ORAL PROPHYLAXIS AGAINST POISON IVY DERMATITIS WITH AQUA IVY TABLETS*

I. A Controlled Experiment and Preliminary Clinical Report

Robert J. Langs, M.D.,** and Margaret B. Strauss, M.S.,*** New York, N. Y.

INTRODUCTION

DERMATITIS venenata from poison ivy or poison oak has been a disturbing entity to many groups of persons who work or spend leisure hours in the countryside.

Protection from ivy poisoning may be developed by administering an ivy extract orally or parenterally. It was a custom among the American Indians[1] to eat the young green ivy leaves to prevent the ivy rash. The beneficial therapeutic effects of oral ivy dates back to the report of Dakin[2] in 1829. Warren[3] produced immunity by administering the extract orally in 1909. Schamberg[4] was the first to popularize the ingestion of the ivy resin which he dissolved in alcohol. Shelmire[5] employed the ivy resin in diluted corn oil and gave it by mouth in daily doses. There have been many reports[6-9] since then on the efficacy of oral ivy therapy. Spain and Cooke[9] showed that the alcoholic ivy resin was stable only in absolute alcohol and that the water present in even 95 per cent alcohol caused its rapid deterioration. Therefore, most oral tinctures of ivy rapidly lose their activity.

Gold and Masucci[7] treated ivy-sensitive patients with capsules containing from 0.5 to 10 mg. of the poison ivy oleoresin in corn oil. Daily treatment with increasing dosages up to fifteen capsules of the 10 mg. concentration through a total of forty-five days was reported. Seventeen of twenty-five ivy-sensitive patients responded favorably in controlled field exposure, but 80 per cent of these patients developed rather severe toxic reactions consisting of erythemas of the extremities, pruritus, vesicular dermatitis, or a papular rash. Kligman[10] has administered orally large dosages of pentadecylcatechol to ivy-sensitive persons, and marked toxic effects were reported.

The chief disadvantage of the liquid oral preparations is the danger of spreading the extract with its active principle upon the hands, lips, and

From the United States Public Health Service St. Louis Outpatient Clinic and the University Hospital, New York University-Bellevue Medical Center.

Read at the annual meeting of the American Medical Association, June 25, 1958.

Received for publication Oct. 13, 1958.

*Alum-precipitated pyridine ivy extract. The Aqua Ivy tablets used in this study were supplied by Syntex Chemical Co., Inc., New York, New York.

**Former chief, St. Louis Outpatient Clinic, United States Public Health Service; Albert Einstein College of Medicine and the Bronx Municipal Hospital Center.

***Allergy Laboratory, University Hospital, New York University-Bellevue Medical Center.

mouth, causing fresh lesions. Toxic side effects, such as pruritus ani, gastric upset, and vesicular dermatitis, have prevented general acceptance of this form of therapy.

Aqua Ivy, A.P.,* the alum-precipitated pyridine-ivy complex described by Strauss and Spain,[11] was the first active ivy preparation to be dispensed in aqueous solution. Successful clinical results have been reported[11-14] on over 500 ivy-sensitive persons treated with Aqua Ivy and virtually no toxic effects were observed. Since Aqua Ivy solved many problems relative to parenteral prophylaxis against poison ivy dermatitis, it was incorporated into tablet form for oral therapy.†

Dermatitis venenata is a problem with the men of the Second Coast Guard District. Poison ivy grows abundantly along the shores of the Mississippi River and its tributaries, and it is the duty of the Coast Guardsmen to clear these areas of overgrowth and other debris. Prior to the first study reported in this article (which was carried out in 1956), a survey was made to ascertain the incidence of poison ivy dermatitis in the District. Data was obtained on 153 men, all of whom were exposed to poison ivy to some extent. Of these, eighty-five men (56 per cent) had some degree of poison ivy dermatitis. The severity of the problem at hand necessitated some type of prophylaxis.

The Coast Guardsmen were stationed on ships which were sometimes away from their base for periods of up to four weeks or more, so that weekly parenteral prophylactic treatment was not feasible since there was no medical officer or pharmacist's mate on many of these ships. Oral prophylaxis against poison ivy was therefore attempted.

This article presents the results of a double-blind, controlled study performed in 1956 and a clinical study without controls performed in 1957. It evaluates Aqua Ivy Tablets as a prophylactic agent against poison ivy dermatitis.

