

Management of occupational allergy to natural rubber latex in a medical center: The importance of quantitative latex allergen measurement and objective follow-up

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When our employees began coming to the Occupational Health Service, Dermatology, and Allergy Clinics with symptoms of allergy to rubber gloves 12 years ago, the Mayo Clinic initiated 3 responses. (1) The Allergic Disease Research Laboratory adapted well-established technology to measure both the IgE antibody specific to natural rubber allergens, and by use of this IgE antibody, the allergens in rubber products and in the air of the workplace. (2) The Division of Allergic Diseases and Internal Medicine reviewed the prevalence and severity of the problem. (3) The Clinical Practice Committee appointed a multidisciplinary task force to implement measures to reduce exposure. The 3 sections of this article describe the Mayo Clinic's experience of successful control of this occupational health problem. Use of only gloves with low or undetectable allergen content greatly reduced the concentration of allergen in the work site, reduced the number of new cases of occupational allergy to rubber, and allowed individuals with latex allergy to work at their usual jobs. (*J Allergy Clin Immunol* 2002;110:S96-106.)

Key words: Latex allergens, latex aeroallergens, immunoassay, environmental control, incidence, intervention measures, health care workers

Section A: Evidence-based Environmental Control of Latex Allergens

Latex-sensitized individuals should minimize their exposure to latex products and latex aerosols. Objective measurements of latex allergens are required to identify and avoid latex products with high amounts of extractable allergens and to examine the effects of various interventions to reduce the concentration of latex aeroallergens.

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Abbreviations used

CBER: Center for Biologics Evaluation and Research of the Food and Drug Administration
HEPA: High-efficiency particulate air
NRL: Natural rubber latex
PBS: Phosphate-buffered saline
PTFE: Polytetrafluoroethylene

This article reviews the establishment of immunoassays to measure latex allergens and the use of these data to establish evidence-based environmental control of latex allergens at the Mayo Medical Center. All studies involving human subjects were approved by the Mayo Institutional Review Board.

METHODS

Latex allergen immunoassays

Assay for finished latex products. Phosphate-buffered saline (PBS) extracts (1:5 wt/vol) of several brands of powdered latex gloves were prepared and used to perform skin prick testing in several latex-sensitive individuals.¹ We selected the most skin-reactive extract, which was then concentrated by pressure filtration to approximately 5 mg protein/mL and coupled to derivatized polyacrylamide beads or to cyanogen bromide-activated microcrystalline cellulose particles to prepare a solid-phase allergen.^{2,3} A plasma pool containing specific IgE to latex allergens was prepared by combining defibrinated plasma samples from 5 latex-sensitive individuals. Several natural rubber products were tested by dicing them into small pieces and extracting them 1:5 (wt/vol) in PBS.

The inhibition immunoassay for latex allergens was performed by mixing solid-phase allergen, pooled IgE antibodies, and several threefold dilutions of test analytes, internal standard (internal control), or assay standard. The solid-phase allergen was then sequentially washed, incubated with radiolabeled anti-IgE, and washed again; particle-bound radioactivity was counted in an automatic gamma spectrometer. A raw nonammoniated latex preparation, provided by the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (lot E5 or E8), was used as the assay standard and assigned an arbitrary potency of 100,000 allergy units (AU)/mL. The latex allergen contents of the various analytes were calculated by interpolation from the standard curve. Assay results were analyzed by a computerized version of the parallel-line assay developed by CBER with predetermined criteria for validity.⁴ The sensitivity of the assay was 100 AU/mL; the interassay coefficient of variation was 15%.

Assay for latex aeroallergens. Calibrated area air samplers (1-3 L/s) or personal breathing zone samplers (5 L/min) equipped with polytetrafluoroethylene (PTFE) filters were operated in various

work areas of the medical center for 1 to 10 hours.⁵ Filters were extracted in 0.5 to 1.0 mL of 100 mmol/L phosphate buffer containing 0.2% bovine serum albumin and 0.01% sodium azide. Latex aeroallergens in filter extracts were measured by an inhibition immunoassay similar to that described previously for latex products, except that plastic microtiter trays instead of polyacrylamide beads served as the solid-phase support. The same latex glove extract described previously was coated to the microtiter wells and also served as the assay standard.⁵ Assay results were calculated by using logistic regression and expressed as mass protein per cubic meter of air. The sensitivity of the assay was 1 to 2 ng/m³; the interassay coefficient of variation was 19%.

