

ATOPIC SENSITIVITY TO CAROID (PAPAIN)

REPORT OF A CASE WITH DISCUSSION OF SOME OF THE PROPERTIES AND USES OF THE DRUG

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THE recent observation of a patient who had developed intense symptoms on exposure to Caroid has prompted me to present the case and to survey the pertinent literature.

Caroid is a proprietary name for papain, *United States Dispensatory*, twenty-third edition. Papain contains proteolytic enzymes and is derived from the papaya tree (*Carica papaya*). The drug is also known as papayotin and papoid.

Allergy to this substance has been reported in the past. Eyermann¹ described the case of a druggist whose vasomotor rhinitis was due to exposure to caroid. The scratch test was positive. The patient's symptoms were reproduced by experimental ingestion and by an overdose during hyposensitizing injections. Walzer² mentioned a patient, sensitive to caroid and pancreatin, whose skin reacted to these in extremely high dilution. Beecher³ reported the case of a druggist who had vasomotor rhinitis and asthma when handling dry caroid. The scratch test was positive, and tasting a solution brought on acute swelling of the lips. Hyposensitization gave improvement. Beecher also mentioned briefly another druggist who had severe asthma on exposure to caroid, being found unconscious therefrom on two occasions, and a third druggist who had angioneurotic edema and dyspnea after ingestion of caroid. Maisel⁴ studied the case of a pharmacist who had vasomotor rhinitis when working with powdered enzymes. He tested the patient with caroid and produced a 2 plus reaction, but could demonstrate no reagins. Both Walzer and Maisel remark that allergy to caroid is not uncommon.

These six cases were the only ones found in a careful search of the literature. They have occurred chiefly among pharmacists, whose exposure presumably was to the dried powder and who were probably sensitized by the common route of inhalation. Sensitization by ingestion might occur, as the substance has a number of uses which will be described later. The case reported herewith, however, was apparently sensitized neither by inhalation nor by ingestion, and therefore presents possibilities not heretofore appreciated.

CASE REPORT

A married woman, aged 41 years, was first seen on April 8, 1944, complaining of severe paroxysmal cough, vasomotor rhinitis, and dyspnea. Her history in brief was as follows:

In July, 1942, she underwent bilateral vein ligations for varicosities of the legs. One wound sloughed open, and, in order to clear up the slough, caroid powder was dusted on for three or four weeks. No untoward local or constitutional symptoms were noted from this treatment, and the wound healed eventually. The history of this exposure to caroid was not obtained until later in her illness.

About March 21 or 22, 1944, her husband for the first time began the use of caroid tooth powder on the advice of his dentist. On March 24, the patient had a rather sudden onset of sneezing and coryza, and her eyes became red and the eyelids swollen. On March

30, a paroxysmal cough developed which rapidly increased in frequency and intensity, associated with dyspnea and orthopnea.

When seen on April 8, the only indications of allergy in her past had been the occurrence since childhood of bronchial colds in the winter and of some sneezing when exposed to certain cosmetic powders. No family history of allergy was elicited.

Examination showed a dry cough with dyspnea. The temperature was 99° F.; pulse, 96; respirations, 26; and blood pressure, 122/80. There were a moderate number of asthmatic wheezes in the lungs. The rest of the examination was essentially negative. X-rays of the chest showed the heart and lungs to be normal. X-rays of the paranasal sinuses showed no fluid or thickened membrane. There were 18 per cent eosinophiles in the differential blood count, and two specimens of sputum showed an eosinophilia. One hundred fifty direct intradermal tests to pollens, molds, inhalants, and foods yielded a number of moderate to marked reactions, the most significant of them being to orrisroot and mattress and house dusts, with lesser reactions to some other inhalants and to a few foods.

Symptomatic treatment and the most careful elimination of the then known reacting inhalants and foods did not control her asthma, which became increasingly severe and for which she was admitted to the Buffalo General Hospital on three occasions. On all admissions her asthma improved greatly before discharge. It recurred severely at home, however, within a few days following her first and second discharges from the hospital.

