REVIEW ARTICLE

Natural Rubber Latex Allergy

A Problem of Interdisciplinary Concern in Medicine

Randolf Brehler, MD; Birgitta Kütting, MD

In the past 10 years, IgE-mediated allergy to natural rubber latex has become a significant health problem in industrialized countries, especially among health care workers, patients with congenital malformations, and children with a history of multiple surgical interventions. Curative treatment inducing immunological tolerance in formerly sensitized patients is experimental and not yet generally available. Therefore, it is important to be aware of the seriousness of latex allergy and to understand the risk factors leading to this allergy. Preventive measures are needed to decrease the incidence of natural rubber latex sensitization. This article gives a brief review of the current state of knowledge concerning latex allergy, including a definition of *latex*, epidemiological data, identified allergens, the clinical spectrum, diagnostic procedures, cross-reactions, preventive measures, the legislative background, and economics. *Arch Intern Med. 2001;161:1057-1064*

In today's health care practice, the use of gloves is indispensable. Because of their low price, high comfort, and tactile properties, natural rubber latex (NRL) gloves are preferred over synthetic ones. Contact dermatitis (allergic and nonallergic) is a well-known problem related to the use of NRL gloves, but during the last 20 years, the immediate reactions to NRL have been the focus. Between 1989 and 1992, the Food and Drug Administration received reports of more than 1000 serious allergic reactions and 15 deaths due to NRL allergy.[1]

Immediate allergic reaction to NRL is a significant occupational problem for employees wearing NRL gloves; about 10% of health care workers are sensitized to NRL. On another level, patients are at risk of anaphylactic reactions due to contact with NRL during medical treatments, especially surgical procedures; about 19% of the anaphylactic reactions associated with anesthesia are caused by NRL allergy.[2] Gloves are not the sole source of contact with NRL in sensitized patients. Natural rubber latex is found in more than 40 000 medical devices and other nonmedical products (**Table 1**). To avoid exposure in daily life, sensitive patients must be able to identify products containing NRL, but the labeling of these products is not regulated in most countries.

From the Department of Dermatology, University of Münster, Germany.

Recent reviews[3-13] focus on different aspects of NRL allergy, such as epidemiology, diagnostic procedures, allergen identification, prevention, and therapy, but despite the increasing awareness and prevention programs, NRL allergy is still a problem. Therefore, the current state of NRL allergy is examined in this review.

DEFINITION OF *LATEX*

To avoid confusion when discussing NRL allergy, clear definitions of the terms *latex* and *rubber* are needed because, depending on the context, they can have multiple meanings:

- *Natural rubber latex* refers to the milky sap produced by more than 2000 species of plants from about 300 genera.[14] Industrial use of NRL is almost exclusively from the rubber tree *Hevea brasiliensis*.
- *Synthetic rubber* is produced by synthesis of polyisoprene or other polymers. The term *latex* is used in referring to NRL and synthetic rubber.
- A technical definition of *latex* is common in some countries, where the term refers to a suspension of different kinds of particles (such as latex wall paint) and does not necessarily indicate the presence of rubber latex in these products.

Table 1. Natural Rubber Latex in Medical and Privately Used Products

Medical Devices	Privately Used Products
Gloves	Balloons
Catheters	Condoms
Face masks	Clothes
Mattresses	Shoe soles
Stethoscope	Sport equipment
Blood tourniquets	Mattresses
Mouth sperrer	Glues
Rubber syringe stoppers	Pacifiers, feeding nipples
Medical vial stoppers	Toys

Table 2. Natural Rubber Latex (NRL) Glove–Related Skin Problems

Type of Reaction	Clinical Manifestation
Nonimmunological irritant contact dermatitis, due to occlusion, mechanical irritation, high glove pH, and sweat	Eczema predominantly on the back of the hands and fingers, with redness, infiltration, scaling, and fissures
T-cell mediated allergic contact eczema, mostly due to rubber chemicals, rarely due to NRL itself	Onset 24-48 h after contact. Acute allergic contact eczema, with redness, infiltration, vesicles and crusts, and itching
	By repeated contact, chronic allergic contact eczema; predominantly scaling, infiltration, lichenification
	Mostly located on the back of the hands and wrists
IgE-mediated immediate-type allergy, nearly exclusively due to NRL proteins, rarely due to casein, cornstarch, or rubber chemicals	Onset mostly within minutes, with localized erythema, itching, and contact urticaria
	Generalized urticaria, rhinitis, conjunctivitis, asthma, and anaphylactic shock

EPIDEMIOLOGY

Since the first epidemiological study among medical personnel by Turjanmaa,[15] the prevalence of NRL allergy has increased. Today, between 10% and 17% of medical personnel in Europe and the US are believed to be sensitive to NRL.[16-26] Children with congenital malformations, especially those associated with spina bifida, are another well-identified risk group. The prevalence of NRL allergy in patients with spina bifida is about 50% in industrialized countries[27-34] and about 5% in less industrialized countries, such as Venezuela.[35] This is believed to be related to contact with NRL during medical treatments, especially surgical interventions in early childhood. A history of multiple surgical interventions has also been reported in the general population of children with sensitivity to NRL.[36] Sensitivity was found in 34.1% of children with a history of 3 or more interventions.[36] Surgical interventions are a risk factor for the development of NRL allergy in children[28,34,36] but not in adults.[37]

Higher prevalence of NRL allergy was also found among hairdressers,[38] housekeeping personnel,[24] latex doll manufacturers,[39] latex glove manufacturers,[40,41] textile workers,[42] and greenhouse workers.[43] The prevalence in the general population is unknown but has been estimated to be less than 1%.[44,45]

CLINICAL REACTIONS

Clinical reactions to contact with latex gloves can be divided into 3 groups (**Table 2**): nonimmunological and delayed- and immediate-type allergy.

