

The ALLERGY ARCHIVES

Pioneers and Milestones

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Food allergens: Landmarks along a historic trail

Extant ancient accounts of foods in the cause and prevention of disease are fanciful, mystic, and bizarre. However, amidst folklore, there is documented indication of antiquity's physicians' and medical writers' familiarity with food "idiosyncrasies," foreshadowing future uncovering of the phenomenon of hypersensitivity. Among the earliest was the Chinese emperors Shen Nong's (fl. 2735 BC) and Huang Di's (2698-2598 BC) *Shi Jin-Jing* ("Interdictions concerning foods").^{E1} (Online-only references are available in the [Online Repository](http://www.jacionline.org) at www.jacionline.org.) Its advice to pregnant women included warnings against eating shrimp, chicken, and meat and incriminated agents of skin lesions (liberally transliterated "ulcerations" whose broad interpretation might encompass eczema and urticaria).

From the texts of Hippocrates (460-377 BC): "Cheese does not harm all men alike; some can eat their fill of it without the slightest hurt.... Others come off badly. So the constitutions of these men differ, and the difference lies in the constituent of the body which is hostile to cheese and is roused and stirred to action under its influence. Those in whom a humor of such a kind is present in greater quantity, and with greater control over the body, naturally suffer more severely. But if cheese were bad for the human constitution without exception, it would have hurt all."¹ Twenty-three centuries later, Hippocrates' concept of a "hostile humor" would be identified and immunochemically characterized as IgE.

A frequently quoted representation of allergy is traced to the Roman philosopher-poet Titus Lucretius Cato's (98-55 BC) poem "De Rerum Natura" ("On the nature of things"): "What is food to one, to another is rank poison." Derivation of this axiom is traced to the 4 centuries earlier theory of atomism advanced by Democritus (460-362 BC), who envisioned all matter to be composed of small particles, called atoms, of varying size, shape, position, and arrangement.^{E2} Inability of the atomic character of a food to fit matching gastrointestinal track configuration resulted in impediment of passage and a resultant idiosyncratic reaction. Replacing conceptual structural elements of atomism are current-day cellular and molecular functional

characterizations of antigens, cell-surface receptors, immune recognition, and allergic mechanisms.

Roman legion surgeon Pedacius Dioscorides (fl. 50 AD)^{E3} and Alexandrian physicians Aretaeus the Cappadocian (120-180 AD)^{E4,E5} and Claudius Galen (130-200 AD) of Pergamen and Rome,^{E6} also noting adverse effects of milk and cheese, additionally recorded inconsistent variations related to derivative animal sources. "Good and bad pasturages" proved to be more than just speculative when in the 1900s corresponding antigens were demonstrated in milk obtained from cows grazing on peanut hay,^{E7} wheat bran,^{E7} and ragweed tops^{E8} or fed with supplements of cottonseed cake and flaxseed meal.^{E9} A human counterpart was identified in Donnally's (1877-1947 AD) 1930 study of neonatal allergic manifestations with egg allergen demonstrated in breast milk obtained from lactating mothers after test ingestion of raw eggs.²

Aretaeus' first precise description of "heterocrania" (migraine cephalalgia), implicating milk and cheese as causative agents,^{E4} was explained 16 to 17 centuries later by identification of tyramine, a monoamine oxidase inhibitor responsible for cranial inflammatory vasodilatation and disruption of blood flow. The finding of phenylethylamine, having a similar property, in some red wines established the relationship of biologist-philosopher Aristotle's (384-322 BC) observation on cerebral symptoms induced by dark wine.^{E10} Until discoveries of these pharmacologic mediators and their sources, migraine was included among disorders triggered by food allergens in milk, cheese, chocolate, egg, wheat, corn, and coffee.

Historian-geographer Herodotus' (484-425 BC) report of Egyptian avoidance of pulses (Lat puls, Gk poltos: legumes)^{E11} was followed by Greco-Roman medical admonitions against cultivated peas, beans, and lentils. Subsequent plant importations of soya from China and peanuts from Peru added popular, widely used, highly allergenic foods to the top of the list of legume-related idiosyncratic reactions.

