AQUA IVY

Toxicity Studies on the Guinea Pig and Treatment of Sensitive Cases

Richard E. Passenger, M.D., Will Cook Spain,† and Margaret B. Strauss, M.S., New York, N. Y.

INTRODUCTION

HYPERSENSITIVENESS to poison ivy develops only after sufficient contact with the leaves or plant parts. Straus[1] reported that 70 per cent of the United States population was sensitive to poison ivy, whereas Heinbecker[2] found no incidence of hypersensitivity among the Eskimos, who never come in contact with it. Deibert[3] found that the American Indians were as susceptible to poison ivy as were the white peoples. Since the American Indian is believed to be closely related to the Eskimos, the difference in incidence of sensitivity to poison ivy was probably due to the great differences in contact with the plant.

Straus[4] reported that feeding the ivy extract alone did not produce cutaneous sensitization, whereas he had previously demonstrated sensitization of newborn infants to poison ivy by means of a cutaneous patch test, or by combined ingestion and cutaneous patch test. He also showed that subcutaneous injection did not produce sensitization; only one of ten infants so treated became sensitized, whereas 73 per cent of forty-eight infants showed sensitization after cutaneous application of an ivy paste.

Ivy leaves or ivy paste applied to nonsensitive persons required ten to twenty-one days for sensitivity to be shown. This was then referred to as a state of hypersensitivity, and it was noted that the incubation period agreed with that found in other types of hypersensitivity. This evidence of an incubation period was first demonstrated by Nestler[5] in 1904 and Low[6] in 1912, and it was confirmed by Field and Sulzberger[7] to be about ten days.

The usefulness of prophylactic therapy for ivy dermatitis by a series of injections or oral doses of ivy derivatives has been reported by many workers. Although the presence of antibodies has not been demonstrated in man and a decrease in skin reactivity has not been noted,* many physicians feel that a refractory state can be produced in patients previously sensitive to contact with Rhus oleoresins and clinically exhibiting dermatitis due to poison ivy or poison oak. The following reports indicate that this can logically be called a

From the Division of Allergy, Department of Medicine, Post-Graduate Medical School, and University Hospital, New York University–Bellevue Medical Center.

Received for publication Aug. 23, 1955.

†Deceased.

*After this paper was submitted for publication, Kligman, of the University of Pennsylvania Medical School, reported that hyposensitization occurred after treatment of ivy-sensitive persons with pentadecylcatechol. However, he encountered many severe reactions, which were difficult to control, when dosages sufficient to cause hyposensitization were administered.

process of immunization or hyposensitization, even though the knowledge of the mechanism is lacking. It is in this broad sense that we (and others) use the word *immunity*. For example, Spain and Cooke[8] wrote: "Although the patient received daily oral treatments for the first five months and regular weekly injections for the next eight months, no change whatsoever in the reaction of the skin was apparent; and, since the result clinically was successful, it must be concluded that the degree of immunity developed by treatment cannot be determined by any change in the cutaneous reaction. This condition is, of course, analogous to that found in hay fever."

ORAL ADMINISTRATION

The American Indians chewed the young tender leaves of the poison ivy plant because of its beneficial effect in preventing ivy dermatitis.

Schamberg[9] described successful immunization by oral use of a tincture of *Rhus toxicodendron* in increasing doses.

Spain and Cooke[8] concluded that a satisfactory degree of clinical immunity to ivy poisoning can be developed by the administration in proper amounts of the active principle of Toxicodendron radicans, in the form of either oral treatments or hypodermic injections. They used a milk sugar tablet of the alcoholic extract of ivy for oral administration.

Shelmire[10] employed the ivy oleoresin diluted in corn oil in daily, gradually increasing doses. In taking liquid oral preparations, special care is necessary to avoid irritation of the lips or mouth.

Besser and Urbach[11] obtained very encouraging results with the oral administration of dried seeds of *Rhus toxicodendron* in capsule form.

Gold and Masucci[12, 13] used poison ivy tablets containing from 0.5 to 10 mg. of the poison ivy oleoresin per tablet. Daily treatment with increasing dosages up to 15 tablets of the 10 mg. ivy resin tablet through a total of forty-five days was reported. Seventeen of twenty-five ivy-sensitive patients responded favorably on controlled field exposure. However, 80 per cent of these patients developed toxic reactions during the second and third weeks of treatment. The concentration of oleoresin in their tablets was many times that used by other workers. An excess of the tincture or of oil of *Rhus toxicodendron* taken orally sometimes causes generalized pruritus, dermatitis, gastrointestinal disturbances, or pruritus ani.

Spain and Cooke pointed out that a daily dosage taken over long periods of time was necessary for satisfactory clinical results with oral therapy. It is very difficult for the average patient, unless constantly supervised, to continue his daily schedule of treatment. Therefore, the injection treatment is usually preferable.