EXPERIMENTAL PROCEDURE FOR CONTROLLED STUDY

One hundred forty-two men were included in the study. All were members of the United States Coast Guard who worked at clearing brush along the banks of the Mississippi River and its tributaries. The period of observation and tablet ingestion was from April 23, 1956, to Nov. 1, 1956.

Exposure to poison ivy was recorded for each man. In general, it may be said that almost all men were exposed; the average man was exposed two or three times per week to heavy poison ivy growth.

Two groups were formed in an entirely random fashion, and each ship had approximately the same number of men in each group. Group A took Aqua Ivy Tablets, and Group B took a placebo which had a chlorophyll base and looked quite like the Aqua Ivy Tablet.

*United States Patent No. 2,456,750. Trademark of Syntex Chemical Co., Inc., New York, New York.

†The suspension of Aqua Ivy for parenteral use is standardized so that the concentrate contains 15 mg. dry alum-precipitated pyridine-ivy per milliliter. Aqua Ivy Tablets are prepared from this concentrate.

The tablets given to Groups A and B were coded; no one aboard ship knew of the difference between tablets. Both groups received identical instructions and took their tablets in identical fashion. Tablet ingestion was supervised by the captains of each vessel every day. The following dosage schedule was used:

(1) *First week:* 0.06 mg. Aqua Ivy Tablet (or placebo) once daily.
(2) *Second week:* 0.06 mg. Aqua Ivy Tablet (or placebo) three times per day.
(3) *Third week:* 0.3 mg. Aqua Ivy Tablet (or placebo) once daily.
(4) *Fourth and fifth weeks:* 0.3 mg. Aqua Ivy Tablet (or placebo) three times per day.
(5) *Sixth week until end of study:* 1.5 mg. Aqua Ivy Tablet (or placebo) once daily.

Observation sheets were kept by the captain of the vessel on all subjects. The diagnosis of poison ivy dermatitis was usually made by the captain of the vessel, who, as a rule, had a great deal of experience with this entity. About 25 per cent of the diagnoses were confirmed by a physician. Cases were rated as mild, moderate, or severe according to the following criteria:

(1) *Mild:* Three or four small isolated blotches, none more than the size of a dime.
(2) *Moderate:* A definite rash on one or both extremities with only mild discomfort. Rash is not weeping and is not greater than 3 square inches in all.
(3) *Severe:* A rash covering a palm-sized area or more. Any rash that causes much discomfort and complaining. Any rash that is oozing noticeably.

RESULTS

Over-all Data.—The over-all results (that is, disregarding duration of observation and the point in the experiment at which the poison ivy dermatitis occurred) are outlined in Table I.

TABLE I. OVER-ALL RESULTS

GROUP	NUMBER OF MEN OBSERVED	NUMBER OF MEN CONTRACTING POISON IVY DERMATITIS
A (Aqua Ivy Tablets)	73	17
B (Control)	69	17
Totals	142	34*

*Over-all incidence 24 per cent.

These figures are not the definitive data. Cases of poison ivy dermatitis which occurred during the first six weeks of observation (and tablet ingestion) are included. Since it takes time to build immunity, it was decided in advance of the study to allow six weeks (the period of increasing Aqua Ivy Tablet

dosage) for the development of adequate levels of protection. Therefore, data which excluded all cases in both groups that occurred during the first six weeks in which the subject took the medication (or placebo) was tabulated (Table II).

Data Excluding First Six Weeks of Observation and Medication.—Table II includes all men observed for a period greater than six weeks and includes only those cases of poison ivy dermatitis occurring in either group after this initial six-week period.

TABLE II. RESULTS AFTER SIX WEEKS OF TABLET INGESTION

GROUP	NO. OF MEN OBSERVED	NO. OF MEN CONTRACTING POISON IVY DERMATITIS	INCIDENCE OF POISON IVY DERMATITIS (PER CENT)
A (Aqua Ivy Tablets)	65	4	6
B (Control)	57	12	21
Totals	122	16	—

$p = 0.035$.

$\frac{1}{2}p = 0.018$.

In the most strict psychologic experiment, a "p" or "½p" equal to 0.05 or less is highly significant. The "½p" value is used here since we predicted the direction of our results. Thus, the "½p" of 0.018 here means that there are 1.8 chances in 100 that our results are due to chance alone and are not due to the difference between Aqua Ivy Tablets and the placebo. Such a "½p" value is enormously significant. For medical experiments, with their many unpredictable variables, a "p" or "½p" of 0.20 is often considered to be significant. The lower the "p" value, the more conclusive the results.