Nonimmunological irritant contact dermatitis is manifested as irritative eczema with redness, scaling, and itching, predominantly on the back of the hands and interphalangeal. In contrast to the others, this type of clinical reaction is not based on an immunological mechanism. It is a general problem of glove wearing that is independent of the chemical composition of the gloves. Gloves can induce skin irritation "mechanically" or by an alkaline pH:

- "Mechanical" irritation can be avoided by use of powder-free gloves. In tests of glove wearing on powdered vs unpowdered hands, laser profilometry demonstrated increased skin roughness after wearing the same glove on prepowdered hands.[46]
- The alkaline pH of most powdered gloves is believed to be responsible for irritative skin reactions.[47] Powder-free gloves offer a lower surface pH that is in the range of normal skin pH. The presence of a long-lasting alkaline skin surface pH after removal of powdered gloves has been reported.[47]

The second type of clinical reaction is manifested by a delayed-type allergic contact eczema caused by glove contact, usually on the back of the hands. Rubber chemicals, mostly accelerators, used for manufacturing latex products are responsible for such reactions.[48] Thiurams have been identified as the predominant contact sensitizers in NRL gloves. Because most manufacturers no longer use thiurams, the delayed-type reactions play a minor role.

Immediate-type reaction to NRL is IgE-mediated, and the term *latex allergy* is usually used to describe this. Localized itching, erythema, or contact urticaria within minutes after NRL exposure are initial symptoms. Progressive sensitization can also lead to generalized urticaria, angioedema, rhinitis, conjunctivitis, asthma, and anaphylactic shock minutes after dermal or mucosal contact with NRL proteins. An increasing number of individuals allergic to NRL report severe reactions to latex, including generalized urticaria, bronchospasm, and hypotension.[49]

The severity of clinical reactions can be classified according to the system of von Krogh and Maibach.[50] Stage 1 of contact urticaria syndrome indicates localized urticaria; stage 2 denotes generalized urticaria with or without angioedema; stage 3 includes bronchial asthma, rhinoconjunctivitis, oropharyngeal, and gastrointestinal symptoms; and stage 4 is severe anaphylactic shock.

Glove powder is believed to play a central role in reactions to NRL products. Natural rubber latex proteins on gloves bind to the glove powder (usually cornstarch powder) and become aeroallergens. Therefore, respiratory tract reactions induced by aeroallergens may occur concomitantly with der-

mal reactions caused by local dermal contact.[51,52] In this case, a clear distinction between a systemic reaction produced by localized dermal contact and reactions caused by allergen inhalation is impossible. Parenteral latex exposure can also trigger reactions.[53,54]

Because of resorption of NRL allergens through mucous membranes, NRL allergy is not only a problem for employees who wear latex gloves but also an increasing problem for sensitized patients undergoing medical treatment by persons wearing gloves. Fatal cases have been reported in the literature,[2,31] especially during surgical interventions. About 19% of all anaphylactic reactions during surgery (anesthesia "accidents") are related to NRL allergy,[2] and the percentage is higher in children.[55] The risk of anaphylaxis to NRL in children with spina bifida has been estimated to be 500 times greater than that in the general population.[56,57]

ALLERGENS

Natural rubber latex derived from *H brasiliensis* contains more than 200 polypeptides, 56 of which have been identified as allergens associated with IgE-mediated reactions. Their molecular weight ranges from 4 to 200 kd. Some of the allergens have been characterized,[58-61] some as general major allergens and others as major allergens only for patients of defined risk groups. Hev b 1, for example, is a major allergen for children with spina bifida but not for health care workers.[62-68] Different routes of NRL exposure and subsequent sensitization may explain this. Hev b 1 and Hev b 3, which are major allergens in children with congenital malformations, are particle-bound proteins and less soluble than other latex allergens, and sensitization to these allergens may result from repeated mucosal contacts.[65] It has been speculated that the aerogen NRL protein exposure associated with the use of powdered gloves in delivery rooms may be responsible for the development of NRL allergy in neonates.[69] Further variation has been identified in mice that have been subcutaneously sensitized to NRL, leading to the development of IgE antibodies recognizing 14-kd and 27-kd proteins. Intratracheally and topically sensitized animals produced IgE antibodies to 14-, 35-, and 92-kd proteins.[70]

Some latex allergens are a part of a plant's defense system (Hev b 2 and class 1 endochitinases). This may explain the increasing prevalence of sensitivity to NRL. It is hypothesized that the amount of NRL obtained from an *H brasiliensis* tree increased in the last few years. There may be a correlation between the production of defense proteins in relation to the frequency and intensity of hurting the trees.[58]

Further complicating the issue, Mäkinen-Kiljunen and colleagues[59] identified an allergen in a surgical glove extract that is not found in natural rubber, suggesting that rubber proteins may be altered during glove manufacture.

DIAGNOSIS

In Vitro

The quantitative measurement of serum-specific IgE antibodies to NRL is generally accepted as a diagnostic tool for latex allergy. However, the sensitivity of specific-IgE analysis ranges from 8% to 100%. For the widely used Pharmacia CAP (Pharmacia AB, Uppsala, Sweden) radioallergosorbent test method, the sensitivity is reported to range from 50% to 80%.[71-73] Data about the specificity of in vitro diagnosis are rare.[71,74,75] Using different assay systems (CAP-FEIA [fluoroimmunoassay; Pharmacia AB] and AlaSTAT [Diagnostic Products Corp, Los Angeles, Calif]), NRL-specific IgE was detected in the serum samples of patients despite negative findings on skin tests and no history of NRL allergy.[74,75] Cross-reacting IgE antibodies binding to plant proteins and NRL are believed to be responsible for this. Mäkinen-Kiljunen and Turjanmaa[74] found IgE specific to banana in the serum of most patients with a false-positive radioallergosorbent test for NRL. Also, IgE antibodies to *Ficus benjamina* (weeping fig) may account for the frequent false-positive finding of specific IgE to NRL.[75] On the other hand, IgE antibodies against carbohydrates were shown to be the cause of IgE reactivity against a broad range of foods, from plant to invertebrate animal origin. These IgE antibodies have been shown to be responsible for positive results in in vitro–specific IgE assays, despite negative skin-prick test (SPT) results and an absence of clinically relevant sensitization.[76,77]

