

Anaphylactic reactions to a psyllium-containing cereal

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Historical data were obtained by questionnaire and telephone survey on 20 of 24 women with reported allergic reactions to a psyllium-containing cereal, Heartwise. Protein fractions from this new cereal, as well as from psyllium mucilloid and a psyllium-containing laxative, Metamucil, were extracted, quantitated, and separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. Patients' sera were collected, and specific IgE and IgG antibodies to these psyllium antigens were detected by immunoblotting techniques. Of the 20 women evaluated, all but six were nurses. Eighteen (90%) of the women had historical and/or laboratory evidence of atopy. Exposures included ingestion or dispensing of psyllium-containing products. Only three women denied prior exposure to psyllium. Symptoms developed shortly after small amounts of the cereal were ingested and most commonly included moderate to severe wheezing, throat and chest tightness, and urticaria. All the women required medical therapy, 11 (55%) in an emergency room. Specific IgE and IgG antibodies to various psyllium protein fractions were documented in all the subjects. It was concluded that individuals sensitized by occupational exposure to psyllium dust are at high risk for allergic reactions to ingested psyllium-containing products. (J ALLERGY CLIN IMMUNOL 1991;88:402-8.)

Key words: Psyllium, immunoblot, anaphylaxis

Psyllium mucilloid is a natural, water-soluble fiber obtained from the seed husk of plants of the *Plantago* genus. Its hydrocolloidal properties have been exploited as a bulk laxative since the 1500s. India provides about 85% of the psyllium of the world, *Plantago ovata*, commonly referred to as blond psyllium. This is the most important variety used commercially in pharmaceutical and other allied health industries. Importing >7000 metric tons per year, the United States has been a major user of psyllium since the 1930s, with more than 4 million Americans using psyllium-containing laxatives each year.^{1, 2}

Processing psyllium involves separation of the seed husk, which contains psyllium mucilloid, from the rest of the seed. After initial screening, the seed is

Abbreviations used

SDS-PAGE: Sodium dodecyl sulfate-polyacrylamide gel electrophoresis
PBS: Phosphate-buffered saline
Ab: Antibody

cleaned, polished, and prepared for the dehusking process, which involves passing seeds through eight separate grinding mills (attrition mills) and 20 mesh screens to separate the husk. The first cut is 99% pure husk and very white in color. The second and third cuts yield 95% purity. Each cut is then passed through a series of blowers to separate further the husk in preparation for market.²

Besides its contribution to bulk laxatives, psyllium mucilloid may also be formulated into food products to increase dietary fiber and improve food texture. The recent observation that psyllium is useful in lowering serum cholesterol levels in hypercholesterolemic patients^{3, 4} has sparked great interest in this product. Allergic reactions after occupational exposure to psyllium have been reported in pharmaceutical and health care workers. Recently, allergic reactions to a psyllium-containing cereal have been reported.^{5, 6} Of 24

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cases reported to the Kellogg Co. between September 1989 and March 1990, 20 cases were evaluated by history and laboratory studies. This article summarizes the allergic symptoms and supporting immunologic evidence for the allergic reactions in this group of patients and the preliminary characterization of the responsible allergen.

MATERIAL AND METHODS

Historical data were obtained by questionnaire and telephone survey on 20 of 24 women with reported allergic reactions to a psyllium-containing cereal, Heartwise (Kellogg Co., Battle Creek, Mich.), between September 1989 and March 1990. The information gathered included occupation, prior exposure to psyllium-containing products, type of reaction, extent of treatment, and history of atopy. Telephone surveys were used to expand and clarify histories of potential psyllium exposure and other allergic disorders. The study was approved by The Johns Hopkins University Institutional Joint Committee on Clinical Investigation.