RESULTS

Latex allergen levels in rubber products

Among consumer rubber products, measurable levels of latex allergen were obtained from rubber balloons and condoms. No allergen was measurable in infant pacifiers or baby bottle nipples. Among medical products, latex allergens were measured in a disposable anesthesia breathing circuit and in many disposable rubber gloves; whereas no measurable allergen was found in intravenous tubing, T-connectors for intravenous sets, or nasopharyngeal airway tubes.²

In 1992 and 1993, 71 lots of boxed disposable latex medical gloves from 22 manufacturers that were in routine use at Mayo Medical Center in Rochester, Minnesota, or at the US Naval Hospital in San Diego, California, were assayed.² The latex allergen levels among different types of gloves are shown in Fig 1. In the case of both sterile surgical gloves and nonsterile examination gloves, powdered gloves usually contained much more allergen than powder-free gloves, whereas chemotherapy gloves contained little extractable allergen. Allergen levels varied by approximately 3000-fold among different brands of gloves.

After this cross-sectional study was completed, a 1-year prospective study was performed from 1993 to 1994 to determine the variability of latex allergen levels in different lots of gloves from the same manufacturers.⁶ Among 10 brands from 9 suppliers, latex allergen levels varied 500-fold in both examination and surgical gloves. The allergen levels showed no consistent trends, increasing over time in 2 brands, decreasing in 2 brands, and remaining unchanged in 6 brands. The allergen contents of gloves from private-label brands, produced and packaged under contract with another manufacturer, were more variable than the allergen contents of gloves from the same manufacturer.

Subsequently, in 1996 and 1997, the allergen contents of latex gloves packaged in sterile kits and trays were measured.⁷ Once again, allergen levels varied by >3000-fold. Allergen levels in gloves from the same kit manufacturer were less variable than allergen levels in gloves from different kit manufacturers. Although the gloves in sterile kits were usually packaged in their own sterile wrapper, some kits contained unwrapped gloves. When these gloves were powdered, the allergen-containing powder could be distributed to drapes or other kit components, theoretically increasing the chances of evoking

an allergic reaction in latex-sensitized persons or medical personnel. Even more disturbing, we found measurable levels of latex allergens in gloves from kits that were labeled as containing nonlatex or synthetic gloves.

On the basis of the findings from these studies, all high-allergen brands of boxed latex gloves were removed from inventory at Mayo Medical Center in Rochester by the end of 1993. Random checks are performed on the gloves presently being stocked to be certain that the latex allergen content in these brands does not increase. Allergy research staff members work closely with personnel in the purchasing department, and vendors wishing us to stock their gloves must first submit samples for allergen testing.

Latex aeroallergens: Quantitation and biologic relevance

In 1992, a cross-sectional study of latex aeroallergen levels in several work areas of the Mayo Medical Center was performed.⁵ Latex aeroallergen concentrations in 11 areas where powdered latex gloves were frequently used ranged from 13 to 208 ng/m³, whereas in 4 areas where powder-free latex gloves or synthetic gloves were used, the levels ranged from 0.3 to 1.8 ng/m³. For individual laboratory technicians, latex aeroallergen exposure ranged from 8.4 to 137 ng/m³, whereas the average allergen exposure among 9 anesthesiologists was 419 ng/m³. In the surgical suites, allergen levels were similar in the conventionally ventilated postanesthesia recovery area (2 to 6 air changes/h), the conventionally ventilated operating rooms (23 air changes/h), and a high laminar flow operating room (225 air changes/h). Particle sizing studies showed that latex allergens were distributed throughout all particle size ranges, with >80% of the recovered allergen being associated with particles >7 μ m in mass median aerodynamic diameter. Latex allergens could be recovered from used laboratory coats and from settled dust in laboratories where powdered rubber latex gloves were being used.

Attempts were made to reduce latex aeroallergen levels in the orthodontics clinic by installing a glove-changing station inside a negative-pressure, high-efficiency particulate air (HEPA)-filtered cabinet.⁵ The latex aeroallergen level was monitored daily for 2 weeks, including both workdays and weekends. Compliance with the use of the changing station was monitored by counting the numbers of gloves discarded inside the cabinet and in other receptacles in the clinic. Before installation of the cabinet, latex aeroallergen levels were undetectable on weekends and ranged from 2.8 to 11.2 ng/m³ on weekdays. After installation of the cabinet, levels ranged from 5.7 to 13.2 ng/m³; the difference was not significant. However, compliance with the use of the glove changing station was only 57%.

