

BRONCHIAL ASTHMA, URTICARIA, AND ALLERGIC RHINITIS FROM TANNIC ACID*†

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RECENTLY one of us (A. G. C.) had the opportunity to investigate a patient who had shown definite allergic manifestations to tannic acid. We believe the case to be important in that it is a clear-cut example of sensitivity to an antigen, either complete or hapten, of simple, non-nitrogenous structure and low molecular weight. To the best of our knowledge this is the first case in which a hydrolytic product of a simple, naturally occurring, non-nitrogenous compound gave immediate whealing reactions by the scratch and passive transfer methods.

CASE REPORT

M. L., a 24-year-old white man, received a mild burn on his foot in 1940 which was treated with a tannic acid solution. This burn took about three months to heal. A short time later he began having nasal symptoms of rhinorrhea, sneezing, nasal obstruction, and itching of the nose. The patient was first seen in 1942 with symptoms of rhinorrhea, sneezing, nasal obstruction and itching of the nose, mostly in the summer months. An extract of alternaria, ragweed, and dust was given at intervals but any improvement was attributable to symptomatic medication as he was never treated for more than a few weeks at a time. In 1949, while in Florida, he had an attack of severe rhinitis and urticaria immediately after using a tannic acid paste for sunburn.

In early July, 1950, the patient was seen as a home emergency with severe bronchial asthma and generalized urticaria. He attributed the attack which had come on suddenly to the use of a sunburn spray containing tannic acid. The label stated that the active ingredients were tannic acid, chlorobutanol, and alcohol. On July 10, 1950, severe asthma and generalized urticaria occurred 20 minutes after a scratch test to this spray which gave a markedly positive reaction with a wheal 25 mm. in diameter. This required two injections of 0.3 ml. of 1:1,000 epinephrine hydrochloride 15 minutes apart for relief. He was completely free of asthma almost immediately, but the urticarial lesions persisted over his shoulders four hours after the onset. The following day tea was omitted from his diet as this beverage contains up to 11 per cent tannic acid. (1) On July 19, 1950, a scratch test to a strong solution of tea produced an immediate whealing reaction, 11 mm. in diameter appearing within five minutes. On August 7, 1950, he reported that his allergic rhinitis had improved. A glass of tea was given at 10:00 A.M. and within a few minutes he developed a "chugging around" in his stomach. At 12:30 P.M. he had another glass of tea and an hour and a half later he had an attack of asthma sufficiently severe to require epinephrine for relief. The patient recalled that his allergic rhinitis had been worse in summer when he drank iced tea. On Sept. 23, 1950, another severe attack of asthma occurred, requiring epinephrine for relief. The patient was unable at this time to account for the attack. On Oct. 17, 1950, while at work, he again developed a severe asthmatic attack requiring epinephrine hydrochloride for relief. At the time of this attack he was watching workmen at the shop setting a saw for cutting cross ties which were made of oak lumber. He then recalled that at the time of the previous attack for which

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he had been unable to ascribe a cause, he had been watching workmen making shelves. Subsequent inspection proved that these shelves were made of oak. Oak lumber is known to contain a large amount of tannic acid.² Since Oct. 17, 1950, by avoiding known sources of contact with tannic acid he has had no asthma and only mild nasal symptoms to date. The family history was known to be positive for allergy in that a sister had severe ragweed hay fever. Skin tests on the patient by the scratch method showed mild reactions to ragweed, grass, alternaria, and house dust.

LABORATORY AND IMMUNOLOGIC STUDIES

The patient was scratch tested with a 1:1,000 solution of tannic acid which gave a marked whealing 11 mm. in diameter in 5 minutes. A solution of egg albumin was added to a solution of tannic acid in excess of the maximum precipitate. The precipitate was washed with water, dissolved in slightly alkalized solution, and a scratch test was made with this solution of egg albumin tannate. It produced a rapid whealing response on the subject. Scratch tests to a crude extract of the saw dust collected from the aforementioned oak lumber produced an immediate type of whealing reaction.

