

Allergens, IgE, mediators, inflammatory mechanisms

Characterization of the allergen(s) in latex protein extracts

Vesna J. Tomazic, PhD, Thomas J. Withrow, MS,
and Robert G. Hamilton, PhD^a Rockville and Baltimore, Md.

Background: Immediate hypersensitivity to latex, induced by natural latex proteins remaining on the finished products, may lead to severe anaphylactic reactions.

Methods: We investigated the distribution of latex proteins by molecular weight and identified the specific allergenic molecules. Proteins extracted from various latex products were compared with those extracted from raw latex sap, both ammoniated and nonammoniated.

Results: Variations in the levels of extractable protein, as well as in the number of molecules and the molecular weight distribution, were observed especially among finished latex products. To identify allergenic (i.e., IgE-binding) molecules, we performed immunoblots with the sera from latex-sensitive persons. The results indicated that antigenic molecule profiles differed among the products and also between the finished products and the raw material. In addition, specificities of the anti-latex IgE antibodies varied among the sensitized persons.

Conclusions: It appeared that persons with the same history of sensitization had similar patterns of antigenic specificities. If the history of exposure, as well as genetic predisposition and medical history of the patient, plays a significant role in the specific IgE response, it may be difficult to select a "standard" antigen and a "standard" antiserum for the evaluation of the latex sensitivity and allergenicity. (*J ALLERGY CLIN IMMUNOL* 1995;96:635-42.)

Key words: latex, allergen, anaphylaxis, type I allergic reaction, IgE antibodies, gel electrophoresis, immunoblotting

Over the last several years, the medical community has become highly concerned with the increased prevalence of immediate hypersensitivity to natural latex products. Although the first description of IgE-mediated type I hypersensitivity to latex was reported in 1979,¹ an increased incidence of severe anaphylactic reactions, including several deaths, was reported only recently.²⁻⁴ On the other hand, type IV rubber sensitivity, manifested as contact dermatitis, has been well documented, especially in the European literature.^{5, 6} While type

Abbreviation used

SDS-PAGE: Sodium dodecylsulfate-polyacrylamide gel electrophoresis

From the FDA, Center for Devices and Radiological Health, Office of Science and Technology, Division of Life Sciences, Rockville, Md., and the ^aAllergy and Asthma Center, Johns Hopkins University, Baltimore, Md.

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Reprint requests: Vesna J. Tomazic, PhD, FDA, Center for Devices and Radiological Health, Office of Science and Technology, HFZ-112, Division of Life Sciences, Health Sciences Branch, 12709 Twinbrook Parkway, Rockville, MD 20852.

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IV sensitivity has mainly been ascribed to the chemical additives in rubber products, source of sensitization in type I hypersensitivity, appeared to be the native proteins in the natural latex sap. A number of investigators have recently demonstrated that native latex proteins are responsible for the observed allergic reactions to a variety of latex products.⁷⁻¹⁰

Latex proteins may be characterized as a family of water-soluble, thermostable proteins or glycoproteins with molecular weights of 5 to 200 kd.^{11, 12} The number of protein molecules and their molecular weight distribution vary among sources of raw latex according to the origin, climate, soil, and method of processing.^{13, 14} Among finished latex

TABLE I. Extractable protein levels from various latex products

No.	Name of device	mg/gm Latex	Mg/Device
1	Exam. gloves—Malaysia	0.87	5.85
2	Exam. gloves—Pharmaseal	0.32	1.86
3	Exam. gloves—China	0.03	0.25
4	Exam. gloves—Ansell	0.02	0.24
5	Surg. gloves—Smith-Perry	0.52	5.92
6	Surg. gloves—Smith-Perry	0.38	4.75
7	Surg. gloves—Triflex-Baxter	0.35	3.60
8	Surg. gloves—Boston	0.01	0.58
9	Surg. gloves—Pharmaseal	0.01	0.12
10	Surg. gloves—HPI-Tillotson	0.01	0.11
11	Urological catheter—Bard	0.00	0.00
12	Foley catheter—Bard	0.00	0.00
13	Dental dams 6 × 6" Hygenic Corp.	0.99	4.46
14	Dental dams 5 × 5" Hygenic Corp.	0.51	1.57
15	Barium Enema Cuffs—MMI	0.04	0.20
16	Barium Enema Cuffs—E-Z-EM	0.07	0.18
17	Condoms—Trojans	0.01	0.17
18	Condoms—Trojans	0.08	0.12
19	Condoms—Trojans	0.03	0.05
20	Condoms—Ramses	0.02	0.03