In a 51-day prospective study, the effect of a single environmental intervention (ie, substitution of low-allergen, powder-free latex gloves for high-allergen powdered gloves) on reducing latex aeroallergen levels in an operating room was examined.⁸ The results are shown in Fig 2. On days when low-allergen gloves were being used, the mean latex aeroallergen level was 1.1 ng/m³, only slightly above the mean allergen level during weekends

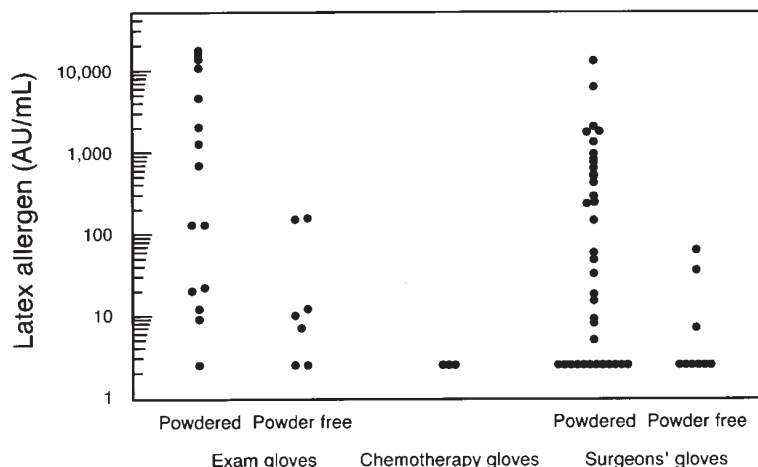


FIG 1. Extractable latex allergens in 1:5 (wt/vol) phosphate-buffered saline extracts of 71 lots of disposable latex medical gloves. AU, Allergy units. (Reprinted with permission from Yunginger JW. Update 18. In: Middleton E Jr, Reed CE, Ellis EF, Adkinson NF Jr, Yunginger JW, Busse WW, eds. Allergy: principles and practice. 4th ed. St Louis: Mosby-Year Book; 1994.)

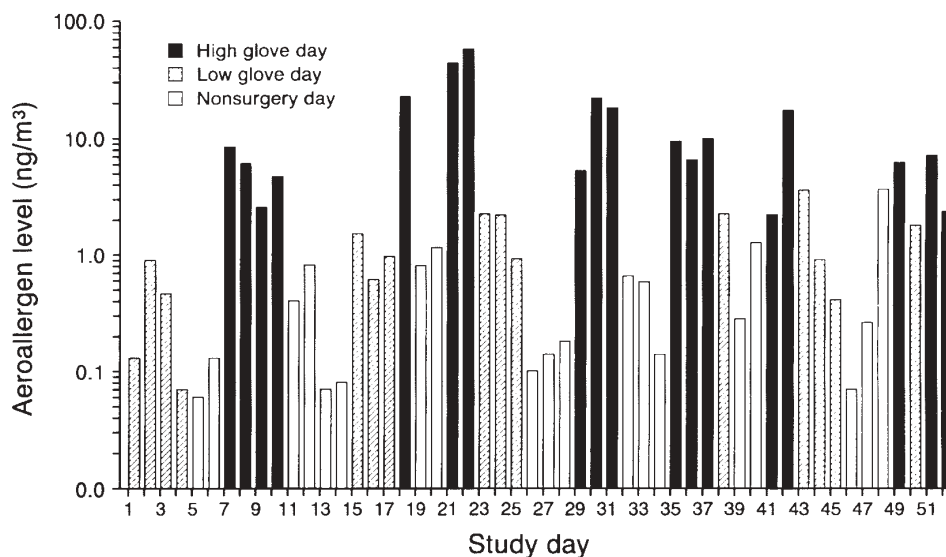


FIG 2. Mean latex aeroallergen levels in a single operating room during a 12-hour sampling period for 52 consecutive days, including nonsurgery days and surgery days when either high-allergen content gloves ("high glove day") or low-allergen content gloves ("low glove day") were in use. (Reprinted with permission from Heilman DK, Jones RT, Swanson MC, Yunginger JY. 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;98:325-30.)

and holidays when the operating room was not in use (0.6 ng/m^3). However, the mean latex aeroallergen level on days when high-allergen gloves were being used was significantly higher (13.7 ng/m^3 , $P < .001$). Moreover, on days when high-allergen gloves were in use, the latex aeroallergen level was significantly correlated with the total number of gloves used during the day ($P = .003$).

To determine the biologic relevance of our aeroallergen measurements, we constructed an inhalation challenge chamber and recruited 11 latex-sensitive volunteers. Subjects were exposed for 60 minutes, in a single-blind fashion, to varying levels of latex allergens (mean, 7600 ng/m^3 ; range, $93\text{--}54,000 \text{ ng/m}^3$) by donning

and discarding high-allergen powdered latex gloves or, as controls, synthetic or low-allergen powder-free latex gloves.⁹ This challenge test was designed to mimic the natural workplace exposure to latex aeroallergens. The latex aeroallergen levels produced were higher than those normally encountered in work areas where powdered latex gloves were in routine use.⁵ Four latex-sensitive volunteers with asthma had reproducible falls in FEV_1 of 20% or greater at cumulative latex aeroallergen doses ranging from $<100 \text{ ng}$ to 1500 ng . The rhinoconjunctivitis and asthma symptom scores reported by the volunteers were significantly lower when the subjects wore HEPA-filtered laminar flow helmets inside the chamber.

