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## Original Articles

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### PURPURA DUE TO FOOD SENSITIVITY

#### USE OF SKIN TESTING IN ETIOLOGICAL DIAGNOSIS

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OSLER<sup>1</sup> in 1914 suggested that purpuras might be manifestations of anaphylaxis. Since that time it has been reported that, in a considerable number of instances, purpuras of both the thrombocytopenic and nonthrombocytopenic types are of an allergic nature. As etiologic factors foods, drugs, inhalant allergens, and infections have been suspected. However, in many cases of purpura there is no evidence of an allergic nature and in others of possible allergic nature the specific allergens are difficult to recognize. The latter may be due to improper use of the available diagnostic procedures, but it is more probably the result of the inadequacies inherent in these methods.

At present there are four procedures which may aid in detecting the specific etiology of an allergic purpura: clinical history, skin tests, elimination of suspected allergens, and clinical trials. The use of other diagnostic methods, such as determination of the leucopenic index (Vaughan),<sup>2</sup> observation of the variation in the number of circulating platelets (Squier and Madison)<sup>3</sup> or rise in the pulse rate after ingestion of the specific allergens (Coca),<sup>4</sup> has not been generally adopted. Of the diagnostic procedures available to the clinician in his attempt to elicit the cause of an allergic purpura, the clinical history is probably the most valuable. A properly taken history in many cases has led to the discovery of the specific noxious substances. The skin tests, invaluable in the etiological diagnosis of other allergic manifestations, such as hay fever, have been found to be of less practical value when applied to the study of purpuras. The early investigators of the relation between purpura and allergy, including Duke,<sup>5</sup> Landsberger,<sup>6</sup> Alexander and Eyermann,<sup>7, 8</sup> Kahn,<sup>9</sup> Barthelme,<sup>10</sup> and Rowe,<sup>11</sup> found that positive skin reactions of clinical value were not common if skin testing with ordinary extracts was done by the scratch or intracutaneous methods. These results have been substantiated by numerous other observations in the last two decades, and the sensitivity or efficacy of skin testing has not been appreciably improved. The patch test method was used by Falconer and

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Schumacher<sup>12</sup> in 1940 to verify the etiologic diagnosis in a patient with thrombocytopenic purpura due to sensitivity to Sedormid,\* with negative results.

More recently Donaldson and Scarborough,<sup>13</sup> and Ackroyd,<sup>14</sup> have applied the patch test technique in purpuras due to sensitivity to drugs and their results deserve further consideration. Donaldson and Scarborough performed patch tests with sulfathiazole in a patient suffering from nonthrombocytopenic purpura. Skin reactions of the usual eczematous type were not observed, but negative pressure applied by Scarborough's technique<sup>15</sup> to the sites of the patch tests revealed definite evidence of a reduced local capillary resistance. Ackroyd<sup>14</sup> investigated patients with thrombocytopenic purpura due to Sedormid. He was unable to obtain positive skin reactions with either the scratch or intracutaneous methods and could not demonstrate evidence of increased local capillary fragility after applying these tests. However, when Sedormid patch tests were applied, positive skin reactions and increased local capillary fragility were observed.

A third procedure, the elimination of suspected foods or drugs or the use of extensive elimination diets, has, in many cases, provided diagnostic clues. The final proof that a suspected allergen is the real offender can only be obtained by the fulfillment of Cooke's<sup>16</sup> postulates: the clinical manifestations should disappear after removal of the suspicious allergen and should be reproduced at will after proper exposure to it. The "provocative method of testing" is based on this concept. With its use one endeavors to reproduce the clinical symptomatology on a small scale by the controlled administration of small doses of the suspected allergen.

We have been able to study and follow a patient who exhibits a nonthrombocytopenic purpura due to sensitivity to crustaceans. The skin tests performed with foods in this individual have shown some peculiarities which, we believe, deserve to be reported. As a result of this study it is now apparent that the food testing materials containing crustaceans can be employed in a manner different from the usual skin testing routine used in the past. Moreover, the presence of multiple, antigenic fractions in some foods (crustaceans) recognized by Tuft and Blumstein,<sup>17</sup> has been reaffirmed and their properties established in relation to their presence or absence in fresh foods, frozen foods or commercial extracts.

#### CASE REPORT

H. T., a 30-year-old white, male teacher, was first seen on Dec. 28, 1947, because of ecchymoses on the back and legs associated with swelling of the left leg and foot.

