

Occupational asthma induced by inhalation and ingestion of garlic

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Repeated exposure to garlic dust induced severe asthma in an atopic patient. Subsequently, the patient also developed marked adverse responses after ingestion of garlic. Immunologic investigations carried out in an asymptomatic period revealed significant skin reactivity and bronchospasm after challenge with both garlic dust and extract. The results of a controlled oral challenge test to garlic dust were also positive. The patient's serum contained unusually high quantities of garlic-specific IgE. Cross allergenicity between garlic and other members of the Liliaceae family were documented by the RAST inhibition technique. (J ALLERGY CLIN IMMUNOL 69:448, 1982.)

The occurrence of asthma has been documented after inhalation or ingestion of a variety of food substances.¹ This article concerns a case of occupational bronchial asthma induced by both inhalation and ingestion of garlic and associated with immediate skin reactions, a positive bronchial provocation response, and immunologically specific IgE antibodies. Other in vitro investigations also revealed cross allergenicity with several other foods of the Liliaceae family.

CASE REPORT

A 30-yr-old electrician worked at a spice processing plant for 9 yr. During the summers of the seventh and eighth years of this employment, he noted isolated episodes of dyspnea and chest tightness at work, which were relieved by breathing "fresh air." During the spring of the ninth year he developed a severe asthmatic attack with cough, dyspnea, and wheezing, which required hospitalization and treatment with corticosteroids. He remained away from work for 1 mo, but after he returned, severe asthma recurred within a

few days and required hospitalization. He was advised to avoid work for 2 mo and the asthma improved. He returned to work a third time and once again developed asthma within a few days. On each occasion the asthma required intensive treatment with bronchodilators, steroids, and immediate removal from the workplace. At this time, he also noted rapid onset of dyspnea and wheezing after eating foods containing garlic.

The patient was responsible for maintenance of electrical machines in all areas of the plant. Fresh garlic bulbs were processed into garlic powder in a separate area of the plant between the months of April and August of each year. Moreover, the patient was required to be in the garlic processing area daily when copious amounts of garlic dust were in the air. Since his asthma symptoms occurred after exposure to garlic powder at work for three successive processing seasons, the patient believed that his illness was occupationally related.

There was no previous history of respiratory illness and no personal or family prevalence of allergy. He had smoked one pack of cigarettes per day for 15 yr.

The physical examination was normal during asymptomatic periods. Prior to the first series of clinical and laboratory tests, the patient had experienced 3 days of wheezing, which he attributed to eating garlic-seasoned sausages. However, he was asymptomatic and pulmonary auscultation was normal on all test days.

MATERIALS AND METHODS

Direct skin tests

Commercial pollen and garlic extracts (Center Laboratories, Port Washington, N. Y.) were used to perform skin prick tests. The garlic tests were performed with extracts containing 1000 and 100 PNU/ml. To eliminate the possi-

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Abbreviations used

RAST:	Radioallergosorbent test
PNU:	Protein nitrogen units
FEV ₁ :	Forced expiratory volume in one second

bility that these extracts might contain nonspecific irritants, seven allergic patients without prior histories of garlic reactions and seven nonallergic patients were skin tested (prick and intracutaneous) with these extracts. No reactions were observed.

Radioimmunoassay

Total IgE was determined by the radioimmunosorbent test (Pharmacia, Inc., Piscataway, N. J.). Specific IgE to garlic was measured by modification of the RAST. Garlic extract (2000 PNU/ml) was coupled to methylcellulose discs activated by cyanogen bromide dissolved in acetone-trile.² Results were expressed as percent binding and were calculated by dividing counts per minute of the test sera by counts per minute of total added radioactivity.

Cross-allergenicity studies with other foods of the Liliaceae family were determined by the RAST inhibition technique.³ Equal volumes of the patient's garlic-specific IgE serum and concentrations of 2000, 200, 20, and 2 PNU/ml of various food extracts (onion, asparagus, chives, and garlic) were incubated at 37° for 2 hr and then centrifuged at 1500 × g for 15 min. The upper two thirds of this mixture was removed and incubated with activated methylcellulose discs coupled with garlic extract (2000 PNU/ml), and percentage RAST binding was determined as previously described. The degree of RAST inhibition was obtained by comparing substrate radioactivity of absorbed samples with that of a control mixture containing reference serum diluted with a comparable volume of normal saline.