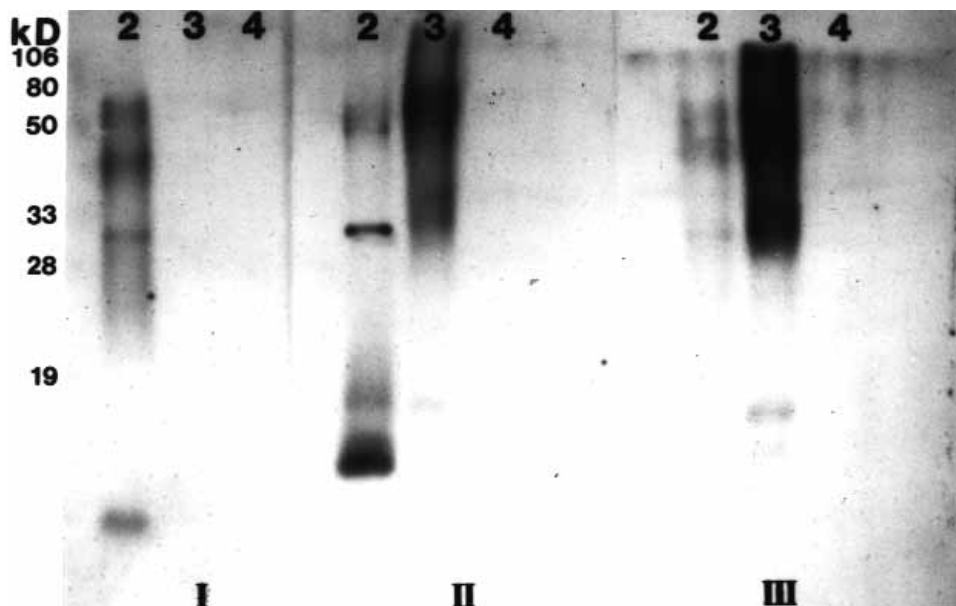


FIG 3. IgE immunoblots with 3 serum samples from individuals sensitive to latex. *Lane 2*, Latex glove extract; *lane 3*, air sample of latex gloves snapped deliberately over an air sampler; *lane 4*, air sample from a laboratory where latex gloves were worn. (Reprinted with permission from Swanson MC, Bubak ME, Hunt LW, Yunginger JW, Warner MA, Reed CE. Quantification of occupational latex aeroallergens in a medical center. *J Allergy Clin Immunol* 1994;94:445-51.)

SUMMARY

This section reviews the establishment and use of inhibition immunoassays to measure either extractable allergens in finished latex products or latex aeroallergens. The highest levels of latex allergens were measured in disposable powdered medical gloves, but the quantity of allergen varied widely among different glove brands. In cross-sectional surveys, aeroallergen levels were highest in work areas where powdered latex gloves were in use. Subsequent prospective studies documented that powdered latex gloves were the major source of latex aeroallergens. Furthermore, use of a HEPA-filtered laminar flow helmet significantly reduced symptoms of rhinoconjunctivitis or asthma in latex-sensitive health care workers deliberately exposed to high-allergen-content latex gloves. Latex aeroallergen levels could be reduced substantially by substitution of synthetic or low-allergen-content powder-free latex gloves for powdered latex gloves.

Section B: Airborne Allergen From Gloves and Other Sources

Most of the allergen is shed into the air from gloves when they are donned or removed. As mentioned in the description of the manufacturing process, a large part of the allergen has been deposited on the inner surface of the gloves in the powder slurry tank.^{10,11} Much of it is carried adsorbed onto the cornstarch powder, but some is dried soluble protein. It is interesting that not all powdered gloves have high allergen content, presumably because of different details in the production line.^{2,12}

During the manufacturing and vulcanization process, the native proteins from the latex sap are aggregated and fragmented, but the allergenic epitopes remain more or less unchanged. Airborne rubber allergen-carrying particles behave like other allergens, and the concentrations at health care delivery sites resemble the concentrations of non-latex allergens in other occupations.