Ten nonallergic subjects gave negative reactions by the prick test to U.S.P. tannic acid in a dilution of 1:3. Using a 1:1,000 dilution of U.S.P. tannic acid by the intradermal technique mild nonspecific reactions occurred. Undoubtedly such reactions are related to impurities in U.S.P. tannic acid or to the irritating quality known to be characteristic of the tannic acid itself.²

Prausnitz-Küstner³ tests on 12 subjects in which serum was injected and tested after 48 hours with 0.025 ml. of U.S.P. tannic acid in dilutions of 1:1,000, 1:10,000, 1:100,000 and 1:1,000,000 gave an immediate whealing response in all subjects which persisted 20 minutes after the control site reaction had disappeared. Prick tests to the passive transfer sites with a dilution of 1:3 tannic acid gave an immediate whealing response with negative controls.

Pure, reagent-grade tannic acid was obtained from two separate manufacturers in order to rule out the possibility of impurities in the U.S.P. tannic acid as the cause of the positive Prausnitz-Küstner tests previously observed. Passive transfer tests of 12 persons all gave good positive reactions to dilution up to and including 1:1,000,000. The dilution of 1:10,000,000 was negative in the one case on whom it was tried. Passive transfer sites in two instances were exhausted by two injections of 0.025 c.c. of 1:1,000 reagent tannic acid. One subject required three injections of 0.025 c.c. of 1:1,000 reagent tannic acid before exhaustion occurred. The patient's serum diluted 1:2, 1:4, 1:8, 1:16, 1:32, 1:64 and 1:100 gave immediate whealing responses with 0.025 c.c. of a 1:1,000 dilution of reagent tannic acid in 48 hours. When tested with 0.025 c.c. of the patient's serum diluted 1:1,000 a two-plus reaction was obtained.

In an attempt to find out whether or not breakdown products of tannic acid (Fig. 1) would also give positive Prausnitz-Küstner reactions we tried gallic acid (Fig. 2) which is produced by hydrolysis of tannic acid. Six control subjects were injected with 0.05 c.c. serum from the allergic patient and 0.025 c.c. of 1:1,000 solution of gallic acid was injected into the sites two days later. Transfer sites gave a good positive wheal in five out of six subjects, while control sites were negative. Gallic acid, prepared one month before testing, failed to

give a positive passive transfer reaction on one occasion. Passive transfer sites were exhausted by one to three injections of 0.025 c.c. of freshly prepared gallic acid.

Resoreinol (Fig. 3) injected into transfer sites failed to produce an immediate whealing reaction in four persons in whom it was tried. Pyrogallol (1, 2, 3 trihydroxybenzene—Fig. 4) gave a positive Prausnitz-Küstner reaction in one out of three cases on whom it was tried, while 1:1,000 pyrogallol triacetate (Fig. 5) and pyrogallol 1, 3 dimethyl ether (Fig. 6) 1:1,000 gave negative reactions when injected into transfer sites in all three patients tested.

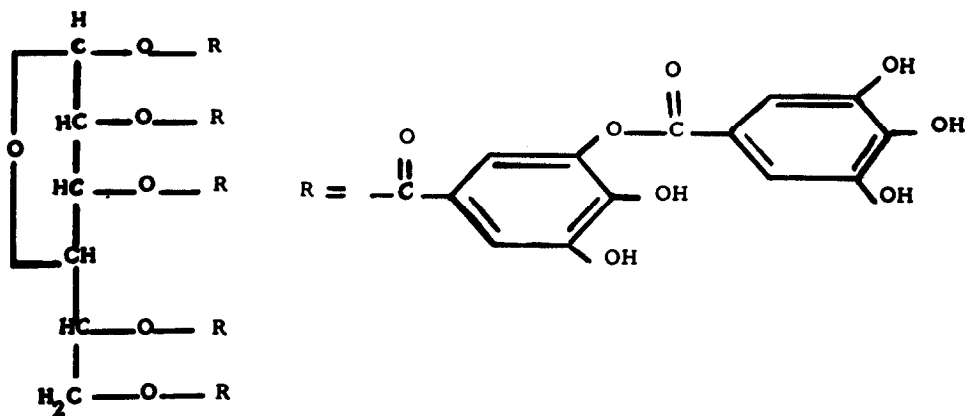


Fig. 1.—The structural formula of tannic acid, a pentadigalloyl esterlike compound of glucose, $C_{76}H_{52}O_{46}$; Molecular weight 1700.

