

## COURIERS OF ASTHMA: ANTIGENIC PROTEINS IN NATURAL RUBBER LATEX

From National Institute for  
Occupational Safety and Health  
Morgantown, West Virginia

Reprint requests to:  
Edward L. Petsonk, MD  
National Institute for Occupational  
Safety and Health  
Division of Respiratory Disease  
Studies  
1095 Willowdale Road  
Morgantown, WV 26505-2888

The opinions and assertions  
contained herein are the views of  
the author and are not to be  
construed as the official policy or  
position of the United States  
government.

Natural rubber latex (NRL)\*, a milky, white liquid from the rubber tree *Hevea brasiliensis*, was known to indigenous people of the rain forests of South America, and was encountered in the 1500s by European explorers.<sup>33</sup> Since the discovery of vulcanization by Goodyear in 1839, NRL has been used in the production of numerous items, and today over 40,000 commercial products may contain natural rubber. Many medical products, from surgeon's gloves to vial stoppers, are currently manufactured using NRL. Aside from dermatitis, for many years the use of NRL had not been associated with health-related problems. However, beginning in 1979 with the report of a housewife developing contact urticaria from dishwashing gloves, there have been increasing reports of hypersensitivity reactions to NRL products, ranging in severity from skin rashes to anaphylaxis and death.<sup>29,31,36</sup> Most reports have associated with onset of allergy with exposure to dipped latex products and, recently, with exposure to powdered latex gloves. This article focuses on the antigens implicated in occupational NRL allergy and, in particular, immediate hypersensitivity responses.

### CLINICAL MANIFESTATIONS

The clinical manifestations of reactions to NRL are fully described elsewhere.<sup>29,31,38</sup> The following are brief summaries of the findings in glove-related dermatitis and latex allergy.

---

\* The term "latex" also is used for some synthetic elastomers that are not derived from plant sources, such as latex in most house paints. Exposure to these synthetic latex elastomers does not represent a risk of IgE-mediated NRL allergy.

## Dermatitis

Irritant and allergic contact dermatitis have long been associated with glove use, and may be manifest by erythema, vesiculation, scaling, and lichenification of skin in glove contact areas. Irritant reactions have been attributed to nonallergic inflammation from skin occlusion in the presence of detergents, perspiration, and other irritating substances. Contact dermatitis has been associated with use of both latex and non-latex gloves, and results from a delayed hypersensitivity reaction to a number of chemicals added during processing of many types of gloves, both latex and non-latex.<sup>31</sup>

## Natural Rubber Latex Allergy

In contrast to glove-related dermatitis, latex allergy is an immediate (IgE-mediated) hypersensitivity reaction triggered by contact with protein allergens derived from NRL products. Initial sensitization occurs among persons exposed to latex allergens through mucous membranes, inhalation, skin, or tissue contact. The specific roles of these routes of exposure is a topic of current research.<sup>39</sup> Children who have had multiple surgeries, particularly those with spina bifida, have high rates of latex allergy.<sup>17,22</sup> Latex allergy also has been reported frequently among workers in a variety of jobs that require NRL contact, most prominently healthcare workers who use natural latex gloves.<sup>29,36</sup>

In a recent survey among 1351 hospital workers, skin prick testing revealed evidence of sensitization to latex allergens in 7.6% (therapists and technicians) to 16.9% (laboratory workers).<sup>21</sup> Symptomatic workers have variously manifest contact urticaria, rhino-conjunctivitis, asthmatic complaints (cough, chest tightness, and wheeze), generalized urticaria, and anaphylactic shock.<sup>34,37</sup> Symptoms appear to progress from skin eruptions, to nasal and ocular inflammation, to bronchospasm, and finally anaphylaxis. This progression of symptoms may not be observed in children with spina bifida.<sup>29</sup>

Allergies to several fruits and other foods have been associated with latex sensitization.<sup>31</sup> A number of studies also have found atopy to be a risk factor in NRL allergy, and atopic healthcare workers can have sensitization prevalences 2 to 5 times their nonatopic colleagues, although overall, only about 10% of atopic healthcare workers have clinical latex allergy.<sup>36</sup> Dermatitis often is reported in association with symptomatic latex allergy, and pre-existing dermatitis may predispose an individual to sensitization.<sup>31</sup> Recent animal studies have supported the hypothesis that damaged skin increases penetration of proteins and allows the antigens to interact with immunocompetent cells in the dermis.<sup>39</sup>