In Vivo

Diagnosis of immediate-type NRL allergy should be based on positive SPT results. Because SPTs with single latex extracts have a sensitivity below 100%, it is necessary to use a panel of different allergen extracts.[71,78-81] In Germany, extracts that are available from allergen manufacturers are generally unstandardized. High-ammoniated NRL milk, available from glove manufacturers, can be used exactly as received; glove extracts can be prepared by a short extraction in isotonic sodium chloride solution.[82,83] Because of the potential risk for anaphylactic reactions associated with SPTs in patients allergic to NRL,[30,81,84] it is recommended that diluted solutions be used initially. Recombinant NRL proteins can be used for SPTs, but a panel of allergens is necessary to get a sufficient sensitivity.[85]

The reliability of NRL glove wearing test results depends on the test protocol and the protein concentration of the gloves used.[86] Increased sensitivity of exposure tests has been obtained by Hamilton and Adkinson[86] by puncturing the skin before contact with the NRL glove. A potential risk for anaphylaxis can be reduced by exposing only 1 finger to a glove finger before exposing the hand to the whole glove.[57]

CROSS-REACTIVE ALLERGENS

Cross-reactions between proteins in NRL and several foods have been demonstrated, and a "latex-food" syndrome has been postulated.[87-89] In one study, 43% of patients with NRL allergy reported reactions caused by the ingestion of foods, particularly tropical fruits. Fruit-specific IgE antibodies are present in about 70% of serum samples of pa-

tients allergic to NRL. However, their presence is of limited significance given the low sensitivity and specificity of in vitro tests relative to a patient's self-reported allergic reaction after fruit ingestion.[89] The relevance of fruit sensitization varies considerably, based on a patient's diet and cultural background. On Spain's Grand Canary island, sensitization to avocado was found to be the predominant food allergen in patients with latex allergy,[87,90] whereas in Germany, reactions to kiwi, banana, and tomato were much more frequent.[89] Patatin,[91-94] profilin,[95,96] chitinases,[97,98] plant endo-1,3-ß-glucosidases,[99] glucanases,[59,94,99,100] and hevein[101] are allergens believed to be responsible for cross-reactions.

Ortiz et al[102] found IgE antibodies to NRL proteins in 85.9% of patients allergic to fruits. Only 10.5% of them had clinically relevant latex allergy. This indicates that patients sensitized primarily by food allergans may also react to NRL.

THERAPY AND PREVENTION

Desensitization

Several recent case reports[103-106] of NRL-specific immunotherapy have been published. Administering oral[103] and subcutaneous [104-106] allergens was demonstrated to be effective in reducing allergic symptoms from NRL contact; SPT sensitivity decreased during specific immunotherapy. In the first randomized, double-blind, placebo-controlled study[107] on 17 patients with NRL allergy, significantly lower rhinitis, conjunctivitis, and cutaneous scores were reported in the patient group, but asthma symptoms were not significantly different in patients vs controls. Therefore, NRL-specific immunotherapy remains an experimental treatment of NRL allergy, and avoidance of exposure remains the mainstay of therapy and prevention.

Protein Concentration of Gloves and Powder

The modified Lowry test is the current standard method for determination of protein content in gloves.[108] A protocol for protein analysis has been issued by the European Union, but there are no guidelines about how many gloves from each batch need to be tested. Therefore, data from manufacturers can be based on the analysis of only a few gloves, with no guarantee that all the gloves, especially if they are from different batches, have the same protein content. Standardized protocols for the quantitative analysis of allergens in gloves are not available. A correlation between the protein concentration and the allergen concentration of gloves has been demonstrated by enzyme-linked immunosorbent assay and radioallergosorbent test inhibition methods and SPT.[109]

Significant variation in the NRL protein concentrations in different types of gloves has been observed by several investigators.[49,109-112] Powder-free gloves normally have low protein concentrations because of special leaching procedures used in their production. The protein concentration of powdered gloves varies between 45 and 1640 µg/g.[109] Heese et al[49] have reported decreasing protein concentrations in gloves manufactured using newer technology.

A correlation between glove wearing and the development of NRL allergy has been demonstrated in other studies:

- Heese et al[20] compared the prevalence of NRL allergy in a group of dental students at 2 time points 3 semesters apart. After the first time point, students regularly wore latex gloves. The prevalence of NRL allergy increased from 2% before glove use to 10.4% 3 semesters later.
- Brehler et al[19] demonstrated that the use of powder-free gloves results in low rates of NRL sensitization. The finding of minimal NRL allergy in 2 English hospitals was attributed to the use of powder-free gloves with a low protein level, whereas the prevalence was much higher in a German hospital where only powdered gloves with high protein contents were worn.

Moreover, powder is an allergen carrier. The air in rooms where powdered NRL gloves are used has high concentrations of allergen,[113] with much lower concentrations where powder-free gloves are used.[114,115] Sensitized persons may have asthmatic and systemic reactions to airborne NRL proteins associated with the use of powder. A hospital's changing from powdered, high-protein content gloves to powder-free or synthetic ones results in a decrease of airborne allergen levels to below the limit of detection within a few days.[116] Strict avoidance of NRL products decreases the risk of latex allergy development even in identified risk groups. After construction of a special NRL-free operating room for children with spina bifida, none of 12 patients studied became sensitized to NRL allergens.[117]

Powdered gloves with a low protein content have become available in Germany, but a reduced risk for the development of NRL sensitization has not been demonstrated with the use of these gloves.

