



INVITED REVIEW

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History of food allergy and where we are today

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ABSTRACT

The food allergy (FA) entity went through a long difficult road which led to much delay in its recognition. After long periods of denial and misdiagnosis, it attained its current designation as food hypersensitivity or allergy. This review will briefly address the evolution of the FA entity from the early BC era until our 21st century and highlight the milestones in the main aspects of diagnosis, treatment, prevention, and research.

A great recognition of the allergy specialty was gained by the discovery of its main mediator -immunoglobulin E in 1967 - which also helped in classifying FA into IgE-mediated (immediate-type) and non-IgE-mediated. The cause of the increasing prevalence during the past few decades may be attributed to an increased food consumption and the consequences of modern lifestyle (the hygiene hypothesis).

In addition to a skillful medical history-taking, helpful tests have been developed involving the skin or blood. The scratch test was modified to the prick test and in certain instances prick-by-prick. The use of intradermal test has been markedly reduced. Blood testing began by measuring specific-IgE antibodies (sIgE) in the serum using the radioallergosorbent test which went through multiple modifications to avoid radioisotope material and increase the test's sensitivity. The test was advanced to measure sIgE to individual allergen components. Recently, cellular tests were developed in the form of basophil activation or mast cell activation. In most cases, FA needs verification by appropriately-designed challenge testing.

Regarding treatment, strict avoidance remains the basic approach. Certain food-labeling regulations led to some improvement in the problem of hidden food allergens but more is desired. Recently some protocols for oral immunotherapy (OIT) showed reasonable safety and efficacy in preventing reactions to accidental exposures. The protocol for peanut has been approved in the United States and other foods are expected to follow. Epicutaneous immunotherapy showed higher safety and promising efficacy. Sublingual immunotherapy might follow as well. Studies on the use of certain biologicals, alone or in combination of OIT, showed promising findings. Very recently, omalizumab was approved in the United States for patients with multiple FA. A major change in the strategy of prevention is the benefit of introducing allergenic foods at an early age (4-6 months). Research on FA markedly flourished in recent decades with increasing numbers of investigators, funding, publications, and education. Despite the major strides, still more awaits exploration with expected better understanding and practice of FA.

Keywords: History of food allergy, Food allergy diagnosis, Food allergy management, Food allergy education, Food allergy research

INTRODUCTION

Food allergy (FA) may be considered the latest entity to develop under the parent branch of allergy which is a late specialty in medicine. For the sake of space in this review, the evolution of the FA entity will be markedly summarized; details with abundance of references are available in previous publications.¹⁻³

EVOLUTION OF THE FOOD ALLERGY DISCIPLINE

The discipline of FA went through a difficult road from its early inception. It passed through multiple stages starting with a long period of "non-recognition" followed with "denial", misdiagnosis as "neurosis", and then the whole subject was considered a "fad" that will not last for long. As convincing cases began to accumulate, the reactions were considered "idiosyncratic" then the term "intolerance" began to prevail followed with "adverse reaction" of which the immunologically-mediated were called "hypersensitivity" or simply "allergy".

During the BC era

The Chinese Emperors Shen Nong (cir 2735 BC) and Huang Di (2698-2598 BC) advised patients with certain skin disorders to avoid certain foods. Hippocrates (460-377 BC) recorded that food could be responsible for adverse symptoms and even death. Titus Lucretius Cato (98-55 BC) coined the famous statement, "What is food for some, may be fierce poison for others" or its modification, "One man's meat is another's poison."

During the AD era

Moises Maimonides (1135-1204), the personal physician of the Sultan of Egypt, in his "Treatise on Asthma", advised asthma patients to avoid certain foods (milk, nuts and poultry). Thomas More (1478-1535) reported that King Richard III of England (1452-1485) reacted with rash to eating strawberries. In 1662, Jean Baptiste van Helmont (1577-1644) noted that eating fish provoked asthma attacks in certain patients. Rober Willan (1798-1808) in his "Treatise on Dermatology" recorded the

occurrence of urticaria following the ingestion of certain foods and of death after eating shellfish. In animal experiments, Magendie (1839) documented the death of dogs following repeated injections with egg white.