**Management** of persons with latex allergy often requires scrupulous avoidance of contact with natural latex products at work, during medical care, and in the home. Latex proteins have been shown to bind to cornstarch glove-donning powders, which become aerosolized during glove use.<sup>6</sup> Consequently, allergy symptoms may be triggered if an affected individual enters an environment in which powdered latex gloves are used, even without direct physical contact with the gloves.<sup>5,10,32</sup> Latex avoidance outside the workplace also may be problematic, since latex content may not be mentioned on consumer product labels (e.g., underwear with latex elastic). Individuals with latex allergy may experience considerable disability and may be unable to return to previous work environments without extensive accommodation.<sup>18,36</sup> Due to its relatively high prevalence and potential severity, prevention of NRL allergy among healthcare workers has become a public health priority.<sup>25</sup>

## WHAT IS NATURAL RUBBER LATEX?

### Raw Material

“Natural rubber latex” is the term for the elastomeric material derived primarily from the laticifer cells of the Brazilian rubber tree, *Hevea brasiliensis*. In fact, over 2500 species of plant are reported to form rubber particles; however, *H. brasiliensis* is the source of raw material for more than 99% of commercial rubber. *Guayule*, a desert shrub that grows wild in Mexico and southern Texas also has been used as a source of latex for dipped rubber products.<sup>28,33</sup> Rubber trees were at one time exclusively found in the Amazon rainforest, but in 1876 a number of seedlings were exported to Britain, and subsequently to southeast Asia and western Africa. In the early 1900s, a blight destroyed the wild rubber trees of South America; thus, current rubber production occurs almost exclusively in Malaysia, Thailand, and Burma, based upon the exported trees. West Africa was also at one time an important commercial source of raw latex, but that region’s role in commercial rubber production has been reduced in recent years. Harvesting of latex involves slashing into the bark of the tree to the phloem and collecting a white liquid that drains from the wounds. This fresh natural rubber contains about 65% water, 30% rubber, 2% resin, and 2% proteins.<sup>33</sup>

### NRL Processing

To reduce microbial contamination and prevent autocoagulation, ammonia generally is added as a sterilizing agent during collection. Ammonia treatment results in precipitation of some of the latex proteins, separation into a liquid phase, and a suspension of rubber particles.<sup>23</sup> Two-dimensional electrophoresis of the material has demonstrated that, after ammonia treatment, there is an increase in the inhomogeneity of the latex proteins, with appearance of new peptides, compared to nonammoniated latex (NAL). This suggests aggregation and conformational changes in the proteins. Using pools of serum from adults and children with latex allergy, in both ELISA and immunoblot assays, Akasawa found that glove extract fully inhibited binding of IgE to ammoniated latex (AL), while NAL did not, suggesting the presence of new antigenic determinants created during ammoniation.<sup>2</sup> In contrast, Lu and colleagues reported that NAL was able to fully inhibit the reaction of rabbit anti-AL antibodies with AL.<sup>23</sup>

The two-phase AL mixture can be coagulated and processed into dry rubber for molded or extruded products, or centrifuged and maintained as a liquid suspension for manufacturing of dipped rubber products, such as gloves, condoms, or balloons. The ceramic molds (also called formers) used in dipping often are coated with powders, which act as coagulants for the rubber and can help facilitate releasing of the product from the mold. Starch donning powder also may be added to medical gloves after dipping. Protein antigens that remain in the latex suspension have been demonstrated to bind to these powders.<sup>6</sup> When powdered latex gloves are worn, the powder-protein particles may transfer to the skin of the glove user and to the tissues of the patient (e.g., during surgery). The powder also becomes aerosolized during glove use and may be inhaled by patients or healthcare workers. (Note that powder-free gloves are widely available. A chlorine wash or polymer coating is used during manufacturing to assure glove lubrication and eliminate the need for cornstarch donning powders.) A number of other chemicals (e.g., antioxidants, stabilizers, accelerants) are added during processing, contributing about 5% of the final weight of rubber products.<sup>15</sup>

