1-1-1943

Seasonal hay fever : with special reference to oral pollen therapy

Robert Sigel Squires
University of Nebraska Medical Center

Senior Thesis

SEASONAL HAY FEVER WITH SPECIAL REFERENCE TO ORAL POLLEN THERAPY

by

Robert S. Squires

Presented to the College of Medicine

University of Nebraska

1943

CONTENTS

PART I Page

THE HISTORY OF HAY FEVER.....1

PART II

THE POLLENS OF SEASONAL HAY FEVER.....6

PART III

THE CLINICAL MANIFESTATIONS AND DIAGNOSIS OF HAY FEVER.....9

PART IV

THE TREATMENT OF SEASONAL HAY FEVER.....15

PART V

A REPORT ON ORAL POLLEN THERAPY OF 130 PATIENTS.....34

BIBLIOGRAPHY.....41

COLORED PLATES

TECHNIC OF SKIN TESTING.....11

PART I

THE HISTORY OF HAY FEVER

The evolution of our knowledge of hay fever from the chaotic conceptions of a mysterious disease to it's present scientific development, forms an interesting chapter in the history of this widespread disease.

It was not until 1819 that hay fever first emerged as a distinct disease and not until 1873 that the etiological relation of pollens was discovered. On March 16, 1819, Dr. John Bostock (1) an English physiologist and clinician, read a paper before the Royal Medical and Chirurgical Society of London on a "Case of a Periodical Affection of the Eyes and Chest", in which he presented the history and clinical symptoms of a seasonal affection which had troubled him since childhood. Nine years later he (2) gave another account of the disease giving it the name of "Catarrhus Aestivus", or summer catarrh, although the affection had, since his earlier publication, obtained the popular name of "hay fever". The credit for being the first to clinically recognize hay fever, as such, belongs to Dr. Bostock. He ascribed the symptoms to external irritants such as dust, but did not suspect plant pollens.

William Gordon (3) came to the conclusion that

hay-asthma was due to the aroma emitted by flowers of the grasses, particularly from those of sweet vernal grasses.

In Gordon's summary he states: "I have said that sweet vernal grass seems to be the principal cause in exciting hay asthma, and I am induced to come to this conclusion: first, because this plant is one of the most scented of the grasses; and second, because as soon as it begins to flower, and not until then, the asthma commences. As the flowers arrive at perfection the disease increases and after they have died away I have remarked that the patient could pass through the most luxurient meadow with total immunity.

Hyde Salter (4) in his classical work on asthma which first appeared in 1859, gave a classical description of hay fever following exposure to animal emination.

That the etiology of hay fever is plant pollens was finally established by Blackley (5) in 1873. For fifteen years, Blackley carried out experiments. In 1859, Blackley noticed a vase full of grasses placed on one of the mantles of his home. In examining the plants he disturbed them and a small cloud of pollen floated from the plants into the air about him. He inhaled the pollen and soon began having a violent sneezing attack.

He tested himself on the pollens of nearly one hundred different species of grasses and flowers in the fresh as well as in the dried stage, and also in alcoholic extracts. He also tested the skin reaction of hay fever subjects by means of pollen applied to the scarified skin.

Like many experimenters before and after him, Blackley suffered from the ailment in which he was interested, and experimented endlessly in various ways. He put pollen in his nose and caused hay fever. He put pollen in his nose out of season and hay fever was produced. He rubbed the pollen into his skin and caused violent eruptions and inflammation, which in reality constituted the first skin test for sensitization. He exposed glass slides coated with glycerin to the outside air and was able to demonstrate pollen under the microscope, thus proving that pollen actually is present in the air. He noted that the amount of pollen was dependent on weather conditions. By exposing slides in kites flown as high as 1500 feet he was able to show that pollen rises to great altitudes. In short, he recorded practically all we know about hay fever today except treatment.

The first American to contribute to our knowledge

of hay fever was Moril Wyman of Cambridge, Massachusetts (6). In 1854 Wyman described hay fever in his lectures at the Medical School of Harvard University, and in 1866 he read a paper on the late form of hay fever at the meeting of the Massachusetts Medical Society, giving it the name "autumnal catarrh".

Marsh (7), of New Jersey, further confirmed the work of Wyman and stated that "autumnal catarrh" like the English hay fever is caused by the presence of pollen of flowering plants in the atmosphere, and its irritant action on the respiratory mucous membrane of susceptible persons.

The acceptance of the pollen theory of hay fever made slow progress, and it wasn't until 1902 that Dunbar (8) published his results from many years work, establishing beyond a doubt the role of pollen as the cause of hay fever.

In 1913, Dunbar (9) advanced the theory that hay fever is a disease caused by vegetable poisons contained in the pollen of certain plants. These substances were connected with the protein of the pollen grain and of a highly specific character.

Clinical allerby apparently became established in 1911 by Noon (10) of London. He reported successful

results in treating pollinosis by the pre-seasonal injection in graduating doses of extracts of the offending substance.

PART II

THE POLLENS OF SEASONAL HAY FEVER

The air-borne pollens are the important etiological factors, but almost any pollen may be a cause when it is present in sufficient concentration. Cooke (11) reports that in the eastern part of the United States it is possible to distinguish three seasonal varieties of hay fever. The "Spring" type, beginning about March 15 and ending May 15, is due to the pollens of trees, especially the oak, elm, birch, hickory, ash, and poplar. The "Summer" type, beginning in the late spring and early summer about May 1 and extending up to July 1, is caused by pollens of grasses, plantain, and sorrel. The "Fall" type begins in the late summer and early fall from about August 1 to October 1, or the first frost. The pollen of the ragweeds is mainly responsible for this group. In the south-western states the amaranths, artemisias and mountain cedar are also important causes of pollinosis.

Hay fever is a fairly common disease affecting between 1 and 2 per cent of the population of the United States. Feinberg (12) estimates that in the United States there are at least 2,000,000 people suffering annually the torments of this disease. It

is a common occurrence to hear the remark that hay fever must be increasing. For example, Beard (13) in 1876 estimated that there were 25,000 to 50,000 hay fever victims in the United States, which had a population of 50,000,000 at that time.

It is quite generally known now that the intensity of the suffering in any hay fever patient depends almost entirely upon one thing - the amount of pollen in the air. Feinberg (12) goes on to state that many factors determine the severity of the attacks, the amount of pollen in the air, sunshine and warmth increasing pollen dissemination, velocity and direction of the wind coupled with the degree of exposure the person is permitted. Heredity has proven to be one of the most important factors in propagating hay fever.

Scheppegrell (14), the founder of the American Hay Fever Prevention Association, gives a very adequate description of pollens in his book Hay-fever and Asthma. The forms of pollens vary. Their size ranges from 6 microns in diameter to 180 microns. They are usually spherical or ovoid in shape. Their markings divide them into two general classes, those having spines or spicules and those without them. The ragweeds form the type of the spiculated pollen and

and the grasses of the unspiculated pollen. The spicules increase the buoyancy of pollen and materially aid them in traveling long distances under favorable wind conditions.

The complete chemical composition of pollens is still a scientific problem. Pollens invert cane sugar. They contain diastase, starch, oils and protein.