These figures show at a very high and conclusive level of statistical significance the ability of Aqua Ivy Tablets to protect persons from poison ivy dermatitis. The difference of incidence when the two groups are compared shows that this is a valid finding and does not appear to be due to chance or any artefact.

Results in Subjects With Prior History of Poison Ivy Dermatitis.—Table III shows the data restricted to men who gave a previous history of poison ivy dermatitis.

TABLE III. RESULTS IN KNOWN IVY-SENSITIVE SUBJECTS

	OVER-ALL		EXCLUDING FIRST SIX WEEKS		
GROUP	NUMBER OBSERVED	NO. OF MEN CONTRACTING POISON IVY DERMATITIS	NUMBER OBSERVED	NO. OF MEN CONTRACTING POISON IVY DERMATITIS	INCIDENCE OF POISON IVY DERMATITIS (PER CENT)
A (Aqua Ivy Tablets)	18*	9	16	3	19
B (Control)	21*	12	17	8	47
Totals	39	21	33	11	—

$p = 0.188$.

$\frac{1}{2}p = 0.094$.

*The approximate equal number of men with a past history of poison ivy in the two groups verifies the evenness of the groups, as no attempt was made to control this in advance.

The figures which exclude the first six weeks of medication are here highly suggestive and may be considered statistically significant.

Results in Subjects Without Prior History of Poison Ivy Dermatitis.—Table IV shows the data for men with no past history of ivy dermatitis, many

TABLE IV. RESULTS IN MEN WITH NO PAST HISTORY OF POISON IVY DERMATITIS

	OVER-ALL		EXCLUDING FIRST SIX WEEKS		
GROUP	NUMBER OBSERVED	NO. OF MEN CONTRACTING POISON IVY DERMATITIS	NUMBER OBSERVED	NO. OF MEN CONTRACTING POISON IVY DERMATITIS	INCIDENCE OF POISON IVY DERMATITIS (PER CENT)
A (Aqua Ivy Tablets)	55	8	49	1	2
B (Control)	48	5	40	4	10
Totals	103	13	89	5	—

of whom were experiencing their first exposure to the ivy leaf. The results appear favorable.

Extent of Rash.—Table V shows the rating of all of the poison ivy dermatitis incidents which occurred, including repeated incidents in the same men.

Once again we shall review only the data after six weeks. Here it is seen that, of the four men in the group taking Aqua Ivy Tablets who contracted poison ivy dermatitis, three had mild cases. From this it is apparent that of the sixty-five men in this group only one man had more than a mild case of the poison ivy dermatitis (a 1.5 per cent incidence) and, of course, only four men had any rash at all. This contrasts with the control group in which four of the fifty-seven men had more than mild cases of poison ivy dermatitis—an incidence of 7 per cent.

TABLE V. INCIDENTS OF POISON IVY DERMATITIS RATED ACCORDING TO SEVERITY

	OVER-ALL					EXCLUDING FIRST SIX WEEKS				
GROUP	NO. OF MEN OBSERVED	MILD	MODERATE	SEVERE	TOTAL	NO. OF MEN OBSERVED	MILD	MODERATE	SEVERE	TOTAL
A (Aqua Ivy Tablets)	17	17	6	4	27	4	6	-	3*	9
B (Control)	17	18	10	2	30	12	11	6†	-	17
Totals	34	35	16	6	57	16	17	6	3	26

*All in the same man.
†In four different men.

Side Reactions.—There were six men (three in each group) who reported side reactions attributed to the tablets taken. These reactions were as follows:

1. Group A (Aqua Ivy Tablets)
   (a) "Makes me sick" (meaning unclear).
   (b) "Nausea."
   (c) A generalized poison ivy dermatitis was reported in a man with a history of recurrent poison ivy dermatitis over many years and a similar reaction to prior attempts at prophylaxis. Subject denied exposure. He stopped the tablets and the rash receded.
2. Group B (placebo)
   (a) "Headaches."

(b) "Drowsiness."

(c) One man contracted poison ivy dermatitis and felt that it was due to the tablets he was taking. He stopped the tablets and the rash receded.

No other reactions were reported. There is virtually no difference in the two groups.