PARENTERAL ADMINISTRATION

Spain and Cooke,[8] in 1927, advocated a schedule of treatment using the alcoholic ivy extract where small doses were used in the beginning and gradually increased. They felt that when the dosage was increased too rapidly, or the interval between injections was too short, a constitutional reaction could

occur. Their method developed a satisfactory degree of immunity. The alcoholic ivy was prepared by extracting 10 grams of the dried poison ivy leaves in 100 ml. of absolute alcohol. After extraction overnight, the extract was filtered and sterilized by filtration through a Seitz filter. All glassware and containers must be thoroughly dry, as moisture causes rapid deterioration of the active principle in the alcoholic ivy extract. This concentrated (10 per cent) alcoholic ivy extract is then diluted in absolute alcohol to dilutions of 1:5, 1:50, and 1:500. Immediately before use, this extract must be diluted in a 1 ml. syringe by diluting 0.1 ml. of the 1:500 alcoholic ivy with 0.9 ml. of sterile saline, mixing, and then administering 0.5 ml. subcutaneously. This dilution containing 10 per cent alcohol causes stinging upon injection. The next dosage would be 1.0 ml. of the same mixture, then this procedure is repeated for the 1:50 and 1:5 dilutions of alcoholic ivy.

Biederman[14] observed that 80 per cent of his patients (with positive patch tests and a history of Rhus dermatitis during at least two preceding summers) received complete protection from ivy and oak after treatment with the alcoholic ivy extract described by Spain and Cooke, whereas all untreated control patients developed dermatitis venenata as they had in previous years.

Molitch and Poliakoff,[15] in 1936, immunized forty boys who were proved by patch test to be susceptible to ivy poisoning. The alcoholic ivy extract of Spain and Cooke was administered in weekly injections. None developed dermatitis venenata during the twenty weeks of treatment with normal exposure to poison ivy. These same authors administered one or two prophylactic injections of commercial poison ivy extract in oil to fifty ivy-sensitive boys; seven developed Rhus dermatitis during the season, while the thirty-nine controls who were not immunized developed the dermatitis.

Strickler[16] reported good results with alcoholic ivy extract which he gave at twenty-four-hour intervals for three to five injections as phylactic treatment, followed by oral administration. "Cure" occurred after four injections, sometimes after two. No untoward results were encountered.

Templeton,[17] reporting on five cases with untoward reactions following poison ivy injections, states: "In spite of the few unfavorable cases, I am convinced that the specific antigenic treatment for dermatitis from the Rhus family is of great value. I have had no untoward reactions since I abandoned the larger doses, and my results seem to be equally good."

Clarke and Hanna[18] treated eighty-two boys from 14 to 18 years of age with the alcoholic iyy extract, with satisfactory results. Fifty-six had no poison ivy, nineteen had a rash which was less intense than the previous year, and seven had a rash as bad as or worse than the previous year.

Caulfeild[19] administered the ivy oleoresin in corn oil by intramuscular injection to ivy-sensitive patients in eight to twenty-six injections. He reported satisfactory reduction in quantitative patch tests and an increase in clinical immunity.

Clock[20] used almond oil as the vehicle for carrying the ivy oleoresin, and Keeney[21] advocated peanut oil.

The discussion of toxicity, which appears later in this article, will indicate that the oily ivy preparations have usually been involved where adverse effects were reported.

Strauss and Spain[22] reported good clinical results following treatment with an alum-precipitated pyridine ivy preparation suspended in aqueous solution. This preparation was named Aqua Ivy,* because all previous ivy extracts used either an oil or alcohol as the vehicle in which the oleoresin was dissolved, but this preparation contained the active ivy principles as an alum-precipitate suspended in an aqueous solution.

The Aqua Ivy is prepared by first extracting 10 grams of dried ivy leaves in 100 ml. of pyridine, a weakly basic tertiary amine. After extraction for twenty-four hours, the 10 per cent pyridine-ivy extract is filtered off and Seitz filtered. This pyridine-ivy extract is the stock solution from which the alum-precipitated pyridine-ivy suspension is made. Under sterile conditions, 100 ml. of the 10 per cent pyridine-ivy is mixed with 250 ml. of distilled water and 100 ml. of 2 per cent potassium alum in ¼ N H_2SO_4. The active principle in the pyridine-ivy extract settles out as a dark green, flocculent precipitate. This precipitate is centrifuged down, the supernatant is decanted, and the precipitate is mixed with three separate large washings of sterile saline solution by centrifugation and decantation to remove all excess pyridine and alum. The alum precipitate is then made up to its initial volume of 100 ml. and is thus a 10 per cent (concentrated) alum-precipitated pyridine-ivy suspension; dilutions of 1:5 and 1:50 of this concentrate with sterile saline solution are readily made with this preparation.

The pyridine-ivy alum precipitate, a large molecular oleoresinous compound, is insoluble and stable in water; it is painless upon subcutaneous injection with a tuberculin or allergy type syringe and 26 gauge ¼ inch hypodermic needle.

Strauss and Spain[22] selected a group of twelve ivy-sensitive patients who had responded with poor clinical results to treatment with the alcoholic ivy extract. They were treated the following year with Aqua Ivy, with good clinical results. Sixteen other sensitive persons experienced a season practically free from poison ivy dermatitis following injections of Aqua Ivy.

