

ACETIC ACID SENSITIVITY AS A CAUSE OF COLD URTICARIA

RICHARD D. WISEMAN, M.D., AND DANIEL K. ADLER, M.D., SYRACUSE, N. Y.

THE subject of cold urticaria has been well documented since Blachez¹ first reported the condition in 1872 after Bourdon² had initially recognized it in 1866. Since then, many others have written on the subject, among them Lewis and Grant,³ Horton and Brown,^{4, 5} Duke,⁶ Bray,⁷ Urbach,⁸⁻¹⁰ Walzer,¹¹ Notier and Roth,¹² Sherman and Seeborn,¹³ Rajka and Asboth,¹⁴ Von Gerd,¹⁵ Illig,¹⁶ Herlitz,¹⁷ and Sheldon, Mathews, and Lovell.¹⁸ These authors have either presented cases describing the syndrome or discussed the probable immunologic mechanisms responsible for it, but no one has presented a case of cold urticaria which has been proved to be caused by a specific antigenic factor. To date, the cure of true allergic cold urticaria by means of allergic management has not been reported. It is the purpose of this discussion to describe a patient with a prolonged history of severe cold urticaria whose symptoms were related to the ingestion of acetic acid and were proved to be caused by a specific sensitivity to this acid. Since this patient had a remarkable clinical course and obtained a complete remission following allergic management, it seemed worth while to present the study of his case, especially with the thought in mind that new fields of investigation regarding causative mechanisms of physical allergies might be opened.

CASE PRESENTATION

P. A., a 35-year-old single male baker, was first seen on Jan. 26, 1954. He gave a four-year history of recurrent bouts of hives on the uncovered parts of the body following exposure to cold. The major areas involved were the head, face, ears, feet, and hands. He also complained of swelling in his throat following the ingestion of ice cream or very cold drinks. During recent years the hives became progressively worse, flaring up each fall at the onset of cold weather. The patient stated that he never had hives after swimming during the summer months. Antihistamines afforded him only temporary relief, and it was often necessary for him to remain in a warm room for over an hour before the swelling subsided. No symptoms suggesting dermatographism were elicited. Hives had occurred intermittently all his life, and as a youngster he used to take Adrenalin under the tongue for relief of acute attacks. During the patient's childhood, citrus fruits, tomatoes, and certain brands of butter seemed to precipitate bouts of hives. He stated that he now ate tomatoes without difficulty, but still avoided citrus fruits. The patient had been a baker for the past ten years. He had lived at home with his parents in the lower half of a two-story house, where he had not been exposed to animal dander and had never followed dust precautions. Cottonseed flour was not used in the bakery, and no association between his symptoms and his work was noted. He used scented aftershave lotions and powders, and was exposed to average quantities of insecticides when the bakery was sprayed once a month by an exterminating service. The diet contained rather sizable quantities of chocolate, nuts, and spices, but the patient admitted a strong aversion to milk. He drank moderate amounts of beer and smoked six or seven cigars a day. Family history was completely negative for allergy as far as could be ascertained. Operations included a hemorrhoidectomy and a tonsillectomy.

Received for publication June 22, 1955.

Complete physical examination was essentially negative except for an injected nasal mucous membrane and marked cloudiness on transillumination of the frontal and antral sinuses. Chest fluoroscopy, urinalysis, blood sugar, sedimentation rate, and Wassermann all gave normal results. The blood count showed a 5 per cent eosinophilia.

Scratch tests for dermatographism were negative. When an ice cube was applied to his skin for three to five minutes, an urticarial lesion quickly formed in the exposed area. Blood was drawn and stored at refrigerator temperature for five weeks. Ice cube tests on sites in normal skin passively sensitized with the five-week-old serum were negative. The patient was seen approximately twice a week for further observation, and at each visit quickly showed a hive wherever an ice cube was placed on his skin.

Since patients with a physical allergy to cold usually get severe urticaria following swimming, the fact that our patient did not respond similarly was most puzzling. After exhaustive questioning, the patient finally remembered that he started to ingest very large quantities of sauerkraut at approximately the same time that his urticaria began four years previously. He was on a reducing diet and ate the sauerkraut because of its low caloric value. He remembered that he did not eat sauerkraut during the summer months, as it was unobtainable. He was therefore told to avoid sauerkraut and was observed for a change in his clinical condition. The following week the patient noticed a very definite diminution in his response to cold. When the ice cube was removed from the skin at this time, the hive did not form as quickly as had been previously observed, taking twenty to twenty-five minutes instead of three to five minutes.