## NATURAL LATEX ANTIGENS

After harvesting, AL typically is centrifuged and separates into three fractions: the cream layer, the C serum, and the B serum. The C serum is a suspension of two populations of particles that each contain the rubber polymer *cis*-1,4-polyisoprene (which is not itself allergenic) as well as a number of particle-associated proteins. Rubber particles are spherical droplets of polyisoprene coated with protein, lipids, and phospholipids, which are present in the laticifer cells of the rubber tree.<sup>29</sup> The B serum contains a number of soluble proteins, including cell structural proteins and enzymes released from the lutoids (vacuoles). The B and C sera have been further fractionated by elutriation on polyacrylamide gels, and a number of antigenic proteins have been identified using immunoelectrophoresis. Of the approximately 240 polypeptides in NRL, nearly 60 have been reported to be antigenic.<sup>20,27</sup>

Ammoniated latex contains proteins with similar physical and immunologic characteristics to NAL, but the addition of ammonia results in rupture of the lutoids and allows interaction of the proteins bound to rubber particles and the soluble proteins, several of which have enzymatic activity. This appears to result in a modification of the proteins, with subsequent fragmentation and/or aggregations and a decrease in the homogeneity after electrophoretic separation. Dipped NRL products such as gloves contain residual soluble antigens that can be removed through water washing, but also have antigens that are more adherent, as evidenced by the ability of washed glove fragments to partially inhibit reaction of NAL with rabbit anti-NAL antibodies, and also with human anti-latex IgE.<sup>23</sup>

When non-ammoniated latex is fractionated on polyacrylamide gels, antigens ranging from 2 to 100 kd have been observed.<sup>11,29</sup> As of this writing, nine antigens from the rubber tree *H. brasiliensis* have been isolated and given official registration, Hev b 1–9, by the World Health Organization–International Union of Immunological Societies' Allergen Nomenclature Subcommittee (Table 1). The specific antigenic proteins that have been isolated from NRL are discussed below, but it is important to emphasize that the proportional concentrations of the different antigens can vary markedly (25 to 100 fold) between different lots

**TABLE 1.** Latex Allergens Registered by the World Health Organization–International Union of Immunological Societies' Allergen Nomenclature Subcommittee

Allergen	Source	Molecular Weight	Function
Hev b 1	Rubber particle	14.6 kd	Rubber elongation factor (REF)
Hev b 3	Rubber particle	23–27 kd	Homology to REF
Hev b 2	Soluble	34–41.3 kd	Endo-1,3- $\beta$ -glucosidase
Hev b 4	Soluble	50–75 kd	Microhelix protein
Hev b 5	Soluble	16 kd	Unknown function Homology to kiwi protein
Hev b 6.01	Soluble	20 kd	Prohevein, hevein precursor
Hev b 6.02		4.7 kd	Hevein, lysozyme/chitinase with homology to other plant defense proteins
Hev b 7	Soluble	46 kd	Patatin, storage protein Homology to potato and tomato proteins
Hev b 8	Soluble	14 kd	Profilin
Hev b 9	Soluble	51 kd	Enolase, 2-phosphoglycerate dehydrogenase

of natural latex materials, related to season of harvest, duration of storage, and other factors.<sup>16,19,40</sup>

### Particle-Associated Antigens

Surface proteins on the rubber particles, including rubber elongation factor (REF) and prenyltransferase, are thought to interact with the isoprene subunits in the formation of the isoprene polymer. Hev b 1 has been identified as the particle-associated REF. Two protein forms, a 14.6-kd monomer and a 58-kd tetramer have been shown to inhibit IgE to REF from latex allergic patients.<sup>13,29</sup> The 24-kd Hev b 3 represents a second particle-associated antigen, and shares a number of immunologic similarities with REF.

Several investigators have noted that specific IgE antibodies to the two particle-associated antigens (Hev b1 and Hev b3) are found in a high proportion of latex allergic children with spina bifida. In contrast, latex allergies among healthcare workers, or children who have not had multiple surgeries, often are associated with serologic responses to other antigens (see below) but less commonly to these two antigens. It has been proposed that these differences relate to the different modes of exposure among individuals who have had multiple surgeries (direct tissue exposure to latex gloves) in contrast to healthcare workers, who generally have either skin contact or mucous membrane exposure to glove powders.