PART III

THE CLINICAL MANIFESTATIONS AND DIAGNOSIS OF HAY FEVER

Hay fever is one of the many allergic manifestations in man. The allergens of hay fever are divided into groups according to their mode of action--inhalants, ingestants, contactants and injectants. The symptoms and physical signs presented by the allergic subject are dependent on the particular shock organs involved, where, in hay fever the person has nasal congestion, itching of the eyes and nose, lacrymitis, and sneezing in varying degrees.

The symptoms of hay fever according to Scheppegrell (14) are fairly constant. The early stage is attended with sneezing and congestion of nostrils due to the swollen mucous membranes resulting from irritation of vasodilators and with a free serous nasal discharge. There is itching of the inner canthi of the eyes. The difficulty of nasal breathing is aggravated when the patient is in a recumbent position. Unlike an ordinary coryza, however, the discharge remains thin and serous.

There is usually considerable general depression, which is due to an abnormal temperature, the discom-

fort of breathing, and the effects of the absorbed pollen proteins on the system generally. Many of these cases are complicated with asthma, which increases the suffering of the patient. Relief is experienced when the supply of pollen from any cause is diminished or disappears, as after a frost or on a sea voyage. A continued rain affords relief.

As Feinberg (12) states in his book, the first essential in the successful management of a hay fever case is the correct diagnosis of the cause of the hay fever. It is necessary to know what the common causes of hay fever are in the patients' locality.

Next in diagnosis after taking the history and making clinical observations is the performance of the skin testing and therapeutic or clinical trial. Suffice it to say that the usual routine tests consist of the cutaneous scratch test.

TECHNIC OF THE CUTANEOUS (SCRATCH) TEST - Ninety-five per cent alcohol is applied to the skin of the volar surface of the forearm and allowed to dry (Fig. 1) in the following colored figures and plates.* For each test, a linear scratch about 1/4 inch long is made with

* The following colored figures and plates were taken from the Sharp and Dohme Seminar, Vol. 1, No. 2 by permission from the Editor, John Henderson, M.D.

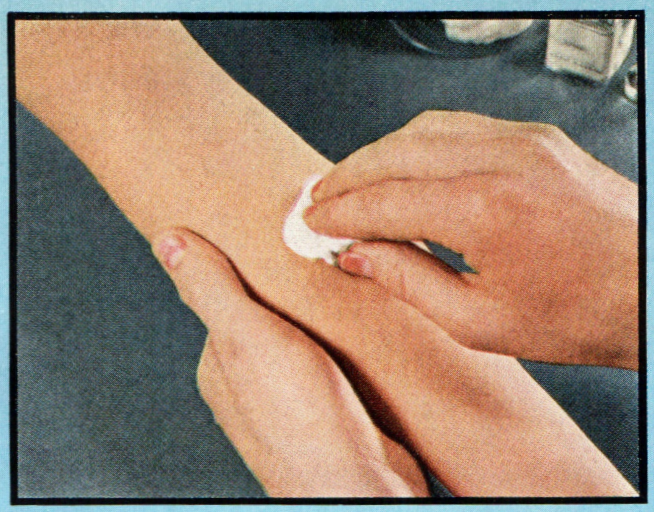

Fig. 1. Scratch Test: Alcohol is applied to the test area and allowed to dry.

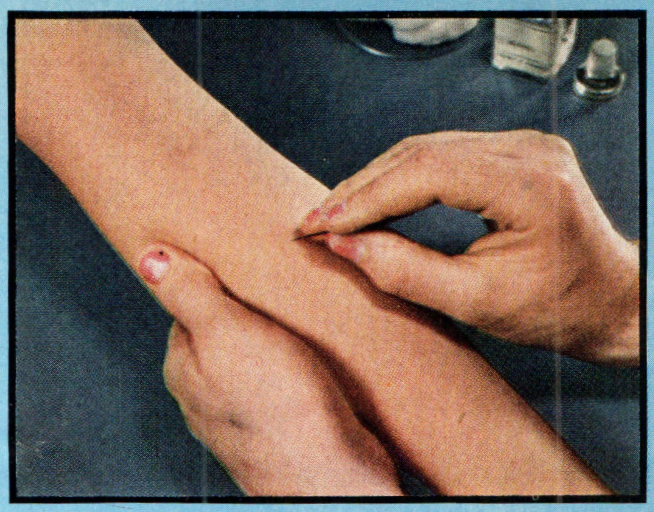

Fig. 2. Scratch Test: A linear scratch is made while holding the skin taut.

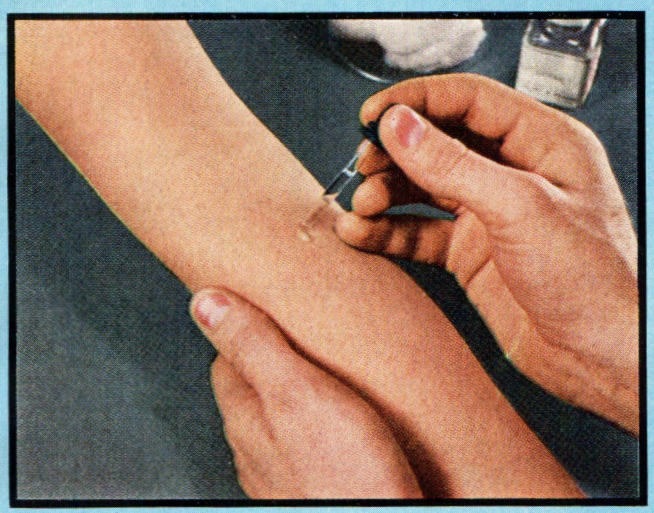

Fig. 3. Scratch Test: A drop of physiological salt solution is applied to the scratch.

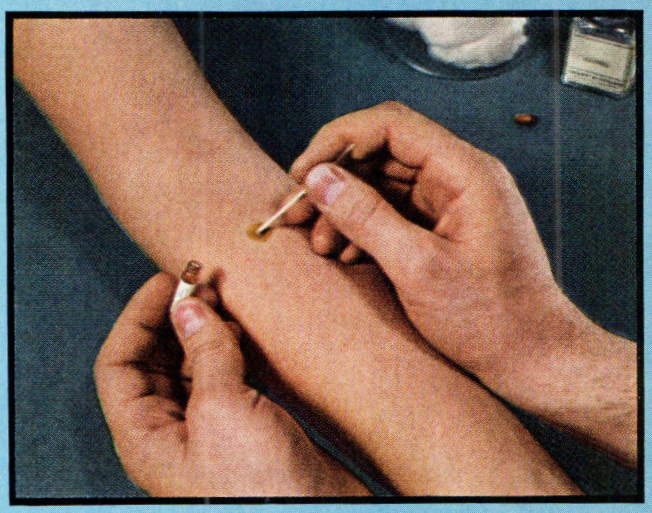

Fig. 4. Scratch Test: A small amount of test material is mixed with the drop of salt solution.