During the twentieth century

In 1902, Charles Richet and Paul Portier explained anaphylaxis by the presence in the patient's blood of a "toxogenin" which in combination with the offending substance precipitated the systemic reaction [Richet received Nobel Prize in 1913]. They coined the term anaphylaxis. In 1906, Clemens von Pirquet coined the term "allergie"; from Greek "allos" [altered] "ergos" [reactivity]. In 1908, Victor Hutinel called FA "alimentary anaphylaxis". In 1930, Henry Donnally (1877-1947) reported neonatal allergy to egg allergen in breast milk. In 1930, Laroche and colleagues believed alimentary anaphylaxis results from too rapid food absorption [incompletely digested]. During early 1990s, Arthur Coca and Robert Cooke coined the term "atopy" [out of place]. In 1963, Philip Gell and Robin Coombs introduced the broader term "hypersensitivity" with its four main types that are still being followed today - with some modifications.

The food allergy epidemic

The twenty-first century witnessed a constant increase in hypersensitivity reactions to food.⁴⁻⁶ According to recent estimates, as many as 520 million people are affected by FA worldwide; 3-10% of children and up to 10% of adults, with 40% of children with FA being allergic to multiple foods.⁷ In the United States, FA has an estimated economic impact of >\$4.3 billion and severe FA reactions is the single leading cause of anaphylaxis treated in the Emergency Department. FA sends a person to the Emergency Department every 3 min, with an increasing number requiring hospitalization particularly among children. In 1989, Strachan⁸ proposed the "hygiene hypothesis" as an explanation for the increase in allergy in general. This was subsequently supported by more studies.⁹ Relevant to FA is the increased consumption of food in quantity and variety without significant seasonal variation.

EVOLUTION OF THE FOOD ALLERGY MECHANISM

1921, Karl Prausnitz (1876–1963) and Heinz Küstner (1897–1963) established that FA could be transferred intradermally by a substance in the serum of the allergic subject. In 1925, John Freeman performed a similar experiment by sensitizing his nasal turbinate with serum from an egg-allergic patient and developed rhinorrhea and sneezing after he ingested egg. During the 1930s, Walzer and his colleagues utilized sera from food-allergic patients to passively sensitize volunteers and demonstrated that intact allergens can cross the gastrointestinal mucosa.

In 1967, a major breakthrough was the discovery of immunoglobulin E (IgE) – the allergy mediator – by 2 different teams simultaneously. Kimishige and Turuco Ishizaka,¹⁰ at the University of Colorado in the United States, were able, by using very sensitive method of measuring serum protein, to identify the “reagin”. In the same year, a similar protein was identified by Gunnar Johansson and Hans Bennich at the blood bank of Uppsala University in Sweden in a myeloma patient.¹¹ Discovering IgE as the mediator of the immediate allergic reactions (type I hypersensitivity) gave a great credibility to the specialty of allergy. It facilitated our understanding of the mechanism of IgE-mediated FA but the non-IgE mechanism(s) remains not clear.

EVOLUTION OF FOOD ALLERGY DIAGNOSIS

The medical history has been and will continue to be the cornerstone of diagnosis in medicine, particularly in FA. The lack of convincing information in the history led to the development of allergy tests; first of the skin and later of the blood.

Skin testing

In 1912, Oscar Menderson Schloss (1882–1952) was the first to diagnose FA (egg) by scratch skin testing [originally introduced by Blackley in 1873 for pollen allergy]. In 1933, Albert Vandeer in his presidential address to the “Society for the Study of Asthma and Allied Conditions,” emphasized that the reading and interpretation of scratch testing should be done by a competent allergist. In 1959,

Helmtraut Ebruster developed prick testing. Intradermal testing with food allergen extracts was done if the scratch or prick test was negative, but was abandoned in the 1990s because of a high rate of false positivity and the risk of systemic reactions. During the 1970s, prick-by-prick with native material was increasingly used in certain cases. Despite some limitations, skin testing remains as the most popular screening test for FA.

Blood testing

In the same year of the discovery of IgE, an assay for allergen-specific IgE (sIgE) in the serum was developed by Wide, Bennich and Johansson in Sweden using a radioimmunoassay in which the allergen was covalently attached to a paper-disc solid phase – the radio-allergosorbent test (RAST).¹² The assay later was switched to enzyme-linked immunoassay and underwent multiple modifications that increased its sensitivity. Using a fluoroenzyme immunoassay, the ImmunoCap test was developed and gained a high popularity.¹³ Despite the abandonment of the radioimmunoassay, the old term RAST continued to be used for many years.