### Soluble Antigens

The laticifer cells of the rubber tree contain lutoids, or vacuoles, which appear to contribute many of the soluble antigens to NRL. Hevein, the related protein prohevein, and hevamine (lysozyme/chitinases) are found in these cells, as well as in AL, in gloves and other dipped rubber products made from NRL, and on the surface of starch donning powders collected from NRL gloves.<sup>36</sup> Hevein (Hev b 6.02), a small protein with only 43 amino acids, is the predominant soluble protein in NRL. It has been reported to represent up to 70% of the total NRL glove allergen.<sup>3</sup> The 4.7-kd protein hevein appears to play a role in wound healing and may inhibit fungal growth through its chitin binding activity. It is synthesized as a preproprotein (prohevein, Hev b 6.01), a 20-kd cysteine-rich chitin-binding protein, which is post-translationally processed to hevein, an N-terminal fragment, as well as to other cleavage peptides.<sup>27</sup> The IgE-binding ability appears to reside primarily in the hevein. Most adult NRL allergic patients have specific IgE antibody to prohevein, although this is found in a minority of spina bifida patients.<sup>12</sup>

Hev b 2 is a soluble 36-kd NRL protein, also found in the lutoids, that has a high degree of homology to enzymes (endo-1,3- $\beta$ -glucosidases) from a number of plant species. IgE antibodies to Hev b 2 have been noted in 21% of NRL allergic patients.<sup>26</sup> Hev b 5, a 16-kd acidic protein with homology to structural proteins from kiwi fruit and potatoes, has been isolated from latex gloves, cloned, and sequenced; IgE antibodies to it have been found in most latex-allergic healthcare workers (92%) and a lesser proportion of spina bifida patients (50–60%).<sup>1,30</sup> A microhelix protein from NRL has been isolated and partially sequenced, and termed Hev b 4.<sup>1</sup> Hev b 7 is a 46-kd NRL protein that has significant homology to a class of plant storage proteins called patatins.<sup>7</sup> Latex profilin, an actin-binding protein with homology to other plant profilins, recently has been isolated and registered as Hev b 8. IgE binding to Hev b 8 was found in 14 of 29 spina bifida patients and 6 of 17 latex-allergic adults.<sup>24</sup> A latex enolase also has been isolated recently and termed Hev b 9.

In addition to the above peptides, sequencing and epitope mapping of NRL proteins have shown significant homologies to a number of previously sequenced plant enzymes, including triose phosphate isomerases and superoxide dismutases, as well as several structural plant proteins.<sup>27</sup> In general, the extensive efforts that have been put forth in the isolation and sequencing of natural latex proteins have resulted in a greatly improved understanding of the proteins that trigger NRL allergies.

## MEASUREMENT OF ANTIGEN ON NRL PRODUCTS

The type and amount of antigenic material present on a given natural latex product varies with the protein content and specific characteristics of the raw latex.<sup>40</sup> Subsequently, the manufacturing process removes a variable amount of the antigenic material that originally was present. Depending on these factors, the quantity of antigenic protein that can be released from a pair of NRL gloves, and thus the related exposure to antigenic stimulation, can vary markedly.<sup>42</sup>

A number of approaches have been used to quantitate the protein that remains on NRL gloves.<sup>9</sup> An approved method for assessing glove protein levels has been published by the American Society for Testing and Materials (ASTM D 5712 Standard Test Method for the Analysis of Protein in Natural Rubber and Its Products), and glove manufacturers are permitted by the Food and Drug Administration to report protein levels on NRL gloves determined using this assay. The ASTM method is a modification of the Lowry assay (with the addition of a precipitation step to reduce interfering substances). Although high protein levels found on a glove by this method generally have been associated with a high level of NRL antigens, the utility of this method of assessing glove antigenicity is diminished by the relatively high limit of quantitation (50 µg protein per gram glove). In tests from 39 NRL-allergic volunteers, Beezhold and colleagues observed that fully 58% of the patients had positive prick skin tests to extracts from gloves that had protein levels below the Lowry test quantitation threshold.<sup>8</sup>