Prevention Guidelines

The primary prevention of NRL allergy is the avoidance of NRL exposure, but because of the ubiquity of NRL in products, this is nearly impossible. Threshold allergen exposure levels to avoid NRL sensitization are not defined. These levels may vary for individuals with atopic vs nonatopic predisposition. Natural rubber latex protein levels should be reduced to the lowest technically possible minimum. Individuals at high risk to develop sensitization should not be exposed to any NRL. These include children with congenital malformations and those with diseases bearing the risk of repeated surgical interventions. Persons who regularly wear gloves in their professions should use NRL-free gloves if eczema of the hand develops, especially if they have an atopic predisposition. Eczema lesions of the hand are opportunisitic for the development of NRL sensitization by allowing protein to penetrate the skin. Less than 1% of NRL proteins penetrate intact skin, whereas 23% penetrate abraded skin.[118]

To identify patients who are sensitized to NRL, screening questionnaires may be used (**Table 3**). In sensitized individuals, NRL avoidance is the cardinal rule of NRL allergy control and to avoid life-threatening anaphylactic reactions.

Aerogen exposure from powdered gloves and other NRL products must be avoided. Contamination of foods with NRL allergens from kitchen personnel wearing powdered gloves can also lead to anaphylaxis.[119] Finally, indirect contact with NRL proteins on surfaces contaminated with NRL, such as clothing,[120] can cause a life-threatening reaction.

Latex-safe environments for patients with NRL allergy should be provided in all medical and dental facilities. Medical procedures in high-risk patients should be performed in a latex-free setting. Substitute products without NRL are available for nearly all products containing NRL.

Table 3. Screening Questionnaires to Determine Latex Allergy in Children and Adults*

Children
Lip swelling, mucosal reactions, or asthma after blowing up balloons
History of atopic diseases
Adults
Contact urticaria rhinoconjunctivitis, asthma, or anaphylaxis after contact with NRL gloves, condoms, or other NRL products
Allergic reaction during medical or dental procedures or anaphylaxis during surgical interventions
Allergies to foods, with special regard to tropical fruits (banana, avocado, papaya, and chestnut)
History of hand eczema and atopic diseases

**NRL indicates natural rubber latex.*

LEGISLATION

In 1997, a joint statement[121] from the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology formulated new guidelines that only powder-free latex gloves should be purchased and used to reduce aeroallergen levels and exposure.

The Food and Drug Administration has begun requiring manufacturers to put allergy warnings on products or packaging containing latex and is regulating the mislabeling of these products as "hypoallergenic."[122] Labels for NRL gloves must include the statement "Caution: This product contains natural rubber latex, which may cause allergic reactions."

In 1995, the American Society for Testing and Materials published standard test method D5712-95 for analyzing protein in natural rubber and NRL products. The Food and Drug Administration is proposing that the recommended limit on water-extractable protein per glove and the actual protein level appear on the label of NRL gloves. The proposed guidance document also recommends that manufacturers of NRL gloves used for surgery or examination limit the amount of water-extractable protein in the gloves to no more than 1200 µg of protein per glove, regardless of glove size. The lowest acceptable amount of water-extractable protein will be limited by the sensitivity of the current American Society for Testing and Materials D5712 test method to 50 µg of protein per gram of NRL product (300 µg of protein per glove for a 6-g glove). The Food and Drug Administration believes that without a more sensitive standard method lower claims would be misleading.

In Europe, no consensus exists for a recommendation to use powder-free gloves only. In Germany, guidelines for the use of NRL gloves were established by the Department of Labor and Social Affairs (Bundesministerium für Arbeit und Sozialordnung) in the Technical Regulations on Dangerous Substances (Technische Regeln für Gefahrstoffe, or TRGS) in December 1997. The TRGS describe the requirements for marketing and use of dangerous substances with regard to safety, occupational medicine, hygiene, and industrial science. TRGS 540 recommends replacing use of powdered NRL gloves with powder-free, low-allergen NRL ones or other suitable gloves. The protein level is required to be less than 30 µg per gram of glove. The standard test method is given in the European Standard EN 455-3 set by the European Committee for Standardization. However, the labeling of NRL protein concentrations on gloves is not required.

ECONOMICS

The issue of NRL allergy bears economic consequences. Addressing occupational latex allergy has direct costs, including the purchase of NRL-free and powder-free gloves, substitution of other hospital equipment, and the cost of installing air filtration and laminar flow changing stations. The costs of implementing a dust-free and NRL-free working environment have been estimated at between $75 000 and $200 000 per year.[123] Indirect costs are worker-related and include job relocation to other areas in the hospital, job change with or without retraining, and additional education for other nonclinical employment.[123] It has been reported that in Canada the employer's cost will be more than Can $200 000 for a registered nurse who has to stop work because of NRL allergy.[124] In Germany, the Employers Liability Insurance Association estimated costs of about $83 000 for each individual with a legally ascertained occupational disease related to NRL allergy (Employers Liability Insurance Association, oral communication, 1997). At present, about 20% of occupational skin diseases and 33% of occupational asthma cases registered by the Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege (the Employers Liability Insurance Association for many health care workers in Germany) are attributed to NRL allergy.

In a recent analysis of 3 health care institutions of different types, the costs of disability due to NRL allergy from continued latex use were compared with the costs of converting the facilities to be latex-safe. It was found that all facilities were likely to benefit economically from becoming latex-safe.[125]

CONCLUSIONS

Because of the elasticity and durability of NRL, products containing

it are widely used at home and in professional occupations, especially in the medical field. For sensitized patients, it is essential to avoid any contact with NRL products. Use of the correct nomenclature and the labeling of NRL-containing products are essential. With current labeling, it is almost impossible to know for certain if a product is safe for patients allergic to NRL. Labeling of "latex" paint is misleading because paint does not contain NRL; here, the term *latex* is a technical description. At the other end of the spectrum, nonlabeling of NRL in glues, ampoule stoppers, and other products may pose an unexpected risk for sensitized patients.

Powder-free latex gloves usually contain lower protein levels than powdered latex gloves. For this reason and because of the potential hazards described herein, a legal ban on the use of powdered latex gloves is expected.

Accepted for publication December 5, 2000.

Corresponding author and reprints: Randolf Brehler, MD, Department of Dermatology, Westfälische Wilhelms Universität, Von Esmarch Straße 56, 48149 Münster, Germany.