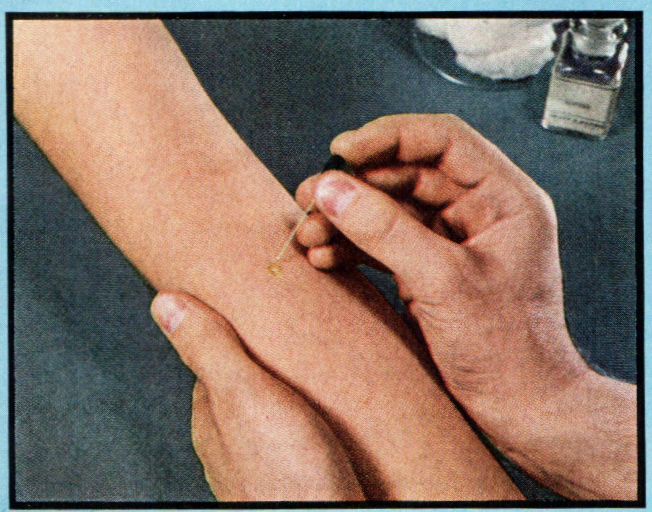

Fig. 5. Scratch Test: The contents of a capillary tube are expelled directly on the scratch.

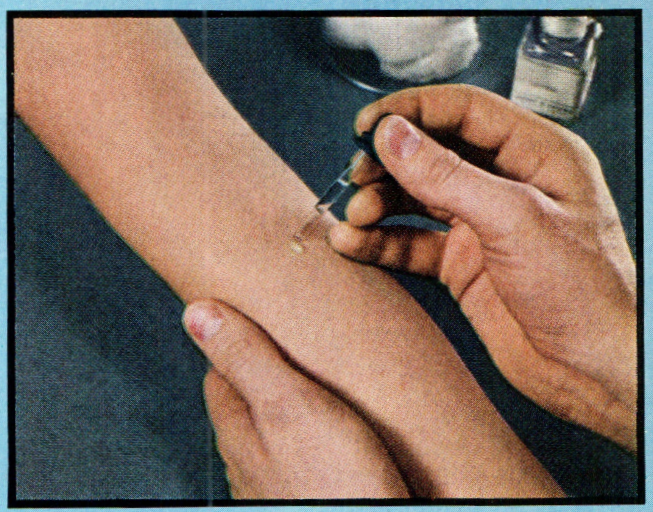

Fig. 6. Scratch Test: 50 per cent glycerin in physiological salt solution is applied to a scratch as a control.

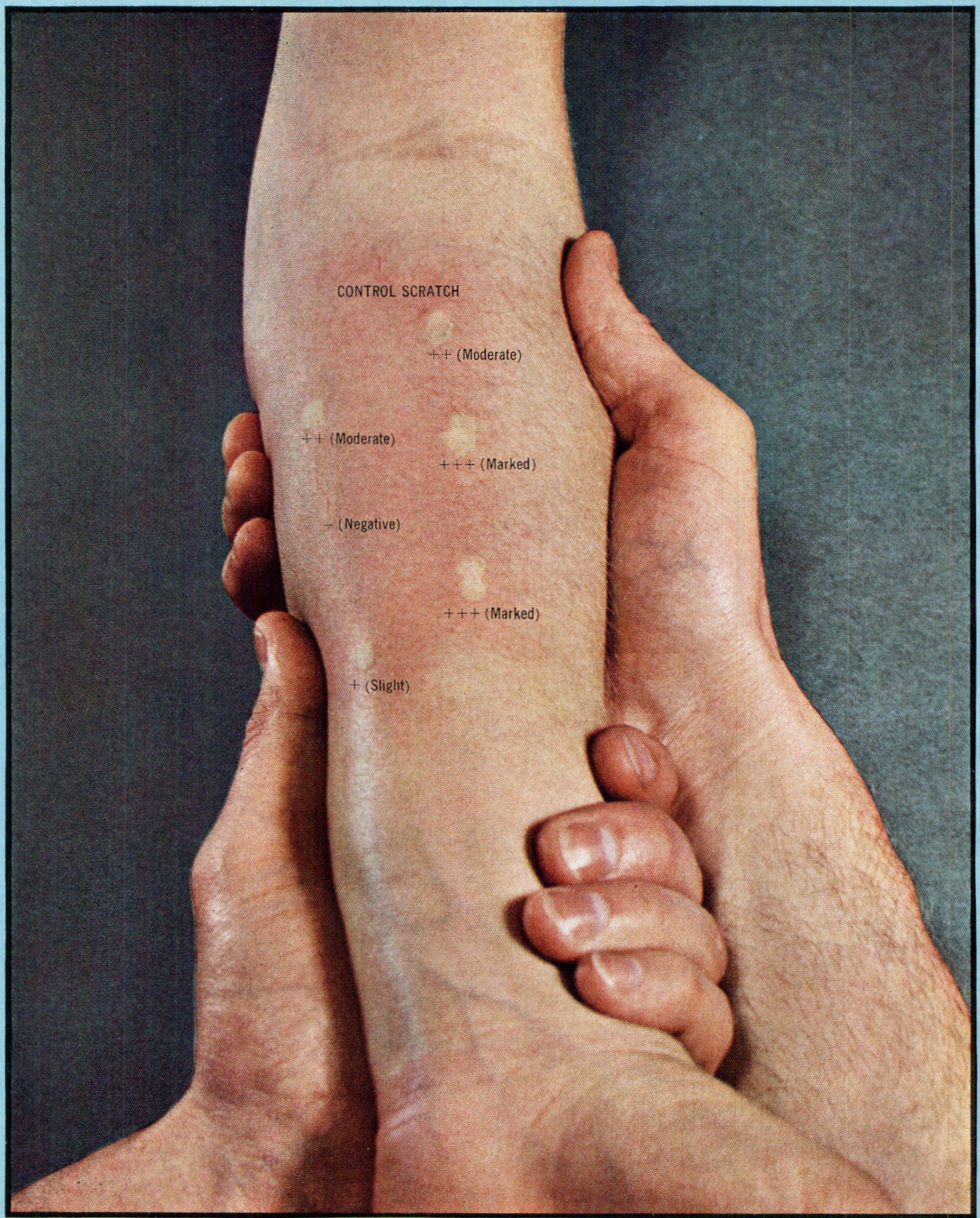

Plate A. Skin reactions obtained with scratch test method. (The skin should be held moderately taut, when reading test.)