Philosopher, rabbi, and physician Moses Maimonides' (1135-1204 AD) *Treatise on Asthma*^{E12} consisted of a series of advisory letters to his asthmatic patient Prince Al-Afdal, son of Saladin, Sabah Ad-din Salah (1137-1193 AD), Ayyub Sultan of Egypt, Syria, Yemen, and Palestine, in whose Cairo court he served. Maimonides' recommendations for specific avoidance of milk, nuts, and legumes at the same time spoke favorably of eggs and wheat, which were also subsequently appreciated allergens.

In the genesis of case reports of specific food hypersensitivity, Belgian physician Jean Baptiste van Helmont (1577-1644 AD) in *Oriatrike*, published in 1662, recorded asthmatic attacks after the eating of fish.^{E13} Sir John Floyer's 1698 discussion of "Food of asthmatics" noted fish idiosyncrasy, production of "a viscid chyle, which stops in the lungs in the spitting asthma, and that oppresses them."^{E14}

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An early account of urticaria from strawberries was not described in the medical literature but rather in a classical masterpiece of English historiography, Sir Thomas More's *History of Richard III*, published in 1513-1518.^{E15} In a setting of intrigue, Richard (1461-1483 AD) displayed a self-induced skin reaction to strawberries, the cause known only to him, as proof of treasonous witchcraft by a political adversary. Food idiosyncrasy and urticaria was clarified in Robert Willan's first original taxonomic classification of skin diseases, a 1798-1808 multivolume publication, *Treatise on Dermatology*. Willan clearly portrayed and described urticaria and its causative relationship to almonds, mushrooms, herring, crabfish, lobsters, and mussels. Fatal outcomes of systemic "urticaria febrilis" were noted to follow eating of muscles or lobsters.^{E16}

A century later, in 1902, the discovery of anaphylaxis by Richet and Portier and von Pirquet's 1906 definition of "allergie" as altered reactivity introduced a new era in uncovering information on adverse reactions to foods. With Prausnitz (1876-1963 AD) and Küstner's (1897-1963 AD) subsequent demonstration of blood serum systemic mediation of hypersensitivity and skin-sensitizing antibody, references to specific food allergens replaced the vague concept of idiosyncrasies.

European physicians, particularly in France, Germany, and Italy, centered clinical investigations on case studies and anaphylactic guinea pig models.³ Initially, they considered American reports on skin testing, other than a marker of the atopic state, to be of little reliability in specific diagnosis.

Journal reports summarized by Laroche et al³ of food allergen-induced systemic reactions, asthma, urticaria, and gastrointestinal manifestations, which European clinicians termed "alimentary anaphylaxis," implicated causative agents: eggs in children from 2 to 16 years of age, milk in nurslings and up to age 16 years, and wheat products in adults. Further experience expanded the initial list, with fish, crustaceans, and mollusks (particularly mussels) as the most frequent. Because of the potential sensitizing property of cow's milk, especially in neonates, its introduction in formulas before breast-feeding was to be avoided. Allergic manifestations were occasionally seen in newborns after first feedings of cow's milk, causing postulation of *in utero* sensitization, but this concept was never proved. Where species specificity was the critical allergic factor, in some instances milk derived from a different foreign source, such as goat or ass, might be tolerated. If not, sources of donor human milk should be sought. Concurrently in the United States, substituted soy-based preparations^{E17} were widely recommended until reports of allergic reactions, duplicating those of cow's milk, led to a decrease in their use.