products the differences were even greater,¹² in both protein profile and total amount of extractable protein.² Several authors evaluated allergenicity levels of extracts from different latex gloves and observed similar variations in the induced skin reaction.^{15, 16} However, the quantitative relationship between amount of extractable protein and the allergenicity of latex product has not been clearly demonstrated to date.

The clinical research community and the manufacturers should develop the best procedure for identifying persons with a high risk of allergic reaction and for determining the potential allergenicity of latex products. The particular proteins responsible for sensitization and induction of allergic reaction need to be identified. In our study we investigated the specific allergen(s) by studying the reactivity of IgE antibodies from a variety of latex-sensitive persons to extracts of different latex products. Our study indicates that most of the evaluated sera recognize from two to four antigenic molecules. Some of these molecules were present in most extracts and may therefore be considered common allergens. Others

are either not present in all extracts or not recognized by all sera.

METHODS

Sources and extraction of latex proteins

Raw ammoniated latex from Malaysian *Hevea brasiliensis* trees was supplied by Guthrie Latex, Inc., of Tucson, Ariz., and Johnson & Johnson, of Arlington, Texas. Nonammoniated Malaysian latex was obtained through the courtesy of Baxter Healthcare Co., of Irwindale, Calif., by collecting *H. brasiliensis* sap directly into Tris buffer without the addition of ammonia. Latex products used for protein extraction in this study were commercially available brands of surgical and examination gloves, catheters, dental dams, condoms, and barium enema cuffs. Selection of the products studied here was based solely on availability.

Water-soluble proteins from unprocessed raw latex, raw ammoniated latex, and latex products were extracted with phosphate-buffered saline (Dulbecco PBS, Gibco, Grand Island, N.Y.), for 1 hour at 37° C as described previously.¹⁷ All extracts were concentrated with an Amicon filtration unit, using a YM1 membrane, MW cutoff at 1000 d, and stored at 4° C for up to 1 week or at -20° C for extended periods.

Protein determination methods

The protein determination for all latex protein extracts in this study were performed by a Lowry method modified in our laboratory.¹⁷ Briefly, we used 2% alkaline tartrate (Reagent A) and a 0.1% solution of copper sulfate (Reagent B) prepared in our laboratory, and Folin-Ciocalteu phenol reagent obtained from Sigma Chemical Co., of St. Louis, Mo. Protein levels were evaluated against serial dilutions of the reference protein Ovalbumin, fraction V (Sigma Chemical Co.) using a UV-Max microplate reader (Molecular Devices Inc., Menlo Park, Calif.) at 595 nm wavelength. The sensitivity of the protein assay method was 20 µg/ml.

Human serum specimens

The sera used in these studies were collected from persons who had clinical symptoms of allergy to latex products, positive skin prick test findings through a rubber glove, and a positive serum IgE antibody level as measured by means of RAST. Most of the sensitized persons were health care workers, 26 to 40 years of age, who acquired their sensitivity through occupational exposure to latex products (R.B., J.S., J.D., S.K., L.B., and J.E.). One serum was obtained from a child (F.T.) with spina bifida, representative of another high-risk population.^{2, 18, 19} One serum was from an atopic individual (G.W.) with a broad spectrum of food allergies. Two control sera (from subjects V.T. and N.T.) were used along with the immune sera. The levels of total IgE and latex-specific IgE in studied sera, ranging from 170 to 8950 ng/ml and 4.4 to 215 ng/ml, respectively, were determined at the Johns Hopkins University DACI Reference Laboratory by solid phase radioimmunoassay as described previously.²⁰ All sera were nor-

malized for the level of latex-specific IgE to 10 to 20 ng/ml before use in immunoassays.

