a double-hubbed 18-gauge needle, in the middle of which an emulsifying valve has been placed. This emulsifying valve contains a meshed disc with perforations of 0.0024 of an inch or 62 microns. As the water and oil mixture placed

*Arlacel A and Tween 80 were procured from the Chemicals Division of the Atlas Powder Company, Washington, Delaware.

†Drakeol 6VR was procured from the Pennsylvania Refining Company, Butler, Pennsylvania.

‡The Conscot Emulsifier is manufactured by the Conscot Company, Rockaway, New Jersey.

in one of the syringes is passed to the other and back and forth by action of the motor, shearing takes place. In addition, due to the turbulence of the flow, electrical charges are produced which result in the aqueous pollen mixture surrounded by a film of light oil. Although presumably suitable for repository injection, the emulsion was examined to make sure. This was done by placing a drop of the prepared emulsion on the surface of water in a beaker. If it did not retain its sphericity it was considered a poor emulsion and discarded. A more exacting test was used on all emulsions before use. That was the careful microscopic examination of a drop of the prepared emulsion. With the high-power lens the emulsion was examined for homogenicity and uniformity of globule size. Just before administration, the emulsion was placed in the Conscot machine for an additional ten minutes.

One milliliter was the amount administered in a dose that duplicated the optimum dose reached by the patient the previous year with aqueous pollen extract therapy. In this kind of therapy, as with the other two previously described, no completely acceptable explanation has been advanced with regard to the mechanism by which the water in oil emulsion produces immunity.

Clinical Evaluation

A clinical evaluation and comparison of results of parenteral prophylactic treatment of hay fever is difficult, for in this disease there is a preponderance of subjective symptoms over objective findings. It is necessary to rely upon the patient's ability to recall, estimate and keep an accurate record of the severity and frequency of symptoms. In evaluating results, the age and sex of the patient, his work, play or exercise, environmental influences, emotional problems, climatic changes, as well as fluctuation of the amount of circulating pollen in the air from day to day and from season to season, must be taken into consideration. In addition, there are psychological factors at work. Some patients are hopeful when they are introduced to a new form of treatment and in their reports tend to minimize their symptoms; others are apprehensive and are apt to magnify them. Some physicians are enthusiastic over every new therapeutic procedure; others are prone to criticize a new method or departure from the type of therapy they have been accustomed to use. These factors all affect the patient's subjective response.

In order to circumvent and prevent or minimize biased reports on a new drug or new method of treatment, double blind studies using placebos have been demanded of clinical investigators. Some such studies are of value, particularly in evaluating drug efficacy, but the variables of age, sex, work, play, exercise, environmental influences and emotional upsets, not to mention the reliance the physician must place on the intelligence of the patient and the exactitude with which he regards and records his discomfort, still remain. That there are no two people exactly alike who can be evenly matched and kept in the same environment is self evident. That physicians attempt to guess, consciously or unconsciously, which is the placebo and which is not, thus becoming prejudiced in one way or the other, is natural. In the last analysis, one must rely upon the credulity of the patient and the exactness of his records. An additional objection to using placebos in determining results of hay fever treatment, particularly when using aqueous pollen in oil emulsion therapy, is based on the fact that the oil phase of the emulsion is an adjuvant. Although it is not entirely proved, some investigators believe or suspect that mineral oil, in itself an incomplete adjuvant, increases the antibody titer in patients who have received antigen injections even several years previously. Since all of the patients in this study who received aqueous pollen in oil repository treatment had had conventional antigen injection treatment previously, the injection of an antigen-free emulsion could hardly have been considered a placebo.

For these reasons no double blind studies were employed in evaluating the results of treatment with the aqeuous pollen extracts, the alum-precipitated pyridine pollen extracts and the aqueous pollen in oil emulsions. The patients were taken in consecutive order as they came in to be treated. In assessing results at the end of the hay fever season, I interrogated the patients with as much objectivity as possible. The patients were urged to give an unbiased, unprejudiced and honest report. Some of those who received aqueous pollen therapy and some who received alum-precipitated pyridine pollen injection therapy had never been treated before with prophylactic pollen injections. All of those who received the aqueous pollen in oil repository treatment had been treated previously with aqueous pollen injections. Since there may be a "holdover" from treatment in a previous year, the results in each group were tabulated separately.