REFERENCES

1. Carey AB, Cornish K, Schrank P, Ward B, Simon R. Cross-reactivity of alternate plant sources of latex in subjects with systemic IgE-mediated sensitivity to Hevea brasiliensis latex. *Ann Allergy Asthma Immunol*. 1995;74:317-320.
2. Laxenaire MC, Cottineau C, Neidhardt M, et al. Agents causing anaphylactic shock during anesthesia: third French multicentric survey (1992-1994). *Ann Fr Anesth Reanim*. 1996;15:1211-1218.
3. Frankland AW. Latex-allergic children. *Pediatr Allergy Immunol*. 1999;10:152-159.
4. Hamann CP. Natural rubber latex protein sensitivity in review. *Am J Contact Dermat*. 1993;4:4-21.
5. Jackson EM, Arnette JA, Martin ML, Tahir WM, Frost-Arner L, Edlich RF. A global inventory of hospitals using powder-free gloves: a search for principled medical leadership. *J Emerg Med*. 2000;18:241-246.
6. Karvonen CA. Latex allergy in health care workers: what are the risks? *Otolaryngol Head Neck Surg*. 1999;47:519-525.
7. Kujala V. A review of current literature on epidemiology of immediate glove irritation and latex allergy. *Occup Med*. 1999;49:3-9.
8. Poley GE Jr, Slater JE. Latex allergy. *J Allergy Clin Immunol*. 2000;105:1054-1062.
9. Reddy S. Latex allergy. *Am Fam Physician*. 1998;57:93-100.
10. Smit J, Faut-Callahan M. Current perspectives on the perioperative management of the latex-allergic patient. *CRNA*. 1999;10:117-123.
11. Wakelin SH, White IR. Natural rubber latex allergy. *Clin Exp Dermatol*. 1999;24:245-248.
12. Woods, JA, Lambert S, Platts-Mills TAE, Drake DB, Edlich RF. Natural rubber latex allergy: spectrum, diagnostic approach, and therapy. *J Emerg Med*. 1997;15:71-85.
13. Yunginger JW. Latex allergy in the workplace: an overview of where we are. *Ann Allerg Asthma Immunol*. 1999;83:630-633.
14. Carey AB, Cornish K, Schrank P, Ward B, Simon R. Cross-reactivity of alternate plant sources of latex in subjects with systemic IgE-mediated sensitivity to Hevea brasiliensis latex. *Ann Allergy Asthma Immunol*. 1995;74:317-320.
15. Turjanmaa K. Incidence of immediate allergy to latex gloves in hospital personnel. *Contact Dermatitis*. 1987;17:270-275.
16. Lagier F, Vervloet D, Lhermet I, Poyen D, Charpin D. Prevalence of latex allergy in operating room nurses. *J Allergy Clin Immunol*. 1992;90:319-322.
17. Yassin MS, Lierl MB, Fischer TJ, O'Brien K, Cross J, Steinmetz C. Latex allergy in hospital employees. *Ann Allergy Asthma Immunol*. 1994;72:245-249.
18. Iacobelli AM, McCullough JA, Ownby DR. The prevalence of latex allergy in high risk medical personnel [abstract]. *J Allergy Clin Immunol*. 1993;91:216.
19. Brehler R, Kolling R, Webb M, Wastell C. Glove powder: a risk factor for the development of latex allergy? *Eur J Surg*. 1997;163(suppl 579):23-25.
20. Heese A, Peters KP, Stahl J, Koch HU, Hornstein OP. Häufigkeit und Zunahme von Typ-I-Allergien gegen Gummihandschuhe bei Zahnmedizinstudenten. *Hautarzt*. 1995;46:15-21.
21. Mace SR, Sussman GL, Liss G, et al. Latex allergy in operating room nurses. *Ann Allergy Asthma Immunol*. 1998;80:252-256.
22. Liss GM, Sussman GL, Deal K, et al. Latex allergy: epidemiological study of 1351 hospital workers. *Occup Environ Med*. 1997;54:335-342.
23. Turjanmaa K, Cacioli P, Thompson R, Simlote P, Lopez M. Frequency of natural rubber latex allergy among US operating room nurses using skin prick testing [abstract]. *J Allergy Clin Immunol*. 1995;95:214.
24. Sussman GL, Lem D, Liss G, Beezhold D. Latex allergy in housekeeping personnel. *Ann Allergy Asthma Immunol*. 1995;74:415-418.
25. Tarlo SM, Sussman GL, Holness DL. Latex sensitivity in dental students and staff: a cross-sectional study. *J Allergy Clin Immunol*. 1997;99:396-401.
26. Kibby T, Akl M. Prevalence of latex sensitization in a hospital employee population. *Ann Allergy Asthma Immunol*. 1997;78:41-44.
27. Michael T, Niggemann B, Moers A, Seidel U, Wahn U, Scheffner D. Risk factors for latex allergy in patients with spina bifida. *Clin Exp Allergy*. 1996;26:934-939.
28. Niggemann B, Kulig M, Bergmann R, Wahn U. Development of latex allergy in children up to 5 years of age: a retrospective analysis of risk factors. *Pediatr Allergy Immunol*. 1998;9:36-39.
29. Drexler S, Strehl E, Heese A, Wenzel D, Stehr K. Prevalence and risk factors of type I latex allergy in children with spina bifida. *Monatsschr Kinderheilkd*. 1995;143:998-1002.
30. Kelly KJ, Kurup V, Zacharisen M, Resnick A, Fink JN. Skin and serologic testing in the diagnosis of latex allergy. *J Allergy Clin Immunol*. 1993;91:1140-1145.
31. 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*. 1994;94:53-61.
32. Konz KR, Chia JK, Kurup VP, Resnick A, Kelly KJ, Fink JN. Comparison of latex hypersensitivity among patients with neurologic defects. *J Allergy Clin Immunol*. 1995;95:950-954.
33. Pittman T, Kiburz J, Gabriel K, Steinhardt G, Williams D, Slater J. Latex allergy in children with spina bifida. *Pediatr Neurosurg*. 1995;22:96-100.
34. Porri F, Pradal M, Lemiere C, et al. Association between latex sensitization and repeated latex exposure in children. *Anesthesiology*. 1997;86:599-602.
35. Capriles HA, Sanchez BM, Von SC, Medina JR. Very low frequency of latex and fruit allergy in patients with spina bifida from Venezuela: influence of socioeconomic factors. *Ann Allergy Asthma Immunol*. 1995;75:62-64.
36. Theissen U, Theissen JL, Mertes N, Brehler R. IgE-mediated hypersensitivity to latex in childhood. *Allergy*. 1997;52:665-669.
37. Golden DBK, Hamilton R, Birenberg A, Krehtool B, Haglauer C, Adkinson NF. Latex sensitization in surgical patients [abstract]. *J Allergy Clin Immunol*. 1995;95:157.
38. van der Walle HB, Brunsveld VM. Latex allergy among hairdressers. *Contact Dermatitis*. 1995;32:177-178.
39. Orfan NA, Reed R, Dykewicz MS, Ganz M, Kolski GB. Occupational asthma in a latex doll manufacturing plant. *J Allergy Clin Immunol*. 1994;94:826-830.
40. Tarlo SM, Wong L, Roos J, Booth N. Occupational asthma caused by latex in a surgical glove manufacturing plant. *J Allergy Clin Immunol*. 1990;85:626-631.
41. Zuskin E, Mustajbegovic J, Kanceljak B, Schachter EN, Macan J, Budak A. Respiratory function and immunological status in workers employed in a latex glove manufacturing plant. *Am J Ind Med*. 1998;33:175-181.
42. Pisati G, Baruffini A, Bernabeo F, Falagiani P. Environmental and clinical study of latex allergy in a textile factory. *J Allergy Clin Immunol*. 1998;101:327-329.
43. Carrillo T, Blanco C, Quiralte J, Castillo R, Cuevas M, Rodriguez de Castro F. Prevalence of latex allergy among greenhouse workers. *J Allergy Clin Immunol*. 1995;96(5 pt 1):699-701.
44. Liss GM, Sussman GL. Latex sensitization: occupational versus general population prevalence rates. *Am J Ind Med*. 1999;35:196-200.
45. Turjanmaa K, Makinene-Kiljunen S, Reunala T, Alenius H, Palosuo T. Natural rubber latex allergy: the European experience. *Immunol Allergy Clin North Am*. 2000;15:71-88.
46. Brehler R, Voss W, Müller S. Glove powder affects skin roughness: one parameter of skin irritation. *Contact Dermatitis*. 1998;39:227-230.
47. Heese A. *Allergien gegen Latexhandschuhe*. Landsberg, Germany: Ecomed Verlagsgesellschaft; 1997.
48. von Hintzenstern J, Heese A, Koch HU, Peters KP, Hornstein OP. Frequency, spectrum and occupational relevance of type IV allergies to rub-