Another difficulty in using the ASTM assay for glove proteins is that non-latex related proteins, such as casein, may be added during the glove manufacturing process, and will be measured by the modified Lowry assay. Ylitalo et al. investigated this using serum from a group of patients who appeared to be reacting to a non-latex protein in the gloves. The patients all reported contact urticaria to gloves, and were skin prick positive to standardized cow's milk antigen but negative to NRL. The investigators tested thirty brands of NRL gloves, and eight were noted to inhibit the RAST positivity to cow's milk casein of these patients' serum, suggesting the presence of casein protein on these eight gloves.<sup>41</sup>

In contrast to measurement of total glove protein, currently no widely accepted method is available for measurement of NRL glove antigen. A number of investigators have used immunologic assays to measure glove antigen levels. For example, Yunginger and colleagues extracted proteins from medical gloves from each of 71 lots of gloves made by 22 different manufacturers. Protein levels were measured and glove allergen levels were determined by the degree of inhibition of a RAST assay, using serum pooled from five NRL-allergic healthcare workers. Levels were compared using a standardized raw NRL allergen. Using this assay, allergen levels from different glove brands were found to vary by more than 3000 fold, with smaller differences between lots from the same manufacturer. A significant correlation was seen between allergen and protein levels ( $R = 0.6$  to  $0.69$ ), but the allergen to protein ratio on the various gloves still varied by nearly 10,000 fold. Powdered gloves had, on average, much higher allergen levels.<sup>42</sup>

As mentioned previously, dipped products also may be manufactured using latex from guayule. The potential for cross-reactivity between antigens in guayule and *H. brasiliensis* was investigated using sera from 46 adults and 16 children with known allergy to natural latex products made from *H. brasiliensis*. No cross-reactivity was noted on RAST testing and Western blots using sera from these individuals. Additionally, antibodies from mice immunized using extracts from each plant species did not react with proteins from the other species, suggesting that products made from guayule might not trigger allergic symptoms in individuals with allergy to NRL proteins derived from *H. brasiliensis*.<sup>28</sup>

Clinical observations have suggested a number of patients with natural latex allergy report triggering of symptoms after exposures to a number of other fruits, vegetables, or plant materials. As discussed above, the plausibility of this observation is enhanced by the multiple investigations indicating that NRL antigens share common epitopes with proteins from these and other plant species.<sup>4,14</sup>

## CONTROVERSIES

The past several years have brought considerable progress in the understanding of the development of clinical allergy to natural latex, and have yielded a number of effective approaches to preventing initial sensitization, as well as to reducing symptoms in individuals who have become sensitized. At the current time, nine allergens have been investigated and given official designation, and the importance of several of these in natural latex protein allergy has been clearly identified. The structure and clinical importance of the approximately 50 other antigens is an area of ongoing investigation. The role of cornstarch glove-donning powders in binding and transferring the NRL antigens to skin, mucosa, and tissues has been extensively investigated and is widely acknowledged. Recommendations for limitation on the use of glove powder and a reduction of total glove protein have been published.<sup>25,35</sup> Although these suggested interventions, as well as other concurrent efforts, are likely to result in a decline in the prevalence of NRL allergies, a number of questions remain under active investigation:

1. It is still unclear why, during the 1980s, there was an increase in the apparent antigenicity of a number of natural latex products, such as barium enema catheter tips and medical gloves.

2. The specific role of skin contact in sensitization to NRL antigens also is a topic of active investigation.

3. It remains unclear whether irritant or allergic contact dermatitis represents a significant risk factor for subsequent development of IgE mediated NRL allergy.