Results with Aqueous Pollen Injection Therapy

Results reported by 175 patients treated prophylactically against spring (grass) hay fever in 1961 with aqueous pollen extracts were as follows:

A—One hundred sixty patients previously treated for one or more years—Excellent or good, 128 cases or 80 per cent; fair, 18 cases or 11.2 per cent; poor, 14 cases or 8.8 per cent.

B—Fifteen patients with no previous treatment—Excellent or good, 9 cases or 60 per cent; fair, 4 cases or 26.5 per cent; poor, 2 cases or 13.5 per cent.

Good to excellent responses indicated that the patient had no symptoms, or if he sneezed a few times or had mild itchy eyes during the hay fever

season, the symptoms were so mild that no additional medication was necessary. A fair response indicated that the patient had symptoms at the height of the hay fever season which required some additional medication such as antihistamines. Poor results indicated that considerable medication was necessary for relief and that the injection treatment afforded very little, if any, relief.

Results with Alum-Precipitated Pyridine Pollen Injection

For 57 patients treated prophylactically against spring (grass) hay fever in 1961 with alum-precipitated pyridine pollen extracts results were as follows:

A—Forty-seven patients previously treated for one or more years with aqueous pollen extracts—Excellent or good, 44 cases or 94 per cent; fair, 1 case or 2 per cent; poor, 2 cases or 4 per cent.

B—Ten patients with no previous treatment—Excellent to good, 7 cases or 94 per cent; fair, 1 case or 3 per cent; poor, 2 cases or 20 per cent.

Dr. Merle Moore of Portland, Oregon, treated a similar but slightly larger series during the spring of 1961. The only difference in his technique was that instead of interrogating the patients himself, he had a third party question them and record the results, thus eliminating the possibility of subconscious bias. Dr. Moore's results were as follows:

A—Ninety patients previously treated for one or more years with aqueous pollen extracts—Excellent to good, 74 cases or 82 per cent; fair, 13 cases or 15 per cent; poor, 3 cases or 3 per cent.

B—Thirty patients with no previous treatment—Excellent to fair, 25 cases or 83 per cent; fair, 3 cases or 10 per cent; poor, 2 cases or 7 per cent.

Results with Aqueous Pollen in Oil Repository Injection Therapy

One hundred thirty patients treated six to eight weeks before the 1961 spring (grass) hay fever season with a single injection of an aqueous pollen in oil emulsion extract reported results as follows:

Excellent to good results, 103 or 79 per cent; fair, 14, or 11 per cent; poor, 13, or 10 per cent.

It should be reemphasized that all of these patients had received previous hay fever injection therapy with aqueous pollen extracts and that their probable optimum dose had been determined.

REACTIONS

In the 175 patients treated with aqueous pollen extract no reactions occurred with the exception of soreness of the arm at the injection site in a few cases. The same was true of the 177 patients treated with alum-precipitated pyridine pollen. However, in the group of 130 patients treated with the aqueous pollen in oil emulsion, 37 (28 per cent) had reactions of various types, ranging from mild soreness at the injection site for periods of a day or two to as long as three months, to the formation of nodules and abscesses. Constitutional reaction occurred in one case.

It has been suggested that the side effects or complications associated with aqueous pollen in oil emulsion injection therapy are due to the use of an improperly prepared emulsion, or to the formula used or to the manner in which the injection is administered. However, the formula, the emulsifying technique and the injection method used in this study were the ones acceptable to most workers in hay fever emulsion therapy.

COMPARISONS

Comparison of clinical results in the treatment of hay fever is difficult and in some cases impossible. In the first place pollen counts vary from one area to another in the same city, winds change, some patients are out of doors more than others, each patient estimates his degree of suffering differently. These are but a few of the factors that must be taken into consideration. Other factors have already been mentioned. Secondly, patients who have received prophylactic injection therapy in previous years may well have a "holdover" effect, and a comparison of the results in these patients with results in patients who have had no previous prophylactic therapy may be unfair. Nevertheless, bearing these considerations in mind the data presented in Charts 1 and 2 are interesting.

In Chart 1, 80 per cent of patients who had never previously received any form of prophylactic injection treatment are shown as having had good to excellent results from the alum-precipitated pyridine pollen injections, while results of that order were reported for only 60 per cent of those treated with aqueous pollen. The patients who received the aqueous pollen injections did better in the "fair" classification—26.5 per cent in contrast to 10 per cent for those treated with the alum-precipitated pyridine pollen. In the "poor" category, there was little difference between the two types of treatment. It is recognized that a further cloud upon the validity of the comparison of these two groups is that there were only 15 in one as against 40 in the other.