Bronchial provocation tests

These tests were performed when the patient's clinical status was normal and his baseline pulmonary function tests were at least 80% of predicted normal. Nonspecific bronchial reactivity was assessed by methacholine challenge.⁴ Bronchial challenge to garlic involved two types of garlic material. Initially, the patient's response to garlic powder from his work environment was determined. This was followed by bronchial challenges to solutions of commercial garlic extract, which were also used for skin testing. Sterile water was aerosolized as a control material for the garlic powder and garlic aqueous-extract studies. Possible irritant effects of the aqueous garlic extracts were evaluated in six clinically stable, garlic-nonsensitive asthmatic patients whose pulmonary function tests were at least 80% of predicted normal. No pulmonary function changes were observed after challenge with the highest garlic concentration (1×10^{-2} gm/ml) subsequently used for challenging the patient.

Garlic dust was generated by transferring the garlic powder from one rectangular (4 by 8 inch) container to another,

the second located in the vicinity of the patient's breathing zone. Two concentrations of garlic powder (w/w, 1:100 and 1:10) were prepared by adding appropriate amounts of lactose powder. Actual quantitation of the generated dust was accomplished with a personal air-sampling device located near the subject's mouth. The personal air sampler contained an open-face particulate filter for gravimetric analysis. For each test, the subject inhaled the generated dust at tidal volume and normal frequency for 2 min.

A special aerosol-generating system (Fig. 1) was used for bronchial challenges with methacholine and aqueous garlic extracts. Compressed air (20 psi) delivered through a number-40 DeVilbiss nebulizer at 10 L/min generated an aerosol that was admixed with compressed air generated at a 56.6 L/min. The final aerosol mixture entered a Plexiglas reservoir (volume = 1056 cubic inches) at a flow of 66.6 L/min. A short tube leading from the reservoir to a one-way valve was connected to the patient's mouthpiece. The expiratory side of the one-way valve was connected to a 13 L Collins spirometer for continuous measurement of expired volume. Excess aerosol was withdrawn from the reservoir by a vacuum system capable of handling the total input flow (66.6 L/min). This allowed the reservoir to remain at atmospheric pressure during breathing.

Mean particle sizes of the aerosol generated by this method were previously evaluated with a solution of uranine, a colored testing reagent for determining mass median diameters of aerosols. According to this technique, aqueous aerosols generated in this apparatus were demonstrated to have had a mass median diameter of 0.65 μ m with a geometric standard deviation of 2.0 μ m. Ninety-five percent of the particles produced by this aerosol were less than 2 μ m in diameter and 70% of the particles were larger than 0.5 μ m.

The aerosol was allowed to equilibrate in the reservoir for at least 60 sec and was delivered to the patient continuously under previously described conditions. The subject, with nose clip in place, inhaled at tidal volume from the reservoir system and exhaled into the spirometer. The amount of inspired aerosol was calculated by multiplying the total expired volume during the test procedure by the aerosol concentration within the reservoir. Previous testing of the reliability of this system had demonstrated good reproducibility of results.

The patient's responses to garlic dust and aerosol solutions were serially monitored with a CPI dry rolling seal spirometer and Wright's peak-flow meter. Forced vital capacity, FEV₁, and peak expiratory flow rate were measured.

Oral challenge tests

On separate days, the patient ingested 1600 mg of garlic powder and 800 mg of lactose in gelatin capsules. The challenge sequence was determined by the investigators but was unknown to the patient.

RESULTS

Skin tests

The patient exhibited a 2 by 2 mm wheal after testing with 100 PNU/ml aqueous garlic extract and a

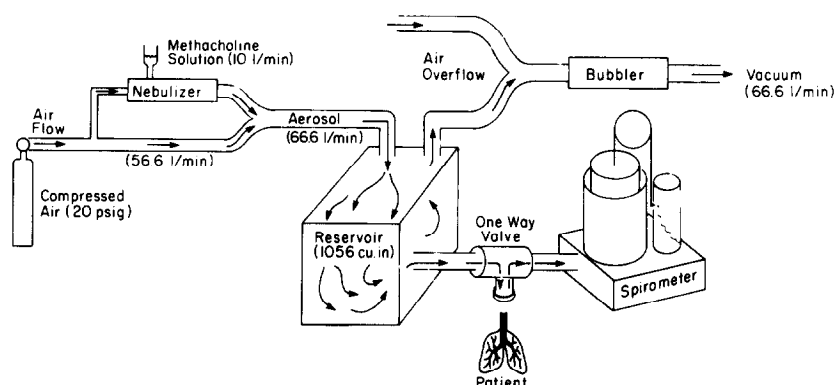


FIG. 1. Apparatus for generating aerosols of methacholine solutions and aqueous garlic extracts.