During the next month, after institution of his elimination diet, he was quite comfortable but continued to keep a food diary. He noted that the ingestion of dill pickles, followed within an hour by a cold beverage, precipitated an edematous response in the mucous membrane of the hypopharynx. It was during a warm period in March that this reaction occurred. Since acetic acid is one of the main ingredients common to both sauerkraut and dill pickles, it was decided to investigate the possibility that sensitivity to this chemical compound was causing his allergic condition. With this in mind, the patient was advised to abstain from all foods which might contain acetic acid. He continued to be asymptomatic and, for the first time in four years, observed no hives following exposure to cold.

The sauerkraut was made from cranberries, cabbage, and salt, while the pickles contained vinegar, spices, thyme, dill, garlic, and sodium benzoate. On infrequent occasions when he had eaten plain cabbage or cranberries no unusual reactions had occurred. After obvious improvement had taken place during the first six weeks of the elimination diet, he again noted mild attacks of urticaria on exposure to cold shortly after adding sauerkraut or dill pickles to his diet. As soon as he avoided these foods, the hives subsided.

In order to eliminate the possibility that psychogenic factors may have influenced the results, special ingestion tests were performed. A thick carbohydrate placebo mixture with a strawberry-peppermint flavor was prepared with lemon juice added in an attempt to simulate an acid flavor. Because of the warm weather at this time, the only way the reaction could be reproduced was to have the patient consume some chilled material following ingestion of the test mixture. He was given about 15 ml. of the placebo mixture on two different occasions, following which he immediately ate some ice cream and noted no unusual reaction. He was then given 15 ml. of the placebo mixture with the addition of about 2 ml. of 2 per cent acetic acid. He again ate some ice cream and within fifteen minutes felt his throat begin to swell. The acetic acid had been obtained from ordinary vinegar. This 2 per cent solution was then diluted 1:1,000, 1:100, and 1:10 for skin testing purposes. Direct skin testing with these dilutions produced no greater reaction in the patient than was obtained on testing control subjects. It was observed that, in spite of his previous supposed sensitivity to citrus fruits, he could now ingest lemon juice, such as was used in the placebo mixture, without any untoward effects, indicating that probably he was no longer sensitive to lemon or other citrus fruits.

After a six-month lapse in observation, the patient has recently been restudied. He had been following the elimination diet very carefully. The ice cube test was now completely

negative, even after application to the skin of the forearm for a period of fifteen minutes. He was able to take pans out of a freezer at 10° F. in the bakery with his bare hands.

Because of the patient's previous history suggesting a possible sensitivity to citric acid and the fact that both lactic acid and acetic acid are found in large quantities in sauerkraut, it was decided to skin test him with chemically pure acetic, lactic, and citric acids. After no signs of cold urticaria had appeared for many months, skin tests on Dec. 7, 1954, with these .1 per cent chemically pure acids were negative. Tests done with .01 per cent acid solutions, followed by application of an ice cube over the skin test area for fifteen minutes, were also negative. When the intradermal tests were repeated, however, with .1 per cent acids, followed by application of an ice cube to the test sites for fifteen minutes, a definite urticarial response was obtained over the acetic acid site which gradually swelled into a wheal larger than a half dollar (4 cm. in diameter) during the next half-hour. No similar reaction was observed over the lactic acid or citric acid sites.



A.

B.

Fig. 1.—A, Skin test with .1 per cent chemically pure lactic acid twenty-five minutes after ice cube was placed over test site. B, Skin test with .1 per cent chemically pure acetic acid twenty-five minutes after ice cube was placed over test site.