He reported that on Christmas Eve he ate a salad which subsequently was discovered to contain minced crab and shrimp. On the following day he noticed that both ankles were swollen and covered with purpuric spots. Gradually the entire left leg and foot became swollen and purpuric spots appeared on both legs and on the back. The history revealed that this was his second attack of purpura. The first one had occurred in June, 1947 in Los Angeles, 12 hours after eating crab meat. At that time the attack began with petechiae on the right and left ankles and swelling of the left ankle. On the following day he noticed severe pain in the right flank and the passage of red urine. He was sent to a local hospital, where examination of the blood revealed a decrease in the number of blood platelets, a slight anemia, and a rapid sedimentation rate. A blood Wassermann test was negative. Vitamins E and C were administered. The hematuria ceased after he had been hospitalized for 9 days.

\* Allyl-isopropyl-acetyl-carbamide, a sedative by Hoffmann-La Roche.

Later, in San Francisco, results of examination of the blood were normal. The blood Wassermann test was negative, and retrograde pyelograms were reported to be normal.

The patient stated that to the best of his knowledge he ate no crab meat between these two attacks.

The history revealed the following pertinent information: He had been in good health until the winter of 1939, when a sinusitis developed. He received numerous treatments for this condition, through the following years, and eventually was operated upon in 1942. A complete remission of the sinusitis followed for about one year.

In the summer of 1942, he developed his first attack of asthma which lasted about six weeks. The asthma recurred again during December of the following year.

In the spring of 1945 and 1946 he developed an oculo-rhinitis and at the height of the attack he had some asthma. No nasal symptoms were present after the patient moved from Los Angeles to Northern California in 1947. The asthma, however, recurred three more times, once in May and June, 1949, prior to the third attack of purpura; and again in November, 1949, without any purpuric manifestations.

In 1943, at the age of 23, he experienced an attack of generalized giant urticaria. This recurred approximately 6 times a year for the next 4 years. The duration of each episode was approximately one week, and relief was always spontaneous. He thought that the ingestion of fresh fruit, such as strawberries or peaches, was responsible for the urticaria. Apparently, however, he could eat such fruits cooked or canned without harmful sequelae.

There has been no other abnormal skin manifestation except the subsequent purpura and a recurrent tinea pedis, and no history of any other manifestation which might be related to allergy.

One paternal uncle and a paternal aunt had asthma and dermatitis, possibly from sensitivity to shell fish.

The physical examination revealed a somewhat obese young man in no apparent pain, but with moderately labored respiration and obviously prolonged expiration. Examination of the skin revealed large ecchymotic areas on the back and legs. There was a mild left epitrochlear adenopathy. The chest was emphysematous. There was a prolonged expiratory note with moderate wheezing throughout both lung fields. The heart was of normal size by percussion. The rhythm was normal. There were no murmurs. Abdominal examination revealed the spleen to be palpable on deep inspiration. The liver was not palpable. There were no other abdominal masses. The left leg and foot were swollen and the left calf was tender. An examination of the blood at this time revealed: hemoglobin 13.8 Gm., red blood cells, 4,580,000 per cu. mm.; platelets 180,000; white blood cells 7,300. A differential count revealed neutrophils 68 per cent (filaments 61, non-filaments 7), eosinophils 2, lymphocytes 26 and monocytes 4. The icterus index was 7.5 units, the sedimentation rate (Wintrobe corrected) 4 mm. per hour and the prothrombin concentration 102 per cent. The nasal secretion showed a large number (4 plus) of eosinophiles. A sternal marrow puncture was performed with the following differential count of the smear:

|                                          |              |
|------------------------------------------|--------------|
| Promyelocytes                            | 1.8          |
| Myelocytes-neutrophilic                  | 10.8         |
| Myelocytes-eosinophilic                  | 8.6          |
| Metamyelocytes-neutrophilic              | 4.0          |
| Polymorphonuclear neutrophils filamented | 1.4          |
| Polymorphonuclear nonfilamented          | 21.4         |
| Polymorphonuclear eosinophils            | 5.6          |
| Lymphocytes                              | 8.6          |
| Plasmacytes                              | 4.8          |
| Proerythroblasts                         | 0.6          |
| Erythroblasts                            | 28.8         |
| Megakaryocytes                           | 3.6          |
| Total                                    | 100 per cent |

The megakaryocytes were seen to be budding a normal number of platelets from their cytoplasm. The smear was interpreted to be within normal limits. On Jan. 7, 1948, the platelets were 240,000 per cu. mm.