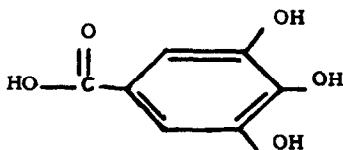
CHEMISTRY OF TANNIC AND GALLIC ACID

Tannic acid U.S.P.² is a yellowish-white amorphous bulky powder with a faint characteristic odor and astringent taste. It is a natural product occurring in the bark and fruit of many plants, the commercial source being Turkish or Chinese nutgalls and is produced when the galls are fermented under special conditions and then extracted with water saturated ether. Emil Fischer⁴ established the structure of tannic acid as a pentadigalloyl esterlike compound of glucose. $C_{76}H_{52}O_{46}$; molecular weight 1700 (Fig. 1). Tannic acid gives insoluble precipitates with albumin, starch, gelatin, most alkaloidal and metallic salts. These precipitates may be dissolved by alkaline solutions. Tannic acid solution quickly combines with a soluble protein forming a tannate which is relatively stable, and insoluble in water. It is partially soluble in alkaline solutions.

Gallic acid, a product of the hydrolysis of tannic acid, forms colorless, odorless prisms which melt with decomposition at 225-250° C. It has been identified as trihydroxy benzoic acid, $C_7H_6O_5$,⁴ molecular weight 170 (Fig. 2).

Attempts to Sensitize Guinea Pigs to Tannic Acid.—To the best of our knowledge no attempts to sensitize animals to tannic acid have yet been reported,

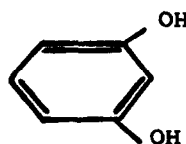
but in an experiment by one of us (H. N. M.), six guinea pigs were given subcutaneously 0.10 ml., 0.20 ml., 0.30 ml., 0.50 ml., 0.75 ml., and 1.0 ml. of a seitz-filtered aqueous 1 per cent solution of U.S.P. tannic acid. No abnormal manifestations except localized cutaneous erythema were seen as the result of this treatment. Two days later, the same animals were given enough tannic acid solution to make the total received 1.1 ml. Fourteen days later, a single intracardiac injection of 0.10 ml. of the original tannic acid was given each animal. No effect was noticed immediately, nor for the six weeks following. The same procedure was repeated using a new set of six pigs with the same results.



GALLIC ACID

Fig. 2.

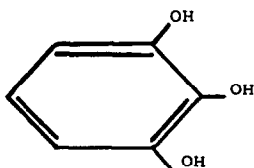
Fig. 2.—The structural formula of gallic acid, trihydroxybenzoic acid, $C_7H_5O_6$; molecular weight 170.



RESORCINOL

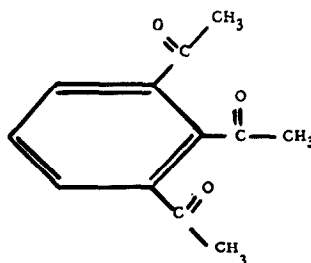
Fig. 3.

Fig. 3.—The structural formula of resorcinol 1,3; dihydroxybenzene.



PYROGALLOL

Fig. 4.



PYROGALLOL TRIACETATE

Fig. 5.

Fig. 4.—The structural formula of pyrogallol 1, 2, 3; trihydroxybenzene.

Fig. 5.—The structural formula of pyrogallol triacetate.