After obtaining informed consent, venous blood was obtained. The serum was separated by centrifugation, shipped, and stored at -20°C until it was needed for specific laboratory investigations. To determine whether or not subjects were predisposed to atopy, the patients' sera were evaluated with two immunoassays. Total serum IgE was determined with a quantitative PRIST assay (Phadezyme IgE PRIST, Pharmacia Diagnostics, AB, Uppsala, Sweden). Serum IgE values $>100\text{ U/ml}$ were considered elevated. In addition, a commercially available multiantigen RAST that detects specific IgE antibodies to seven common allergens (Phadiatop, Pharmacia Diagnostics AB) was used. It is a qualitative assay that yields a positive or negative result for atopy and has been demonstrated to have both a sensitivity and specificity of 90% in the detection of atopy.⁷ To investigate prior sensitization to a common, related lawn weed found in the United States, English plantain (*Plantago lanceolata*), a commercially available RAST (Phadiazyme RAST, Pharmacia Diagnostic AB,) was performed on patients' sera. Patients' sera were also used in immunoblotting studies to detect IgE and IgG Abs specific to psyllium fractions. Control sera were drawn from five subjects who had been ingesting Heartwise regularly for at least 6 months but who had no history of adverse allergic reactions.

Protein extraction techniques were used to prepare samples of pure psyllium powder, the psyllium-containing cereal, and Metamucil (Procter and Gamble, Cincinnati, Ohio) for further studies. Metamucil, a psyllium-containing bulk laxative, was included in the analysis because of its widespread and apparently safe use during many years without reported allergic reactions. Two grams of each sample were added to 200 ml of PBS, pH 7.4, and rotated for 30 minutes at 4°C . Samples were clarified by centrifugation at 700 g for 10 minutes, and then supernatants were removed and lyophilized overnight. The protein content of each sample was determined with a Bio-Rad protein assay kit (Bio-Rad Laboratories, Richmond, Calif.).⁸

With SDS-PAGE, 100 mg of lyophilized sample was

dissolved in 1 ml of distilled water, diluted 5:1 in sample buffer concentrated five times (0.01 mol/L dithiothreitol, 10% SDS, 0.4 mol/L Tris HCl [pH 6.8], and 50% glycerol, bromophenol blue, and pyronin Y), and then boiled at 100°C for 10 minutes. Seventy-five microliters of each extract was loaded in separate gel lanes. The proteins were resolved in a discontinuous SDS-PAGE system according to a previously published method.⁹ Briefly, the samples were electrophoresed through a 3% stacking gel at 80 mV for 1 hour and then through a 13.5% running gel at 160 mV for 3 hours. The running gel was prepared from a stock of 33.5% acrylamide and 0.3% *N,N'*-bis acrylamide to a final concentration of 13.5% acrylamide. The stacking gel was prepared from a stock of 30% acrylamide and 0.44% *N,N'*-bis acrylamide to a final acrylamide concentration of 3% in 0.5 mol/L of Tris HCL, pH 6.8. Both gels contained 0.1% SDS and were polymerized with 3% ammonium persulfate and *N,N,N',N'*-tetramethyl-ethylenediamine. The electrode tank buffer was 25 mmol/L of Tris and 192 mmol/L of glycine with 1% SDS.

For immunoblotting studies (Western blots), the separated protein subunits were electrophoretically transferred from the gels onto nitrocellulose paper overnight at room temperature with 0.15 amps in 50 mmol/L of Tris-glycine buffer (pH 9.1) containing 20% methanol. A 0.1% amido black staining technique was used to define specific protein bands. The nitrocellulose blots were blocked in 0.5% porcine gelatin in PBS, pH 7.4, with 0.05% Tween 20 and 0.001% merthiolate for 8 hours at room temperature. The blots were then probed for antigen-specific IgE binding to the protein bands. They were initially incubated for 2 hours at room temperature on a rocking platform in a 1:25 dilution of sera from a patient or control subject in 0.5% porcine gelatin in PBS with 0.001% merthiolate. After the incubation step, the blots were washed with five 5-minute exchanges of 0.05% Tween 20 in PBS. Peroxidase-labeled, affinity-purified rabbit antihuman IgE or antihuman IgG (DAKO Corp. Santa Barbara, Calif.) was then incubated with the blots for 2 hours at room temperature in 0.5% porcine gelatin in PBS, and then the wash step was repeated. Rabbit antisera were chosen as the second Ab because our earlier studies demonstrated nonspecific binding of mouse IgG and goat IgG Abs to the nitrocellulose-bound psyllium protein fractions. This binding was probably the result of lectins in the psyllium fractions. The blots were developed for 2 to 3 minutes in 10 mmol/L of potassium phosphate, pH 6.8, with 1 mmol/L of ethylenediaminetetraacetic acid containing 0.009% hydrogen peroxide and 0.3 mg/ml 3,3'-diaminobenzidine. The reaction was stopped by washing the developed blots in PBS.¹⁰