ber chemicals. *Contact Dermatitis*. 1991;24:244-252.
49. Heese A, Lacher U, Koch HU, Kubosch J, Ghane Y, Peters KP. Latex allergy: an update. *Hautarzt*. 1996;47:817-824.
50. von Krogh G, Maibach HI. The contact urticaria syndrome: an updated review. *J Am Acad Dermatol*. 1981;5:328-342.
51. Baur X. Allergic reactions to airborne latex allergens. *Allergologie*. 1995;18:568-571.
52. Tomazic VJ, Shampaine EL, Lamanna A, Withrow TJ, Adkinson NF, Hamilton R. Cornstarch powder on latex products is an allergen carrier. *J Allergy Clin Immunol*. 1994;93:751-758.
53. Slater JE. Latex allergy. *J Allergy Clin Immunol*. 1994;94:139-149.
54. Cohen DE, Scheman A, Stewart L, et al. American Academy of Dermatology's position paper on latex allergy. *J Am Acad Dermatol*. 1998;39:98-106.
55. Laurent J, Malet R, Smiejan JM. Latex hypersensitivity after natural delivery. *J Allergy Clin Immunol*. 1992;89:779-780.
56. Gold M, Swartz JS, Braude BM, Dolovich J, Shandling B, Gilmour RF. Intraoperative anaphylaxis: an association with latex sensitivity. *J Allergy Clin Immunol*. 1991;87:662-666.
57. Warshaw EM. Latex allergy. *J Am Acad Dermatol*. 1998;39:1-24.
58. Yagami T, Sato M, Nakamura A, et al. Plant defense-related enzymes as latex antigens. *J Allergy Clin Immunol*. 1998;101:379-385.
59. Mäkinen-Kiljunen S, Turjanmaa K, Palosuo T, Reunala T. Characterization of latex antigens and allergens in surgical gloves and natural rubber by immunoelectrophoretic methods. *J Allergy Clin Immunol*. 1992;90:230-235.
60. Posch A, Chen Z, Raulf-Heimsoth M, Baur X. Latex allergens. *Clin Exp Allergy*. 1998;28:134-140.
61. Breiteneder H, Scheiner O. Molecular and immunological characteristics of latex allergens. *Int Arch Allergy Immunol*. 1998;116:83-92.
62. Posch A, Chen ZP, Wheeler C, Dunn MJ, Raulf-Heimsoth M, Baur X. Characterization and identification of latex allergens by two-dimensional electrophoresis and protein microsequencing. *J Allergy Clin Immunol*. 1997;99:385-395.
63. Posch A, Chen Z, Raulf HM, Baur X. Latex allergens: review of current knowledge. *Pneumologie*. 1997;51:1058-1062.
64. Alenius H, Kalkkinen N, Yip E, et al. Significance of rubber elongation factor as a latex allergen. *Int Arch Allergy Immunol*. 1996;109:362-368.
65. Yeang HY, Cheong KF, Sunderasan E, et al. The 14.6 kd rubber elongation factor (Hev b 1) and 24 kd (Hev b 3) rubber particle proteins are recognized by IgE from patients with spina bifida and latex allergy. *J Allergy Clin Immunol*. 1996;98:628-639.
66. Chen ZP, Posch A, Lohaus C, Raulf-Heimsoth M, Meyer HE, Baur X. Isolation and identification of hevein as a major IgE-binding polypeptide in Hevea latex. *J Allergy Clin Immunol*. 1997;99:402-409.
67. Chen ZP, Cremer R, Posch A, Raulf-Heimsoth M, Rihs HP, Baur X. On the allergenicity of Hev b 1 among health care workers and patients with spina bifida allergic to natural rubber latex. *J Allergy Clin Immunol*. 1997;100:684-693.
68. 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*. 1993;92:690-697.
69. Worth J. Neonatal sensitization to latex. *Medical Hypotheses*. 2000;54:729-733.
70. Woolhiser MR, Munson AE, Meade BJ. Immunological responses of mice following administration of natural rubber latex proteins by different routes of exposure. *Toxicol Sci*. 2000;55:343-351.
71. Shah S, Cawley M, Gleeson R, O'Connor J, McGeady S. Latex allergy and latex sensitization in children and adolescents with meningomyelocele. *J Allergy Clin Immunol*. 1998;101:741-746.
72. Ownby DR, McCullough J. Testing for latex allergy. *J Clin Immunoassay*. 1993;16:109-113.
73. Blanco C, Carrillo T, Ortega N, Alvarez M, Dominguez C, Castillo R. Comparison of skin-prick test and specific serum IgE determination for the diagnosis of latex allergy. *Clin Exp Allergy*. 1998;28:971-976.
74. Mäkinen-Kiljunen S, Turjanmaa K. Laboratory evaluation of latex CAP-FEIA [abstract]. *Allergy*. 1995;26:39.
75. Brehler R, Abrams E, Sedlmayr S. Cross-reactivity between Ficus benjamina (weeping fig) and natural rubber latex. *Allergy*. 1998;53:402-406.
76. Mari A, Iacovacci P, Afferni C, et al. Specific IgE to cross-reactive carbohydrate determinants strongly affect the in vitro diagnosis of allergic diseases. *J Allergy Clin Immunol*. 1999;103:1005-1011.
77. Van Ree R, Aalbertse RC. Specific IgE without clinical allergy. *J Allergy Clin Immunol*. 1999;103:1000-1001.
78. Turjanmaa K, Palosuo T, Alenius H, et al. Latex allergy diagnosis: in vivo and in vitro standardization of a natural rubber latex extract. *Allergy*. 1997;52:41-50.
79. Yunginger JW. Diagnostic skin testing for natural rubber latex allergy. *J Allergy Clin Immunol*. 1998;102:351-352.