The same reaction was repeated on three separate occasions within a period of one week and each time, after removal of the ice cube from the acetic acid test site, the wheals began to form within five minutes and reached their maximum size five to ten minutes later (twenty to twenty-five minutes following the original contact of the ice with the acetic acid test site). Application of ice to the skin concomitantly for fifteen minutes in an area not previously skin tested, or in an area where a skin test with a .1 per cent lactic acid test had been performed, produced no urticarial response in either site (Fig. 1). The patient further stated that the lesion produced in the acetic acid test site definitely itched and felt like a typical hive. Placing an ice cube for fifteen minutes over a skin test with .1 per cent chemically pure acetic acid on several control subjects (nonallergic persons) gave completely negative reactions. Unfortunately, during the preliminary passive transfer studies of the

patient's serum, a skin test with acetic acid followed by an ice cube over the test site was not done. When this procedure was eventually carried out on the original serum after it had been refrigerated for ten months the test was negative.

Six weeks after the positive direct skin tests had been obtained, serum was withdrawn for additional passive transfer studies. Nonallergic persons were then sensitized with four-day-old filtered serum and were tested by placing an ice cube over an area previously injected with .1 per cent chemically pure acetic acid. No positive reactions were obtained. A few days later nonallergic subjects were sensitized with unfiltered serum four hours after it had been withdrawn. Skin testing of these sites with acetic acid plus an ice cube over the test site produced no positive responses, regardless of whether the tests were performed immediately or twenty-four hours following sensitization. Direct skin testing of the patient at this time with acetic acid in the presence of cold also produced a negative reaction. (See Table I for summation of testing results.)

TABLE I. SUMMATION OF TESTING RESULTS

DIRECT TESTING			INDIRECT TESTING		
DATE	TESTING MATERIAL	RESULTS	DATE	TESTING MATERIAL	RESULTS
3/20/54	Acetic acid .01%	Negative	2/ 1/54	Serum drawn	
3/20/54	Acetic acid .1%	Negative	3/ 8/54	Ice cube test on 2/1/54 serum	Negative
3/20/54	Ice cube test	Positive	12/ 7/54	.1% C.P.A.A. and ice cube over test site on 2/1/54 serum	Negative
12/ 7/54	.1% C.P.A.A.*	Negative	1/14/55	Serum drawn	
12/ 7/54	.1% C.P.A.A. and ice cube over test site	Positive	1/18/55	.1% C.P.A.A. and ice cube over test site on 1/14/55 serum	Negative
12/ 7/54	Plain ice cube test	Negative	1/24/55	Serum drawn	
12/ 7/54	.1% C.P.L.A.†	Negative	1/24/55	Tests performed on unfiltered serum with .1% C.P.A.A. and ice cube over test site 4 hours following withdrawal on 1/24/55	Negative
12/ 7/54	.1% C.P.L.A. and ice cube over test site	Negative	1/25/55	Tests performed on unfiltered serum with .1% C.P.A.A. and ice cube over test site 24 hours following withdrawal on 1/24/55	Negative
12/ 7/54	.1% C.P.C.A.‡	Negative			
12/ 7/54	.1% C.P.C.A. and ice cube over test site	Negative			
12/ 9/54	.1% C.P.A.A. and ice cube over test site	Positive			
12/ 9/54	.1% C.P.L.A. and ice cube over test site	Negative			
12/12/54	.1% C.P.A.A. and ice cube over test site	Positive			
12/12/54	.1% C.P.L.A. and ice cube over test site	Negative			
1/24/55	Plain ice cube test	Negative			
	.1% C.P.A.A. and ice cube over test site	Negative			

*C.P.A.A. chemically pure acetic acid.

†C.P.L.A. chemically pure lactic acid.

‡C.P.C.A. chemically pure citric acid.

He was then instructed to eat foods made with acetic acid to see if the hives would recur. During the next three months, he continued to ingest sauerkraut frequently without developing hives or any symptoms suggesting a mucous membrane hypersensitivity to cold.

The fact that we were not able to passively transfer the patient's reaction to acetic acid in the presence of cold means that if reagins were present they probably were produced for only a short time and that, if the studies could have been done at exactly the same time the direct reactions were obtained, reagins might have been demonstrated. Knowing that the reagenic sensitivity, which does occasionally occur in drug sensitivities, is usually of a transient nature, it is not surprising that our patient may have had a similar response.