The patient was free of purpura until the end of June, 1949, when he again ate some shrimp and crab. Forty-eight hours later he noted hemorrhagic skin lesions over the face, neck, scrotum and lower part of the legs. A blood count at that time was reported as essentially within normal limits.

Shortly after leaving his doctor's office, and upon returning home, he experienced a hemorrhage in the muscles of the buttock and about the hips which forced him to remain in bed for 2 weeks. He was given Neoantergan and Pyribenzamine, but purpuric skin manifestations continued to be present.

On August 2, 1949, he exhibited an ecchymosis, 6 by 8 cm., on the dorsum of the left foot. Several small areas of ecchymosis were seen on the right foot and ankle. Many ecchymoses, varying from 2 mm. to 5 mm. in diameter, were noted about the scrotum, over the perineum and inner aspects of the thighs, some of which were ulcerated from scratching. A hard, tender area, 3 by 4 cm., probably a fibrosed hematoma, was present in the left posterior cervical triangle, and caused some pain. The spleen was palpable at the left costal margin and was not tender. At this time the blood count was essentially normal. The blood platelets were 310,000 per cu. mm. The bleeding time was 3½ minutes. A sternal marrow puncture revealed little change from the specimen of marrow previously obtained. The clotting time was 10 minutes, and the clot showed good retraction at 3 hours. A heparin protamine titration was within normal limits.

The patient was hospitalized for a short period, during which time the severity of the lesions decreased considerably. He was given rutin, Neoantergan and Benadryl with subsequent clearing of the crural ecchymotic areas. A capillary fragility test on Aug. 20, 1949, showed 20 petechiae when a negative pressure of 10 mm. Hg was applied to the right antecubital fossa for one minute. He continued to note some edema of the ankles at the end of the day.

On Sept. 13, 1949, after discharge from the hospital he still had slight edema of the ankles, but by November, 1949, the edema had subsided. Capillary fragility was definitely increased.

It was during this period that a series of skin tests was performed with a large number of commercial extracts of pollens, fungi, epidermals and miscellaneous inhalants by the scratch and intracutaneous methods. Positive reactions were elicited with the pollens of most of the grasses. These were considered to be of clinical value, since they correlated well with the seasonal recurrences of asthma and hay fever as reported by the patient.

Skin tests with foods were made with a large series of commercial extracts by the scratch and intracutaneous methods; with 50 raw frozen foods by the scratch method; and with a few fresh foods suggested by the history, including crab, prawns, strawberry, and peach, by scratch method.

The use of frozen raw foods as a skin testing material has recently been introduced. Ancona and Schumacher<sup>18</sup> have emphasized that greater sensitivity and potency are demonstrated with these materials than with the commercial extracts.

Positive skin reactions (Table I) were obtained by scratch testing with fresh, frozen, and boiled crab meat. No positive reactions were obtained with the commercial extracts of crab and other crustaceans from three different reputable manufacturers when the scratch as well as the intracutaneous methods were used.

Patch tests were performed with fresh, frozen and boiled crab meat and with the very same three commercial crab extracts which had not induced positive skin reactions by either the scratch or intracutaneous methods. At the end of 24 hours the reading showed strong positive reactions characterized by erythema, edema, vesiculation and petechiae.

Passive transfer tests were done in order to prove the presence in the serum of skin-reacting antibodies to crab. The sensitized sites when tested with a variety of fresh\* and commercial extracts by the intracutaneous and patch test methods showed uniformly negative results.

Simultaneous controls were run in allergic and nonallergic individuals. All the positive skin tests were repeated and showed the same positive results.