Observations on egg in alimentary anaphylaxis generated information on immune system relevance. In

mild and chronic cases, tolerance to egg allergens could overcome sensitization caused by continuing feedings of small subanaphylactogenic amounts or, if not withheld until early childhood years, might be prevented by avoidance of overfeeding during infancy.^{E18}

Laroche et al,^{E19} searching for an explanation of predisposition to development of alimentary anaphylaxis, considered possibilities of (1) too rapid food absorption, (2) inefficient digestive juices, (3) special fermentations produced by digestive juices, and (4) a theoretical possibility advanced by Charles Richet. Relating to his discovery of anaphylaxis, Richet envisioned the blood of susceptible individuals to contain a toxogenin, which in combination with antigen, precipitated "the anaphylactic condition." Richet's "toxigen" was subsequently transformed from concept to demonstrable entities of Coca's atopic reagin and Ishizakas' IgE.

By contrast, in American allergy clinics and clinical practices, skin tests played a major role in identifying food allergens. In 1912, the controlled, in-depth study of Oscar Schloss (Fig 1) established the practicability of scratch tests for clinical hypersensitivity. Applying von Pirquet's tuberculin abrasion technique in investigating a child's rhinitis, asthma, and eczema, he correlated cutaneous, erythematous wheal responses with clinically manifested "idiosyncrasies" to egg, almond, and oats.⁴

In retrospect, there had been earlier instances of cutaneous reactivity to a food. In a 1656 investigation of a case of food intolerance, application of an egg's content to the patient's skin raised a "blister."^{E20} A 1929 summary of the European literature cited the report of a woman, clinically sensitive to egg, who inadvertently pricked her finger with a pin that had been used to pierce an egg shell; a papular wheal appeared moments later at the minute wound site.^{E21} Smith, Thayer, and Cole reported the study of a patient with buckwheat-induced cough, itching, throat discomfort, hives, and giant swellings, which they believed to be a manifestation of buckwheat poisoning, which was known only in cattle. In adapting the tuberculin test technique, rubbing buckwheat into scarified skin evoked an immediate wheal response and a severe, systemic anaphylactic reaction.^{E22} The documented constitutional reaction induced by a skin test to a food foreshadowed potential danger in such a diagnostic procedure, especially with Cooke's intracutaneous technique.^{E23}

With the scratch test for diagnostic leads in atopic disorders, Schloss⁴ introduced chemically extracted food fractions as reagents. Further development of chemical extraction procedures was extensively pursued by Coca.⁵ As commercial endeavors followed, practicing physicians found easy accessibility to a large and loosely categorized array of food skin test materials. Consequent opportunities for abuse or deviation from state-of-the-art diagnostic approaches extended beyond the control of clinical experts.



FIG 1. Oscar M. Schloss, MD (1882-1952), Johns Hopkins University, 1905. Dr Schloss held the positions of professor and chairman in the Departments of Pediatrics at Cornell Medical College and at Harvard and was director of Pediatric Services at New York Nursery and Childs Hospital and at Boston Children's Hospital. Figure courtesy of the Bret Ratner Collection, History of Medicine Division, National Library of Medicine.

In his 1933 presidential address to the Society for the Study of Asthma and Allied Conditions, Albert Vandeever decried: "We must combat the general attitude which seems to be gradually gaining ground that allergy testing consists of scratching the skin with a few food tests and putting the patient on a weird and impracticable diet which usually accomplishes no result.... The reading of these tests and their interpretation should be done by a competent allergist." Understanding the utility of the diagnostic tests required additional defined characterization of allergens, standardization of reagents, and correlated clinical studies. Seminal in bringing integrated application of such undertakings into the clinical arena was May's introduction of the double-blind, placebo-controlled food challenge,^{E24} a diagnostic model that became the gold standard in evaluating adverse reactions to foods.