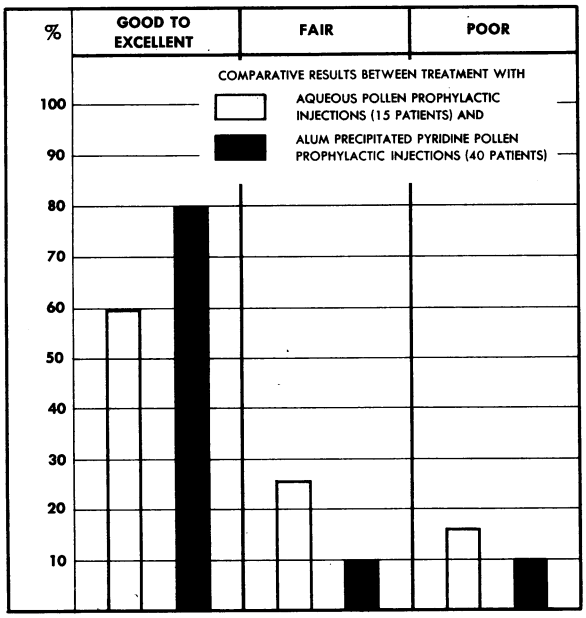
In Chart 2, data on results of all three forms of treatment in all the patients treated are compared.

DISCUSSION

If any conclusion can be drawn from the comparisons available in the present study, it is that alum-precipitated pyridine pollen prophylactic treatment has a slight edge in efficacy of treatment, but it probably is unfair to compare results with aqueous

CHART 1

SPRING (GRASS) HAY FEVER SEASON—1961
NONE OF PATIENTS HAD RECEIVED DESENSITIZATION PROPHYLACTIC TREATMENT IN PREVIOUS YEARS.

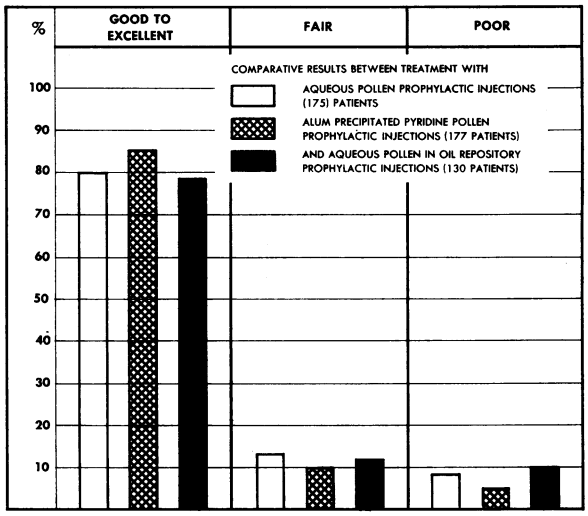


pollen extracts which have been in use for fifty years with the results obtained by treatment with alum-precipitated pyridine extracts, which are only now being investigated, and with the even newer aqueous pollen in oil emulsion therapy.

There is no doubt that both the alum-precipitated pyridine extract and the aqueous pollen in oil emulsion possess an advantage—fewer visits to the physician's office. If there is no danger to the patient with these newer methods and the results are equal, they will of course supplant the aqueous pollen injections. The repository treatment requires from one to four or five injections annually, depending upon the patient's sensitivities. The alum-precipitated pyridine method requires about 12 to 16 injections,

CHART 2

SPRING (GRASS) HAY FEVER SEASON—1961



sometimes fewer. Apparently any number of antigens can be included in the alum-precipitated extract and the number of injections depends primarily upon the degree of the patient's sensitivity. Aqueous pollen treatment usually requires 20 to 35 or more injections, depending upon the number of the patient's sensitivities and the degree.

In the series of cases reported, all patients were given what was considered to be their optimum dose. With aqueous pollen extract, the optimum dose was determined by the degree of local reaction obtained at the site of the injections and the relative freedom of symptoms by the patient. A similar method was employed to determine the optimum dose for the patients who received the alum-precipitated pyridine pollen extract. Patients who received the aqueous pollen in oil emulsion injection were given the optimum dose they had reached previously with aqueous pollen extract administration.

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