Protein separation and Western blots

The molecular weight distribution of latex protein extracts was analyzed by means of sodium dodecylsulfate–polyacrylamide gel electrophoresis (SDS-PAGE). All samples were diluted with 10 mmol/L Tris-HCl, pH 7.4, and sample buffer (62.5 mmol/L Tris-HCl, pH 8.0, 2% mercaptoethanol, 0.01% bromophenol blue, and 1 mmol/L ethylenediamine tetraacetic acid) to a concentration of 4 mg/ml. Gel electrophoresis was performed with commercial 8% to 25% gradient minigels (Phast System, Pharmacia/LKB Biotechnology, Piscataway, N.J.), applying 1 μ l of each sample per run. Gels were subsequently stained with Coomassie R-350 or double stained with Coomassie and silver stain.

For Western blotting, proteins from gels were transferred to a PolyScreen transfer membrane (New England Nuclear Research Products, Boston, Mass.) using 40 mA per gel for 45 minutes. Successful transfer of proteins was verified by means of a prestained molecular weight marker. The blots were blocked with a 3% solution of bovine serum albumin in TBS for 3 to 6 hours at room temperature. After being washed three times with blocking buffer containing 0.05% Tween-20, the blots were incubated with the sera from latex-sensitized patients for 12 to 15 hours. The blots were then washed three times with Tris buffer with 0.05% Tween-20 and incubated with alkaline phosphatase–conjugated polyclonal anti-human IgE (Cat. No. A-3525; Sigma Immunochemicals). Specificity for human IgE was confirmed by the manufacturer using an ELISA test. An alkaline phosphatase–conjugated substrate kit (BIO-RAD Laboratories, Richmond, Calif.) was used for visualization of antibody binding.

RESULTS

Evaluation of molecular weight distribution and total amounts of latex proteins

Variations in levels of the water-soluble proteins were determined among different types of products, as well as among samples of the same type of product obtained from different sources. The amount of extractable proteins varied markedly, not only among various types of products but also among products of the same group (Table I). Various lots of products from the same manufacturer were not evaluated. Variability in the extractable protein level of surgical gloves ranged up to 50-fold. Two samples of dental dams both had rather high amounts of protein (0.5 to 1.0 mg/gm of latex), while condoms and barium enema cuffs in general had low levels of extractable protein. No protein was detected in the extracts from the two types of catheter used in our study.

Our earlier analysis of the protein profiles (comparing extracts from finished products with extracts

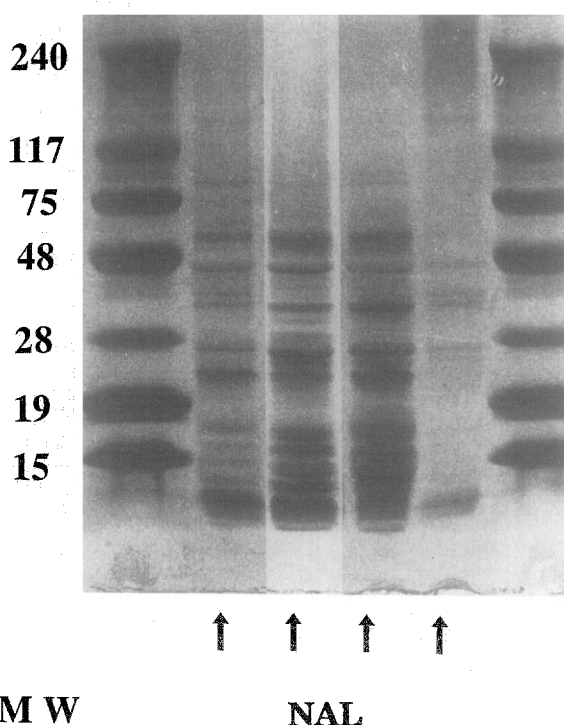


FIG. 1. Comparison of molecular weight distributions in four samples of nonammoniated latex proteins.