Just before her third hospital admission, when making a visit to her home to administer epinephrine, I discovered a container of caroid tooth powder in the bathroom. The patient did not use this brand, but she then recalled that her husband had begun to use it shortly before the onset of her symptoms. She also remembered an incident a few days past, when she had had a particularly sharp paroxysm of asthma after cleaning her teeth for the first time with her husband's powder. She was positive that she had had no contact with caroid prior to March 21 or 22, 1944, except for the use of it in the wound in July, 1942.

During her third stay in the hospital, all traces of the caroid tooth powder were removed from the home. Since her return there she has had no further asthma. Hyposensitizing injections of orrisroot and dust were begun on June 27, and have been continued uneventfully to the present.

A quantity of powdered caroid was secured and an extract was prepared in Coca's solution after defatting.

The patient was tested intradermally with about 0.02 c.c. each of 1:500 and 1:50 dilutions of this extract. The surrounding skin immediately flushed strongly. Within one minute the patient complained that her hands felt hot and her face flushed. She was placed recumbent, where she rapidly became confused, pale, and sweating. She vomited, her respirations became labored, her pulse became imperceptible, and she lost consciousness. Epinephrine was immediately injected beneath the two skin-test sites and a tourniquet was applied above them. More was injected into the other arm, followed by massage of the areas to speed the dispersal of the drug. One-half hour after the tests her systolic blood pressure was 60 mm. Hg, but the pulse had become palpable.

During the succeeding two hours, the pulse strengthened, her mind cleared, and recovery took place slowly. Two and one-half hours after the tests her pulse was 90, the blood pressure 130/80, and the patient felt well except for some weakness.

She had severe urticaria for the following five days. On the third day after testing redness and superficial necroses the size of a dime appeared at the test sites, and her arm swelled from shoulder to forearm. The swelling lasted three days, and the scabs fell from the necrotic areas nine days later. Redness at the test sites was followed after several weeks by pigmentation which was still present at the time of this report. Subcutaneous nodules persisted under the sites for four months.

REAGIN, PRECIPITIN, AND COMPLEMENT FIXATION STUDIES

On September 12, blood was obtained from the patient. Passive transfer was done on a nonallergic individual who had been shown previously to be a good receptor and who was skin negative by intradermal tests to caroid. Numerous sites were made with various dilutions of the patient's serum and were tested with serial dilutions of the caroid extract and with certain controls. No site was tested more than once. The results are given in Table I.

TABLE I. PASSIVE TRANSFER STUDIES

DILUTION OF PATIENT'S SERUM	DILUTION OF CAROID EXTRACT					
	1:50	1:500	1:5,000	1:50,000	1:500,000	1:2,500,000
Undiluted		+++++	++++	+++	+++	
1:5				+++	+++	++
1:25				+++	++	+
1:125				+++	++	±
1:625				++	+	0
1:3,125				+	0	0
1:15,625			+	±		
1:78,125			±	+		
Tests on Unsen- sitized skin	0	0	0	0		
Saline Control on Sensitized Site	Negative	8				

Doubtful reaction but not negative, ±; negative, 0; minimal definitely positive reaction, +; marked reaction + + + + +.

No reagins were demonstrated in the patient's undiluted serum to orris, feathers, ragweed, or carrot; control tests with these on unsensitized skin of the receptor were also negative.

Precipitin tests were done with the undiluted serum and with various dilutions of the same against serial dilutions of the caroid extract. No precipitins were demonstrated.

Complement fixation tests were done, using a 1:5 dilution of the patient's inactivated serum with serial dilutions of the caroid extract plus guinea pig complement against the usual antisheep cell amboceptor and 4 per cent sheep cell suspension, and with suitable controls. No deviation of complement was shown.