In the 1990s, a further advance in serum testing led to measuring sIgE to individual allergen components that can predict the clinical relevance of the result and possibly the reaction’s severity or prognosis. Two methods were developed; the immuno solid-phase allergen chip (ISAC) and the component-resolved diagnostics (CRD).¹⁴

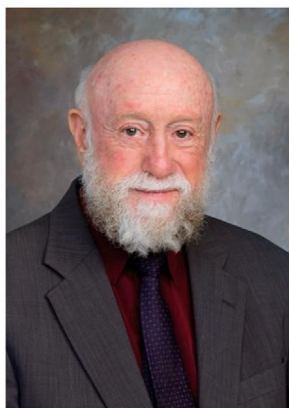
In the 2000s, the basophil activation test (BAT) was developed, with varying degrees of reliability, and has been slowly gaining availability.¹⁵ Other blood tests in development are sIgE to allergen peptides or epitope profiling^{16,17} and mast cell activation test (MAT).¹⁸

Food challenge testing

Very early on, there has been a call that FA diagnosis should not rely solely on skin or blood testing and that it should depend on reproducing the patient’s symptoms with re-introduction of the suspected food in a safe and unbiased method. To that effect, some criteria were proposed by three academicians (Fig. 1). My mentor, Douglas C. Heiner (1925–2018) at the University of California-Los Angeles was of the opinion to document 2



Douglas C. Heiner
(1925-2018)



Armond Goldman
(1930-2023)



Charles D. May
(1908-1992)

Fig. 1 Leaders who contributed to the development of food allergy challenge testing.

negative placebo challenges and 2 positive active challenges. Such a very rigid approach did not receive sufficient acceptance. Armond S. Goldman (1930-2023) at the University of Texas-Galveston proposed that avoidance of the suspected food should lead to resolution of symptoms and that three active challenges should reproduce the symptoms. He applied this approach in a large study on milk allergy¹⁹ but was not widely accepted due to its impracticality and potential risk. Charles D. May (1908-1992) at the University of Colorado-Denver proposed the double-blind, placebo-controlled food challenge (DBPCFC)²⁰ which involves documentation of a negative placebo challenge and a positive active challenge in a blind manner to both the patient and the observer. The approach was increasingly accepted, particularly for research, and emerged as the “gold standard.” In clinical practice, situations evolved where single-blind or open challenge testing can be carried out with a high reliability.²¹

In 2009, per assignment by the Adverse Reactions to Food Committee of the American Academy of Allergy, Asthma and Immunology (AAAAI), a Work Group published a report on oral food challenge testing, primarily to promote the use of challenge test to confirm the diagnosis of FA.²² In 2012, a consensus document (PRACTALL) was published by the AAAAI and the European Academy of Allergy and Clinical Immunology (EAACI) to standardize the double-blind placebo-controlled food challenge test.²³ Subsequently

multiple publications encouraged the use of food challenge in clinical practice by guidelines for the open, single-blind placebo-controlled and double-blind placebo-controlled tests. In some cases, the reproduction of the allergic reaction requires the inclusion of certain co-factors, best understood is exercise. Food-dependent, exercise-induced FA (post-prandial FA) was described first in 1979 by Maulitz et al.²⁴

Unproven tests for FA

Over the years, many tests were used by certain practitioners or laboratories but without a proven validity.^{25,26} They include the provocation-neutralization test, increase in heart rate, electrodermal (Vega) test, kinesiology, AlphaCore test, and iridology. Laboratory tests included specific IgG or IgG4 antibody level, cellular allergen stimulation test (CAST), antigen leukocyte cellular antibody test (ALCAT), leukocyte cytotoxic test, hair analysis, and trace or heavy metal analysis. In late 2023, the US Food and Drug Administration (FDA) expressed concern about many medical laboratory tests being used without validation and called for the need for regulation.