Particularly important was the work of Matthew Walzer, identifying, sorting out, and developing a compilation of food source allergens and their roles in atopic hypersensitivity disorders⁶ and in investigations concerned with clinical applications of the Prausnitz-Küstner (P-K) passive sensitization technique.^{E25} In 1927, with Abraham Walzer (1893-1951 AD), description of orally ingested foods and their absorbed, incompletely digested products or raw protein sources evoking positive P-K reactions at distal



FIG 2. Warren T. Vaughan, MD (1893-1944), University of Michigan, 1926. Dr Vaughan was founder and director of the Vaughan-Graham Allergy Clinic (Richmond, Va), author of *Practice of Allergy*, 1939, and editor of the *Journal of Laboratory and Clinical Medicine*. Figure courtesy of Victor Clarence Vaughan III (as a gift to the author).

skin test sites led to the definition of routes of transportation of food allergens through internal channels.^{E26}

Selected highlights of other investigative studies of interest and relevance to food allergens were as follows:

- The major allergenic property of cow's milk was identified in one specific fraction, lactoglobulin, the destruction of which by heat with retention of the least common offending fractions, lactalbumin and casein, provided dietary guidelines.^{E27}
- Although heat and chemical treatment destroyed or inactivated antigenic fractions of a food, in some instances reverse action created new allergens: (1) Helmont's patient's reaction to fried fish^{E13}; (2) Küstner's P-K passive transfer reactivity only to cooked, and not raw, fish^{E28}; (3) a patient whose asthmatic sensitivity to peanut was expressed only after eating peanuts that had been roasted and salted^{E29}; and (4) Rowe's observation of hypersensitivity to cooked, but not raw, fruits.^{E30}
- Unlike the plant toxins—prussic acid/hydrogen cyanide retained in the tissues of quails eating bitter almond sources and transmitted to human subjects and similarly ciguatera in fish feeding on algae in coves—the model of hatchery brook trout raised on beef liver or cereals demonstrated that ingested allergens were metabolized beyond passage to the next link in the food chain.⁷

- Aristotle's centuries-old observation that some can eat fruit and others not^{E10} found relevance in Tuft and Blumstein's 1942 study of patients allergic to fruit, which detected: (1) lack of concordance between clinically manifested, pharyngeal, immediate hypersensitivity reactions and corresponding skin test reactions and (2) fallibility of skin tests caused by heat lability of extracted, antigenic, fresh fruit enzymes. In explaining the enigma of demonstrably sensitized patients' abilities to eat causative fruits altered by cooking and canning processes without adverse effects, they coincidentally provided the first report of the disorder known as the oral allergy syndrome.^{E31}
- Studies of immune-related properties of the peach, plum, and almond family demonstrated nonidentity between antigenic fractions of the fruits and corresponding tree pollens.⁷
- Initiation and expression of immediate hypersensitivity to food allergens bypassing the gastrointestinal route exemplified the roles of inhalation in workers grinding and sifting coffee beans^{E32} and bakers exposed to wheat and rye flours,^{E33} cutaneous contact with raw fish and vegetables (eg, onion, potato, garlic, and radish^{E34}), and parenteral injections of pharmaceutical liver extract.^{E35}

In 1930, Vaughan (Fig 2),⁸ in collaboration with Frances Wilson, an academic botanist, initiated studies of shared characters of plant-derived foods as the first stage in the development of a classification intended to serve as a rational and workable basis for selecting test allergens representative of members of a group. Their findings of shared structural and functional allergen-related properties both within phylogenetically common and diverse foods could ultimately be explained as the evolutionary outcome of Darwinian natural selection and both induced and natural mechanisms of hybridization of source plants. Other critical factors recognized by plant scientists related to changes within a single lineage responsible for deviation from ancestral properties and chance development of similar allergens in unrelated plants with resultant cross-reactivity.

Current-day tools for an anatomic study using electron and scanning microscopy, immunologic techniques with raised antisera precipitins for identification of corresponding component antigens fractionated by electrophoresis or differential diffusion in agar, biochemical characterizations, and RNA and DNA sequencing have enabled plant and food scientists to expand and refine taxonomic classifications and phylogenetic applications.⁹ Of special interest is a 75-year retrospective view of Vaughan's contribution, noting that with few exceptions his compilation was valid and met the test of time (John V. Freudenstein, PhD, personal communication).

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