TABLE I. Specific IgE to garlic extract measured by RAST

Experiment No.	% Binding of ^{125}I anti-IgE	
	Patient	Control
1	16.1	4.6
2	13.1	2.5
3	16.3	3.2
4	14.3	2.9
5	14.2	4.3
Mean	14.8	3.5

5 by 6 mm wheal after application of 1000 PNU/ml of the same extract. Positive prick tests to aqueous pollen extracts were also observed.

IgE measurements

The patient's serum IgE concentration was 4566 U/ml, a markedly elevated value in this laboratory (normal range, 10 to 250 U/ml).

A RAST battery screen to common pollen aeroallergens was also performed. The percentages of RAST binding to short ragweed, timothy grass, and box elder were 20.8%, 11.6%, and 16.5%, respectively.

Results of garlic-specific IgE determinations are summarized in Table I. The patient's serum contained a high level (14.8%) of garlic-specific IgE on at least five occasions, and this level was at least 4.2 times higher than that of negative control sera.

RAST inhibition

Significant inhibition of RAST activity by garlic and other members of the Liliaceae family are shown in Fig. 2. There is a linear relationship between the amount of inhibition and the concentration of the absorbent. RAST inhibitions at equivalent concentrations of 2000 PNU/ml were 74% for onion, 72% for

TABLE II. Relative inhibitory capacities of several foods in the Liliaceae family

RAST absorbent	50% Inhibition concentrations (PNU/ml)
Garlic	160
Onion	60
Asparagus	40
Chives	2000

asparagus, 68% for garlic, and 50% for chives. Table II lists the relative inhibitory capacities of members of the Liliaceae family. It is of interest that several heterologous food allergens (onion and asparagus) were more potent inhibitors of garlic-specific RAST than garlic itself.

Bronchial challenge testing

Airway hyperactivity was documented by a positive methacholine challenge. The patient's FEV₁ decreased more than 20% after an aerosol challenge dose of methacholine at a concentration of 10 mg/ml.

Results of garlic bronchial provocation are summarized in Figs. 3 and 4. The concentrations of dust measured at the patient's breathing area for various garlic powder concentrations were as follows: (1) garlic powder (1:100 with lactose), 2.5×10^4 parts per cubic foot; (2) garlic powder (1:10 with lactose), 3×10^5 ppcf. Exposure to 2.5×10^4 ppcf (1:100 garlic:lactose) failed to elicit a response, while inhalation of 3×10^5 ppcf garlic powder for 2 min induced a maximum reduction (37%) of FEV₁ (Fig. 3). The concentrated aqueous garlic extract (2000 PNU/ml) contained 324 $\mu\text{g}/\text{ml}$ protein, as determined by the Lowry method.⁵ The dose-response bronchial challenge experiment was performed with three dilutions (w/v, 1×10^{-7} , 1×10^{-5} , and 1×10^{-2} gm/ml) of this extract. At these dose levels the calculated amounts of total protein inhaled by the patient were