Gaillard[23] summarized 113 ivy-sensitive patients treated with Aqua Ivy with 77 per cent satisfactory results after one season's treatment and the percentage of good results increased with successive years' treatment. Of forty-six cases treated for two years, 84 per cent had success the second season of treatment. Similar favorable results are being reported by him in more than 300 additional cases.[24] In his report on "The Modern Treatment of Poison Ivy," 78 per cent had satisfactory results after the first season of treatment; 86 per cent had success after the second year of treatment; and 95 per cent had success after the third year of treatment. Gaillard felt that after three years of treatment the immunity might be lasting. Neidorff[25] has treated 318 ivy-sensitive patients with Aqua Ivy, with excellent results.

Loveless[26] patch tested one ivy-sensitive patient before and after an accelerated treatment schedule with Aqua Ivy. Before treatment the patient showed a one plus reaction to 1:100 Aqua Ivy, consisting of one flat vesicle,

*Obtainable at the Allergy Laboratory, University Hospital, 303 East 20th St., New York 3, N. Y., until commercially available.

and after treatment there was "almost nothing" to a patch test with the same dilution of Aqua Ivy and the patient reported being 98 per cent cured.

Fontana[36] treated fifteen ivy-sensitive children with Aqua Ivy, with good clinical results. Most of these patients had been treated previously without success with other ivy preparations.

DISCUSSION OF TOXICITY REPORTS

Some workers have reported on harmful local and generalized reactions following Rhus toxin therapy in patients given treatment orally, or by injection with alcoholic or oily extracts of poison ivy or poison oak. To date, 759 cases in which Aqua Ivy has been used with no untoward local or general reactions have been reported. Shaffer, Burgoon, and Gosman[27] reported, in the *Journal of the American Medical Association,* on a fatal and near-fatal case of acute glomerulonephritis following administration of Rhus toxin administered intramuscularly. Since an intramuscular injection was used, an oily ivy preparation was probably administered, but the authors failed to report the actual preparation used. (Aqua Ivy was not used.) A series of four daily intramuscular Rhus toxin injections was administered to each patient, but there is no indication as to the concentration of the active material in each daily injection. This serves to illustrate the general lack of appreciation of the importance of properly regulated dosages, especially when administered to patients with active dermatitis venenata. These authors extensively reviewed the literature where local and general reactions were noted, but failed to cite numerous reports of beneficial results without toxicity.

Spain and Cooke, in 1927, warned against reactions that occur when large doses are given. Reyer[28] more recently reported upon the flare-up of dermatitis in four patients following treatment with Rhus antigen. It was suggested that Rhus injections were harmful and of no benefit when administered to a patient with dermatitis venenata due to poison ivy. No effort was made to correlate the resultant flare-up with overdosage due (1) to daily intramuscular injections in three cases of from four to eight days' duration and (2) to the concentration of the administered oily ivy preparation.

Rytand and associates[29, 30] reported on the appearance of renal disturbances in seven patients three days to two months after the onset of poison oak contact dermatitis, and only two of these seven patients had received Rhus toxin for the active treatment of their dermatitis. Renal disturbances were therefore shown to occur following the poison oak dermatitis *without* treatment of the dermatitis with a Rhus toxin injection. The question arises as to whether the patients developing the renal disturbances following treatment might not also have done so had no active Rhus toxin been administered, simply as a result of severe poisoning from the direct contact as must have happened in the untreated cases. This also re-emphasizes the need for Rhus toxin in a form such as an aqueous solution which may be easily diluted with saline solution to make higher dilutions of the material readily available when

necessary in the treatment of very sensitive persons or children, and in a slowly absorbed form so that it does not reach the shock organ quickly and in a concentrated dosage.

Howell and associates[31] showed that concentrated poison ivy extract was not nephrotoxic for the rabbit. In fact, they stated: "There is insufficient and inadequate evidence that Rhus dermatitis or extracts administered to ivy sensitive individuals result in systemic injury." They suggested that kidney damage may be caused by a secondary infection, as shown by Callaway and O'Rear.[32]

TOXICITY STUDIES IN THE GUINEA PIG

Toxicity studies with Aqua Ivy on guinea pigs were performed by administering the human prophylactic dosage of Aqua Ivy subcutaneously to twelve normal white guinea pigs, even though the guinea pig weighs only 1/300 that of an average man.

The human prophylactic series of injections of Aqua Ivy consists of the following dosages:

0.3 ml. of 1:50
0.5 ml. of 1:50
0.7 ml. of 1:50
0.2 ml. of 1:5
0.4 ml. of 1:5
0.6 ml. of 1:5

The last dosage is repeated each four to eight weeks.

The interval between dosages for human beings is one week, but the guinea pigs were given their injections every third day in order to intensify any toxic reactions (should they appear) due to the shorter interval between injections causing greater concentration of the active material in the body during this period.

These guinea pigs injected with Aqua Ivy remained completely normal throughout the test period; they gained weight and their coats remained sleek and luxuriant. It has generally been noted that the coat of sensitized guinea pigs became very sparse and gave a mottled appearance following a dermatitis from a positive contact test. None of the above treated pigs showed any abnormality in their coats.