ASSAY METHOD: ADVANTAGES AND PITFALLS

The two critical components of assay of airborne allergens are sample collection and immunochemical analysis. As discussed in the article on industrial hygiene,⁵ sample collection requires a calibrated sampler that can be either an area sampler that collects a large volume of air at the work site or a personal sampler that collects air from the personal breathing zone of the worker. It is critical that the particles be collected on a PTFE filter membrane to allow recovery of the allergens into a small volume of buffer, an important step for adequate analytic sensitivity.

Immunochemical analysis includes an IgE inhibition assay carried out on Immulon plates (Dynex Technologies Inc, Chantilly, Va) coated with a latex reference standard reagent. The air samples are incubated with a serum pool from allergic donors selected to have a high titer of IgE antibody to natural rubber allergens. Inhibition of binding of the IgE to the antigen-coated plate by the allergen in the samples is measured by ELISA or radioimmunoassay and compared with dilutions of the reference standard by the CBER straight line assay criteria.⁴ As Drs Hamilton and Tomazic-Jezic have discussed (see p S47 and p S40 in this issue), the two critical com-

TABLE I. Latex aeroallergen levels (in a laboratory environment) associated with airborne particles of various sizes*

Dp50 (μm)	Latex aeroallergen levels	
	ng/m ³	Total (%)
14	3.0	67
7	0.6	14
4	0.3	7
2	0.3	6.5
<2	0.3	6.5

*Particle size cutoffs (in microns) at 50% collection efficiency for spherical particles with unity mass density at 25°C and 760 mmHg are designated Dp50.

ponents of the immunochemical assay are the reference standard and the selection of the human sera containing IgE antibody. Western blot analysis of the IgE-binding molecules from ammoniated or nonammoniated latex sap, glove extracts, and extracts from airborne particles show interesting differences as a result of denaturation during manufacture. In particular, many of the IgE-binding natural rubber epitopes eluted from air samples migrate with a molecular mass of around 100 kd, although originally they were a part of much smaller proteins⁵ (Fig 3). Analyzing the allergens in glove extracts or air samples is not unlike analyzing raw egg albumin extracted from a ham and cheese omelet. Because Western blot analysis of individual serum samples shows considerable variation in the binding to different rubber proteins, the sera selected for the assay must have a high titer of IgE antibody, and several donors should contribute to the pool to ensure that the assay is comprehensive. A major advantage of the IgE inhibition assay is that it detects the actual allergenic epitopes. One disadvantage is that the sera for the pool require careful selection, and the pool is finite; a new pool must be carefully compared with the old one. Although research laboratories can share and compare pools, the sera are not universally available. Another disadvantage is that measurement of protein content of the reference standards is not absolute, and also calculation of the concentration of these epitopes in air samples in terms of the protein concentration of the reference standard is unavoidably arbitrary. The results of this method are comparable within an assay, but only roughly comparable between different laboratories and between assays for different allergens. Therefore, many investigators prefer to express the results of IgE inhibition assays as "allergy units." We prefer to express the results in mass units, realizing that though the comparisons are only rough, they are the best available. The results of this method are internally consistent but not necessarily comparable between laboratories.

AIRBORNE ALLERGEN AT MAYO: NATURAL RUBBER LATEX AIRBORNE ALLERGEN CONCENTRATIONS AND RECOMMENDATIONS

In 1993 we measured the level of latex allergen at a number of sites in the Mayo Medical Center (see Section A

for details).⁵ In areas where many latex gloves were used, the concentrations ranged from about 14 to about 200 ng/m³. Personal task samples ranged from about 10 ng/m³ up to about 900 ng/m³. Anesthetists had the highest rate of exposure. Since then, assays at other hospitals and dental offices have yielded similar results. In general, the level of airborne allergen correlates with the frequency of donning powdered gloves with high allergen content. Symptoms of rhinoconjunctivitis and asthma very rarely occurred at sites where the concentration was below 10 ng/m³ but did occur where the concentration was 10 to 100 ng/m³. After Mayo adopted a control policy, repeated measurements at these sites were consistently below 10 ng/m³ and usually below 1 ng/m³. Several other studies have confirmed that the level of allergen in hospitals where high-allergen-content gloves are used can range from 10 to 500 ng/m³.^{13,14} It is interesting that 5 years later in 1998, the aeroallergen levels at St Joseph's Hospital in Denver, where powdered gloves were used regularly, were substantially lower (<10 ng/m³) than they had been at similar sites at Mayo in 1993.¹⁵ During this time, the level of allergen in gloves has declined.¹⁶

Particle size, rate of settling, and airway deposition sites

We determined the aerodynamic particle size of the aeroallergen with an Andersen sieve impinger (Andersen Samplers Inc, Atlanta, Ga) (Table I). Two thirds of the allergen is carried on particles >14 μm, and only about 20% on particles that could be expected to remain suspended in the air stream to be deposited in the lungs. This is consistent with the more frequent occurrence of upper airway symptoms in the eyes and nose as compared with symptoms of asthma.