The only previously recorded case of a patient who was thought to have cold urticaria from a specific chemical sensitivity was described by Herlitz.¹⁷ He discussed a 15-month-old girl who appeared to have urticarial-like lesions on the exposed parts of her body after being out in cold weather. She was being treated at the time with Tulo tablets (throat lozenges containing menthol). The skin eruption had been present for only a few days and appeared to be directly related to the ingestion of these tablets, since the reaction stopped shortly after she was taken off the lozenges and reappeared following reinstitution of this medication. A confusing aspect of the case report, however, was the fact that when the patient was again given the lozenges, her skin lesions recurred following exposure to cold weather, but the ice cube test was negative. It is difficult to understand how one with active cold urticaria can have a negative ice cube test, especially when it was previously positive.

Abramson¹⁹ reported a case of nonallergic cold urticaria which responded well to psychiatric therapy. There was no evidence in the patient's personal or family history to indicate that it was an allergic problem.

Urbach, Linneweh, and Greenberg²⁰ described a patient who developed urticaria after the ingestion of pork sausage which contained large amounts of pork blood. Following repeated exposures to the material, he eventually developed cold urticaria, as the lesions would only occur on areas just previously bathed with cold water. When given plain pork sausage which did not contain any pork blood, the reaction to cold did not take place. Since the patient signed out of the hospital prematurely, no further investigative studies could be conducted to determine what factor in the pork blood was responsible for the reaction.

Two additional cases of cold urticaria which responded well to treatment have also been reported by Urbach.^{8, 9} One was a patient with a localized tooth infection whose urticaria cleared following removal of the tooth. The other was a 25-year-old woman with an intermittent twelve-year history of cold urticaria following the onset of her menses at age 13. The only periods free of urticaria during this time were while she was pregnant. The pelvic findings were normal, and the urticaria ceased after she received injections of posterior pituitary hormone combined with x-ray therapy to the pituitary gland.

Because of the belief that acetic acid is a normal constituent of body metabolism, it may be questioned whether hypersensitivity to acetic acid can occur. Personal discussion of this point with Dr. W. W. Westerfeld,²¹ professor of biological chemistry at New York State College of Medicine, Syracuse, New York, has revealed the fact that currently it is believed that acetic acid is not a normal intermediate in body metabolism. As early as 1933, Himwich and his group²² observed that no free acetic acid could be found in the blood following the metabolism of ethyl alcohol. Later, in 1939, Friedemann and Kmiecik²³ confirmed the work of Himwich and his associates,²² adding further evidence to show that free acetic acid is not a normal breakdown product of body metabolism. In so far as is known, acetic acid is not present in the free state in any measurable quantity but is present in combination with a coenzyme,

CoA, as acetyl CoA. Because free acetic acid is not a normal product of body metabolism, it is possible that hypersensitivity to this compound could occur in human beings.

It would appear that the patient discussed in this article had a specific chemical sensitivity which produced the cold urticaria and that, following the elimination of this chemical from his diet, the allergic activity quickly subsided. The findings suggest that, in the presence of cold, either (1) the acetic acid acted as a hapten to form a complex antigen responsible for the allergic reaction or (2) the cold acted as a more suitable medium to permit the acetic acid hypersensitivity to take place. In this respect, the cold could have been a catalyst in the allergic reaction.

We believe that these findings are also significant because a new technique of testing for drug sensitivity may have been demonstrated. This type of testing may be especially valuable in the study of patients with physical allergies due to chemical sensitivities.

CONCLUSION

1. The case history has been presented of a patient who has apparently been cured of recurrent cold urticaria and mucous membrane hypersensitivity to cold of four years duration by avoidance of foods containing acetic acid.

2. After diet elimination, ingestion of a placebo mixture followed by ice cream produced no mucous membrane response. When a minute quantity of acetic acid was added to this mixture and the ingestion was followed by ice cream, pharyngeal edema quickly developed.

3. Direct skin testing with .1 per cent chemically pure acetic acid was negative, but when an ice cube was immediately placed over the test site for fifteen minutes an urticarial reaction resulted. Ice cube tests performed concomitantly over untested skin or over an area tested with .1 per cent chemically pure lactic or citric acid were negative. Similar testing with .1 per cent chemically pure acetic acid plus an ice cube over the test site in normal control subjects gave negative reactions.

