

STUDIES IN FOOD ALLERGY

II. SENSITIZATION TO FRESH FRUITS: CLINICAL AND EXPERIMENTAL OBSERVATIONS

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IT IS a well-recognized and generally accepted fact that allergy to fruits is a frequent cause of allergic disturbances, particularly of the cutaneous variety. Urticaria, angioneurotic edema, burning or itching sensations of the mouth, canker sores, and diarrhea are the usual types of disturbance caused by such sensitization, although it occasionally may be responsible for such manifestations as migraine, allergic coryza, or even asthma. Symptoms more often follow the eating of the raw fruit than when it is cooked, canned, or preserved. This explains the greater incidence of urticaria in the summer when more fresh fruits are ingested than at any other time of the year.

Almost any type of fruit may cause symptoms of allergy; however, statistical evidence as to the frequency is quite variable. This is undoubtedly due to the fact that most of this evidence is obtained from the results of skin tests rather than from clinical findings. Fruit allergens used for skin testing usually are prepared in a rather concentrated solution, yet negative skin reactions often are obtained in individuals who give definitely positive clinical histories and in whom the symptoms may be induced by ingestion of the suspected fruit. Attempts have been made to explain this discrepancy usually upon the basis of the symptoms being produced by some intermediate—or split—product, but as yet no acceptable evidence has been offered in substantiation of these claims. Other related facts awaiting suitable explanation are that the skin of the fruit (e.g., orange or lemon peel or peach skin) may provoke symptoms in some patients when the edible portion of the fruit does not; also that group allergies exist, for example, among all citrus fruits or to apples and pears or to peaches, cherries, apricots, and plums.

Our interest in this particular phase of food allergy began in 1936 while studying three patients who repeatedly displayed symptoms typical of food allergy following the ingestion of certain fresh fruits. Skin tests, however, even with the concentrated stock extracts of these fruits were consistently negative. We decided at that time to test the patients with the freshly extracted juices. To our surprise markedly

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positive reactions were obtained. This formed the basis of the further studies which are included in the present initial report.

Before detailing the results of these studies, it might be well first to review briefly the clinical histories of these three patients as well as that of a fourth more recent addition belonging to the same group.

CASE REPORTS

CASE 1.—E. L., female, aged 24 years, was first seen on July 9, 1938, because of asthma beginning in childhood and recurring each week since. Each spell lasted from five to fifteen minutes and subsided spontaneously. In 1926 she developed typical fall hay fever and in 1933 mild spring hay fever, lasting three weeks during the month of May. She was subject to paroxysms of sneezing while riding a horse. The ingestion of fresh fruits (watermelon, honeydew melon, cantaloupe, pears, peaches, pineapple, and grapes) produced swelling of the mouth and throat. This occurred throughout the year but was more noticeable during the hay fever seasons. This peculiar reaction to fresh fruits (except plums) was first noted in 1927. Canned or stewed fruits failed to produce the reaction.

CASE 2.—V. B., male, aged 45 years, was first seen April 20, 1936, with fall hay fever present since 1922 and complicated by pollen asthma in 1929. The ingestion of pears, peaches, cantaloupe, bananas, oranges, and grapes caused an itching of the soft palate that was much more noticeable during the pollen season than at any other time. There was no aggravation of this hay fever syndrome following the ingestion of these foods. Canned and stewed fruits failed to produce this reaction.

CASE 3.—J. R., male, aged 40 years, was first seen on April 9, 1936, because of hay fever that began in 1929 and lasted from late April to late June and from mid-August to late September. Mild pollen asthma accompanied the fall hay fever. Tightness of the neck and itching of the throat followed the ingestion of oranges, watermelon, peaches, and cantaloupes. This was particularly annoying during the hay fever seasons, being mild and negligible at other times of the year.

CASE 4.—D. H., male, aged 23 years, medical student, was first seen on Feb. 6, 1941, because of severe seasonal hay fever and asthma that started in childhood and recurred from early April to late June. He experienced swelling of the mucous membrane of the mouth following ingestion of fresh green peas, apples, and peaches. Cooked or canned fruits failed to produce this swelling.