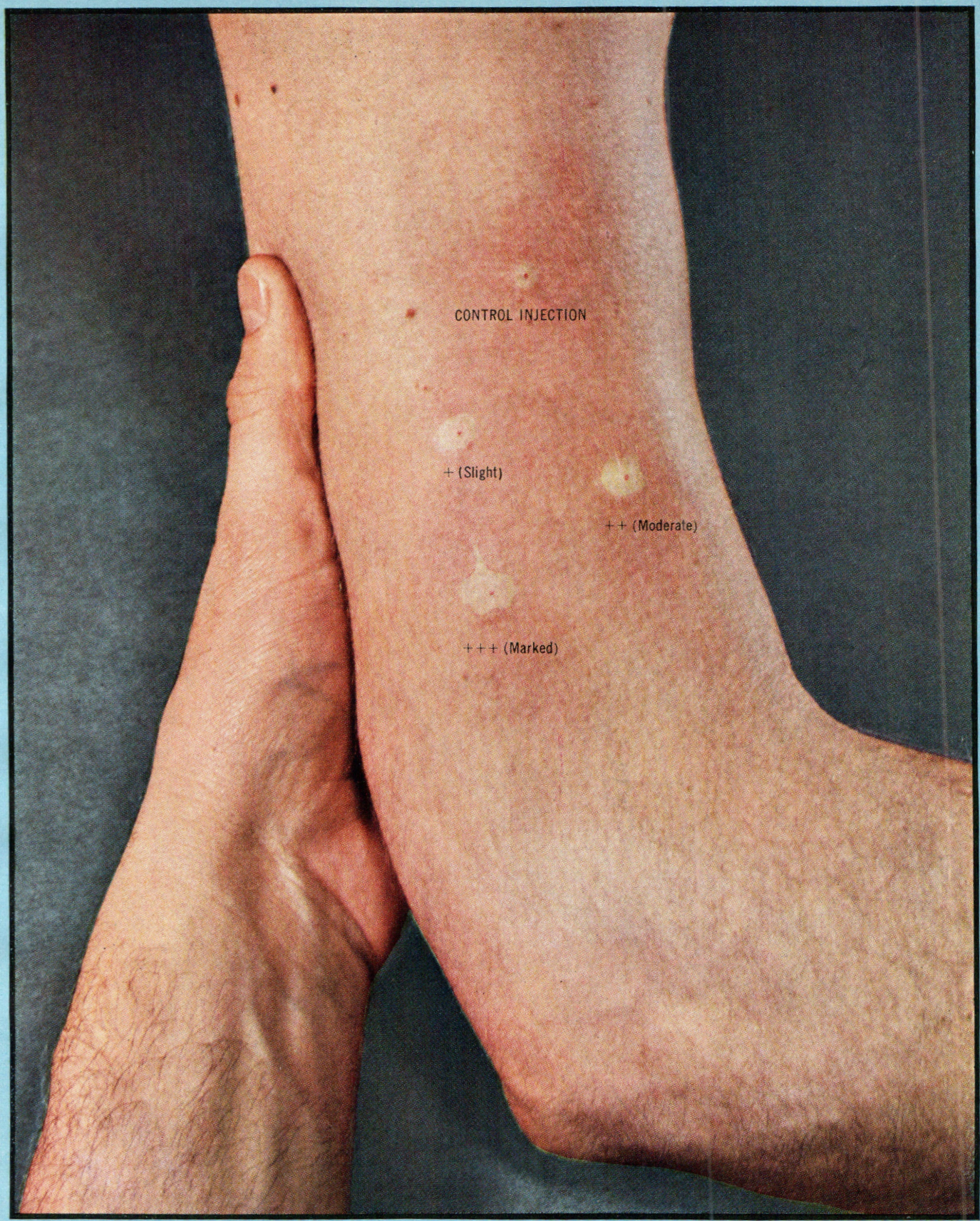

Plate B. Skin reactions obtained with the intradermal test method. (The skin should be held moderately taut, when reading test.)

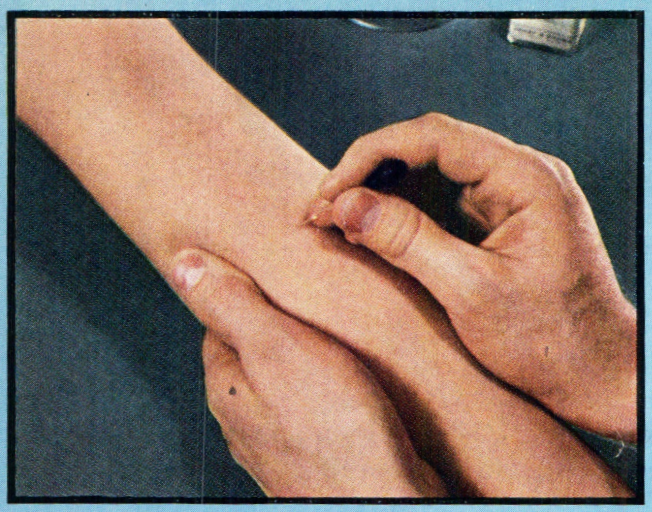

Fig. 7. Scratch Test: For scratch testing with 'Tube-Points,' scarifier-applicator, the scratch is made with the point of the tube.

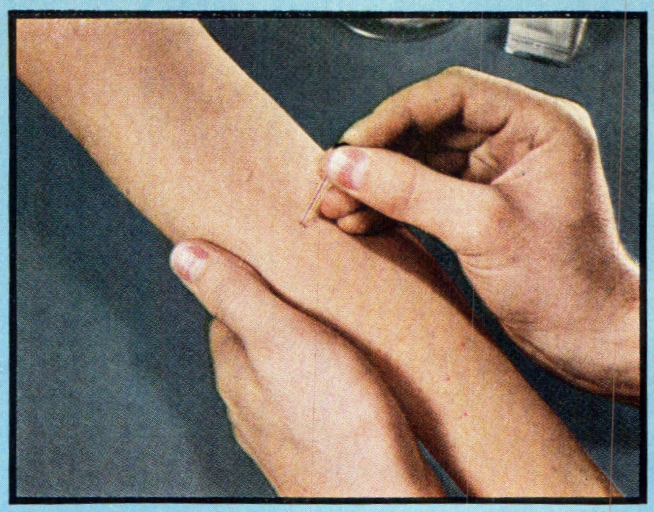

Fig. 8. Scratch Test: The contents of the 'Tube-Points,' scarifier-applicator, are expelled directly upon the scratch.

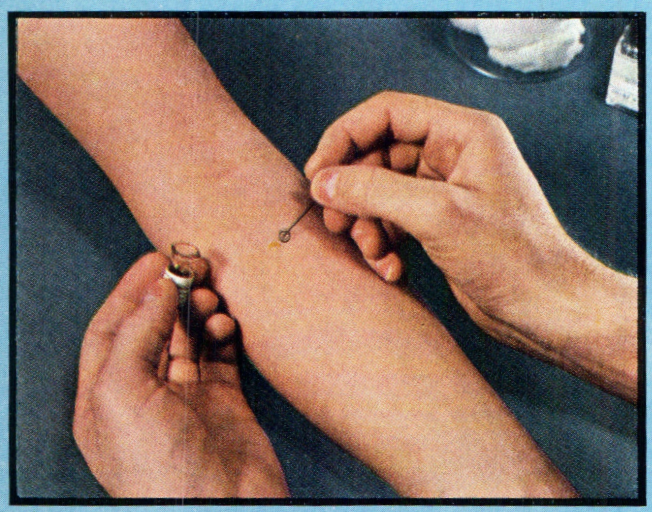

Fig. 9. Scratch Test: If the test material is supplied in a vial, it is transferred by means of a wire loop from the vial to the scratch.

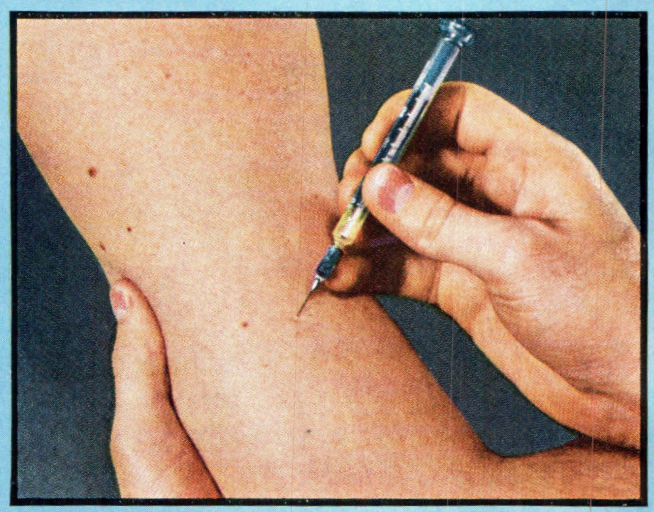

Fig. 10. Intradermal Test: The point of the needle is engaged in the superficial layers of the tautly held skin at an angle of 45 degrees.