CLINICAL STUDY

Experimental Procedure.—One hundred twelve men of the Second Coast Guard District participated under work conditions and exposure similar to those in the controlled study. The period of observation was from April 4, 1957, to Oct. 15, 1957. Aqua Ivy Tablets, 1.2 mg., were utilized exclusively in this study (there were no controls), and the following dosage schedule was followed by all subjects:

½ tablet (0.6 mg.) every other day for two weeks, then ½ tablet (0.6 mg.) daily for two weeks, and then 1 tablet (1.2 mg.) daily until 100 tablets had been ingested (three months).

Observation sheets were kept, as before, and the same rating scale for episodes of poison ivy dermatitis was used. At the end of the study, during the first week in December, patch tests* were performed on fifty-seven men.

TABLE VI. RESULTS OF CLINICAL STUDY

	NO. OF MEN CONTRACTING POISON IVY DERMATITIS								
	WEEKS 1 TO 6 ONLY					AFTER WEEK 6 ONLY			
	NONE	MILD	MOD-ERATE	SE-VERE	TOTAL	MILD	MOD-ERATE	SE-VERE	TOTAL
Men with a past history of poison ivy	41	1	1	-	2 (5%)	3	2	-	5 (12%)
Men with no past history of poison ivy	71	2	-	-	2 (3%)	1	-	-	1 (1.4%)
Totals	112	3	1	-	4 (4%)	4	2	-	6 (5%)

Clinical Results.—Table VI reveals that Aqua Ivy Tablets afforded complete protection against poison ivy dermatitis for 88 per cent of subjects with a past history of dermatitis after six weeks of tablet ingestion. The results are somewhat better in light of our rigid rating scale, since 93 per cent of the "sensitive" men achieved good protection (had only mild poison ivy dermatitis) over-all and 95 per cent received good protection after six weeks. The absence of a severe dermatitis in any subject is also worthy of note.

The results in those men with no past history of poison ivy (many of whom had never been exposed to poison ivy previously) are, as expected, somewhat better; no man had more than a mild dermatitis at any time.

*Patch tests were performed as follows: A fresh 10 per cent alcoholic ivy extract was prepared and one drop of a 1-10 dilution from a 26 gauge needle was placed on a ¼ inch disc, placed on the upper arm, and secured with a Band-Aid. After twenty-four hours the patch was removed, and the reaction was read twenty-four hours after this.

Results of the Patch Testing After Treatment With Aqua Ivy Tablets.—Since no patch testing was performed before tablet ingestion in this study, the results of patch testing after treatment are of limited value.

Twenty-seven men with no history of poison ivy dermatitis were patch tested, and all patch tests were negative. Fifteen men with a past history of poison ivy dermatitis were patch tested; thirteen were negative to patch test and two were positive.

Results of Patch Testing Men Not Treated With Aqua Ivy Tablet.—For comparison, men with a past history of poison ivy dermatitis and definite exposure, who did not take Aqua Ivy Tablets, were also patch tested. Of the fifteen men patch tested, twelve had positive patch tests and three had negative patches.

These results suggest two interesting ideas: first, that Aqua Ivy Tablets do not sensitize nonsensitive persons and, second, that Aqua Ivy Tablets may very well desensitize, as measured by patch testing, persons who are sensitive to poison ivy.

Side Effects.—Three men (2.5 per cent) reported very mild incidents of poison-ivy-like lesions in the web of the fingers during the first six weeks of tablet ingestion, at times when they were not exposed to poison ivy. In each case, the rash lasted about three days, caused no notable discomfort, and disappeared spontaneously without any sort of therapy. Tablet ingestion was not interrupted. No other side effects were reported.

Only thirty men participated in both the 1956 and 1957 studies. This small number does not provide sufficient material for meaningful analysis; the trends, however, are along the lines of our other data. Combining the clinical data of the two studies, we find that 86 per cent of the men with a past history of poison ivy dermatitis had complete protection against the dermatitis, while 98 per cent of the men without a history of the dermatitis were fully protected.

DISCUSSION

The results tend to show that Aqua Ivy Tablets offer immunity against poison ivy dermatitis. This conclusion appears warranted on the basis of the double-blind, controlled study which gave statistically significant results, as well as the clinical study in which 88 per cent of men with a past history of poison ivy dermatitis, under conditions of heavy exposure, had no dermatitis at all.