Latex allergen particles settle rapidly from the air. After 24 hours, very little, if any, airborne latex allergen remains in an unused operating room.⁸

Transport of allergen to adjacent rooms

Not all airborne latex allergen arises directly from gloves. Respiratory symptoms can be caused by airborne latex allergen in rooms where high-allergen-content gloves are not used.^{17,18} Allergen in settled dust can be resuspended. Ventilation ducts can become contaminated and disperse the allergen.¹⁹ Allergen can be carried on clothing or bedding from one room to another.

Exposure challenge studies

Two important practical questions that must be answered to make recommendations for control of occupational respiratory allergy to natural rubber are: how much airborne allergen is required to elicit respiratory symptoms? and what are permissible exposure limits for natural rubber latex (NRL)? Two approaches have been adopted in an attempt to answer these questions. One approach is to measure the concentration at the work site and compare it with symptoms. Using this approach, we have estimated that few symptoms occur at levels below 10 ng/m³. Levels approaching 1000 ng/m³ can result in severe asthma. Baur et al^{20,21} in Bochum, Germany,

arrived at a similar but somewhat lower recommended safe value, 0.6 ng/m³.

The other approach has been to challenge patients under controlled exposure conditions.^{9,22-26} This method indicates that a higher value, 100 to >1000 ng/m³, is required to provoke mild symptoms. There are several reasons for this difference, such as bias in case selection toward milder cases for the challenge studies and the priming effect of daily exposure to the allergen. In recommending guidelines, it is appropriate to adopt the lower value. Our recommendation is to consider values below 10 ng/m³ as "low," 10 to 50 ng/m³ as "moderate," and more than 50 ng/m³ as "high." However, presently available technology and information are not sufficient to establish a formal threshold limit value. Nor is it possible to estimate a concentration that can cause initial sensitization.

Exposure during glove manufacture

Not surprisingly, the concentration of airborne allergen is very high at the site of the plant where the dried gloves are stripped off of the formers (Table II).^{11,27} The concentration at this location ranges in micrograms per cubic meter rather than nanograms per cubic meter. The concentrations in many areas of glove manufacturing plants where workers are present are similar to those in locations in medical care facilities where the concentrations are high, but in some locations, are considerably higher. However, the reported prevalence of allergy is no greater in these workers than it is in hospital personnel.²⁸ Allergen carried on powder is not the only source of exposure. Actually, the highest aeroallergen concentration was recorded at a plant producing chlorinated gloves during the auto-stripping process where no workers were present.¹¹ Airborne allergen has also been reported in the plantations when the sap is being harvested from the rubber trees.²⁷

Allergen from rubber balloons

Patients with respiratory allergy to latex have reported symptoms associated with toy balloons, especially when blowing them up. For a science fair project in Rochester, a student brought 30 helium-filled toy balloons into a medical center examining room. The air was sampled for 2 hours. Then the balloons were batted around for 10 minutes. After another 2 hours of sample collection, the balloons were popped, one every 30 seconds, and sampling was resumed for 2 more hours. No allergen was detected while the balloons were quietly present. After they were batted around, the level rose to 4 ng/m³. After they were popped, it rose further to 20 ng/m³.

Outdoor allergen from rubber tires

Whether airborne particles from rubber tires along the highway can be a source of exposure is controversial. Studies from Los Angeles and Denver have demonstrated the presence of allergen in tire particles and air samples collected along freeways.²⁹⁻³¹ Our laboratory has not been able to confirm these results; however, we found that extracts from dust from a truck tire retreading plant (car tires are made from synthetic rubber) contained

TABLE II. Airborne concentrations of NRL allergens within glove production facilities

Location	Average concentrations (ng/m ³)	
	Plant 1	Plant 2
Auto-stripping	23,679	4,162
Hand-stripping	17,647	3,140
Dry tumblers	4,947	5,847
Beading	536	278
Compounding	232	858
Tunnel dryer	81	886
QC packing	27	52
Protein lab	13	NT
Office area	14	26

NT, Not tested.

hardly any protein and only trace amounts of allergen as determined by the IgE inhibition assay. Nor in the solid phase did tire dust extract bind IgE from our NRL-sensitive patients. The air of this plant, though dusty, did not contain detectable NRL allergen. Thus, it seems likely that truck tire rubber, unlike dipped products, contains little if any allergen. The positive results from outdoor air sampling are more likely due to cross-reactions with pollen and other plant proteins.