from raw latex) indicated significant variations in both the number of protein molecules and their molecular weight distribution.¹² In this study all latex protein extracts with measurable protein levels were evaluated by means of SDS-PAGE to (1) characterize the individual protein molecules and (2) compare the variations in the molecular weight distribution of proteins from finished products with the variations observed with nonammoniated and ammoniated unprocessed raw latex. In Table II we summarize a molecular weight distribution of the major bands observed in the various extracts from nonammoniated and ammoniated latex in comparison with the extracts from latex gloves. The amounts of water-soluble protein extracted from four samples of nonammoniated raw latex, all from Malaysian plantations, were comparable, and the protein profiles showed only minor differences (Fig. 1). In these latex extracts we detected about 20 to 25 protein bands with a similar distribution. The samples of the ammoniated latex extracts differed significantly from nonammoniated latex specimens in their molecular weight distributions, while containing comparable amounts of water-soluble protein. The four samples we prepared had a lesser total number of protein bands than did the nonammoniated latex specimens. In general, the larger molecular weight proteins were not found in

TABLE II. Protein molecule distribution in various latex extracts observed on SDS-PAGE

Extract	Molecular weight range										
	<14	14	15	18	20	25	30-35	40-45	50-55	80-90	>100
NAL-A	+	—	+	+	+	+	+	+	+	+	—
NAL-B	+	—	—	+	+	+	+	+	—	+	+
NAL-C	+	—	+	—	—	+	+	+	—	+	—
NAL-D	+	+	+	+	+	+	+	+	+	+	+
AL-A	+	—	—	—	+	+	—	—	—	—	—
AL-B	+	+	—	—	—	+	—	—	—	—	—
AL-C	+	+	—	—	—	+	—	+	—	—	—
AL-D	+	+	—	+	+	+	—	+	—	—	—
GL-A	+	+	—	+	—	—	+	—	—	—	—
GL-B	+	+	—	+	—	—	+	+	—	+	—
GL-C	+	+	+	+	+	+	+	—	—	—	—
GL-D	+	+	+	+	+	+	+	—	—	+	—

*Multiple bands observed in a specified range.

the ammoniated latex preparations. The variability in protein profile among samples of ammoniated latex was much greater than that observed among nonammoniated latex samples. However, the greatest diversity in protein profile was observed among various finished latex products (Table II).

Identification of the IgE-positive proteins

To identify the total number of proteins that are actually allergens and their molecular weights, we studied a number of latex protein extracts by Western blot analysis using sera from latex-sensitized persons. Immunoblots of various latex protein extracts obtained with serum from one latex-sensitive individual (S.K.) revealed that some of the protein molecules are common to most of the extracts (Fig. 2). Most extracts contained a 45 kd and 20 kd protein molecule recognized by S.K. serum IgE antibodies. However, some of the IgE-positive bands, such as 25 kd and 35 kd molecules, were observed in only two extracts. Antibodies of this particular serum appear to recognize proteins of various molecular weights in different latex protein extracts.

The specific binding of anti-latex serum antibodies from seven latex-sensitive persons was evaluated with ammoniated and nonammoniated raw latex proteins. Sera from four of five health care workers (R.B., J.D., L.B., and J.E.) reacted strongly with 45 kd protein in nonammoniated latex extract (Fig. 3). Weakly positive lines were detected in the 35 kd and 25 kd range with sera from J.S., J.D., and L.B. The R.B. serum, however, had strong positive reaction with 28 kd and 40 kd molecules, neither of which was recognized by IgE antibodies in other sera. J.S. and

G.W. sera showed a weaker reaction with 45 kd protein, while reacting with 15 kd and 35 kd molecules. Serum from the patient with spina bifida (F.T.), however, had a significantly different pattern than did others; it did not react with 45 kd protein, but did react strongly with proteins in the range of 14 to 15 kd and 25 kd.

Relatively similar patterns were observed with immunoblots by using the same panel of sera with ammoniated latex extract (Fig. 4). The 45 kd molecular weight protein appeared as the predominant allergenic molecule in this extract also, although R.B. serum reacted more strongly with 28 to 30 kd molecules than with 45 kd molecule. In general, however, fewer antigens were detected in the ammoniated than the nonammoniated latex specimens. The exception was again F.T. serum, which recognized the same lower molecular weight proteins as in nonammoniated latex samples, but exhibited a much greater reaction.