From the above studies, it is apparent that the patient had a true atopic sensitivity to caroid (papain), with specific reagins in high concentration in her blood. The skin was sensitized to such a degree that typical Arthus necrosis occurred at the skin-test sites. The extremely severe constitutional reaction on testing demonstrates again the need for the utmost caution and the use of weak dilutions when testing with untried allergens*

This patient had evidently been sensitized by absorption of the caroid antigen through the wound in July, 1942. The American Ferment Company, manufacturer of the drug, in response to a query, reported that besides the caroid from *Carica papaya*, the tooth powder contained oil of peppermint and other "standard ingredients which are considered to be hypo-allergic." The caroid itself contains "no added substances of plant or other origin." The questions arise therefore as to other evidences of the antigenicity of papain (caroid) and as to its uses which would constitute sensitizing and "shocking" exposures.

ANTIGENICITY OF PAPAIN

The plant *Carica papaya*, from the latex of which papain is derived, is a dicotyledonous angiosperm belonging to the family *Archichlamydeae*, genus *Caricaceae*. It has no near botanical relatives in use.⁵

Animal experimentation by several workers has indicated that papain is a very active antigen. It can induce anaphylaxis in dogs⁶ and in guinea pigs.⁷⁻⁹ Specific precipitins and complement fixing antibodies follow its injection into rabbits.^{7, 9} Specific sensitization of the uterus can be shown by the Schultz-Dale technique in injected guinea pigs.⁹ The antigen in papain is not the same as that in the proteolytic enzyme pepsin.⁹ Papain contains powerful proteolytic enzymes and has certain other actions.¹⁰⁻¹³ It has been prepared in crystalline form.¹⁴

*Nitrogen determinations on the 2 per cent extract, which had not been done at the time of the testing, showed: total nitrogen, 0.99 mg. per cubic centimeter and phosphotungstic acid precipitable nitrogen, 0.76 mg. per cubic centimeter.

MEDICINAL USES OF PAPAIN

There are a number of parenteral uses of papain reported in the literature, all of which could constitute either sensitizing or "shocking" exposures. Intraperitoneal instillation of a sterile solution of papain (up to 1 liter) for the prevention of postoperative adhesions was used in a large number of patients in the 1930's.¹⁵⁻¹⁷ It has been used topically in solution for the treatment of sloughing wounds.¹⁸ It is said to be very effective in clearing up the discharge of chronic purulent otitis media¹⁹ and for dissolving the eschar of burns²⁰ and the membrane of diphtheria.⁷ It has also been used through the bronchoscope for loosening the exudate in membranous tracheobronchitis. It has been used locally for the treatment of carbuncle²¹ and by injection of the synovial sac in the treatment of ganglion,²² the latter with serious results.

No evidence that ingestion of papain can induce sensitivity has been disclosed. Its ingestion, however, has elicited symptoms in already sensitized persons.^{1, 3} For this reason the following list of oral preparations containing papain²³ may be useful:

All the "Caroid" preparations, American Ferment Co.
 Caripeptic Liquid and "Carica" preparations, The Upjohn Co.
 Bisodol.
 Digestone Elixir, Robert McNeil.
 Elixir Caricans, Fraser Tablet Co.
 Protenzamy, R. J. Strassenburgh Co.
 Liquor Diastos, Sharp and Dohme, Inc.
 Panpasoda, G. D. Searle and Co., Inc.
 C. M. S. Compound, Walker Pharmacal Co.

There are probably other oral preparations containing it as it seems to have some popularity as a digestant.

COMMERCIAL AND INDUSTRIAL USES OF PAPAIN

The fruit of *Carica papaya* (also called papaya or pawpaw) has considerable popularity for eating purposes in regions where it is available (Tropical America, West Indies, Florida, California, Ceylon, and Malaya). The juice is canned and sold at delicatessen and special food stores in the United States. It is entirely distinct from the North American pawpaw (*Asimina triloba*).