RESULTS

Of the 20 patients evaluated by history and laboratory studies, all were female, ranging in age from 27 to 73 years (median age, 53 years). The patient population and allergic reactions to the psyllium-containing cereal are summarized in Table I. Twelve of the subjects, seven of whom were previously eval-

TABLE I. Historical data on 20 psyllium-allergic patients

	No.	(%)
Reported atopic symptoms (evaluated by allergist)	12 (7)	(60)
Laboratory data supporting atopy	18	(90)
Positive RAST to English plantain	0	
Health care workers (nurses)	14	(70)
Previously dispensed psyllium-containing laxatives	15*	(75)
Previously taken psyllium-containing laxatives	7†	(35)
Previously eaten the cereal	2‡	(10)
No prior exposure to psyllium	3	(15)

*11/15 had symptoms.

†4/7 had symptoms.

‡Both subjects had nausea/abdominal cramping.

uated by an allergist, reported atopic symptoms. Interestingly, of the eight who denied atopic symptoms, six had laboratory evidence suggestive of atopy by either a positive Phadiatop and/or an elevated total serum IgE (>100 U/ml). Overall, 18 of the women had laboratory data suggesting atopy. No patient had a positive RAST to English plantain. Fourteen of the women were nurses, and of the remaining six non-health care workers, one woman had dispensed Metamucil to her cat, and two other workers had previously taken bulk laxatives. Only three subjects denied any prior exposure to psyllium. Eleven of 15 women who had previously dispensed psyllium-containing laxatives experienced allergic symptoms while they were dispensing these products (Table II). Seven patients had previously taken psyllium-containing laxatives; four of these patients experienced nausea and abdominal cramping. Two patients had previously eaten one serving of the cereal and suffered abdominal side effects, including nausea and cramping.

Allergic reactions in this group developed within 2 to 30 minutes after ingesting small amounts of the cereal. Each patient reported ingestion of an amount less than one cup of cereal before symptoms appeared. The most common symptoms (appearing in $>70\%$ of all patients) included moderate to severe wheezing, tightness in the chest or throat, and urticaria. The wide array of symptoms reported are summarized in Table III. All the women required some form of medical therapy; 14 (70%) of the women were treated by a physician, 11 (55%) were treated in an emergency room setting, and the remaining six women were self-medicated. Nearly three quarters of the patients received antihistamines, and $>20\%$ were treated with epinephrine and corticosteroids.

TABLE II. Allergic symptoms experienced while 11 subjects were dispensing psyllium-containing laxatives

Symptom	No.	(%)
Nasal congestion/itching	10	(91)
Watery, itchy eyes	5	(45)
Chest tightness	5	(45)
Cough	4	(36)

To implicate an immunologic etiology, a search was undertaken for laboratory evidence of psyllium-specific IgE Abs. Amido black staining of the psyllium protein fractions separated by electrophoresis and transferred to nitrocellulose revealed 13 protein bands ranging in molecular weights from 12,200 to 66,100 daltons (Fig. 1). The major bands included three in the 20 to 22 kd range and two bands in the 30 to 34 kd range. Likewise, similar migration of protein fractions was noted when the psyllium-containing cereal, psyllium powder, and Metamucil were compared. Immunoblotting studies revealed that all the patients possessed IgE and IgG Abs specific to some psyllium fractions. All the patients had IgE Abs to bands 4 to 9 in the 20,000 to 36,000 dalton range. In addition, five patients had IgE Abs to bands 12 and 13 in the 60 to 66 kd range (high molecular weight). One patient had IgE Abs to bands 2 and 3 in the 12,000 to 14,000 dalton range (low molecular weight), and one patient had IgE Abs to all bands in the high, middle, and low molecular weight ranges. Representative patient immunoblots with both IgE and IgG Abs against Heartwise, psyllium powder, and Metamucil are depicted in Fig. 2 and illustrate the different patterns of patient reactivity described above. A representative control patient is also depicted. The control patients had no detectable IgE Abs to the protein fractions, but all possessed specific IgG Abs. Neither the patients nor the control subjects had evidence of IgE Abs to wheat or oat, two cereal grains contained in Heartwise.