EVOLUTION OF FOOD ALLERGY TREATMENT

Elimination diet

Avoidance of the offending food has been and continues to be the basic treatment of FA. A major

problem in following a strict elimination diet is the incorporation of hidden food allergens in restaurants and in packaged foods. For a very long time, the food industry resisted the call for accurate and complete labeling. It is only in 2004 that the US Food Allergen Labeling and Consumer Protection Act enforced listing the 8 most common food allergens: milk, egg, peanut, tree nuts, soybean, fish, shellfish, and wheat. On Jan 1, 2023, sesame was added. There is a need for international guidelines for FA labeling laws.²⁷

Injection immunotherapy for FA

Subcutaneous immunotherapy (SCIT) started to develop during the early 1900s and was reported in the literature in case reports or small series. In the mid 1990s, a DBPCFC clinical trial of peanut SCIT²⁸ was aborted because of frequent systemic reactions, including 1 fatality caused by an error. Consequently, the procedure was abandoned.

Oral immunotherapy (OIT) for food allergy

In 1905, Finkelstein reported a case of successful “desensitization” in a milk-allergic child. In 1908, Alfred Schofield described the successful treatment of a child with egg “poisoning”. In 1923, Unger reported food desensitization in bronchial asthma. Subsequently a few scattered case reports were followed with a series of 50 patients by Keston et al in 1935²⁹ and another of 13 patients by Edwards in 1940.³⁰ During 1980s-1990s, Brunello Wuthrich and his colleagues in Zurich, Switzerland, published a few studies on food desensitization, mostly in the German literature, but the EAACI did not approve the procedure because the studies were not placebo-controlled.² In a debate session during an international symposium on FA in Lugano, Switzerland, in 1995, Wuthrich³¹ presented data on successful OIT with milk and another speaker was assigned the contra side but without having convincing data to the contrary!³²

During the early 2000s, many multicenter studies were carried out in the United States and Europe using different protocols on OIT with promising results and various adverse effects.³³ Recently, some protocols for OIT showed reasonable safety and efficacy in raising the threshold of reactivity to the food allergen and

could prevent reactions to accidental exposures. High-quality clinical trials led to the development of protocols with adequate efficacy and acceptable side effects. The first approved OIT product in the United States was for peanut allergy (AR101).³⁴ Other foods are expected to follow.

Promising results were reported by a few studies using the sublingual³⁵ and epicutaneous routes.³⁶

Biologics for food allergy treatment

Multiple biologic agents have been tried for FA treatment either alone or in combination with OIT, with varying favorable results.³³ Anti-IgE was the first tried, starting with talizumab (TNX-901) then omalizumab, and lately ligelizumab.^{37,38} In early 2024, omalizumab was approved in the United States for patients with multiple FA.³⁹ Other biologic agents recently in early trials are disruptors of IgE-FcεRI complexes, anti-alarmins/anti-TSLP, JAK1 inhibitors (abatacept, abrocitinib, and ibrutinib), anti-BTK (acalabrutinib), and allergen nanoparticles.³³

EVOLUTION OF FOOD ALLERGY PREVENTION

In 1936, Grulee and Sanford⁴⁰ reported that exclusive breast feeding reduced the development of atopic dermatitis (AD) by 7-fold. During 1980s –1990s, multiple studies demonstrated the benefit of exclusive breast feeding or the use of hydrolyzed infant formulas in the prevention of AD and cow milk allergy.^{41,42} In 2015, Gideon Lack, George Du Toit and their colleagues⁴³ showed the advantage of early (at 4-6 months) feeding of peanut. Subsequent studies reported a similar finding for some other foods.

FOOD ALLERGY EDUCATION AND RESEARCH

At the time when the FA discipline was not given significant attention, some Italian allergists took the lead in research and educational programs. Allergy societies in other parts of the world followed. At present, FA became a constant and popular topic in all local, regional, national, and international allergy educational programs.