When the same sera were evaluated against extracts from latex gloves, we detected mostly one or two positive bands. A summary of the allergenic protein profiles with the seven sera tested against two types of latex glove extracts is presented in Fig. 5. Findings obtained with extracts from a surgical glove and an examination glove were compared with the pattern observed with nonammoniated raw latex. We observed variations in individual serums' recognition of antigenic molecules in different latex samples studied, as well as variation in the recognition of the same molecules by various sera. However, Fig. 5 clearly demonstrates that most antigenic molecules fall primarily in the range from 20 kd to 45 kd. The only exception is,

IgE - POSITIVE PROTEINS IN VARIOUS EXTRACTS

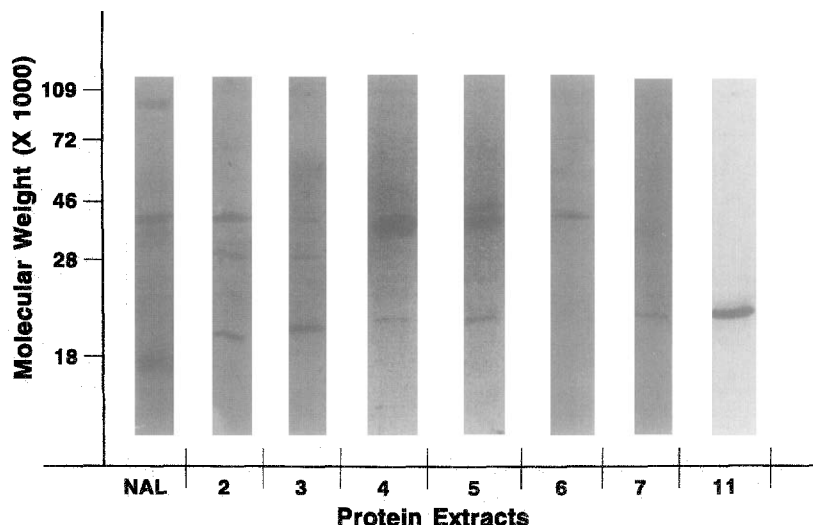


FIG. 2. Identification of allergenic proteins in latex products. Immunoblots performed with serum S.K. against extracts of nonammoniated latex and extracts from surgical gloves (2, 3), examination gloves (4, 5), condom (6), barium enema cuff (7), and household glove (11). The figure represents a summary of several experiments.

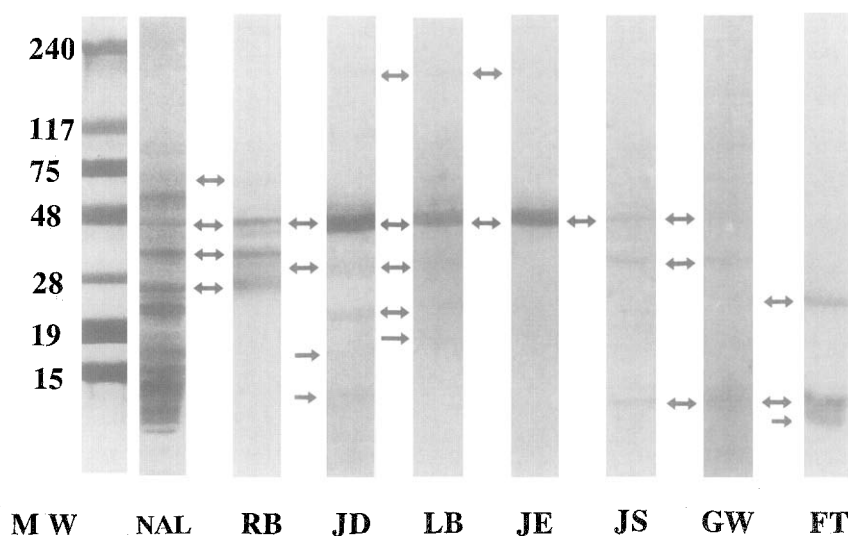


FIG. 3. Specificity of anti-latex IgE antibodies from panel of human sera evaluated against protein extract from nonammoniated latex.

again, the serum from the patient with spina bifida (F.T.), which identified a unique pattern of lower molecular weight proteins (14 to 15 kd and 25 kd).