PROCEDURES AND RESULTS

Direct skin tests with the freshly extracted juice of most of the clinically reacting fruits were performed in the above patients. The juice used in the tests was obtained by first removing the skin of the fruit, then squeezing the whole fruit or its slices through ordinary gauze over a beaker and centrifuging the filtered material. The supernatant fluid then was removed and used in the skin tests as the fresh juice. Strict asepsis was not possible, but the operation was carried out as carefully as possible to avoid contamination. That little or no bacterial contamination occurred is indicated by the fact that not a single instance of infection was encountered in spite of the large number of

tests done with the fresh juice obtained in this way. Whenever possible and unless the conditions of the experiment demanded otherwise, the material always was stored in the refrigerator to prevent bacterial growth.

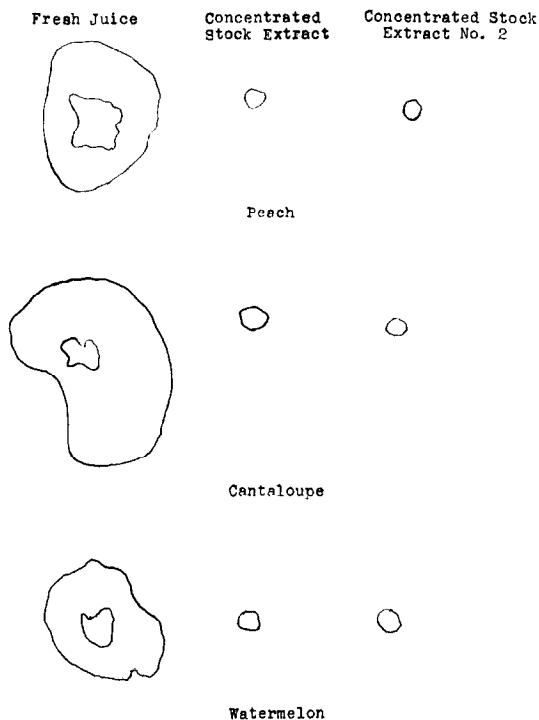


Fig. 1.—Direct skin tests on E. L.

As already stated, we were considerably surprised when definitely positive skin tests were obtained in the first three patients with the freshly extracted fruit juices to which they were clinically sensitive (including peach, apple, pear, pineapple, plum, cantaloupe, watermelon, and grape). On the other hand, similar tests with the concentrated stock extracts, both in the liquid and powdered states, were negative. By contrast, positive reactions to both the stock extract and freshly prepared juice of tomato were obtained in the patient in Case 2. The tomato juice was tested because it induced similar clinical symptoms after ingestion. The patient in Case 4, seen first in 1941, was tested only with peach and apple extracts. He likewise showed positive reactions to the fresh juices and negative reactions to the stock extracts.

The type of reaction occurring in the patient in Case 1, who was tested with the freshly extracted juice, is illustrated in Fig. 1 and may be taken as representative of the entire group. In order to be certain that failure to get reactions with the stock extracts was not attribu-

table to their impotency, the patients also were tested with the concentrated stock extracts obtained from two other allergy laboratories (L. C. and A. B.). The latter reacted in the same manner as our own extracts (Figs. 1 and 3). Control skin tests with the fresh juices likewise were performed upon a group of normal nonallergic persons and a group of allergy patients with negative clinical histories so as to determine the specificity of the reactions. Negative reactions were obtained in all instances, indicating that the material used was non-irritating and that the positive reactions were specific.