To exclude the possibility that a contaminant unique to the Indian psyllium was responsible for the allergenicity, Australian psyllium was compared to Indian psyllium and the psyllium nugget used in the preparation of the cereal. The major protein fractions were present in comparable amounts in all preparations, and Abs to the psyllium fractions were detected with sera from the 20 patients (Fig. 3). An investigation was then undertaken to determine if the allergenic portion of the crude psyllium could be eliminated. Psyllium powder (85% purity) was passed through a series of three different mesh screens with progressively smaller diameters, 20, 30, and 40 mesh size. When

TABLE III. Symptoms experienced by 20 patients after ingesting psyllium-containing cereal

Symptom	No.	(%)
Moderate to severe wheezing	17	(85)
Tightness in throat and chest	16	(80)
Urticaria/angioedema	14	(70)
Itching or tingling in mouth	11	(55)
Nasal congestion/pruritus	11	(55)
Vomiting	9	(45)
Swelling of lips/tongue	7	(35)
Watery, itching eyes	7	(35)
Diarrhea	4	(20)
Hypotension recorded	3	(15)

psyllium was passed through a 20 mesh screen and retained material was examined, no allergenic protein fractions were detectable by SDS-PAGE and immunoblot analysis. However, after passage through a 30 mesh screen, there was a trace of allergenic protein in retained material, and after passage through a 40 mesh screen, there was a significant amount of the allergenic fractions. Finally, psyllium powder passing through all screens contained the most allergenic protein. It was concluded that highly purified psyllium mucilloid, that is, psyllium mucilloid retained on the 20 mesh screen, contained only traces of the responsible allergen.

To determine whether a reformulation of Heartwise with more purified psyllium would result in a potentially less allergenic product, immunoblots were run to compare the cereal without psyllium to the cereal with psyllium of 85%, 95%, and 98% purity. These studies demonstrated virtually no detectable Ab binding to allergenic fractions in the highly purified psyllium products (Fig. 4).

DISCUSSION

Occupational allergy to psyllium has been described in pharmaceutical workers and health care workers. Symptoms, including rhinitis, wheezing, and gastrointestinal distress, have been reported.¹¹⁻¹³ Goransson and Michaelson¹⁴ reported allergic symptoms in 27 of 64 (42%) pharmaceutical workers exposed to psyllium dust. In larger studies, Kirby et al.¹⁵ found that 47 of 188 (25%) employees in two pharmaceutical companies became sensitized to psyllium, and Bardy et al.¹⁶ reported that 27.9% of 130 workers were sensitized as determined by prick skin testing; 3.6% wheezed on later exposure.

In a medical department with high exposure to psyllium dust (dispensing bulk laxatives), 4/20 nurses were found to be sensitized to psyllium, as demon-