Another group of fifteen new guinea pigs were treated with ivy by contact on the unbroken epilated skin. The skin was first denuded by cutting the hair with an electric animal hair clipper and the skin was then treated with a cream depilatory* which proved to be nonirritating. Then 0.02 ml. of a 1:10 dilution of pyridine-ivy extract† was deposited on the denuded skin by filling an 0.02

*Nudit, Helena Rubenstein.

†10 Grams of dried leaves, extracted in 100 ml. of pyridine and filtered, gives the concentrated pyridine-ivy extract. The alum-precipitated pyridine ivy suspension (Aqua Ivy) is prepared from this pyridine-ivy stock solution, but the alum-precipitated product is not sufficiently absorbed through the unbroken skin for adequate patch or contact test. Therefore, the stock solution of 10 per cent pyridine-ivy is used for contact sensitization, but dilutions of the 10 per cent pyridine-ivy to make a 1:10 dilution were made in absolute alcohol to prevent any irritating reaction of pyridine itself upon the skin.

ml. pipette to the mark and touching the tip of the pipette to the skin. This minute deposit was allowed to air dry, the tip was touched to the same spot, and the procedure was continued until 0.02 ml. was delivered. In this way, the ivy deposit was confined to a small area and direct contact with the skin was assured. After twenty-four hours, all of the fifteen animals showed an intense inflammatory reaction consisting of vesiculation, redness, and swelling at the site of the patch test. After two or three days, hard, crusty scabs formed which lasted sometimes for weeks. That it was possible to administer 195 times this concentration in Aqua Ivy form by parenteral route to guinea pigs without any signs or symptoms of sensitization, inflammation, or toxicity indicates the safety of this product when administered subcutaneously.

Experiments were planned in order to determine whether the guinea pigs which received the prophylactic series of injections of Aqua Ivy had developed any increased sensitivity to poison ivy. In order to do this, it was first necessary to determine the strongest dilution of poison ivy extract which would just fail to give a positive reaction after contact for twenty-four hours on the denuded skin of normal (new) pigs; a slightly higher concentration of ivy extract giving positive reactions. By titrating out a particular batch of extract in this way, it is possible to show that a particular dilution of ivy extract gives no skin patch reaction in a majority of normal (untreated) pigs. This same dilution was then tested on the series of guinea pigs which had received the prophylactic series of injections and on another group of guinea pigs which previously were actively sensitized to poison ivy.

Preliminary testing showed that 0.02 ml. of a 1:10 dilution of the concentrated (10 per cent) pyridine-ivy gave a marked positive reaction in all of fifteen guinea pigs tested. This patch dosage was therefore a primary irritant and could not be used for any comparative tests. Any other type of ivy extract in sufficient concentration would act similarly. Table I shows that a 1:20 dilution, on the other hand, gave negative patch tests on nine out of twelve new normal pigs when performed in the identical manner. The positive reactions were in no way comparable to the violent reaction of the 1:10 material (described previously); the reactions to the 1:20 dilution of pyridine-ivy consisted of faint pinkness on the patch area and were not followed by crusting or scabs. A 1:50 and a 1:100 dilution of pyridine-ivy gave negative reactions to patch tests in all twelve pigs which had received no other treatment (normals).

When the guinea pigs which had received the human prophylactic series of Aqua Ivy injections were patch tested with 1:20, 1:50, and 1:100 dilutions of pyridine-ivy, exactly similar reactions were noted as with the normal untreated group of pigs. This is clearly seen in the table. There is no evidence of any increased sensitivity following the injection of Aqua Ivy in the complete human dosage administered.

In contrast to these two groups are the results in guinea pigs which were previously sensitized by skin contact with ivy. Ten guinea pigs were sensitized by a single application on the denuded skin of 0.02 ml. of 1:20 pyridine-ivy,