80. Hamilton RG, Adkinson NF. Natural rubber latex skin testing reagents: safety and diagnostic accuracy of nonammoniated latex, ammoniated latex, and latex rubber glove extracts. *J Allergy Clin Immunol*. 1996;98:872-883.
81. Hamilton RG, Adkinson NF. Diagnosis of natural rubber latex allergy: multicenter latex skin testing efficacy study. *J Allergy Clin Immunol*. 1998;102:482-490.
82. Turjanmaa K, Reunala T, Räsänen L. Comparison of diagnostic methods in latex surgical glove contact urticaria. *Contact Dermatitis*. 1988;19:241-247.
83. Lahti A, Turjanmaa K. Prick and use tests with 6 glove brands in patients with immediate allergy to rubber proteins. *Contact Dermatitis*. 1992;26:259-262.
84. Bonnekoh B, Merk HF. Safety of latex skin testing in allergic patients. *JAMA*. 1992;267:2603-2604.
85. Yip L, Hickey V, Wagner B, et al. Skin prick test reactivity to recombinant latex allergens. *Int Arch Allergy Immunol*. 2000;121:292-299.
86. Hamilton RG, Adkinson NF. Validation of the latex glove provocation procedure in latex-allergic subjects. *Ann Allergy Asthma Immunol*. 1997;79:266-272.
87. Blanco C, Carrillo T, Castillo R, Quiralte J, Cuevas M. Avocado hypersensitivity. *Allergy*. 1994;49:454-459.
88. Frankland AW. Food reactions in pollen and latex allergic patients. *Clin Exp Allergy*. 1995;25:580-581.
89. Brehler R, Theissen U, Mohr C, Luger T. "Latex-fruit syndrome": frequency of cross-reacting IgE antibodies. *Allergy*. 1997;52:404-410.
90. Blanco C, Carrillo T, Castillo R, Quiralte J, Cuevas M. Latex allergy: clinical features and cross-reactivity with fruits. *Ann Allergy*. 1994;73:309-314.
91. Beezhold DH, Sussman GL, Kostyal DA, Chang NS. Identification of a 46-kd latex protein allergen in health care workers. *Clin Exp Immunol*. 1994;98:408-413.
92. Beezhold DH, Sussman GL, Liss GM, Chang NS. Latex allergy can induce clinical reactions to specific foods. *Clin Exp Allergy*. 1996;26:416-422.
93. Kostyal DA, Hickey VL, Noti JD, Sussman GL, Beezhold DH. Cloning and characterization of a latex allergen (Hev b 7): homology to patatin, a plant PLA(2). *Clin Exp Immunol*. 1998;112:355-362.
94. Sowka S, Wagner S, Krebitz M, et al. cDNA cloning of the 43-kDa latex allergen Hev b 7 with sequence similarity to patatins and its expression in the yeast Pichia pastoris. *Eur J Biochem*. 1998;255:213-219.
95. Jaggi KJ, Hovanec BD, Unver E. Existence of profilin in latex allergen [abstract]. *J Allergy Clin Immunol*. 1995;95:212.
96. Vallier P, Balland S, Harf R, Valenta R, Deviller P. Identification of profilin as an IgE-binding component in latex from Hevea brasiliensis: clinical implications. *Clin Exp Allergy*. 1995;25:332-339.
97. Sowka S, Hsieh LS, Krebitz M, et al. Identification and cloning of Prs a 1, a 32-kDa endochitinase and major allergen of avocado, and its expression in the yeast Pichia pastoris. *J Biol Chem*. 1998;273:28091-28097.
98. Diaz Perales A, Collada C, Blanco C, et al. Class I chitinases with hevein-like domain, but not class II enzymes, are relevant chestnut and avocado allergens. *J Allergy Clin Immunol*. 1998;102:127-133.
99. Alenius H, Kalkkinen N, Lukka M, et al. Prohevein from the rubber tree (Hevea brasiliensis) is a major latex allergen. *Clin Exp Allergy*. 1995;25:659-665.
100. Scheiner O, Aberer W, Ebner C, et al. Cross-reacting allergens in tree pollen and pollen-related food allergy: implications for diagnosis of specific IgE. *Int Arch Allergy Immunol*. 1997;113:105-108.
101. Chen ZP, Posch A, Cremer R, Raulf-Heimsoth M, Baur X. Identification of hevein (Hev b 6.02) in Hevea latex as a major cross-reacting allergen with avocado fruit in patients with latex allergy. *J Allergy Clin Immunol*. 1998;102:476-481.
102. Ortiz JCG, Moyano JC, Alvarez M, Bellido J. Latex allergy in fruit-allergic patients. *Allergy*. 1998;53:532-536.
103. Toci G, Shah S, Al-Faqih A, Beezhold D, McGeady SJ. Oral latex desensitization of health care workers [abstract]. *J Allergy Clin Immunol*. 1998;101(suppl):161.
104. Pereira C, Rico P, Laurento M, Lombardero M, Pinto-Mendes J, Chieira C. Specific immunotherapy for occupational latex allergy. *Allergy*. 1999;54:291-293.
105. Pereira C, Tavares B, Carrapatoso I, Rico P, Lombardero M, Chieira C. Latex immunotherapy: efficacy and safety. In: Program and abstracts of the XVII International Congress of Allergology and Clinical Immunology; October 15-20, 2000; Sydney, Australia.
106. Dahl R, Larsen BB, Jensen EJ. Specific immunotherapy in a latex-allergic patient. In: Program and abstracts of the XVII International Congress of Allergology and Clinical Immunology; October 15-20, 2000; Sydney, Australia.