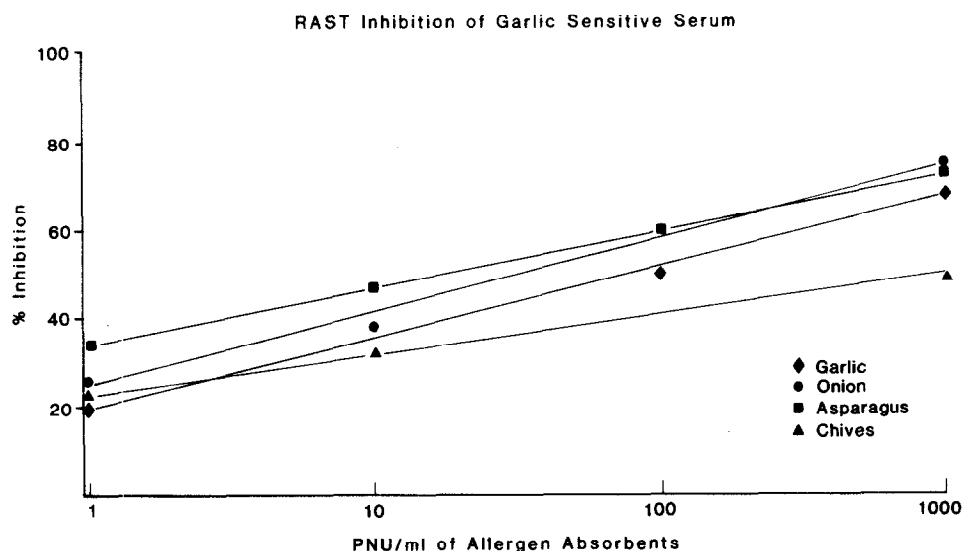


FIG. 2. RAST inhibition experiments with garlic-sensitive serum. Each curve was plotted from dose-response RAST assays of serum obtained after absorption with each of the designated members of the Liliaceae family.

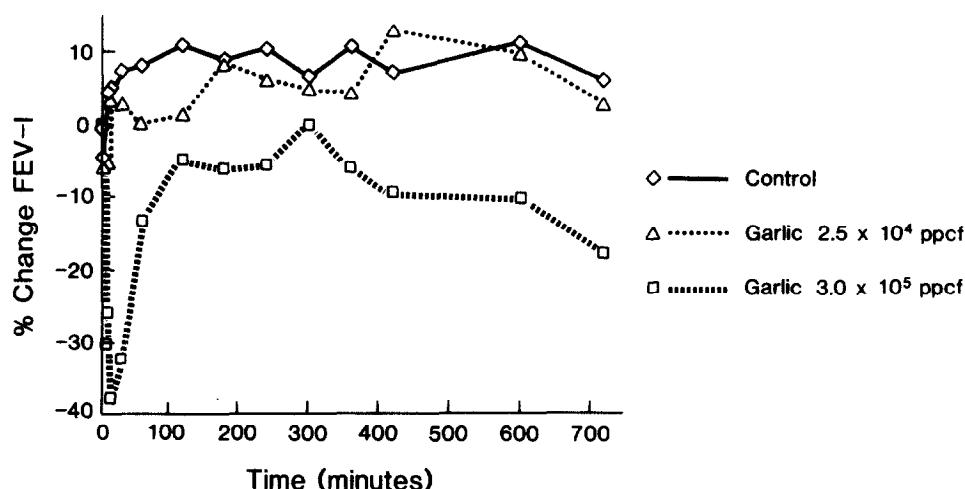


FIG. 3. Sequential changes of FEV₁ over a period of 12 hr after bronchial challenge with control solution and garlic powder (1:100 and 1:10, w/w).

1.14×10^{-12} , 1.18×10^{-9} , and 1.15×10^{-7} gm/ml, respectively. Bronchial challenge with the 1:100 dilution of aqueous garlic extract produced a 35% decrease of FEV₁ (Fig. 4). No significant fall in FEV₁ was noted after provocation with smaller doses of garlic powder and aqueous extract or with the control solution. In both dust and aqueous extract aerosol challenges, the decrease of FEV₁ occurred within 15 min and returned to the baseline level within 2 hr. No bronchodilator medication was required for this reversal. Clinically, the patient described symptoms of dyspnea and cough on each occasion and wheezes were also heard by the examiner.

The patient was pretreated with 40 mg of cromolyn

sodium at bedtime and 30 min prior to a morning challenge with the 1:100 dilution of garlic aqueous extract, which had previously caused a 35% reduction in FEV₁. The patient's bronchial response was partially blocked by cromolyn pretreatment. This was determined by comparing the declines of FEV₁ with (14%) or without (35%) cromolyn sodium pretreatment.