TABLE I. RESULTS OF TOXICITY WITH AQUA IVY IN GUINEA PIGS

ANIMAL NO.	TREATMENT BEFORE PATCH TEST	REACTION TO SKIN PATCH TEST WITH PYRIDINE IVY EXTRACT (0.02 ML.)					
		1:20 DILUTION		1:50 DILUTION		1:100 DILUTION	
		24 HR.	48 HR.	24 HR.	48 HR.	24 HR.	48 HR.
51	None	0	0	0	0	0	0
52	None	0	0	0	0	0	0
53	None	0	0	0	0	0	0
54	None	0	0	0	0	0	0
55	None	+	+	0	0	0	0
56	None	0	0	0	0	0	0
57	None	+	+-	0	0	0	0
58	None	+	+	0	0	0	0
59	None	0	0	0	0	0	0
60	None	0	0	0	0	0	0
61	None	0	0	0	0	0	0
62	None	0	0	0	0	0	0
70	Human dosage (Prophylactic) of Aqua Ivy injected*	0	0	0	0	0	0
71	Human dosage (Prophylactic) of Aqua Ivy injected*	0	0	0	0	0	0
72	Human dosage (Prophylactic) of Aqua Ivy injected*	+	+	0	0	0	0
73	Human dosage (Prophylactic) of Aqua Ivy injected*	+	+	0	0	0	0
74	Human dosage (Prophylactic) of Aqua Ivy injected*	0	0	0	0	0	0
75	Human dosage (Prophylactic) of Aqua Ivy injected*	+-	+	0	0	0	0
76	Human dosage (Prophylactic) of Aqua Ivy injected*	0	0	0	0	0	0
77	Human dosage (Prophylactic) of Aqua Ivy injected*	0	0	0	0	0	0
78	Human dosage (Prophylactic) of Aqua Ivy injected*	0	0	0	0	0	0
79	Human dosage (Prophylactic) of Aqua Ivy injected*	0	0	0	0	0	0
80	Human dosage (Prophylactic) of Aqua Ivy injected*	0	0	0	0	0	0
81	Human dosage (Prophylactic) of Aqua Ivy injected*	0	0	0	0	0	0
82	Human dosage (Prophylactic) of Aqua Ivy injected*	0	0	0	0	0	0
8	Pyridine-Ivy placed on denuded skin†	++	+++	+	++	0	0
9	Pyridine-Ivy placed on denuded skin†	0	++	0	0	0	+
10	Pyridine-Ivy placed on denuded skin†	+++	++++	++	+++	+	0
13	Pyridine-Ivy placed on denuded skin†	+	+++	++	+	0	+-
15	Pyridine-Ivy placed on denuded skin†	0	+	+-	+	0	0
16	Pyridine-Ivy placed on denuded skin†	++	++++	++	+++	0	+-
17	Pyridine-Ivy placed on denuded skin†	+	++	0	++	0	0
19	Pyridine-Ivy placed on denuded skin†	++	+++	+	+++	0	0
21	Pyridine-Ivy placed on denuded skin†	0	+	0	+	0	0
23	Pyridine-Ivy placed on denuded skin†	0	0	0	0	0	0

*Aqua Ivy was injected subcutaneously every third day in the following dosages: of the 1:50 dilution, 0.3 ml., 0.5 ml., and 0.7 ml.; of the 1:5 dilution, 0.2 ml., 0.4 ml., and 0.6 ml.: the last dosage was repeated three times.

†Sensitized by the application of 0.02 ml. of a 1:20 dilution of the 10 per cent pyridine ivy upon the denuded skin and allowing it to remain in situ for four days.

which was allowed to remain in situ for four days. Ten days after the patch had been applied and sensitization had theoretically developed, a hitherto untouched area of the skin was patch tested with the same 1:20, 1:50, and 1:100 pyridine-ivy dilutions as used in the other experimental groups of animals. In marked contrast to the normal or prophylactically treated group of pigs, this sensitized group reacted not only to the 1:20 dilution in most cases, but also to the more dilute 1:50 dilution.

These results are recorded in Table I.

AUTOPSY STUDIES

Six guinea pigs were administered the complete human prophylactic series of Aqua Ivy injections subcutaneously every three days and the top dosage was repeated three times. One week after the last dosage, the guinea pigs were killed and examined macroscopically, and the kidneys were examined microscopically by Dr. A. Hochwald.* The macroscopic examination showed nothing unusual. The microscopic examination showed the usual finding in old guinea pigs of marked congestion in the kidneys. There were no glomerular, vascular, or tubular lesions.

CLINICAL STUDIES

The following patients, reporting for phylactic treatment of existing dermatitis as well as prophylactic courses, were recorded until 101 patients, a number comparable to the Gaillard series, had been summarized as to age, past history, existing dermatitis at time of treatment, dates and amounts of injections, and results. In each case, patients were examined before and after each season to determine the presence or absence of lesions and the extent of severity of lesions following phylactic and prophylactic treatment.

Of the 101 patients studied, ranging in age from 2 to 62 years, it was noted that most commonly those having a history of difficulty were exposed by virtue of living and gardening near newly built suburban homes or by their occupational exposure as gardeners, farmers, and highway and utility maintenance men.

PROPHYLACTIC TREATMENT: METHOD AND RESULTS

In the case of hay fever symptoms, results can be evaluated on the basis of considerable degree of exposure for everyone, even though the pollen crop varies from year to year. With Rhus dermatitis, however, a patient may become cautious after a severe dermatitis. The apparent result of treatment may depend, therefore, not only on the use of immunizing extract, but also on the lessened degree of exposure due to unpleasant past experiences. The cases studied were not ones in which a drastic change of environment, job, or habit was concerned in the results. Spontaneous remissions in some cases cannot be ruled out. The psychotherapeutic effect of a series of injections may conceivably account for some favorable reports in patients regardless of what material is injected; placebo controls were not used. With all these limitations in mind, we

*Pathology Department, University Hospital, New York University–Bellevue Medical Center.

still consider the use of Aqua Ivy so consistently valuable in clinical practice that we wish to report our results in order to encourage others to further evaluation of the product. Prophylactic treatment series were given 121 times. At the end of the calendar year, each season was recorded as excellent, good, or poor. Each patient either had existing dermatitis typical of the eruption caused by poison ivy or oak, or began treatment because of a history of one or more years of difficulty recurring each year.

An excellent result was taken to be one in which the rest of the year elapsed with less than three or four 12 mm. macules or papules appearing. Larger areas of macules and papules regarded as inconsequential by the patient were considered "good results" unless the area involved was greater than about 3 square inches (20 sq. cm.).