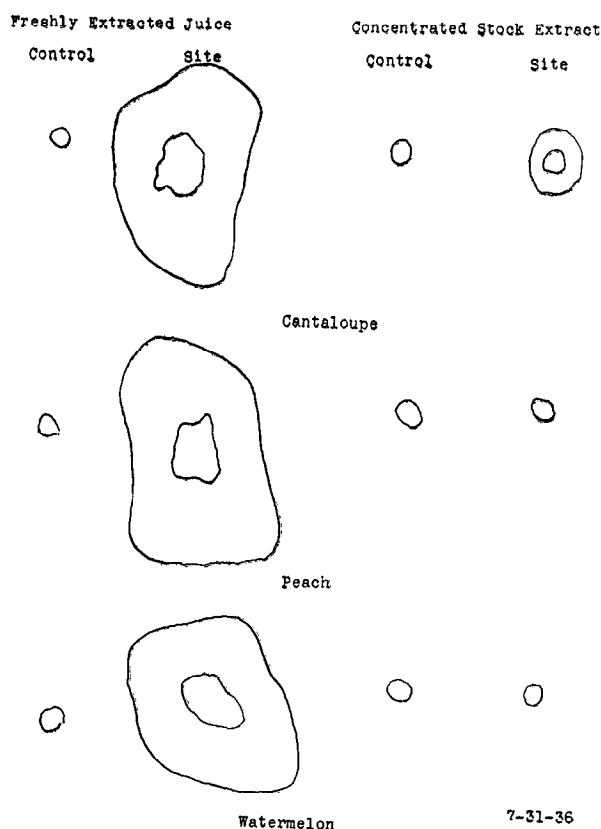


Fig. 2.—Passive transfers with E. L. serum.

Blood was withdrawn from all of these patients and the serum used for passive transfer by the usual Prausnitz-Küstner technique. Positive reactions similar to those of the direct skin tests were obtained in all instances in the sensitized sites with negative reactions in the nonsensitized or control sites, as illustrated in Fig. 2. It was evident, therefore, that sufficient reagins were present in the serum of these patients to induce passive sensitization.

These findings, obtained originally in 1936, were considered extremely significant at that time, but it was deemed inadvisable to report them until they could be corroborated and the basis investigated. When we attempted to repeat them in 1937 and 1938 (during the early summer when fresh fruits were in abundance) we failed to obtain the same results. In fact it was not until the appearance of Case 4 in 1941 that the original findings were duplicated. Careful review of our original experiments indicated that the initial results followed the use

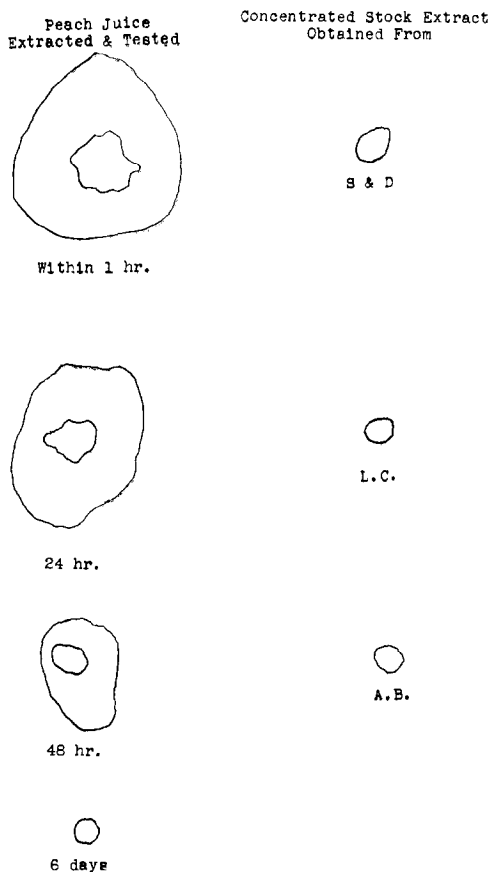


Fig. 3.—Direct skin tests on D. H.

of freshly extracted juice that had been used immediately in the skin tests, whereas in the later attempts on the same patients, the juices used had been prepared several days in advance of the time when the skin tests were performed. This naturally accounted for our inability in 1937 and 1938 to verify the initial observations. When we adhered to the original technique and tested with the freshly extracted juice, we were able to confirm our earlier findings both by direct skin reactions and passive transfer.

In order to determine the time required for the deterioration of the fresh juice to occur, freshly extracted juice was allowed to remain in the refrigerator and samples withdrawn at periodic intervals. Each sample was then tested both directly on the patient and in passively sensitized sites to ascertain the relative potency. The results illustrated in Figs. 3 and 4 demonstrate the rapid diminution in the potency of these extracts. Deterioration was greatest apparently within the first twenty-four hours and was complete within three to four days.