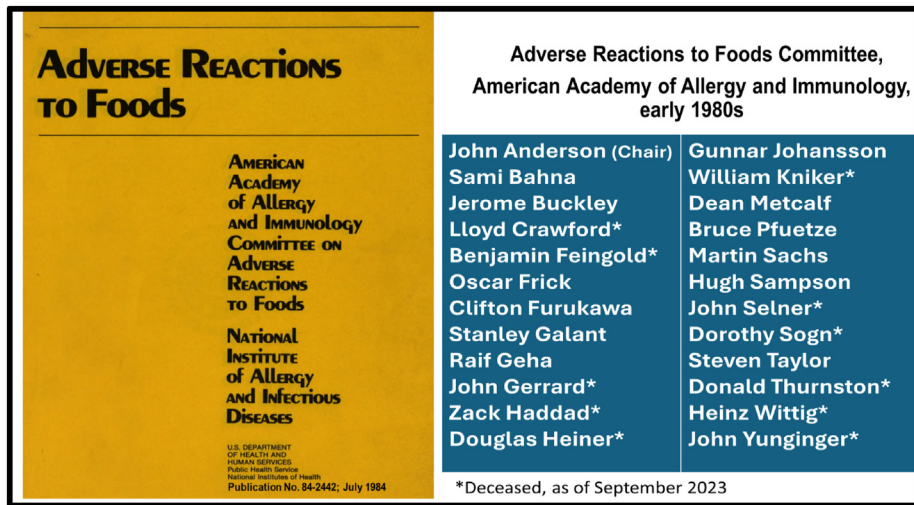


Fig. 2 Monograph of the first symposium on adverse reactions to foods held by the American Academy of Allergy and Immunology in 1983 and members of the adverse reactions to foods Committee in the early 1980s.

The programs of the American College of Allergy, Asthma and Immunology (ACAAI) annual meetings in earlier years included some segments by practitioners promoting their diagnostic or therapeutic methods – some of which were not validated or did not have a scientific basis, which generated much criticism. Attention towards improvement began in the early 1970s and the ACAAI organized an International Food Allergy Symposium for presenting sound studies and promoting validated practices. The symposium was well received and was held periodically, initially as a stand-alone program for many years and later was on the day before the main annual program – and is still continuing.

The AAAAI, with leaders primarily academicians, remained skeptical about the FA entity until 1983 when it allowed a one-day “Adverse Reactions to Foods Symposium” before its annual meeting. The symposium was co-sponsored by the Adverse Reactions to Foods Committee of the AAAAI and the National Institute of Allergy & Infectious Diseases (NIAID) (Fig. 2) It was markedly successful with speakers mostly academicians and was attended by > 500, primarily allergists. The presentations were published in a Monograph (Fig. 2) by the National Institutes of Health (NIH).⁴⁴ The event’s success made the AAAAI’s door wide open for the FA topic.



Fig. 3 The National Institute of Allergy and Infectious Diseases (NIAID) expert panel of the Guidelines for the Diagnosis and Management of Food Allergy in the United States, 2009.

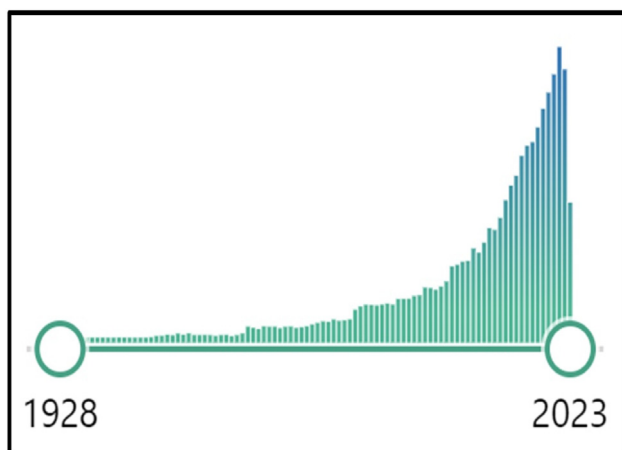


Fig. 4 Trend of number of published articles on food allergy listed in PubMed during 1928 to September 2023 (total 33, 926). Accessed September 25, 2023 using search filter at PubMed <https://pubmed.ncbi.nlm.nih.gov/>.