Palm-sized or larger areas, vesiculation of any area, or failure of the injection to help, in the opinion of the patient, automatically placed the series in the "poor result" category.

Using these rough criteria, the results were as follows:

Prophylactic Result	*Courses*	*Per Cent*
Excellent	63	52
Good	50	41
Poor	8	7
Total	121	100

Patch tests were not done, as it was not considered necessary to determine closely the degree of sensitivity.

ILLUSTRATIVE CASE HISTORIES

CASE 1.—R. A., 5 years old, reported with a history of having been seen by a family doctor every summer for three years for a rash on the arms, hands, and exposed areas of the lower legs, considered typical of poison ivy dermatitis. Aqua Ivy dosage used at seven- to fourteen-day intervals, beginning in April, was:

April 26	0.2 ml. of 1:50
May 15	0.5 ml. of 1:50
May 22	0.7 ml. of 1:50
May 29	0.1 ml. of 1:5
June 12	0.5 ml. of 1:5
July 3	1.0 ml. of 1:5
August 2	1.0 ml. of 1:5
August 24	1.0 ml. of 1:5

A few papules, not related to the injection, were noticed during August, but the patient's mother felt that this was a great improvement over the prior years with similar opportunity for exposure. This was considered a good result.

CASE 2.—A. C., a 34-year-old salesman, gave a history of a vesicular rash on the forearms each summer for ten years, attributed to week-end exposure in gardening and at picnics. He required several days of hospitalization for the first three summers. Due to lack of exposure to poison ivy, he had slight or no difficulty for two years. This interval was

followed by increasingly troublesome ivy dermatitis of the forearms every summer during the next five years. He came in for treatment and was given the following limited series of Aqua Ivy injections:

June 20	0.3 ml. of 1:50
June 22	0.5 ml. of 1:50
June 24	0.7 ml. of 1:50
June 28	0.1 ml. of 1:5

He had a satisfactory result which lasted all summer, even though his exposure was essentially unchanged.

CASE 3.—A. C., a 62-year-old salesman with profuse ivy growth in his suburban gardening area, suffered a repeated maculopapular rash with intense itching on the wrists and forearms each summer for four years. Week-end outdoor work was usually followed by an eruption. The diagnosis of ivy poisoning was confirmed by two physicians. The initial series of Aqua Ivy injections was given at the same time that pollen extract was administered and the intervals were therefore longer than usual. The dosage was as follows:

May 28	0.3 ml. of 1:50
June 18	0.5 ml. of 1:50
July 2	0.7 ml. of 1:50
August 2	0.2 ml. of 1:5

From October, 1951, through December, 1954, a 0.7 ml. dose of 1:5 dilution of the alum-precipitated pyridine extract was given monthly through the summer and a 0.5 ml. dose was given each month through the winter. Although the exposure remained the same, or even increased as the patient felt free to do more work in the garden, absolutely no lesions appeared and his four years of treatment were rated "excellent."

CASE 4.—L. A., 8 years old, had a history of dermatitis venenata each summer since the age of 3 years. Her Aqua Ivy doses were:

April 22	0.3 ml. of 1:50
April 28	0.7 ml. of 1:50
May 6	0.2 ml. of 1:5
May 20	0.4 ml. of 1:5

This patient remained free of dermatitis, in the suburban environment in which the dermatitis usually occurred, until about August 1, when her usual maculopapular eruption of the hands and face developed. The mother had not understood the need for booster doses and relied on the initial series, which also fell short of the 0.7 ml. we had intended to reach before a four-week booster interval. This result was recorded as "poor," and the eight-week interval of control, followed by recurrence, can be interpreted as supporting our feeling that booster doses of 0.5 to 0.7 ml. of 1:5 Aqua Ivy should be maintained every four to six weeks for best results.

PHYLACTIC USE OF AQUA IVY: DISCUSSION AND RESULTS

Eighty-five patients appearing with poison ivy dermatitis were treated with Aqua Ivy. Mild dermatitis responds well to topical applications and antihistamines, and may not require further treatment of any kind. In more protracted or more disturbing cases, phylactic injections at two- to four-day intervals of minute doses of Aqua Ivy may alleviate the discomfort and shorten the period of attack. In the more severe or extensive attacks of dermatitis venenata, where exacerbations of symptoms may follow injection therapy, the steroid hormones have proved especially helpful. This is due to the self-

limited character of the condition, which consequently does not demand protracted treatment.[33] These hormones do not permanently alter the original hypersensitivity to the Rhus toxin. It is recognized that the hormones act by suppressing the inflammatory reaction rather than by affecting the immune mechanism. This is observed when premature discontinuance of the hormone is followed by reappearance of the rash. The evaluation of steroid therapy for the relatively minor ailment, such as ivy dermatitis, hinges upon further knowledge about the degree of adrenal suppression found with even a few doses of cortisone. Severe infection or surgery has been reported to precipitate shock and even result in death. The advisability of treatment of relatively mild ivy dermatitis with such a potent hormone is therefore questionable.