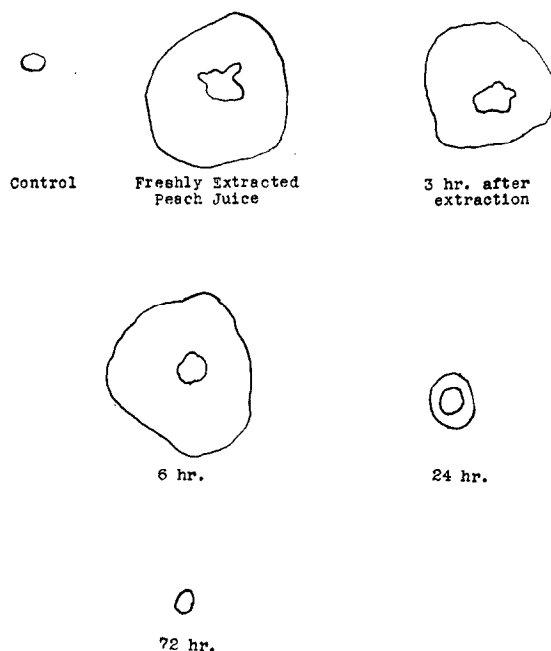


Fig. 4.—Passive transfer tests with D. H. serum.

It will be noted that these patients were able to take stewed or canned fruits with impunity. Evidently, therefore, the antigen must have been destroyed or altered in the process and skin tests with extracts of the denatured fruit were negative. We also were interested in the effect of rapid freezing (frozen fruits) upon the allergenic qualities of fresh fruits. Individual extracts were prepared from the stewed, canned, and frozen peaches in the same manner as from the fresh fruits. Direct and indirect skin tests with these extracts showed that the stewing and canning process rendered the extracts inactive while freezing did not destroy their allergenic properties (Fig. 5). The extracted juice of the frozen fruit deteriorated in the same manner and approximately at the same rate as that of the fresh fruit.

While attempting to sterilize the freshly extracted juices by Seitz filtration, it was noted that a marked diminution in activity occurred

(see Fig. 5). This procedure was repeated several times with identical results on each occasion.

Although the original direct skin tests were carried out with the fresh juices of those fruits to which the patients gave positive clinical histories, nearly all the subsequent observations herein reported were made with the peach extracts. We have suggestive evidence from other experiments that other fruit juices behave in a similar manner and hope to be able to include it in subsequent communications when the evidence is more definite and conclusive.

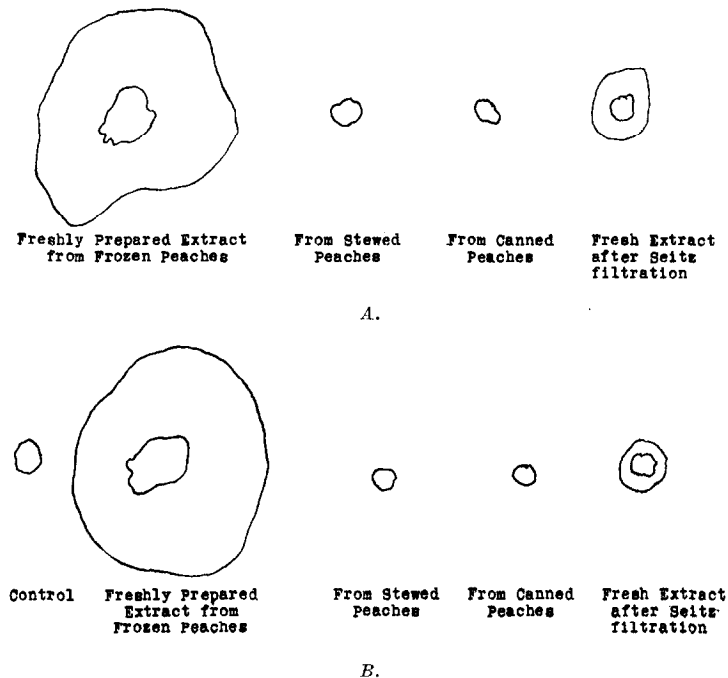


Fig. 5.—A, Direct skin tests on D. H.; B, Passive transfers with D. H. serum.

DISCUSSION

It is evident, therefore, from these results that the juices of fresh fruits, exemplified by the peach, contains a labile antigen which may be responsible for the clinical manifestations of fresh fruit sensitization. In the four patients studied, the symptoms produced by clinical trial with the offending fruit were quite similar and constant in each patient. Since skin tests with the stock extracts even in concentrated form were consistently negative, it was assumed that some change had taken place in the course of its preparation to render it impotent. This deterioration was indicated by the rapid diminution in the size of the skin test reactions obtained with the peach juice at various intervals after its extraction, even though it was kept in the refrigerator during this period.