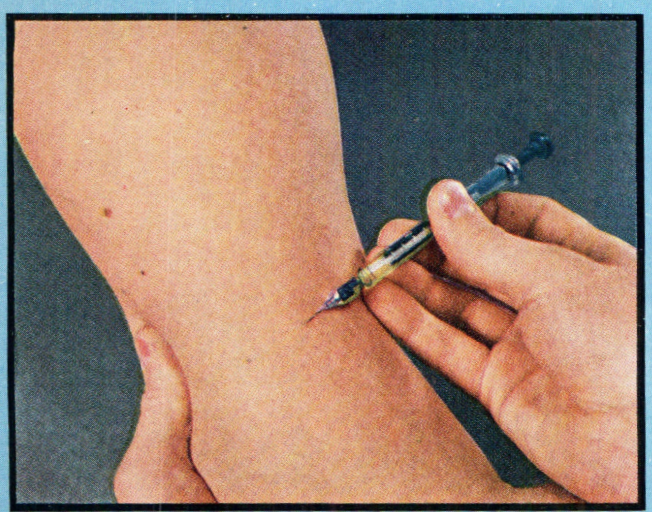

Fig. 11. Intradermal Test: Holding the needle parallel to the arm, it is inserted so that the bevel remains visible through the thin layer of epidermis covering it.

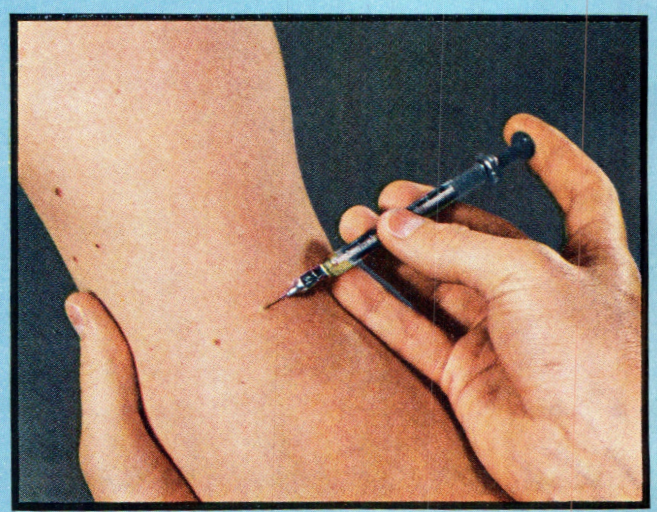

Fig. 12. Intradermal Test: Tension on the skin is relaxed and 0.02 cc. of test material is injected.

a needle, dull scalpel, or other especially designed instrument; care should be taken not to penetrate too deeply (Fig. 2). The scratch should go only through the surface layer of the skin, and not draw blood. One scratch for each series of tests serves as a control.

To each scratch, a drop of physiological salt solution is applied (Fig. 3). Using a small blunt instrument such as a toothpick, thoroughly mix a small amount of the test material with each drop of the salt solution (Fig. 4), except the one which is to serve as the control. A separate toothpick must be used for each test. If a capillary tube of pollen extract is employed for testing, the material is expelled from the tube onto the scratch (Fig. 5). If a control is desired a mixture of fifty per cent glycerine in physiological saline may be applied to one scratch (Fig. 6).

READING THE SCRATCH TEST - Scratch tests are read in 15 minutes after the application (See Plate A). If however, there is a marked reaction at any site prior to that time, the material causing the reaction should be immediately wiped off with a piece of gauze.

Positive reactions are distinguished by being more swollen than the control, and present a wide zone of erythema. Strongly positive reactions show a large

whitish raised center or urticarial wheal, which may have irregularly protruding borders (pseudopods). Moderate reactions display the same characteristics to a lesser degree. Mild reactions exhibit erythema, with or without a small wheal. Negative reactions are similar to the control scratch.

TECHNIC OF THE INTRADERMAL TEST - Diagnostic testing may also be carried out effectively by means of the intradermal method. The intradermal test with clinically standardized test extracts is especially valuable for the diagnosis of more obscure allergies and sensitivity to foods.

The test is made by injecting 0.02 cc. of test material into the skin, using a No. 26 or No. 27 guage needle. A more detailed description is found beneath Figures 10 to 12.

READING THE INTRADERMAL TEST - The intradermal test is read ten minutes after completion. (See Plate B). A positive reaction is characterized by an urticarial wheal at the injection site, surrounded by a zone of erythema. If the reaction is negative, there is no erythema, no itching and only slight elevation.

PART IV

THE TREATMENT OF SEASONAL HAY FEVER

Prophylactic

Since heredity is a most potent factor in determining the onset of hay fever, it would seem that hay fever disease could be reduced by discouraging intermarriage between allergic people or even the marriage of any allergic person. From the practical standpoint this, however, is not successful.

Feinberg (12) discusses the prophylactic treatment in his book stressing that nose or throat operations during, or immediately before, the hay fever season should be avoided. Anything that decreases the amount of pollen inhaled reduces the hay fever symptoms. The simplest advice is to stay indoors, avoid rides in the country, supply filters for your house, wear nose-filters or take a temporary trip to a locality free of the pollen causing the person's distress.

Specific

The principle of the specific treatment of hay fever is the immunization by hypodermic injection or oral ingestion of gradually increasing amounts of the pollen to which the patient is sensitive. The first amounts are very small. As the patient attains an

increasing tolerance to it, the amounts are increased until finally at the time his hay fever is at its height the person can be exposed to large amounts of pollen without having ill effects. The first essential in pollen treatment is the selection of the proper pollen to be used. The pollen selected must fulfill the following requirements: it must be wind-borne, it must be spread during the season in which the patient's symptoms occur, the plants must be in the patient's environment and be there in sufficient numbers, and there should be a positive diagnostic test.

1. Cutaneous injection method - the first report of the subcutaneous method of treatment of hay fever was made by Noon (10) in 1911. This was a pre-seasonal injection treatment which brought fair results. About seventeen years ago Duke (15), Phillips (16), and Thommen (17) were the first to report coseasonal intracutaneous treatment. Phillips (16)(18) reported his first observations in 1926 and submitted a further report in 1933 on a group of 322 patients treated over a period of six years. Satisfactory results were obtained in 91 per cent. Twelve general reactions occurred out of 625 injections. Phillips used an initial dose of 0.02 cc. of the 1-5,000 solution.

Doses were increased until a dose of more than 0.17 cc. was needed, then the dosage was divided and given in two sites. In 1932 and 1935, Anderson (19)(20) reported on a group of 350 patients, in which 299 never received a total of more than 0.10 cc. of a 1-4,000 solution. All treatments were given by the intracutaneous route at intervals of one day in severe cases and every ten to fourteen days in mild cases. Anderson recommended for the first injection 0.1 cc. of a 1-40,000 dilution.

Matzger (21) also treated patients with the intracutaneous method until the patient was symptom-free and continued either subcutaneously or intracutaneously as needed.