Topical application of hydrocortisone not only has been disappointing, but at times it seems to be responsible for the spread of the rash beyond its original limits; this is thought at times to be due to the oily nature of the vehicle in which it is sometimes dispensed. A recent confirmation of this was by Eskind and associates,[34] who found no significant difference in seventy-seven patients treated by topical hydrocortisone in various vehicles and fifteen given placebo therapy. Exceptions were four patients relieved where angioedema, rather than vesiculation and erythema, was the primary complaint.

Average phylactic treatment for adults with mild to moderate cases of dermatitis venenata consisted of subcutaneous injections every two to four days as follows:

Dosage:	No. 1	0.1 ml. of 1:50 Aqua Ivy
	No. 2	0.2 ml. of 1:50 Aqua Ivy
	No. 3	0.3 ml. of 1:50 Aqua Ivy

In a few severe cases, the initial dosage was repeated or the interval lengthened to avoid overdosage. The dermatitis usually dries up by the second or third injection and the patient reports general improvement.

Phylactic treatment is no longer necessary for general use since the advent of corticosteroids, but it is reported here to substantiate the safety of Aqua Ivy and its usefulness even during active dermatitis venenata. Local applications varied according to the degree of oozing and vesiculation. These varied from wet dressings with potassium permanganate 1:20,000 in severe cases to antipruritic agents for milder maculopapular stages. We feel that the application of ointments and creams early in the dermatitis is often responsible for mechanically spreading the poison ivy oleoresin to adjacent skin.

Among the 101 patients studied, there were eighty-five times when a series of one to four injections was given for ivy dermatitis present at the time of the initial visit. The need to withhold ivy injections exists chiefly in the acute vesiculation or oozing of relatively large areas from intimate exposure to ivy leaf or vine, or in cases where there have been several full doses of ivy in oil during the preceding ten days. There have been many warnings in reference to such radical treatment with injections of ivy in oil, and we heartily endorse caution.

In this series, the results were as follows:

Phylactic Results	*Courses*	*Per Cent*
Excellent	42	49
Good	37	43
Poor	6	8
Total	85	100

DISCUSSION

Aqua Ivy, being alum precipitated, is very slowly absorbed so that larger dosages are administered both as an initial dose and as a final concentration in the prophylactic immunization series. This slower absorption and high dosage level, which is greater than that obtainable with the alcoholic or oily ivy preparations, probably explains, in part, (1) the freedom from toxic reactions and (2) the more successful clinical results seen with this Aqua Ivy preparation. Aqua Ivy, being in the body for a longer period of time and in greater concentration than has heretofore been possible with other preparations, gives the body defenses a greater opportunity to develop immunity. Coulson and Stevens[35] showed that ovalbumin which was alum precipitated had a sensitizing capacity in guinea pigs from four to nearly 400 times greater than that of ovalbumin in saline solution, depending upon the route of administration. Exacerbation of the dermatitis is rare with this preparation (in spite of the higher initial and final dosages to known sensitive persons) because of the nature of this new pyridine-oleoresin compound and its slow absorption. The maximum doses of the alum-precipitated, pyridine-ivy extract can be given at much longer (eight-week) intervals with very little fear of any type of untoward reaction, such as may occur at times with the usual ivy extracts.

SUMMARY

1. Guinea pigs who received the full human dosage of Aqua Ivy subcutaneously were not made more skin-sensitive to poison ivy, as demonstrated with quantitative serial dilutions by contact test.

2. Nephritis, even when large dosages of Aqua Ivy were administered, was not found on autopsy in guinea pigs.

3. A group of 121 prophylactic series of Aqua Ivy injections were administered, with 93 per cent excellent or good results.

4. There was no incidence of nephritis or exacerbation of dermatitis in this series, even when Aqua Ivy was administered to children as young as 2 years of age.

5. Observations on the phylactic use of Aqua Ivy in mild to moderate ivy dermatitis are included only to emphasize the lack of exacerbations (with good clinical results) following its use as described. Current therapy of choice is systemic hydrocortisone for the acute severe case and Aqua Ivy for subsequent prophylaxis.