The present report differs from those in the literature in several important aspects: First, we have reported a controlled study performed in a "blind" fashion which produced statistically valid results. Second, we recorded exposure to the ivy leaf and have been able to verify heavy and fairly constant exposure. Third, we have set very stringent criteria with which to measure the clinical efficacy of Aqua Ivy Tablets; many would consider mild lesions, as we have defined them, as constituting excellent clinical results.

One problem must be acknowledged. Tablet ingestion in both studies was not preseasonal but coseasonal. During the first six weeks of the double-blind study (1956), thirteen men in the experimental group contracted the dermatitis, as compared with five men in the control group. Although the thirteen men in the first group did not develop a dermatitis again during the season, after more prolonged therapy, the early appearance of the dermatitis must be explained. One can only speculate at this time since a definite answer can come only from later studies which begin at least six weeks preseasonally. It is our impression, however, that many of these reports of "poison ivy dermatitis" were actually minor side effects—mild cases of dermatitis due to ingestion of the Aqua Ivy Tablets. To support this concept, we refer to the one subject in the controlled study and the three subjects in the clinical study who reported such mild lesions as "side effects" because they were certain that they had not been exposed to the ivy leaf. On the other hand, subjects being exposed would consider such lesions to be due to their contact with the leaf. Walzer[15] has shown that such an absorption is quite possible for molecules of this size.

There are minor drawbacks to the experimental procedure which should be mentioned. One is the lack of a physician's confirmation of the diagnosis of poison ivy dermatitis in 75 per cent of the cases. However, the captains are fairly competent in this regard, and their errors (if any) would have tended to be balanced out in the controlled study and toward an increased incidence of ivy dermatitis in the clinical study.

The relative absence of side reactions and the complete absence of toxicity are extremely important findings. No pruritus ani, mouth irritation, lesions of the hands due to handling the tablet, or significant gastrointestinal upset was reported. Incidental complete blood counts done on several subjects during the study were without abnormality. The key here seems to be the use in the Aqua Ivy Tablets of the pyridine-ivy resin complex which is alum precipitated and slowly absorbed. From this, it appears that previous side reactions which had rendered oral prophylaxis impractical were due to the native solubility and toxicity of the unaltered ivy resins in oil or alcohol. This impression certainly merits more detailed confirmation with more complete laboratory studies. These were not possible in these studies, but it should be noted that no clinical indication for such laboratory work appeared.

The duration of immunity remains unanswered and awaits further work.

SUMMARY

1. A controlled, double-blind study and a clinical study were performed in an effort to evaluate the use of Aqua Ivy Tablets as a means of providing oral prophylaxis against poison ivy dermatitis.

2. In the controlled study, the following pertinent results were obtained:

(a) Allowing a six-week incubation period for the formation of immunity, Aqua Ivy Tablets provided full protection for 94

per cent of the subjects who took the drug, so that only 6 per cent showed any form of poison ivy dermatitis. This is statistically a highly significant difference from the 21 per cent incidence of the dermatitis in the control group ($\frac{1}{2}p = 0.018$).

(b) Aqua Ivy Tablets protected 81 per cent of the men with prior history of poison ivy dermatitis, so that only 19 per cent of these men showed the dermatitis. This compares well with the 47 per cent incidence of poison ivy dermatitis in the "sensitive" men in the placebo group ($\frac{1}{2}p = 0.094$).

(c) There was only one man in the entire Aqua Ivy Tablet group who had more than a mild case of poison ivy dermatitis (1.5 per cent).

3. In the clinical study, after six weeks of tablet ingestion, 88 per cent of "sensitive" subjects had no dermatitis at all and 95 per cent of "sensitive" subjects had good results (that is, they had only minimal poison ivy dermatitis). In the entire group of 112 men, 95 per cent had complete immunity after six weeks and 98 per cent had good results.

4. No significant side effects appeared in the controlled study. In the clinical study, three "sensitive" subjects (2.5 per cent) reported a minimal and transient dermatitis in the web of the fingers which did not require therapy or necessitate interruption of tablet ingestion.

5. The over-all findings tend to show that Aqua Ivy Tablets provide a safe and effective means of oral prophylaxis against poison ivy dermatitis.

The work of Drs. G. P. Ferrazzano, United States Public Health Service Hospital, Chicago, Illinois, and John P. Schlemmer, United States Public Health Service Clinic, St. Louis, Missouri, in aiding in the collection of the data is gratefully acknowledged. We wish to express our appreciation to the men of the Second Coast Guard District for their participation and assistance.

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