Hausel (22) in his review on coseasonal treatment stated that Harris advocated daily injections until relief was obtained, and then injections every two or three days. He gave a 0.01 cc. initial dose of 1-10,000 dilution. A combination treatment of intracutaneous and subcutaneous injections was used by Davidson, according to Hausel (22). Davidson started treatment with the strongest dilution the patient could stand. He noted that patients could stand a stronger solution intracutaneously than subcutaneously.

Stoesser (23) reported the results of treating

413 children with seasonal hay fever from 1936 to 1941 at the outpatient dispensary of the University of Minnesota College of Medicine. Of this number 180 began their symptoms before the age of 5 years. The long preseasonal and perennial forms of pollen therapy gave best results. Coseasonal treatment was unsatisfactory. He also tried oral therapy with pollens, histaminase orally, and potassium chloride and Coli metabolin with poor results in all.

Markow and Rosen (24) made a comparison of two forms of treatment in 1940. In the perennial group of 118 patients, there were satisfactory results in 87 per cent. In the preseasonal group of 70 patients there were 77 per cent with satisfactory results. In those patients receiving their third to eighth consecutive year of treatment, the perennial method yielded results superior to preseasonal methods.

Tests have been made by varying the composition of the solution used for injection. Wenkenwerder (25) treated 57 ragweed patients preseasonally with extract made of short ragweed pollen granules which had first been disrupted in the ball-mill. The results were as good, but not superior to the results obtained in a control group of 57 treated the same season with a

buffered extract (Coca solution) made from defatted but intact cells of the ragweed pollen.

Natermann (26), in an attempt to improve the injection treatment, precipitated the active material of pollen extract by using tannic acid, and the precipitate was taken up in buffered saline to make a suspension which would be slowly absorbed after injection. Natermann treated 77 ragweed sensitive patients this way. Ninety per cent had good or excellent results.

Spain et al (27) states that the disadvantages of injection therapy for hay fever are due in many instances to too rapid absorption of the antigen. He treated 95 adult patients with pollen extract containing gelatin. A greater tolerance for this new extract was noted, higher maximum doses were given with fewer injections, and constitutional reactions were infrequent and mild. A control group of 95 patients was treated with the standard aqueous extract. Spain decided that the chief value of the gelatin extracts is in the treatment of hay fever cases so sensitive as to accept poorly the usual aqueous pollen therapy.

The preceding reports showed that satisfactory relief can be obtained by injection methods of treatment. Systemic reactions may occur during the course

of the hay fever treatment. They may be of a hay fever, asthma, or marked generalized urticaria. The prompt use of some form of adrenalin will relieve it. It has been agreed by most physicians that 65 to 85 per cent relief can generally be expected in the average case by the injection method of treatment.

2. Oral administration of the pollen - This is the other form of specific treatment for hay fever. Although this form of treatment dates back further than the injection method, it has only been in recent years that this method has been given a good test for its therapeutic value.

It is the purpose of the author to discuss the oral therapy in detail giving the entire history, development, and present day status of this means of treating hay fever.

The earliest report of suggesting oral pollen treatment for hay fever was given by Curtis (28) in 1900. Curtis had a patient with severe attacks of hay fever combined with an energetic spasmodic asthma, which completely prostrated the patient and lasted two weeks. He immunized his patient by giving internally the watery extract of a sterilized infusion of roses. In all, Curtis treated ten cases this way and claimed

remarkable results.

In 1909, Scheppegrell (14), although not treating his patients orally, had them snuff dried pollen into their noses two to three times daily to immunize them against hay fever. He made no mention of any gastro-intestinal symptoms.

Touart (29) of New York in 1921 treated six hay fever patients by ingestion of pollen protein in the form of a tablet triturate, salol coated for intestinal absorption, containing 0.1 mgm. of protein for each indicated pollen. It was administered daily on a fasting stomach. Where possible, the treatment was begun ten weeks before the attack was due and continued up to the date of pollination, otherwise, it was administered during the season. Of the six patients, one of them having the late type of hay fever obtained complete relief; two of the early type obtained relief of symptoms already begun; one of the early type obtained relief from asthma and about seventy-five per cent relief from symptoms already begun. Two of the late type previously treated preseasonally by hypodermic method without relief did not benefit either by ingestion of the antigen.

It was Touart's belief that insufficient doses

were used, and that a much larger amount of antigen could be administered by mouth without producing any unfavorable effects.

Black (30), in 1927, treated himself with pollen extract of giant ragweed. The initial dose was .1 cc. of 5 per cent extract diluted with approximately 200 cc. of water and taken on an empty stomach with the belief that it would be passed rapidly into the intestine without stimulating gastric secretion. The dose was increased by doubling it until 1.0 cc. was reached after which .1 cc. increments were used. The total amount taken was 34.5 cc. in seven days time. His summary was to the effect that this treatment was apparently devoid of danger and caused no unpleasant symptoms, and that an appreciable amount of pollen was absorbed as shown by its presence in the circulating blood and its elimination in the urine. That some of it was not absorbed was shown by its presence in the feces.

In 1928, Black (31) reported administration of ragweed pollen orally to patients at the onset of their symptoms. The extract was dispensed in dropper-stopper bottles. The initial dose was 10 drops of 1-20 extract and each succeeding dose was increased by 10 drops

until 60 drops were being taken at a dose. The extract was dropped into a glass of water, stirred well and drunk. Black also treated 61 patients hypodermically. The hypodermic extracts were made with 46 per cent glycerin in 7 per cent sodium chloride, as recommended by Stier. The results with hypodermic therapy were better than those with pollen given orally. Six patients treated orally complained of nausea, diarrhea and abdominal distress.

In 1937, Stier and Hollister (32) reported satisfactory results in 78 per cent of 383 hay fever patients treated orally over a period of three years. Their best results were obtained with the coseasonal method of oral administration. The pollens used consisted of a large variety but did not include ragweed pollen. The doses consisted of 3 drops of 1-100,000 dilution of pollen to a maximum dose of 21 drops of 1-100 dilution. Most of the patients required a quantity of the 1-100 dilution daily. When too large doses were administered orally the patients in a few cases complained of diarrhea, irritated eyes, nausea, headache, stuffy nose, dizziness and eczema. Stier and Hollister treated about the same number of patients with the parental method. The advantages seen in the oral therapy by these men

were: 1. The oral administration of pollen extracts gives comparable results with those of cases treated by hypodermic methods.

2. It is easy to administer. Should appeal to children.

3. Gives a wider margin of safety.

4. May be home treated.

5. Doses may be individualized.

The fact that a number of hay fever sufferers claimed they obtained relief by eating honey produced in their vicinity led McGrew (33) to suspect, in 1936, that the pollen in the honey was responsible for the results. He therefore tried oral pollen therapy. A 1 per cent extract of pollen was employed coseasonally, 1 to 10 drops being given three times daily for the immediate relief of an individual attack.

McGrew noted that when too much oral extract was taken, an increased intensity of the hay fever symptoms was noted in most cases, with an occasional case of mild urticaria. In either instance, the number of drops per dose was reduced to the number of drops giving the most relief from symptoms within an hour. No other reactions were noted. Of 33 patients thus treated, 29 were improved. He also reported that the extract retained its potency in dark bottleskept in a refrig-

erator for at least a year.