107. Leynadier F, Herman D, Vervloet D, Andre C. Specific immunotherapy with a standardized latex extract versus placebo in allergic healthcare workers. *J Allergy Clin Immunol*. 2000; 106:585-590.
108. Koch HU. Regulatory aspects of latex allergy (CEN; extractable protein and allergen assays for latex gloves). *Rev Fr Allergol Immunol*. 1997; 37:1201-1210.
109. Palosuo T, Mäkinen-Kiljunen S, Alenius H, Reunala T, Yip E, Turjanmaa K. Measurement of natural rubber latex allergen levels in medical gloves by allergen-specific IgE-ELISA inhibition, RAST inhibition, and skin prick test. *Allergy*. 1998;53:59-67.
110. Jones RT, Scheppmann DL, Heilman DK, Yunginger JW. Prospective study of extractable latex allergen contents of disposable medical gloves. *Ann Allergy*. 1994;73:321-325.
111. Alenius H, Mäkinen-Kiljunen S, Turjanmaa K, Palosuo T, Reunala T. Allergen and protein content of latex gloves. *Ann Allergy*. 1994;73: 315-320.
112. Baur X, Chen Z, Raulf-Heimsoth M, Degens P. Protein and allergen content of various natural latex articles. *Allergy*. 1997;52:661-664.
113. Newsom SWB, Shaw M. A survey of starch particle counts in the hospital environment in relation to the use of powdered latex gloves. *Occup Med*. 1997;47:155-158.
114. Tarlo SM, Sussman G, Contala A, Swanson MC. Control of airborne latex by use of powder-free latex gloves. *J Allergy Clin Immunol*. 1994;93: 985-989.
115. Heilman DK, Jones RT, Swanson MC, Yunginger JW. A prospective, controlled study showing that rubber gloves are the major contributor to latex aeroallergen levels in the operating room. *J Allergy Clin Immunol*. 1996;98:325-330.
116. Allmers H, Brehler R, Chen Z, Raulf-Heimsoth M, Fels H, Baur X. Reduction of latex aeroallergens and latex-specific IgE antibodies in sensitized workers after removal of powdered natural rubber latex gloves in a hospital. *J Allergy Clin Immunol*. 1998;102:841-846.
117. Cremer R, Kleine Diepenbruck U, Hoppe A, Blaker F. Latex allergy in spina bifida patients: prevention by primary prophylaxis. *Allergy*. 1998;53: 709-711.
118. Hayes BB, Afshari A, Millecchia L, Willard PA, Povoski SP, Meade BJ. Evaluation of percutaneous penetration of natural rubber latex proteins. *Toxicol Sci*. 2000;56:262-270.
119. Schwartz HJ. Latex: a potential hidden "food" allergen in fast food restaurants. *J Allergy Clin Immunol*. 1995;95(1, pt 1):139-140.
120. Karathanasis P, Cooper A, Zhou K, Mayer L, Kang BC. Indirect latex contact causes urticaria/anaphylaxis. *Ann Allergy Asthma Immunol*. 1993; 71:526-528.
121. AAAAI and ACAAI Joint Statement concerning the use of powdered and non-powdered natural rubber latex gloves. *Ann Allergy Asthma Immunol*. 1997;79:487.
122. Kohn P. The legal implication of latex allergy. *RN*. 1999;62:63-65.
123. Taylor M. Cost of latex device related occupational illness: workmens' compensation and legal issues. *Eur J Surg*. 1997;163(suppl 579): 49-51.
124. Cameron M. Cost implication of allergy and recent Canadian research findings. *Eur J Surg*. 1997;163(suppl 579):47-48.
125. Phillips VL, Goodrich MA, Sullivan TJ. Health care worker disability due to latex allergy and asthma: a cost analysis. *Am J Public Health*. 1999;89: 1024-1028.