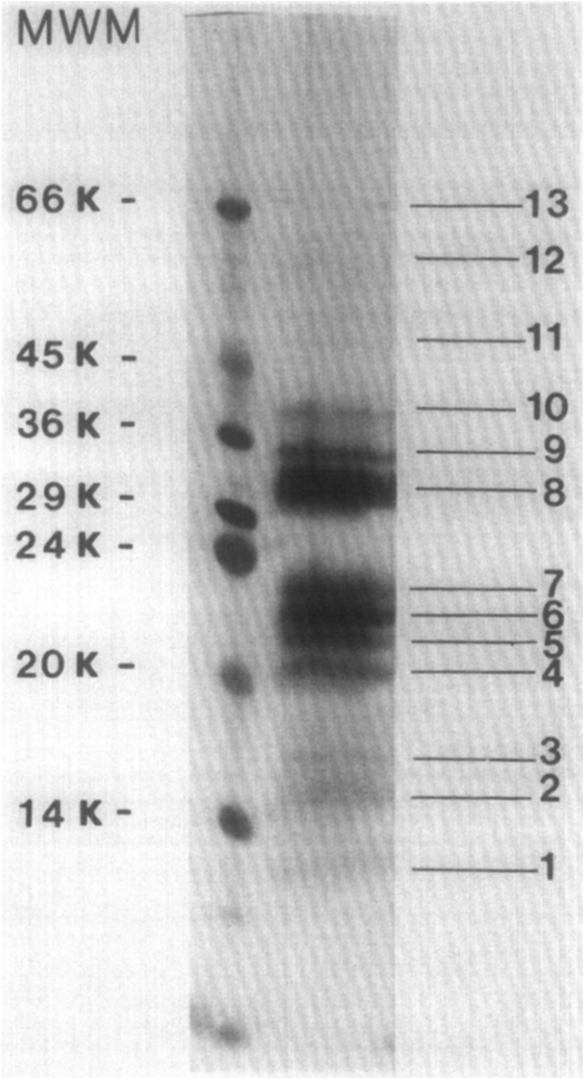


FIG. 1. Psyllium protein fractions (right) separated by SDS-PAGE, transferred to nitrocellulose and stained with amido black are compared to standard molecular weight markers (left).

strated by provocative challenge tests.¹⁷ Cartier et al.¹⁸ documented wheezing in five nurses exposed to psyllium-containing laxatives; four of these nurses had positive skin tests and RAST to psyllium. A survey of 743 health care workers in eight hospitals revealed that 136 (18%) experienced allergic symptoms while they were dispensing psyllium-containing laxatives, and 19 workers (2.6%) required treatment by a physician.¹⁹

There have been three case reports of anaphylactic-type reactions after the ingestion of psyllium-containing bulk laxatives.²⁰⁻²² A group of six nurses who reported respiratory symptoms secondary to occupational exposure to psyllium were orally challenged at a later date. The challenges precipitated