Oral challenge

Ingestion of the lactose placebo caused no reaction. Ingestion of 1600 mg of garlic caused symptoms of apprehension, marked facial and trunk flushing, and nausea within 10 min. Diarrhea appeared within 2 hr,

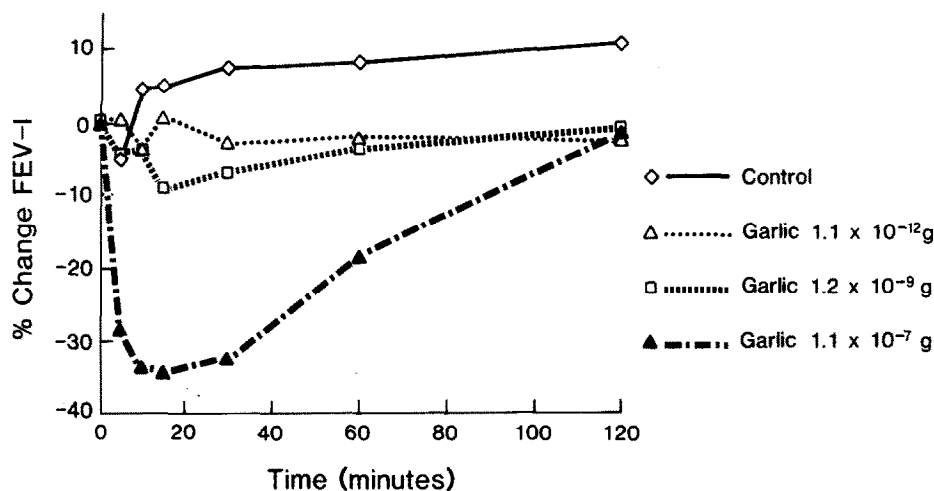


FIG. 4. Sequential changes of FEV₁ over a period of 120 min after bronchial challenge with control solution and various concentrations of garlic extract.

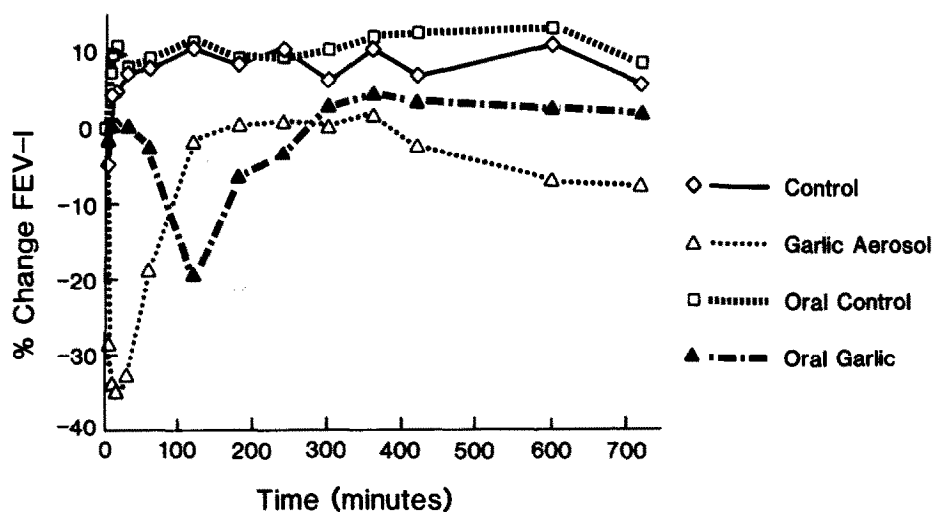


FIG. 5. Sequential changes of FEV₁ over a period of 12 hr after ingestion of 800 mg of lactose (control test) and 1600 mg of garlic powder (challenge test). The data of control and garlic aerosol at a concentration of 1.1×10^{-7} gm/ml are superimposed on this graph for comparative purposes.

the pulse rate increased to 130 per/min, and there was a 21% reduction in FEV₁ (Fig. 5). The peak intensity of this clinical reaction occurred 2 hr after ingestion of the garlic capsule in contrast to inhalation challenge, where the maximum effect was observed at 15 min. Although symptoms of nasal stuffiness, facial flushing, and nausea suggested hyperhistaminemia, this was not substantiated by an increase of venous plasma histamine.