Attempts to Sensitize Guinea Pigs to Protein Tannate.—Freshly separated guinea pig serum was precipitated with a slight excess of 1 per cent tannic acid solution. The precipitate was removed by centrifugation, washed once with slightly acid water, and redissolved in water made slightly alkaline by a drop of NaOH solution and adjusted to equal the volume of serum originally used. Six guinea pigs were given two subcutaneous injections of 0.1 ml. of this preparation on alternate days. Fourteen days later, a single 0.10 ml. intracardiac injection of (a) serum protein tannate or (b) normal untreated guinea pig serum was made. In neither case was any degree of anaphylaxis observed. This procedure was repeated using a new set of six pigs with the same result.

THE SOURCES OF CONTACT AND USES OF TANNIC ACID^{5, 6}

Tannic acid is found: in various concentrations in the bark or fruit of most plants; in various species of oak, hemlock, and sumac; in myrobalan, chestnut bark, and coconut fiber; in some perfumes for color and astringency; in sunburn lotions and ointments; in solutions in the treatment of bed sores; in some douche powders, in almost all fruits, vegetables, nuts, and fibrous foods; in the manufacture of ink; in some hemorrhoidal ointments; in antidotes to some metals; in some medicines for diarrhea; in the leather industry for tanning leather; in detoxifying diphtheria toxin; in combination within insulin to prolong its action; with barium sulfate in x-ray studies of the gastrointestinal tract; in some astringents, some syptics, and in some antiseptics; and in some enemas for the treatment of bacillary, amebic, or flagellate dysentery. According to the American Institute of Cleaners and Dyers, tannic acid is a source of much permanent staining of clothing in spilled fruit juice stains. Tea, coffee, and cocoa contain an appreciable quantity of tannic acid, although they do not serve as commercial sources. Green tea may contain up to 11 per cent tannic acid.¹

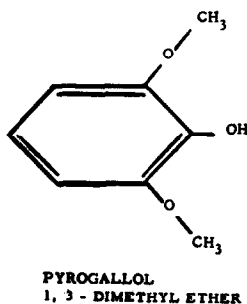


Fig. 6.—The structural formula of pyrogallol 1, 3; dimethyl ether.

DISCUSSION

On the day following direct skin tests with the tannic acid spray mentioned above, July 11, 1950, both skin test sites were raised, indurated, brawny and 33 mm. in diameter. There was no vesiculation or desquamation. The reaction disappeared in 72 hours. The possibility has been suggested that this might be the missing link between atopic and contact reactions.

The passive transfer reaction seems specific for the trihydroxyphenyl structure of tannic acid and gallic acid since the dihydroxyphenyl compound, resorcinol, gave a negative result.

Tannic acid appears to be the allergen or hapten which is capable of producing asthma, urticaria and allergic rhinitis, as well as gastrointestinal symptoms in this case. It presumably has induced the formation of a large amount of antitannate reagin. The severity of the symptoms caused by the minimal degree of exposure to tannic acid has produced a degree of sensitivity in this case equal to that of other known allergens.

To the best of our knowledge sensitivity to tannic acid or gallic acid has not previously been reported. Nor have other allergens on hydrolysis produced compounds of such small molecular weight which were capable of demonstration by direct and passive transfer tests.

SUMMARY AND CONCLUSIONS

1. A case of allergy to tannic acid and gallic acid is reported.
2. Symptoms have occurred from both ingestion and inhalation to tannic acid.
3. The presence of antibodies to tannic acid and gallic acid has been demonstrated by means of direct skin testing and by the Prausnitz-Küstner technique.
4. The fact that reagins have been demonstrated to both tannic acid and gallic acid and were absent to resorcinol would suggest that the antigen in our patient has a trihydroxyphenyl configuration.
5. The fact that simple chemical compounds such as tannic acid and gallic acid can be potent allergens raises the question of the possibility of other simple chemicals as the etiological cause for heretofore unexplained allergic diseases.

The authors wish to express their appreciation to Dr. Charles H. Eyermann for additional confirmation of the passive transfer reaction to tannic acid and for many helpful suggestions.

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