Investigators became increasingly attracted to the FA discipline and the National Institute of Allergy and Infectious Diseases embraced the topic and assembled a large Expert Panel of scientists interested in the subject (Fig. 3). They prepared the landmark “Guidelines for the Diagnosis and Management of Food Allergy in the United States” that was published in multiple journals in 2010.⁴⁵

Multiple additional significant documents promoted the science and practice of FA. A Joint Task Force by the AAAAI and ACAAI published a series of practice parameters including one on FA in 2006,⁴⁶ with subsequent periodical updates. Alessandro Fiocchi in Italy assembled an international group under the auspice of the

- Manifestations (rare or unexplored)
 - Gastrointestinal: Eos disorders, ^aFPIES, ^bNCGS
 - Respiratory: Heiner syndrome
 - Skin: vasculitis
 - Cardiovascular: Kounis syndrome
 - Autoimmune/rheumatologic
- Mechanisms
 - Non-IgE
 - Cross-reactivities
 - Role of microbiome
 - Hidden food allergens in medications & blood products
- Diagnosis
 - Standardization of ST (extracts, testing methods, interpretation)
 - Biomarkers for resolution of FA
 - Allergenic epitope analysis
 - Basophil activation test
 - Mast cell activation test
- Treatment
 - Immunotherapy, Biologics, Pre-/probiotics
 - Food labeling
- Prevention
 - Population
 - Targets
 - Realistic protocols
- Education:
 - Medical students/residents curricula, clinical rotations
 - Postgraduate courses
- Literature scrutiny

Table 1. Current gaps in the discipline of food allergy. ^aFPIES, food protein induced enterocolitis syndrome. ^bNCGS, non-celiac gluten sensitivities

World Allergy Organization (WAO) to publish Guidelines on the Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA). The first was published in 2010⁴⁷ and was followed with a series that addressed various aspects of CMA (10 so far). The relevant literature was assessed using the evidence-based GRADE approach (Grading of Recommendations, Assessment, Development, and Evaluations). The EAACI recently published Guidelines on the Diagnosis of IgE-mediated Food Allergy.⁴⁸ Also very recently, an international group prepared a WAO consensus on definition of FA severity.⁴⁹

According to PubMed, journal articles relevant to FA began in the literature in 1928 at a rate of 1-2 per year and gradually increased except during World War II. The number exponentially increased, reaching a peak of 2299 articles in 2021 then declined in the subsequent couple of years attributed primarily to COVID-19 pandemic (Fig. 4). The idea of founding a special journal for FA floated around for many years until was fulfilled in 2019 when the "Journal of Food Allergy" was published by Oceanside Publication (www.JFoodAllergy.com). A plethora of books has been published on FA both for health providers and the public.

CURRENT GAPS IN THE FOOD ALLERGY DISCIPLINE

Though FA has taken major strides over the years, still much more awaits to be done on various aspects (Table 1). Not all clinical manifestations of food hypersensitivities have been identified and some rare manifestations are not included in the differential diagnosis. Knowledge about the non-IgE mediated FA mechanisms is markedly deficient. Except for the challenge test or a convincing medical history, there is no single test that could diagnose FA with 100% certainty. In the interpretation of skin or blood test result, the effect of the duration and degree of avoidance of the food before the time of testing may need to be taken into account.

Available FA treatment methods so far are not providing a cure or even an optimal degree of protection. The potential therapeutic role of newer biologics is worth exploring such as tezepelumab (anti-

TSLP), lircatelimab (anti-siglec-8), mepolizumab/reslizumab (anti-IL-5), benralizumab (anti-IL-5R), lebrikizumab (anti-IL-13), and MEDI-528 (anti-IL-9). The area of prevention lacks well-defined targets and optimal protocols. The role of probiotics and prebiotics remains to be defined.

Education of health providers is still far from being adequate; medical students are getting minimal or no knowledge on FA and medical residents' rotation in the allergy clinic is elective and short. Last, but not least, is the information that goes into the literature without sufficient scrutiny particularly regarding the study design, methodology and diagnostic criteria. The field of FA is wide open for more work.

Abbreviations

AAAAI, American Academy of Allergy, Asthma & Immunology; ACAAI, American College of Allergy, Asthma & Immunology; AD, atopic dermatitis; CMA, cow's milk allergy; DBPCFC, double-blind, placebo-controlled food challenge; DRACMA, Diagnosis & Rationale for Action against Cow's Milk Allergy; EAACI, European Academy of Allergy & Clinical Immunology; FA, food allergy; IgE, immunoglobulin E; OIT, oral immunotherapy; sIgE, specific immunoglobulin E.

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Declaration of competing interest

The author reports no competing interests.

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