DISCUSSION

Respiratory sensitization to dust generated in the workplace has been reported with increasing frequency.⁶ The prevalence of such reactions may be

even greater among food handlers and processors.¹ However, specific respiratory sensitization to garlic has been documented in only two previous case reports.^{7, 8} This is consistent with the fact that relatively few workers are exposed to this particular food substance under optimal conditions for allergic sensitization. In the first case report of respiratory sensitization, the diagnosis was not proved immunologically but the history of association between immediate symptoms and exposure to garlic, positive skin tests, and improvement after removal from further exposure suggested a causal relationship between onset of asthma and exposure to garlic dust.⁷ Recently, a similar instance of garlic-induced asthma was documented

by direct skin tests, positive bronchial challenge tests, and the presence of immunologically specific IgE anti-garlic antibodies.⁸ It is noteworthy that the patient in the latter study was able to tolerate ingestion of cooked garlic or onion without symptoms, but controlled oral challenge tests with uncooked garlic were not performed.

Contact dermatitis is not uncommon in professional cooks or food helpers who handle garlic bulbs, but respiratory or gastrointestinal symptoms do not occur after this route of exposure.⁹ On the other hand, the special conditions of dust generated by garlic processing in our patient's work environment presumably provided the ideal milieu for sensitization of his respiratory tract. In addition, his susceptibility to sensitization to garlic dust might have been enhanced by his pre-existing atopic status, as manifested by positive skin reactivity and RAST to some of the common inhalant aeroallergens as well as by a high serum IgE level. Subsequent development of anaphylactoid symptoms after ingestion of garlic suggested that the degree of specific IgE antibody response had progressed to the point where sensitization of tissue mast cells in the gastrointestinal tract and basophils within the intravascular compartment was more widespread. It also appeared that the allergic determinant(s) was similar for both respiratory and oral routes of sensitization and that it was not destroyed during the process of digestion. The temporal associations of reactions occurring after respiratory exposure and ingestion of garlic were both corroborated by controlled bronchial and oral provocation testing. Moreover, the allergenic properties of garlic were revealed by positive direct skin tests and a high circulating level of IgE, which was found to be specifically directed against garlic allergen(s) by the RAST inhibition technique.

Food allergens that induce respiratory sensitization may be classified into two principal categories. The first group consists of those foods that induce respiratory sensitivity without symptoms after oral administration. Common examples of this group are flour and coffee dusts.^{10, 11} One previous case report of asthma induced by garlic dust could also be included in this group.⁸ It has been assumed that the appropriate allergenic fractions are denatured during baking, roasting, or cooking processes of these foods and simply are not available for combination with sensitized mast cells in the gut. It is also possible that allergenic determinants of these foods could be destroyed by enzymatic digestion in the gastrointestinal tract. The second main category of foods may cause a heterogeneous immune response, which, as illustrated by the current case, may produce reactions after both respira-

tory and oral exposure. Buckwheat, pineapple protease, and garlic have these common characteristics.^{12, 13} The allergenic properties of garlic are of further interest because contact with this food also causes an allergic dermatitis. This delayed form of immune response has been attributed to sensitization by protein constituents of garlic.⁹

The existence of crossreacting contact allergenic determinants in several food members of the Liliaceae family was previously demonstrated by endermal patch tests in patients with garlic dermatitis.⁹ Direct immunologic evidence for the presence of humoral cross-allergenicity was demonstrated for the first time in this patient. Several closely related food members of the Liliaceae family (onion, asparagus, chives) exhibited parallel slopes of their respective RAST inhibition curves. Since the inhibitory capacities of both onion and asparagus food extracts were 2.5 to 4 times higher than that of the homologous garlic allergen, it is possible that these related foods may contain even higher concentrations of the common allergenic determinant. Such an inverse relationship had already been documented among several members of the Compositae.³ For example, the pollen of *Franseria tenuifolia*, a species of false ragweed, contains more antigen E than *Ambrosia elatior* (short ragweed), from which antigen E was originally purified. Direct substantiation of this premise for members of the Liliaceae family requires further immunochemical characterization of the crossreacting allergen described in this article.

In conclusion, this case of occupational asthma induced by sensitization to garlic dust was documented by direct skin-test reactivity, a positive bronchoprovocation response under controlled conditions, and immunologically specific IgE in the patient's serum. Subsequently, the patient also developed gastrointestinal sensitivity documented by a controlled oral challenge with garlic. Immunologic evidence of cross allergenicity with other related members of the Liliaceae family was also demonstrated.

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