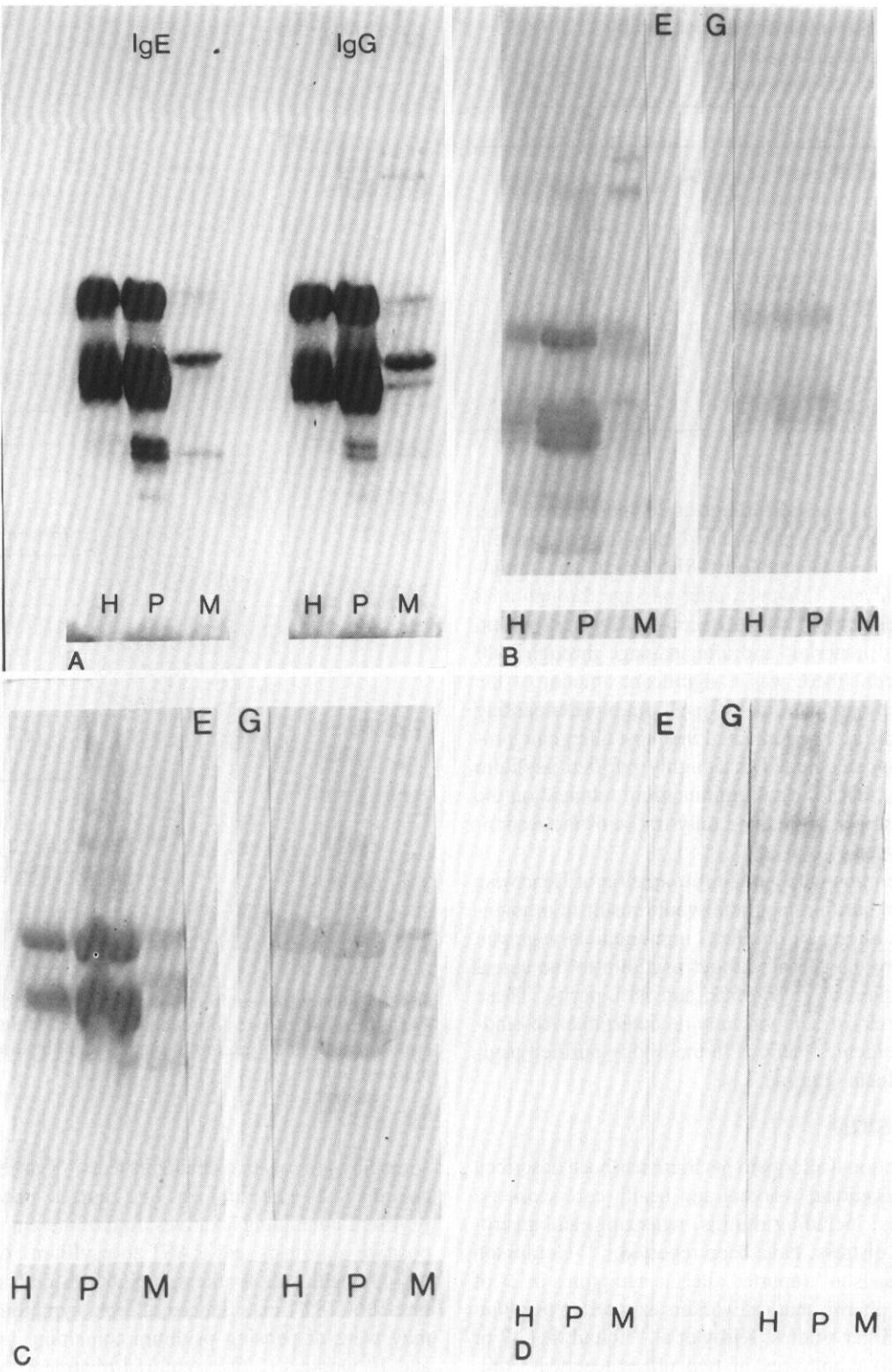


FIG. 2. Representative patient immunoblots with both IgE (left) and IgG (right) Abs against Heartwise (H), psyllium powder (P), and Metamucil (M), illustrating the different Ab patterns of IgE specificity. **A**, Patient with IgE Abs to bands 4 to 9 in the 20 to 36 kd range. **B**, Patient with IgE Abs to psyllium protein bands, including low molecular weight bands 2 and 3. **C**, Patients with IgE Abs to psyllium protein bands, including high molecular weight bands 12 to 13. **D**, A control patient with no detectable IgE Abs to psyllium protein bands but IgG Abs to these proteins.

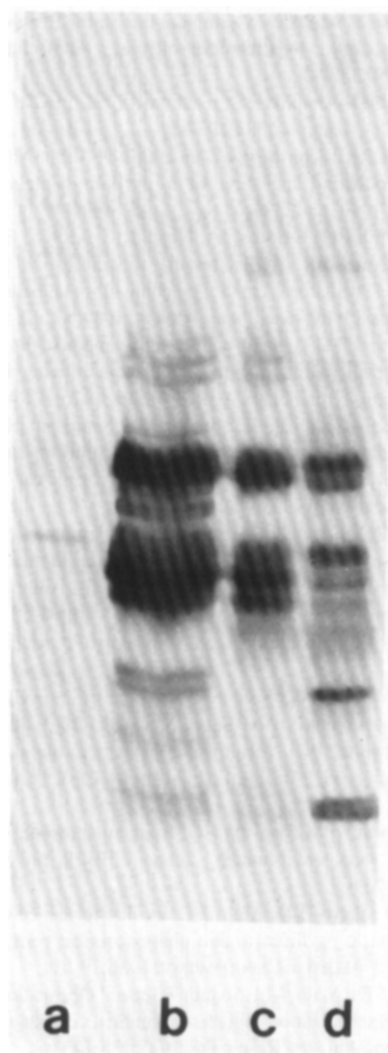


FIG. 3. Representative patient immunoblot comparing the IgE Ab binding to the major protein fractions in Metamucil (a), psyllium nugget (b), Indian psyllium (c), and Australian psyllium (d).

rhinitis in all the subjects, nausea and abdominal cramps in three subjects and wheezing and a rash in two subjects.²³

In 1989, two psyllium-containing cereals were introduced by manufacturers attempting to take advantage of high dietary fiber and cholesterol-lowering effects of psyllium (Heartwise, Kellogg Co., and Benefit, General Mills, Minneapolis, Minn.). Since its introduction, 50 allergic reactions after the ingestion of Heartwise have been reported⁵; most of the women were nurses. Before it was discontinued in December 1989, 26 complaints were received about probable allergic reactions to Benefit.⁶