4. Finally, although recent studies have suggested that the use of powder-free NRL gloves can reduce exposure to NRL antigens, decrease the risk of immunologic sensitization, and help to control symptoms among some NRL-sensitized workers, it remains to be seen if NRL gloves with intermediate levels of protein and/or starch powder can be safely adopted.<sup>5,32</sup>

## REFERENCES

1. Akasawa A, Hsieh L-S, Martin BM, et al: A novel acidic allergen, Hev b 5, in latex. *J Biol Chem* 271:25389-25393, 1996.
2. Akasawa A, Hsieh S, Lin Y: Comparison of latex-specific IgE binding among nonammoniated latex, ammoniated latex, and latex glove allergenic extracts by ELISA and immunoblot inhibition. *J Allergy Clin Immunol* 97(5):1116-1120, 1996.
3. Alenius H, Kalkkinen N, Lukka M, et al: The main IgE-binding epitope of a major latex allergen, prohevein, is present in its N-terminal 43-amino acid fragment, hevein. *J Immunol* 156(4): 1618-1625, 1996.

4. Alenius H, Makinen Kiljunen S, Ahlroth M, et al: Crossreactivity between allergens in natural rubber latex and banana studied by immunoblot inhibition. *Clin Exper Allergy* 26(3):341-348, 1996.
5. Allmers H, Brehler R, Chen Z, et al: Reduction of latex aeroallergens and latex-specific IgE antibodies in sensitized workers after removal of powdered natural latex gloves in a hospital. *J Allergy Clin Immunol* 102(5):841-846, 1998.
6. Beezhold D, Beck WC: Surgical glove powders bind latex antigens. *Arch Surg* 127(11):1354-1357, 1992.
7. Beezhold DH, Sussman GL, Kostyal DA, Chang NS: Identification of a 46-kd latex protein allergen in health care workers. *Clin Exp Immunol* 98:408-413, 1994.
8. Beezhold D, Pugh B, Liss G, Sussman G: Correlation of protein levels with skin prick test reactions in patients allergic to latex. *J Allergy Clin Immunol* 98(6 Pt 1):1097-1102, 1996.
9. Beezhold D, Swanson M, Zehr BD, Kostyal D: Measurement of natural rubber proteins in latex glove extracts: Comparison of the methods. *Ann Allergy Asthma Immunol* 76(6):520-526, 1996.
10. Brehler R, Kolling R, Webb M, Wastell C: Glove powder—A risk factor for the development of latex allergy? *Europ J Surg (Suppl 579)*:23-25, 1997.
11. Breiteneder H, Scheiner O: Molecular and immunological characteristics of latex allergens. *Int Arch Allergy Immunol* 116(2):83-92, 1998.
12. Chen Z, Posch A, Lohaus C, et al: Isolation and identification of hevein as a major IgE-binding polypeptide in Hevea latex. *J Allergy Clin Immunol* 99:402-409, 1997.
13. Czuppon AB, Chen Z, Rennert S, et al: The rubber elongation factor of rubber trees (*Hevea brasiliensis*) is the major allergen in latex. *J Allergy Clin Immunol* 92:690-697, 1993.
14. Fuchs T, Spitzauer S, Vente C, et al: Natural latex, grass pollen, and weed pollen share IgE epitopes. *J Allergy Clin Immunol* 100(3):356-364, 1997.
15. Hamann CP: Natural rubber latex protein sensitivity in review. *Am J Contact Derm* 4(1):4-21, 1993.
16. Kekwick R, Bhambri S, Chabane MH, et al: The allergenic properties of fresh and preserved *Hevea brasiliensis* latex protein preparations. *Clin Exp Immunol* 104(2):337-342, 1996.
17. Kelly KJ, Pearson ML, Kurup VP, et al: A cluster of anaphylactic reactions in children with spina bifida during general anesthesia: Epidemiologic features, risk factors, and latex hypersensitivity. *J Allergy Clin Immunol* 94(1):53-61, 1994.
18. Kujala VM, Karvonen J, Laara E, et al: Postal questionnaire study of disability associated with latex allergy among health care workers in Finland. *Am J Ind Med* 32(3):197-204, 1997.
19. Kurup VP, Kelly KJ, Turjanmaa K, et al: Immunoglobulin E reactivity to latex antigens in the sera of patients from Finland and the United States. *J Allergy Clin Immunol* 91(6):1128-1134, 1993.
20. Kurup VP, Alenius H, Kelly KJ, et al: A two-dimensional electrophoretic analysis of latex peptides reacting with IgE and IgG antibodies from patients with latex allergy. *Int Arch Allergy Immunol* 109(1):58-67, 1996.
21. Liss GM, Sussman GL, Deal K, et al: Latex allergy: Epidemiological study of 1351 hospital workers. *Occ Environ Med* 54(5):335-342, 1997.
22. Lu LJ, Kurup VP, Hoffman DR, et al: Characterization of a major latex allergen associated with hypersensitivity in spina bifida patients. *J Immunol* 155(5):2721-2728, 1995.
23. Lu LJ, Kurup VP, Fink JN, Kelly KJ: Comparison of latex antigens from surgical gloves, ammoniated and nonammoniated latex: Effect of ammonia treatment on natural rubber latex proteins. *J Lab Clin Med* 126(2):161-168, 1995.
24. Nieto A, Mazon A, Estornell F, et al: Profilin, a relevant allergen in latex allergy. *J Allergy Clin Immunol* 101:S207, 1998.
25. NIOSH Alert: Preventing Allergic Reactions to Natural Rubber Latex in the Workplace. Pub. No. 97-135. Cincinnati, OH. Department of Health and Human Services, 1997, pp 1-11.
26. Palosuo T: Latex allergens. *Revue Francaise D'Allergologie et D'Immunologie Clinique* 37(8):1184-1187, 1997.
27. Posch A, Chen Z, Wheeler C, et al: Characterization and identification of latex allergens by two-dimensional electrophoresis and protein microsequencing. *J Allergy Clin Immunol* 99:385-394, 1997.
28. Siler DJ, Cornish K, Hamilton RG: Absence of cross-reactivity of IgE antibodies from subjects allergic to *Hevea brasiliensis* latex with a new source of natural rubber latex from guayule (*Parthenium argentatum*). *J Allergy Clin Immunol* 98(5 Pt 1):895-902, 1996.
29. Slater JE: Latex allergy. *J Allergy Clin Immunol* 94(2 Pt 1):139-149, 1994.
30. Slater JE, Vedvick T, Arthur-Smith A, et al: Identification, cloning, and sequence of a major allergen (Hev b 5) from natural rubber latex (*Hevea brasiliensis*). *J Biol Chem* 271(41):25394-25399, 1996.
31. Sussman GL, Beezhold DH: Allergy to latex rubber. *Ann Intern Med* 122(1):43-46, 1995.
32. Tarlo SM, Sussman G, Contala A, Swanson MC: Control of airborne latex by use of powder-free latex gloves. *J Allergy Clin Immunol* 93(6):985-989, 1994.