4. A new technique for skin testing for drug sensitivities in patients suffering from physical allergies has been suggested.

REFERENCES

1. Blachez: Observation d'urticarie, Bull. et mém. Soc. méd. hôp. Paris 9: 270, 1872.
2. Bourdon, H.: Note sur l'urticarie intermittente, Bull. et mém. Soc. méd. hôp. Paris 3: 259, 1866.
3. Lewis, T., and Grant, R. T.: Vascular Reactions of the Skin to Injury. Part II. The Liberation of a Histamine-like Substance in Injured Skin; The Underlying Cause of Factitious Urticaria and of Wheals Produced by Burning; and Observations Upon the Nervous Control of Certain Skin Reactions, Heart 11: 209, 1924.
4. Horton, B. T., and Brown, G. E.: Cold Allergy, Report of Two Cases, Proc. Staff. Meet., Mayo Clin. 2: 276, 1927.
5. Horton, B. T., and Brown, G. E.: Systemic Histamine-like Reactions in Allergy Due to Cold: Report of 6 Cases, Am. J. M. Sc. 178: 191, 1929.
6. Duke, W. W.: Treatment of Physical Allergy, J. ALLERGY 3: 642, 1932.
7. Bray, G. W.: A Case of Physical Allergy; A Localized and Generalized Allergic Type of Reaction to Cold, J. ALLERGY 3: 367, 1932.
8. Urbach, E.: Kälteurticaria auf Grundlage einer Zahnneiterung Zentralbl. Haut- u. Geschlechtskr. 50: 646, 1935.

9. Urbach, E.: Kälteurticaria auf Grundlage Ovariell-endokrines Störungen, Zentralbl. Haut- u. Geschlechtskr. 50: 646, 1935.
10. Urbach, E., and Gottlieb, P. M.: Allergy, New York, 1946, Grune & Stratton, Inc.
11. Walzer, M.: A Critical Review of the Recent Literature on Physical Allergy, Intrauterine Sensitization, the Mechanism of Specific Treatment in Hay Fever, Hypersensitiveness in Monkeys, J. ALLERGY 9: 64, 1937.
12. Notier, V. A., and Roth, G. M.: Treatment of Hypersensitiveness to Cold With Benadryl: Report of a Case, Proc. Staff. Meet., Mayo Clin. 21: 170, 1946.
13. Sherman, W. B., and Seebohm, P. M.: Passive Transfer of Cold Urticaria, J. ALLERGY 21: 414, 1950.
14. Rajka, E., and Asboth, A.: Cold Urticaria, Ann. Allergy 9: 642, 1951.
15. Von Gerd, F.: Behandlung der Kälteurticaria mit Antistin (Ciba) Med. Klin. 47: 966, 1952.
16. Illig, L.: Experimentell—Therapeutische Untersuchungen Bei Kalteurticaria, Klin. Wchnschr. 30: 642, 1952.
17. Herlitz, G.: Cold Urticaria on Nutritional—Allergic Base With Contralateral Urticarial Reaction After Exposure to Cold, Internat. Arch. Allergy 4: 10, 1953.
18. Sheldon, J. M., Mathews, K. P., and Lovell, R. G.: The Vexing Urticaria Problem: Present Concepts of Etiology and Management, J. ALLERGY 25: 525, 1954.
19. Abramson, H. A.: Psychodynamics and the Allergic Patient, ANN. ALLERGY 6: 219, 1948.
20. Urbach, E., Linneweh, F., and Greenberg, S.: Blood Urticaria, Including a Contribution on Metallergic Genesis of Cold Urticaria, Arch. Dermat. & Syph. 39: 987, 1939.
21. Westerfeld, W. W.: Personal communication.
22. Himwich, H. E., Nahum, L. H., Rakieten, N., Fazikas, J. F., Dubois, D., and Gildea, E. F.: The Metabolism of Alcohol, and J. A. M. A. 100: 651, 1933.
23. Friedemann, T. E., and Kmiecik, T. C.: Free Volatile Acidity of Blood and Tissues Following Ingestion of Ethyl Alcohol, Proc. Soc. Exper. Biol. & Med. 40: 669, 1939.