The proteolytic properties of papain have been applied to a variety of uses. Much of the papain imported into the United States is used in preparations for rapidly tenderizing tough meat.¹⁴ It acts more evenly when mixed with ground meat. Since the enzyme is relatively resistant to heat it is smeared on, or mixed with, the meat just before cooking and acts during the cooking.

Papain has been used for many years in the brewing industry for making "chillproof" beer, preventing turbidity on cooling by digesting the traces of protein dissolved in the beer.¹⁴ It has been estimated that 80 per cent of American beer is so treated. The dilution, however, is very weak. Papain is used in the tanning industry for bating skins and hides,²⁴ and the latex is used in chewing gum manufacture.⁵

Of incidental interest is the fact that papain will inactivate ragweed pollen extract resistant to animal proteases.²⁵ It will inactivate several bacterial toxins.²⁸ Animal proteins digested by papain apparently form excellent bases for culture media.²⁷ The practicability of these uses would seem to be doubtful, however, because of its high antigenicity.

DISCUSSION

From the experimental work referred to and from the several case reports, it is evident that papain is actively antigenic and is capable of sensitizing human beings both by inhalation of the dry powder (apparently the common mode) and by absorption through granulation tissue. This sensitivity is of the atopic type, not a true drug-sensitivity. I believe that the atopen probably is related to the water-soluble plant extractives and is independent of the actual proteolytic enzymes present, although this question will bear further study.

Most of the cases reported heretofore have been in pharmacists, who were presumably sensitized by inhaling the powdered papain. In recent years the introduction of papain in the form of caroid tooth powder has created the conditions for sensitizing persons in the general population by inhalation.

Through its use medicinally, papain has elicited symptoms in sensitized persons by inhalation, by ingestion, by injection, and by local application. It may be an excitant of symptoms through exposure to it in the brewing and tanning industries, in chewing gum, and in food preparations.

How common this sensitivity is and how widespread is the exposure we do not yet know. I have tested intradermally forty patients with dilutions of 1:50,000, 1:10,000, 1:5,000, and 1:1,000 of caroid without untoward results. Four of these patients (10 per cent) gave moderate skin reactions and seven more gave slight reactions, a total of eleven (27 per cent). Six patients admitted the use of caroid tooth powder. One of these, a pharmacist, gave a moderate reaction, and two others gave slight reactions. The significance of these reactions has not been finally determined.

SUMMARY

1. Papain is an active antigen.
2. Sensitivity to it in human beings is atopic in type and is not uncommon.
3. Its several uses medicinally, industrially, in dentifrice (caroid) and chewing gum, and in food preparation create exposures in the general population which the allergist must keep in mind.

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SKIN SENSITIVITY IN THE AGED—FATALITY FOLLOWING INTRADERMAL TESTS

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CONSTITUTIONAL reactions following intradermal testing or hypodermic injections have been recognized for some time. Cooke¹ (1922) and Lamson² (1929) were among the earliest to report fatalities after intradermal testing.

The cases reported have usually been in younger patients in whom the skin is supposed to be more reactive than in the aged. We are reporting a death following intradermal testing in a woman, 78 years of age, who had marked positive reactions to many of the allergens with which she was tested. The skin of elderly people is usually considered to be relatively inactive and positive reactions generally not to be expected, but we were able to find in the literature only two references to this subject. Fineberg³ wrote, "An atrophic skin, a skin with poor circulation or the skin of the aged may be so diminished in reactivity that what would be ordinarily moderate reactions may become negative." Tuft⁴ stated that "especially in older individuals or in those who have had their condition for some time, the skin is likely to be of the nonreactive type."

CASE REPORT

The patient, Mrs. C., a small, elderly-appearing but mentally active widow, aged 72 years, was first seen at the Allergy Clinic of the Syracuse Free Dispensary in January, 1938. She gave a history of asthma since the age of 4 years, usually occurring in the fall or winter