33. Truscott W: The industry perspective on latex. *Immunol Allergy Clin North Am* 15(1):89–121, 1995.
34. Turjanmaa K, Alenius H, Makinen-Kiljunen S. et al: Natural rubber latex allergy. *Allergy* 51(9):593–602, 1996.
35. U.S. Department of Health and Human Services, Food and Drug Administration: Draft Medical Glove Guidance Manual (released for comment on July 30, 1999).
36. Vandenplas O: Occupational asthma caused by natural rubber latex. *Europ Resp J* 8(11):1957–1965, 1995.
37. Vandenplas O, Delwiche JP, Evrard G, et al: Prevalence of occupational asthma due to latex among hospital personnel. *Am J Respir Crit Care Med* 151(1):54–60, 1995.
38. Woods JA, Lambert S, Platts-Mills TA, et al: Natural rubber latex allergy: Spectrum, diagnostic approach, and therapy. *J Emerg Med* 15(1):71–85, 1997.
39. Woolhiser MR, Munson AE, Meade BJ: Immunological responses of mice following administration of natural rubber latex proteins by different routes of exposure. *Toxicol Scis* (in press)
40. Yeang HY: Impact of biologic variation on latex allergenicity [letter]. *J Allergy Clin Immunol* 101(1 Pt 1):145–146, 1998.
41. Ylitalo L, Makinen-Kiljunen S, Ahlroth M, et al: Cow's milk casein, a hidden allergen in natural rubber latex gloves. *J Allergy Clin Immunol* 104(1):177–180, 1999.
42. Yunginger JW, Jones RT, Fransway AF, et al: Extractable latex allergens and proteins in disposable medical gloves and other rubber products. *J Allergy Clin Immunol* 93(5):836–842, 1994.