In this study, 18/20 women had histories and/or laboratory evidence of an atopic disposition. Eleven

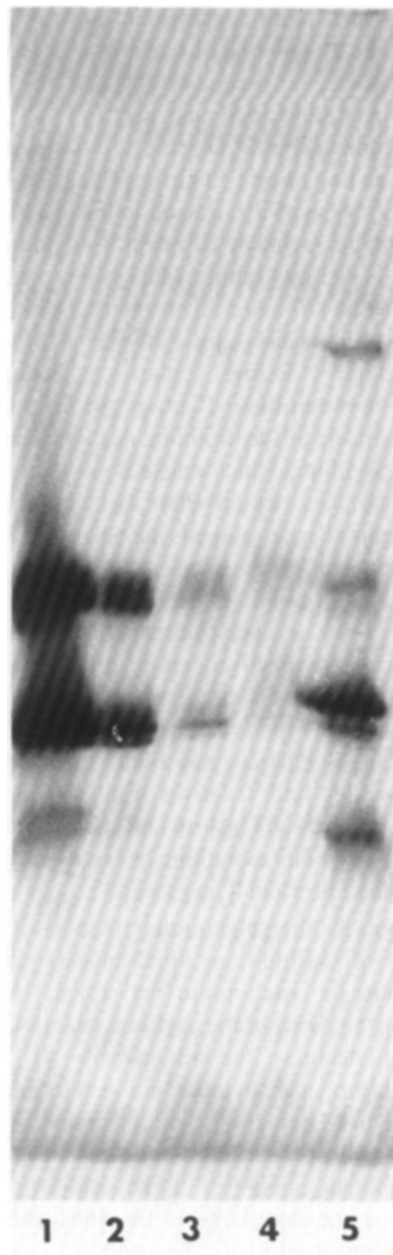


FIG. 4. Immunoblot compares Heartwise with psyllium of 85% purity (1), Heartwise with psyllium of 95% purity (2), Heartwise with psyllium of 98% purity (3), Benefit (4), and Metamucil (5).

of 15 subjects who dispensed psyllium-containing laxatives had experienced allergic symptoms while they were handling this product. Furthermore, all but three of the women had prior known exposure to psyllium, such as dispensing or ingesting bulk laxatives containing psyllium. Most patients were sensitized by inhaling psyllium dust. After their first ingestion of Heartwise, the sensitized individuals experienced an allergic reaction. These studies suggest that suscep-

tible individuals with occupational exposure to psyllium dust are at high risk of reacting to ingested psyllium products.

It has been suggested that reactivity to psyllium (*P. ovata*) may occur as a result of cross-reactivity to the common lawn weed, English plantain, or *Plantago lanceolata*. None of the women in this study had IgE Abs to English plantain. However, this finding is not surprising since our studies (data not presented) and recent studies of other investigators have demonstrated no cross-reactivity between *P. ovata* and *P. lanceolata*.²⁴ Earlier studies suggesting cross-reactivity between these *Plantago* species used goat anti-IgE antisera as the detecting Ab. The lectin properties of psyllium, which cause nonspecific binding of goat IgG Abs, would elicit the false impression that plantain-allergic patients possessed IgE Abs to psyllium as well.

Seven of 20 women had previously taken psyllium-containing laxatives, and four experienced abdominal discomfort while they were taking the laxative. In the course of this investigation, two other women (both nurses) called in reports of allergic reactions after the ingestion of Metamucil, and both nurses had previously dispensed bulk laxatives. This specific type of occupational exposure history and subsequent allergic reaction to psyllium-containing laxatives may be more common than previously appreciated.

In summary, allergenic protein associated with the seed husk of psyllium mucilloid appears responsible for the allergic reactions to the cereal, Heartwise. Increasing the purity of the psyllium mucilloid powder used may decrease the allergenicity to psyllium-containing products. Indeed, after a reformulation of Heartwise in March 1990, with psyllium of 95% purity, only two minor allergic reactions have been reported (Victor Fulgoni, PhD, Kellogg's Co.). Whether or not the allergenic fractions can be completely removed awaits further study.

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