DISCUSSION

Latex allergens have been identified in a variety of molecular weights, ranging from 14 to 30 kd,^{16,21} 30 and 66 kd,²² 20 to 45 kd,¹¹ and 50 to 65 kd.²³ This apparent variability may have resulted in part

from interlaboratory differences in the methods used in extraction, protein purification, and allergen identification, but most likely from the diversity of latex sources and the specificity of immune sera used for immunoblot evaluation.

In our study we evaluated the amounts of total extractable protein and allergenic protein profiles in extracts from raw materials and latex-containing medical products. The amounts of protein ob-

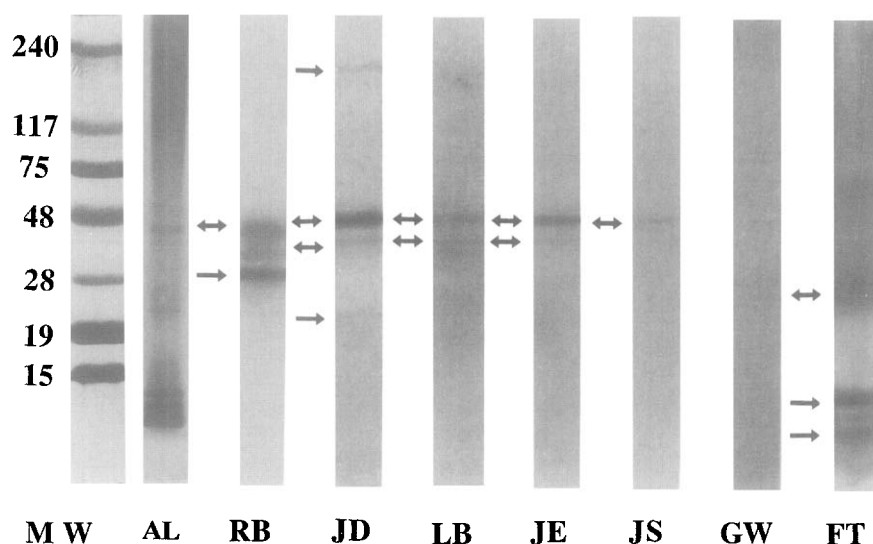


FIG. 4. Specificity of anti-latex IgE antibodies from panel of human sera evaluated against protein extract from ammoniated latex.

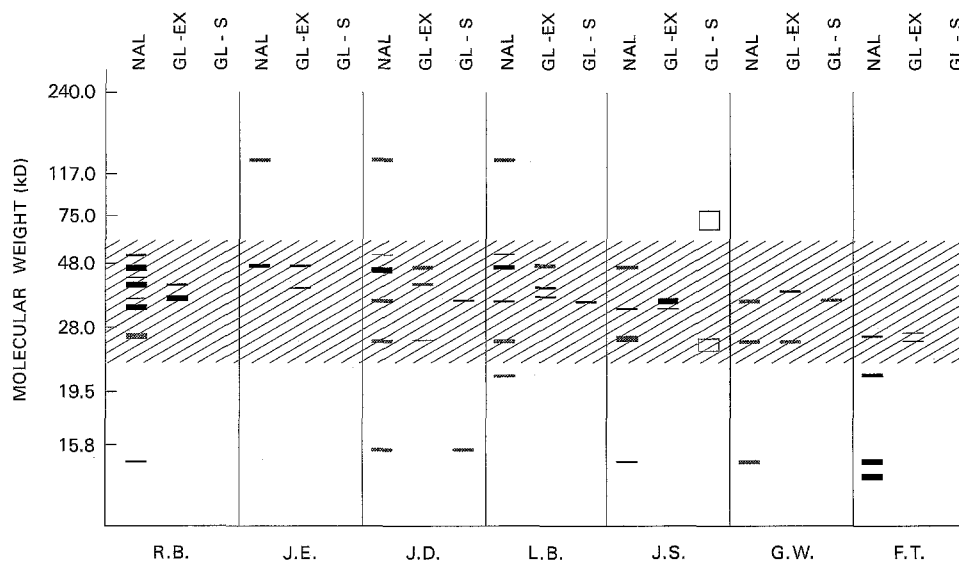


FIG. 5. Comparison of the IgE-positive protein profiles in extract from nonammoniated latex, and extracts from one surgical (GL-S) and one examination glove (GL-EX). Three extracts were exposed to antisera of seven patients. The open boxes represent a smear of protein.