Comparison of latex with other occupational allergens

The airborne concentration of latex allergens in health care settings lies within the range of other occupational allergens (Table III).³² It is significant that the highest occupational allergen concentration we have measured is egg proteins in egg-cracking plants, where egg aeroallergen levels are tens of thousands an order of magnitude higher. As a result of this heavy exposure, up to 30% of the workers in these egg-cracking plants have occupational asthma; often, the asthma is severe and poorly reversible. Although eating eggs is a recognized cause of anaphylaxis, anaphylaxis from airborne exposure has not been reported among these workers, and they can eat eggs without reactions. Nor has anaphylaxis been reported in patients with asthma caused by other occupational exposure.³³

SUMMARY

Airborne allergen from gloves and other sources can cause dose-related occupational respiratory disease. These allergens can be measured by the same technology used for other airborne allergens. In this assay, calibrated volumetric air samplers, PTFE filter membranes, and IgE inhibition immunoassay are used. In areas of hospitals and other health care locations where large numbers of high-allergen-content gloves are used, the concentration ranges from tens to hundreds of nanograms per cubic meter. Concentrations <10 ng/m³ rarely cause symptoms. The concentrations required to cause sensitization are still unknown. In glove manufacturing plants, the concentration is much higher, up to 20,000 ng/m³ at the point where the gloves are removed from the formers. Toy rubber balloons are an additional source of low to moderate indoor

TABLE III. Maximum concentration of occupational aeroallergens in various locations

Agent	Approximate concentration (ng/m ³)	Location
<i>Aspergillus fumigatus</i>	1,200	Quiet dairy barn in winter
<i>Lepidoglyphus destructor</i> (storage mite)	12,000	Quiet dairy barn in winter
Cow epithelium	16,000	Quiet dairy barn in winter
Mouse urinary protein	60	Animal quarters
Rat urinary protein	1,200	Animal quarters
Guinea pig urinary protein	17,000	Animal quarters
Egg albumin	360,000	Egg-processing plant
Papain	5,000	Meat-processing plant
Esperase	180	Detergent-packing plant
Soybean dust	30,000	Outdoors, Port of New Orleans
Soybean dust	10,000	Outdoors, Barcelona, Spain
Latex natural rubber protein	1,000	Surgical suite
Latex natural rubber protein	23,000	Glove manufacturing plant

concentrations. Whether dust from tires on highways carries allergen is controversial. Rubber tires are not a significant source of allergen, if they are a source at all.

Section C: Long-term Clinical Follow-up of Health Care Workers With Latex Allergy

Health care workers are among several groups believed to be at risk for development of latex allergy. Other groups include patients with spina bifida or other urogenital abnormalities, atopic subjects, latex industrial workers, individuals who have had multiple surgeries or who have preexisting hand dermatitis, and possibly patients with fruit allergy.³⁴ Latex allergy as a clinical entity is defined as having evidence of IgE-mediated sensitivity as determined by either skin prick testing or latex-specific IgE measurement in combination with symptoms on latex exposure.^{1,35,36} Health care workers are at risk for latex allergy from frequent contact with disposable rubber gloves, particularly those that are powdered and of high protein content.^{14,37} The risk of latex allergy is proportional to the number of these gloves used.³⁸⁻⁴⁰ The outcome of clinical latex allergy appears to depend on several variables including the natural history of latex allergy and whether it is possible to modify incidence, symptoms, or degree of sensitivity to latex through intervention measures. Other outcome issues involve cost-benefit analysis of intervention measures and the potential to rehabilitate health care workers with latex allergy when necessary.

The natural history of latex allergy is difficult to determine because many subjects with latex allergy undertake some degree of self-modification of occupational latex exposure when symptoms begin. Many voluntarily relocate or avoid specific locations that cause symptoms or change the type of gloves they use on their own. The best estimate of natural history can be derived from hospital and institutional reports before the implementation of any intervention measures. These reports have described the spectrum of symptoms including contact urticaria, rhinoconjunctivitis, asthma, and occasionally, anaphylax-

is.⁴¹ Prevalence statistics of latex allergy in health care workers vary widely, depending on the occupational group studied and testing methods. Questionnaire surveys show that up to 53% of health care workers report some degree of symptoms associated with the use of rubber gloves.⁴² When sensitization to latex is defined as a positive skin prick test response or latex-specific IgE measurement, the rates vary from 5% to as high as 17%.^{38,40,43} Clinical latex allergy, defined as an index of specific IgE sensitivity to latex in the presence of symptoms, most likely has a lower prevalence. There is surprisingly little information on the prevalence of clinical latex allergy. Turjanmaa³⁸ screened health care workers with a scratch-chamber test and then skin tested those who had positive results and found a prevalence of 4.5%. Vandenplas et al⁴⁴ similarly found a 4.7% rate of positive skin prick test responses and symptoms in health care workers. In our cohort of 187 latex-allergic health care workers at the Mayo Clinic, we have calculated a prevalence rate of latex allergy of 1.6% based on an estimate that 12,000 workers regularly use gloves.