TABLE I. SKIN TESTS WITH CRAB

| TYPE OF MATERIAL<br>USED | METHODS USED |                     |          |                     |          |
|--------------------------|--------------|---------------------|----------|---------------------|----------|
|                          | DIRECT       |                     |          | PASSIVE TRANSFER    |          |
|                          | SCRATCH      | INTRACU-<br>TANEOUS | PATCH    | INTRACU-<br>TANEOUS | PATCH    |
| Fresh raw                | positive     | —                   | positive | negative            | negative |
| Fresh boiled             | positive     | —                   | positive | negative            | negative |
| Frozen raw               | positive     | —                   | positive | negative            | negative |
| Commercial extracts      |              |                     |          |                     |          |
| manufacturer I           |              |                     |          |                     |          |
| powder                   | negative     | —                   | positive | —                   | negative |
| manufacturer II          |              |                     |          |                     |          |
| powder                   | negative     | —                   | positive | —                   | negative |
| manufacturer III         |              |                     |          |                     |          |
| glycerinated             | negative     | —                   | positive | —                   | negative |
| manufacturer III         |              |                     |          |                     |          |
| aqueous                  | —            | negative            | —        | negative            | —        |
| manufacturer IV          |              |                     |          |                     |          |
| aqueous                  | —            | negative            | —        | negative            | —        |

Table I summarizes the results of the various types of skin tests performed with crab. Prawns, because of their common antigenic properties with crab (Tuft and Blumstein),<sup>19</sup> produced similar results. The skin tests positive to crustaceans were considered of clinical value in indicating the cause of the purpura, and therefore the patient was advised to avoid ingestion of all crustaceans. At the present time, nineteen months from the last attack, no purpuric manifestations have developed. Diagnostic ingestion tests (provocative tests) were not performed. These tests were believed to be of great danger to the patient since the clinical manifestations during his last attack had been very severe and it would have been too difficult to foresee accurately the degree of reaction to the ingestion of even a small amount of crab. It was believed, moreover, that the clinical history, the results of the skin tests, and the subsequent clinical course had given sufficient proof of the etiological diagnosis of the purpura. The specific factors responsible for the occurrence of the urticaria or for the asthma in the wintertime could not be positively identified.

#### DISCUSSION

The analysis of Table I allows some speculation on the results of the skin tests.

Raw, frozen, boiled, or autoclaved crab meat induced positive reactions by the scratch method, although the usual commercial crab extracts prepared by

\*For the intradermal testing of the passively sensitized sites, exclusively, a crab meat extract was prepared as follows: Fresh raw crab meat was reduced to pulp, mixed with an equal volume of distilled water, extracted for two hours at refrigerator temperature and then centrifuged. The supernatant fluid, after passage through a Swinney filter, was used immediately for testing. This extract was obviously a crude one, and the possibility of loss of potency through filtration was considered.

several reputable firms failed to give positive reactions by the scratch or even by the intradermal method. All the crab materials, i.e., raw, raw frozen, boiled, autoclaved, and powdered or glycerinated commercial extracts had in common the property of eliciting positive skin reactions to patch tests. This would appear to indicate the existence of two antigenic fractions in crab meat: one fraction present in the fresh raw, raw frozen, boiled, or autoclaved meat is apparently thermostabile and is absent in the commercial extracts. It is possible that this fraction may either have been retained in the Seitz filtration used by most of the manufacturers or suffered deterioration in time at room temperature. Similar results were reported in 1942 by Tuft and Blumstein<sup>19</sup> for the antigens present in some fresh fruits. However, the labile fraction present in the fruits was destroyed by canning or cooking, while this first fraction present in crab meat exhibited thermostability.

The results of the patch tests were all positive no matter what type of crab material was used, fresh, frozen, cooked, or commercial extract. This observation suggests that all these testing materials contain a second antigenic fraction which, although unable to provoke positive reactions by scratch tests in our patient, elicited the positive reactions in the patch tests. This second antigenic fraction also appears to be thermostabile, but unlike the first fraction, it does not lose its potency through the various steps of extraction, filtration and drying encountered in the manufacture of the commercial extracts. Moreover, this fraction in powder form as well as in glycerinated solution maintains its activity for years at room temperature.

#### CONCLUSIONS

1. A patient with nonthrombocytopenic purpura has been studied. History, skin tests and subsequent course point to the allergic nature of his condition. The specific allergen has been recognized as meat of crustaceans (crab).

2. Once more it has been demonstrated that the use of fresh, raw and frozen crab or shrimp meat in tests by the scratch method is more apt to detect a specific state of sensitivity than the use of corresponding commercial extracts by the same scratch method or even by the intracutaneous method.

3. The use of foods as materials for patch tests has been found of diagnostic aid and is recommended in the search for the etiological diagnosis of purpuras.

4. The presence of at least two antigenic fractions in the meat of crustaceans has been suggested by the results of the skin tests performed with raw fresh or raw frozen or cooked material as compared with those using the corresponding commercial extracts. The characteristics of these antigenic fractions have been discussed.

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