tained from samples of ammoniated and nonammoniated raw latex materials were quite similar, but a great variability was observed among surgical and examination gloves, where the amounts of extractable protein ranged from 0.1 mg to 5.9 mg per glove. The observed variations may be attributed to differences in the specific manufacturing procedures,²⁴ or to differences in the initial protein levels of the raw material used in the production. Although our samples of raw material yielded

similar amounts of protein, the different processing of raw latex may result in a selective reduction in the protein levels.¹⁴ The greatest differences in protein profiles were observed among samples from finished latex products. It is not clear if different molecular weights, identified by means of SDS-PAGE, indicate proteins of distinct structure and antigenic specificity, or if they originate from cleavage of a few protein molecules that appear as distinctive bands on the final gels.

IgE immunoblots of the raw latex proteins and latex product extracts indicated that some protein molecules can be considered "major allergens," present in most of our extracts and identified by almost all sera studied. Some immunoblot bands appear to identify less common, or "minor," allergens, as they are detected with only select sera. The two most common allergenic molecules had molecular weights of 45 kd (seen in seven of eight samples) and 20 kd (seen in four of eight samples). Minor, or less common, allergens had molecular weights of 15 kd, 18 kd, 25 kd, 35 kd, and 100 kd. Our results are comparable with findings of Jaeger et al.,²⁵ who reported that most sera they evaluated reacted with proteins in a similar range of molecular weights.

Comparison of antigenic molecules in the extract of raw latex with those in latex products indicate that in the latter some antigenic specificities may be lost, probably as a result of protein hydrolysis, either by added ammonia or during the manufacturing processes. Several new positive bands identified in the glove extracts were not observed in the untreated raw latex extract. These new bands may represent molecules with the same antigenic specificities but different molecular weights, or they may indicate different antigens resulting from variations in the source material. The manufacturing process may lead to selective enrichment of chemical- and heat-resistant proteins that were not visualized in raw material. Furthermore, the proteins either denatured during the manufacturing procedure or coupled to added chemical components may indeed present new antigenic specificities.

The evaluation of a panel of human sera against the raw latex proteins indicates that individual antibody responses are quite diversified. Most of the sera reacted with major antigenic molecules (45 kd, 35 kd, and 25 kd), with the 45 kd band being predominant. The sera of five health care workers presented common pattern of IgE responses, whereas two other sera (G.W. and F.T.) had quite distinct patterns. A similar observation was recently reported by Beezhold et al.²⁶

In summary, our studies indicate that the antigenic specificities of proteins in the extracts of the finished products differ from those proteins extracted from the raw material. Most of the evaluated sera detected more positive protein bands with raw material than was possible with extracts from latex products. Furthermore, the specificity of IgE antibodies also varied among patients, possibly indicating the significance of the patient's

exposure history. For example, G.W. had a wide spectrum of food allergies and had no occupation-related exposure to latex products. The patient's serum antibodies reacted very weakly with 45 kd protein but demonstrated stronger reaction with 15 kd and 35 kd proteins. The positive reaction to latex proteins in this case may result from a cross-reactivity with some food allergens, as already reported for banana, chestnuts, and avocado.²⁷⁻³¹ An alternative cause could be exposure to latex rubber consumer products. Serum from the child with spina bifida (F.T.) also showed a different pattern of allergen recognition than did sera from the group of health care professionals. Exposure to a variety of latex products occurs early in the life of these patients during multiple corrective surgeries and other procedures. Similar differences among children and adults have been observed by other investigators,³²⁻³⁴ indicating that a patient's age, medical history, genetic predisposition, and history of exposure all play significant roles in determining the specificity of the anti-latex IgE antibodies.

We believe that the identification of specific allergen(s) and the determination of allergenicity levels for latex products may require further research into the structure, specific properties, and biologic activities of individual latex proteins. Although extracts of raw latex, especially nonammoniated, appear to contain the most antigenic molecules, new antigenic specificities can be identified in the extracts from finished latex products.

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