REFERENCES

1. Straus, H. W.: Artificial Sensitization of Infants to Poison Ivy, J. ALLERGY 2: 137, 1930.

2. Heinbecker, P.: Studies in Hypersensitiveness; the Susceptibility of Eskimos to an Extract From Toxicodendron Radicans (L), J. Immunol. **15**: 365, 1928.
3. Deibert, O., Menger, E. F., and Wigglesworth, A. M.: Studies in Specific Hypersensitiveness; Relative Susceptibility of the American Indian Race and the White Race to Poison Ivy, J. Immunol. **8**: 287, 1923.
4. Straus, H. W.: Experimental Study of the Etiology of Dermatitis Venenata, J. ALLERGY **5**: 568, 1934.
5. Nestler: Quoted by Low.[6]
6. Low, R. C.: Anaphylaxis and Sensitization, New York, 1925, William Wood & Company.
7. Field, H., and Sulzberger, M. B.: Experiments in Poison Ivy Sensitivity, J. ALLERGY **7**: 139, 1936.
8. Spain, W. C., and Cooke, R. A.: Studies in Hypersensitiveness. XXVII. Dermatitis Venenata: Observations Upon the Use of a Modified Extract From Toxicodendron Radicans, J. Immunol. **13**: 93, 1927.
9. Schamberg, J. F.: Desensitization of Persons Against Poison Ivy, J. A. M. A. 73: 1213, 1919.
10. Shelmire, B.: The Poison Ivy Plant and Its Oleoresin, J. Invest. Dermat. **4**: 337, 1941.
11. Besser, J. P., and Urbach, J.: Peroral Prophylaxis of Poison Ivy. Dermatitis, Ann. Allergy **10**: 169, 1952.
12. Gold, H., and Masucci, P.: Oral Prophylaxis Against Poison Ivy, J. ALLERGY **13**: 606, 1941-42.
13. Gold, H., and Masucci, P.: Prophylactic Oral Therapy Against Poison Ivy, J. ALLERGY **13**: 157, 1941-42.
14. Biederman, J. B.: Observations on the Relation of Poison Ivy and Poison Oak, New Eng. J. Med. **219**: 117, 1938.
15. Molitch, M., and Poliakoff, S.: Prevention of Dermatitis Venenata Due to Poison Ivy in Children, Arch. Dermat. & Syph. **33**: 725, 1936.
16. Strickler, A.: The Toxin Treatment of Dermatitis Venenata, J. A. M. A. **77**: 910, 1921.
17. Templeton, H. J.: Untoward Reactions Following Toxin Treatment for Dermatitis Venenata, Arch. Dermat. & Syph. **20**: 83, 1929.
18. Clarke, J. R., and Hanna, C. M.: The Treatment of Rhus Poisoning by Alcoholic Extracts in a Small Group Controlled by Preliminary Patch Tests, J. ALLERGY **13**: 599, 1942.
19. Caulfeild, A. H. W.: Prevention of Poison Ivy Dermatitis by the Intramuscular Injection of "Rholigen," Canad. M. A. J. **37**: 18, 1937.
20. Clock, R. O.: Rhus Dermatitis: Its Treatment With Poison Ivy Extract, M. J. & Record **122**: 93, 1925.
21. Keeney, E. L., Sunday, S., Gay, L. N., and Lynch, K.: Poison Ivy Dermatitis; the Diagnostic Value of the Patch Test Made With an Ether Extract From Fresh Leaves and Stems of the Poison Ivy Plant, Bull. Johns Hopkins Hosp. **69**: 482, 1941.
22. Strauss, M. B., and Spain, W. C.: Studies on Poison Ivy and Other Dermatitis Producing Plant Parts Wherein Active, Resinous Principles Are Suspended in Aqueous Solution, J. ALLERGY **17**: 1, 1946.
23. Gaillard, G. E.: Poison Ivy: A Summary of One Hundred Cases Treated With Aqueous (Alum Precipitated Pyridine) Extract, J. ALLERGY **21**: 55, 1950.
24. Gaillard, G. E.: Fundamentals of Modern Allergy; The Modern Treatment of Poison Ivy, New York State J. Med. **56**: 2255, 1956.
25. Neidorff, H. A., Altoona, Pa.: Personal Communication.
26. Loveless, M. H., New York, N. Y.: Personal Communication.
27. Shaffer, B., Burgoon, C. F., and Gosman, J. H.: Acute Glomerulonephritis Following Administration of Rhus Toxin, J. A. M. A. **146**: 1570, 1951.
28. Reyer, W. A.: Exacerbation of Ivy Dermatitis by Rhus Antigen Injections, Ann. Allergy **11**: 91, 1953.
29. Rytand, D. A.: Fatal Anuria, the Nephrotic Syndrome and Glomerular Nephritis as Sequels of Dermatitis of Poison Oak, Am. J. Med. **5**: 548, 1948.
30. Rytand, D. A., Burna, D. W., and Cox, A. M.: Periarteritis Nodosa Following the Dermatitis of Poison Oak and of Primrose, Stanford Med. Bull. **6**: 319, 1948.
31. Howell, J. B., Goth, A., and Fashena, G. J.: Rhus Toxicodendron—Possibility of Systemic Effects, A. M. A. Arch. Dermat. & Syph. **70**: 426, 1954.
32. Callaway, J. L., and O'Rear, H. B.: Pyogenic Infections of Skin—Etiologic Factor in Acute Glomerulonephritis of Children, A. M. A. Arch. Dermat. & Syph. **64**: 159, 1951.

33. Ekblad, G. H.: The Use of Corticotrophin (ACTH) and Cortisone in Urticaria and Dermatitis, U. S. Armed Forces M. J. 3: 839, 1953.
34. Eskind, I. B., Sigafoos, R. B., and Kelso, R. W., Jr.: Treatment of Rhus Dermatitis With Topical Hydrocortisone; a Clinical Evaluation, Arch. Dermat. & Syph. **69**: 410, 1954.
35. Coulson, E. J., and Stevens, H.: Quantitative Studies in Anaphylaxis. III. Effect of the Alum Adjuvant and Route of Administration on the Sensitizing Dose, J. Immunol. **61**: 119, 1949.
36. Fontana, V. J.: Eczematous Dermatitis in Children, GP **10**: 47, 1954.