Barksdale (34), in 1936, also reported favorable clinical findings following the administration of oral pollen extract for hay fever.

Rockwell (35) states that all hay fever treatment, whether it be perenial, preseasonal, or coseasonal, resolves itself into seasonal treatment. By this is meant that it is absolutely necessary in all methods to give frequent doses of the pollen extract during the hay fever season. In oral therapy it appears that the beneficial effect of a dose does not last as long as a hypodermic dose, according to Rockwell. Hence, he continues, in oral therapy more frequent doses are required during the hay fever season. It was his belief that if the build-up doses are completed by the beginning of the hay fever season, and if the maximum dose is sufficiently large and administered often enough, most of the patients will be kept free from symptoms. At that time, he believed, that under those conditions results would be obtained comparable to the injection method and superior with respect to convenience, absence of severe systemic reactions and lower cost of treatment.

Rockwell's (35) method of oral pollen therapy

differed somewhat during the three seasons in which he administered it. During the third year, 1937, he gave dry ground pollen in capsules. The beginning doses were 500 pollen units (15 mgm.) and the maximum doses 120,000 units (120 mgm.). Treatment was given either preseasonally or coseasonally. In the preseasonal method the doses were given once or twice weekly until the pollen season, then several times weekly. In the coseasonal method doses were given three times daily until symptoms were controlled, and then several times weekly, or as often as was necessary to control symptoms. In the ragweed cases the satisfactory results with preseasonal method were:

1935.....66.6%
1936.....58.4%
1937.....61.5%

The coseasonal method during 1937 produced 75 per cent satisfactory results, and only 2 individuals had urticarial reaction. About 10 per cent of the cases complained of some degree of malaise.

The amount of extract to use in oral therapy is still a debatable question. Also, another question of raised is, "Does the cutaneous reaction remain the same throughout the treatment?"

Rackemann (36) believes that the successful treat-

ment of hay fever patients will regularly result in a reduction of the size of the cutaneous reaction.

Baldwin and Glaser (37) found a reduction in half their patients. The degree of sensitivity was also reduced, if the patient was clinically improved.

Urback (38) published a communication in which he claimed to have obtained satisfactory results in hay fever by use of peptones of the specific pollen administered orally. He also reported similar results with the use of peptones made from the entire pollinating flower.

Bernstein and Kirsner (39) in 1937 administered 5 grain capsules of ragweed pollen orally, and were unable to demonstrate enteral absorption sufficient to cause a reaction in the passively sensitized skin of four non-allergic persons. They also corroborated previously recorded observations that digestion of pollen by gastric juice caused only a moderate diminution of cutaneous reactivity of ragweed pollen.

Bohner (40) in 1938 fed ragweed pollen in large quantities to 21 patients orally, and 13 were relieved. He also treated 21 other patients with subcutaneous injections and 16 were relieved.

London (41) using a combined oral and subcutaneous

treatment for ragweed pollinosis concluded that patients adequately treated by the subcutaneous method can expect no further benefit from the supplementary oral administration of pollen.

In 1938, Zeller (42) treated 22 patients preseasonally with oral pollen, and 20 per cent obtained good results. Of the five obtaineng good results, two had had from 3 to 4 years of good results, two had had poor results from hypodermic therapy. In the discussion of Zeller's paper, Vaughan mentioned that he obtained relief by the oral method in 10 to 20 per cent of his cases treated preseasonally.

Levine and Shulsky (43) report that work done in 1938 showed that in children better results were obtained by oral therapy than in adults. They noted excellent results in 8 of 10 children treated for uncomplicated fall hay fever by the oral route.

In 1940, Levine and Shulsky (43) made a comparison of parental and oral therapy. Two groups of patients were studied. One group of 13 received ragweed pollen extract hypodermically and the other group of 10 received extract orally. Patients were between 8 and 13 years of age giving typical histories of ragweed hay fever and had not been previously treated.

Oral pollen treatment was an initial dose of 1/256 grain of mixed short and giant ragweed pollen. The dose was doubled each day until 2 grains of mixed pollen were being given twice a day. There were very few untoward reactions. These consisted of nausea or mild abdominal pain in a few of the children.

Hypodermic treatment used was an extract of equal parts of short and giant ragweed prepared in 5 per cent alkaline glucose solution using .4 per cent phenol as a preservative. An attempt was made to reach a dose in excess of .5 cc. of 3 per cent pollen extract (30,000 Noon units per cc.). The top dosage was then continued until after the peak of the pollen season at three to seven day intervals.

Results

	Hypodermic	Oral
Excellent	7	2
75 per cent	3	4
50 per cent	3	2
No improvement	0	1
Stopped Rx.	0	1

Bernstein and Feinberg (44) reported on a group of 20 patients with ragweed hay fever and asthma who were given oral doses of pollen extracts, beginning with 1 drop of 1-33 dilution and reaching a maximum of 10 to 30 drops three times daily. Eighteen did not benefit and 2 obtained moderate relief. These men felt they

were justified to conclude that in ragweed hay fever in the middle west, coseasonal oral pollen therapy is of little value.

In going over Bernstein's and Feinberg's report, the author noted that four of the 20 patients were treated six days or less and no improvement resulted. The majority of those with the most severe reactions of nausea and cramps occurred in patients treated only 4 to 11 days. Only 2 of the 20 patients were treated for more than 15 days. This might be evidence for believing that preseasonal therapy and smaller doses are in order. Twelve of the same twenty patients were also treated with hypodermic therapy and they were unrelieved.

In 1939, Black (45) reported that of 40 patients treated orally in 1938, results were as follows:

2 - Nausea and abdominal distress.
4 - Excellent results.
12 - Good results.
6 - Poor results.
18 - Failure (no improvement).

Of this group, 40 per cent got satisfactory results. He states that oral therapy, for ragweed hay fever, does not compare favorably with results obtained by hypodermic treatment. In 3 patients, it was found that the oral administration of pollen made it possible to

increase the hypodermic dosage much more rapidly than it could be done before pollen was administered orally.

In 1940, Foran and Lichtenstein (46) reported the results of treatment of thirty two patients with oral pollen for ragweed pollinosis. A similar group was treated parentally. Of those treated orally, 25 per cent were improved, as compared with 56 per cent of those treated parentally. Severe G. I. symptoms were in 12.5 per cent of those treated orally, and the same percentage in the parentally treated ones.

Schwartz (47) reports extremely satisfactory results in a group of sixty-five patients treated orally in the region of El Paso, Texas. The treatment was, in most cases, coseasonal, and consisted generally of a mixture of equal parts of Bermuda grass, careless grass, and Russian thistle extracts. In some cases, other extracts were added to the mixture. The usual starting dose was 1 drop of the mixed extract in a concentration of 1-100, given well diluted two or three times daily. The dosage was increased by 1 or 2 drops daily until the symptoms were controlled. The dosage which controlled symptoms ranged from 2 to 17 drops of the extract twice daily, and averaged from 4 to 6 drops two or three times daily.

Of the sixty-five patients treated, twenty-six received complete relief and thirty-one had satisfactory results; 85 per cent were satisfactory in securing relief.

From the foregoing reports, it is seen that no unanimous agreement has been reached as to the specific type of therapy which should be used for seasonal hay fever.