Deterioration begins apparently within a few hours after extraction and may be complete within one to three days. The demonstration of the lability of the active agent in the peach juice upon standing explained our failure to verify our original observations made in 1936, because subsequent experiments were carried out with juice that was several days old. When we used the fresh juice shortly after extraction upon the same patients, positive reactions could again be obtained.

It will be noted both from the histories and the result of the skin tests with the fresh juice that each patient showed reactions to more than one fresh fruit but these were not always in the same botanical group. Thus Case 1 (E. L.) developed symptoms from peaches but not from plums, even though both are in the same botanical group. Further study will be necessary however in order to determine more definitely whether a common antigen is present in the various botanical groups of fruits.

The absence of positive skin reactions to the juices of stewed and canned fruits is in accord with the patients' clinical histories and with general clinical experience in food allergy. Denaturization of fresh fruits seems to alter or destroy the allergenic factor in such a way as to enable patients clinically sensitive to the fresh fruit to ingest the denatured fruit without untoward effect. Rapid freezing on the other hand does not alter the allergenic property of the fresh fruits that we have thus far investigated.

Seitz filtration materially reduces the antigenic property of fresh fruit extracts. This raises the question of sterilization of these extracts by some other means that will not alter or reduce their allergenic properties. Other means of sterilization have been tried but have not yet been considered sufficiently satisfactory for present report.

SUMMARY

1. We have demonstrated the presence of a labile antigen in fresh fruit extracts. Deterioration is rapid, occurring in largest proportion within twenty-four hours and being complete within one to three days.
2. This antigen is either altered or destroyed by heat during both the canning and stewing processes.
3. Rapid freezing (as in frozen fruits) seems to preserve the allergenic properties of fresh fruits.
4. Seitz filtration materially reduces the potency of the freshly extracted juice.
5. The lability of the antigen in fresh fruit juice probably accounts for the frequent failure to obtain positive skin reactions in clinically sensitive patients even with the concentrated stock extracts.

DISCUSSION

DR. LEO H. CRIEP.—This is a very timely subject. I suppose there is nothing that has helped to shake the confidence of the practicing physician in allergy more than these negative skin reactions that are obtained in clinically sensitive patients.

This is also a problem in which every allergist is interested because it deals with extracts, their preparation, preservation, and deterioration. Perhaps we could spend an afternoon some day in discussing the subject in order to arrive at some sort of standardization and uniformity. This is merely a pious wish.

Now, the authors have rendered us a very valuable service. They indicate that manipulation of materials frequently leads to loss of potency. For example, Seitz filtration, dialysis, and heating caused them to lose strength. That confirms the view that the less one fools with the material in preparing the extracts, the more likely it is that the extracts will be more potent. I certainly believe that is so.

The other point which Dr. Tuft and Dr. Blumstein emphasize, which is of particular interest to me, is the fact that freezing does not deteriorate the extract. We are now engaged in preparing extracts or at least in preserving them by drying through freezing, and our results have been very encouraging in that connection.

The pH of the extract, I think, is probably of more importance than we are accustomed to believe. For that reason, I often wonder to what extent phenol, which is used as a preservative by some of us, may interfere with keeping up the potency of the extract.

I remember one particular patient who had a rather unusual type of allergy manifested by vertigo, in whom I obtained a constitutional reaction by allowing a small amount of garlic to be introduced under his tongue. That patient gave a negative intradermal and a negative scratch test to garlic extract.

I often wonder whether the active principle which is lost is always a protein. Dr. Coca some time ago was subjecting some extracts to tryptic digestion and showed that they did not lose their potency.

DR. RACKEMANN.—Every once in a while something really important is presented to our meeting and I think this is one of those papers. I would like to congratulate Dr. Tuft and Dr. Blumstein on a fine piece of work.

DR. COOKE.—I merely wanted to add a word of commendation and verification of this in an experience which happened a good many years ago in a woman who had a very clear-cut history of reaction to raspberries, then in season. We tested her with our usual extract and got nothing at all. We then expressed the juice and immediately did a scratch test and got a very excellent positive reaction. She came in the following day and we again used the juice which had been prepared the day before, and to our amazement the test was negative. We confirmed the fact that a positive reaction could be obtained with the fresh juice of the raspberry but nothing further was done about it.