Eyermann (48) considers the factors which are to be evaluated before the efficacy of any therapy can be determined. He discusses the variability of pollen counts, and the influence upon them by meterologic conditions, such as rain, wind direction and velocity. He also points out that symptoms may vary due to auto inoculation. Other allergens than pollen may be contributing to the patient's disconfort and so interfere wihh properly evaluating the therapy being used.

The question of digestion of the pollen preventing its absorbtion is still a contoversial one. Grove and Coca (49), Black (50), Black and Moore (51), and Bernstein and Kirshner (39) believe that the active principle of pollen is not destroyed by peptic or trypeptic digestion, while Caulfield, Cohen and Eadie (52), and Moore and Unger (53) claim that it is destroyed.

MacQuiddy (54) in his search for pollen in the stool, also stained pollen with carmine and noted that the pollen recovered in the stool showed very little trace of the stain. While not conclusive, MacQuiddy believes that some digestion occurrs while pollen is passing through the alimentary canal.

MacQuiddy has been treating hay fever patients with oral pollen extract since 1940 and the following Part V of this thesis discusses his treatment in detail, giving the latest clinical reports available to the author.

PART V

A REPORT ON ORAL POLLEN THERAPY OF 130 PATIENTS

The successful treatment of seasonal hay fever in Nebraska and the neighboring mid-western states has been an important and also difficult task. Early in 1940, E. L. MacQuiddy, a member of our staff, began a series of tests to determine the value of oral therapy. His reason for starting trials of oral therapy was that there were too many objections to the parental method of treatment. The disadvantages to the parental method were: 1. There is considerable danger inherent to this method unless dosages are carefully chosen and the patient is watched at least twenty minutes after each injection.

2. The method requires from fifteen to thirty visits to a doctor's office or to a clinic. While to some doctors this may not be objectionable, it is at least quite a task for the patient.

3. The cost of this form of treatment is necessarily high and because of this and the fact that there is considerable danger of reactions, too many of the hay fever sufferers are not receiving treatment.

In selecting one method of treatment for trial, MacQuiddy felt that the oral administration of the extract had certain distinct values inherent to other methods. In dispensing the solution it is possible for the patient to take out measured doses in drops. They can measure out each dose in turn. If reactions occur it is easy for the patients themselves to drop the dosage back. This method also lends itself easily to the mixing of several types of pollens and extracts. The elasticity of this method makes it a desirous one to use and it is because of these facts that he choose this particular method.

Each patient was skin tested by the scratch method and a treatment set of three bottles of extract prepared. Solutions were made up in 1-33, 1-100, 1-1,000 and 1-10,000 dilutions. One cubic centimeter of the 3 per cent solution contained approximately 100,000 units of pollen. Thus:

1 cc. of 1-100	=	33,000 units
1 cc. of 1-1000	=	3,300 units
1 cc. of 1-10000	=	330 units
1 gtt. of 1-10000	=	20 units

Instructions for taking the pollen extract were given to each patient in the following form:

"Place one drop of the 1-10,000 dilution, which is bottle number one, in a glass of cool water, and

take about twenty minutes before breakfast. On the second morning take two drops, increasing one drop each day until ten drops have been taken.

After finishing the first bottle, repeat in the same manner with the 1-1,000 dilution, which is bottle number two. Continue in the same manner with the 1-100 dilution, which is bottle number three.

If you experience any reactions, such as abdominal cramps, excessive sneezing, or discharging nose, do not increase the dosage but repeat the same as the previous day. Do not increase until the symptoms have passed. Please make a note on the accompanying chart".

The chart given to each patient to record the number of drops taken each day, is as follows:

Name: Age: Sex: Occupation:
Type of Hay Fever: Duration:
Residence (past) (present)
Family History:
Asthma:
Previous Treatment: Results:
Associated Pathology:
Associated Reactions:
Treatment:

Date	1-10000	Date	1-1000	Date	1-100	Date	1-33
____	____	____	____	____	____	____	____
____	____	____	____	____	____	____	____
____	____	____	____	____	____	____	____
____	____	____	____	____	____	____	____
____	____	____	____	____	____	____	____
____	____	____	____	____	____	____	____
____	____	____	____	____	____	____	____

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___ ___	___ ___	___ ___	___ ___
___ ___	___ ___	___ ___	___ ___
___ ___	___ ___	___ ___	___ ___

Results: Fair ( ) Good ( ) Complete relief( )
No relief( )

Total Units Taken:

In 1940, MacQuiddy and his associates selected a group of twelve cases. The results of oral therapy were quite satisfactory. In 1941, he treated 80 cases by the oral route with satisfactory results again.

In 1942, MacQuiddy selected a group of 160 cases of seasonal hay fever. There were reactions to 17 different specific pollens in this group. Ten of the patients were given their treatment at the University Hospital Allergy Clinic. The rest were MacQuiddy's private patients.

The author worked with MacQuiddy in preparing a report on these patients. Of the 160 patients who received the oral pollen extract, we received reports from 130 cases. A good many of the patients were treated for more than one type of hay fever. We divided this treatment into another two groups. One group was composed of patients who had taken extract up to only the 1-100 dilution and the second group was made up of those whose treatment included the 1-33 dilution extract.

The following tables are our results:

EARLY SPRING	Failure	Fair	Good	Complete Relief
Blue grass	0	1	5	1
Timothy	0	0	4	1
Crab grass	1	0	6	0
English plantain	0	1	1	0
LATE SPRING				
Lamb's quarter	4	2	9	2
Pigweed	2	1	6	2
EARLY SUMMER				
Hemp	9	15	15	0
Russian thistle	3	6	10	0
FALL				
Ragweed (G,S, and W)	20	24	38	2
Cockleburr	2	2	2	0
Kochia	3	3	6	1
Burrweed marsh elder	5	5	8	0
Western water hemp	1	0	2	0

The seasonal groups evaluated in percentages were:

	Failure	Fair	Good	Complete relief
Early spring	5%	10%	75%	10%
Late spring	21%	10%	56%	13%
Early summer	20%	36%	44%	0%
Fall	25%	27%	45%	3%
1-100 dilution (85 patients)	22%	25%	49%	4%
1-33 dilution (45 patients)	28%	26.5%	45.5%	0%

After treating more than 200 hay fever patients with the oral pollen extract, MacQuiddy feels that the results justify continued work and trial with this method of treatment. The relief of hay fever symptoms is about equal to the injection method, and with the definite advantages which the oral method has over the parental, it is the hopes of those using the oral method that it will in the near future replace the injection method.

G. N. Best of Council Bluffs, Iowa, who is also a member of our staff, treated 8 patients with hay fever by oral pollen extract. Two patients reported excellent results, three estimated relief at 75 %, and two reported about 50 % relief of symptoms. One patient could increase her dosage no further than 1 drop of the 1-100 dilution, suffered cramps and diarrhea, and reported the entire seasonal treatment as unsatisfactory.

The oral method of treatment is now confronted by a new difficulty, namely, that the mixing and dispensing of the extract at the physician's office is too difficult and time-consuming. At the present time it is difficult for the physician to employ a person capable of mixing and dispensing the oral ex-

tract and as a result, action is being taken to have a local drug firm mix and dispense the extract at the physician's order.

The report of the oral treatment of 130 hay fever patients, although unpublished to date, was presented by E. L. MacQuiddy in the fall of 1942 at the Omaha Midwest Clinical Society held in Omaha, Nebraska

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