Intervention measures for latex allergy are specific activities that are targeted toward either reduction of latex allergen exposure or host modification of the allergic response. Reduction of allergen exposure consists of attempts to reduce or eliminate symptoms in workers who have latex allergy, and secondly, to prevent sensitization in workers not yet sensitized to latex. Latex-allergic health care workers also require their own medical care, and the methods of creating latex-safe environments for dental and surgical procedures are well described.⁴⁵ Modification of the host response is the attempt to lower the degree of sensitivity among individuals who are allergic to latex by reducing or eliminating the allergen exposure over time, theoretically allowing spontaneous diminution of sensitivity, or possibly modifying the host response by means of immunotherapy with latex allergen protein.

METHODS

Intervention measures at the Mayo Clinic were initiated after the formation of a multidisciplinary task force in 1990. After an initial assessment of the scope and potential magnitude of the problem, an action plan was developed.⁴⁶ This plan included the development of assays for measurement of latex allergen protein in latex products

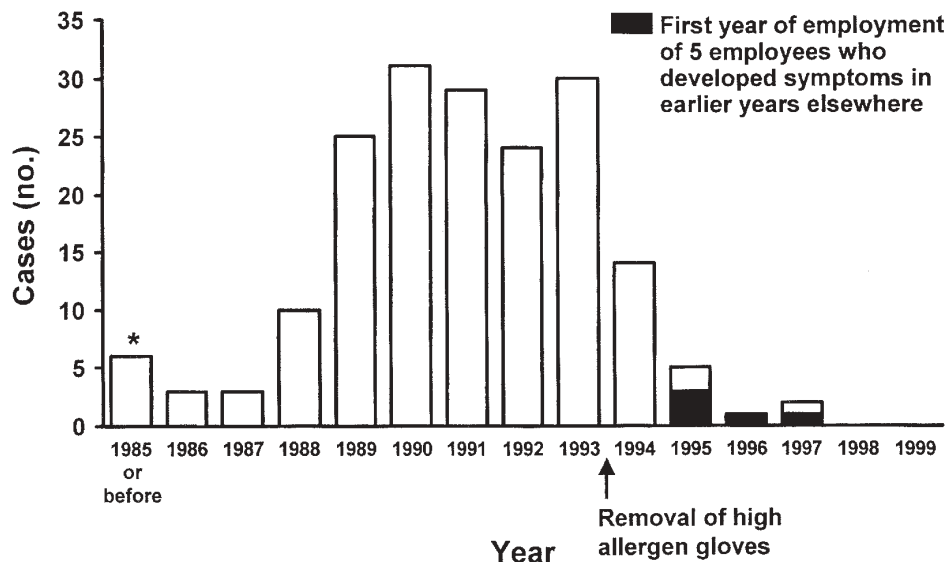


FIG 4. The number of new-onset cases of latex allergy at the Mayo Clinic between the years 1985 and 1999 is shown. *Six cases were in 1985 or earlier, with the earliest in 1971. Five latex-allergic subjects who transferred to the medical center in the years 1995 to 1997 had onset of their symptoms in earlier years elsewhere. Using an estimated 12,000 employees who regularly use gloves per year, we calculated crude incidence rates of 0.15% for the listed years before the 1993 interventions and 0.027% for the years after 1993.

and aeroallergen concentrations in varied medical center environments.^{2,5} It was also necessary to develop a skin testing extract with which to test persons believed to have latex allergy.¹ Policies of personal latex avoidance were developed for latex-allergic health care workers, as well as for latex-allergic patients. Using latex product allergen quantification information, we then obtained centralized control of all glove purchasing and allowed only latex gloves that had low or undetectable allergen content to enter the medical center work environments. No other latex allergen reduction measures were undertaken. Educational measures were also implemented to provide rapid access to information for any health care workers with suspected latex-related symptoms and to provide a mechanism of tracking and reporting such that information from the medical center work areas could be relayed back to the Latex Allergy Task Force. Finally, subsequent follow-up measurements of latex product allergen content and work area aeroallergen concentration were performed for ongoing quality management.⁴⁷ These measures were implemented in their entirety on December 31, 1993.

RESULTS

Fig 4 shows the number of new cases of latex allergy at the Mayo Clinic during the years 1990 to 1999. We identified 187 Mayo Medical Center employees with latex allergy as determined by skin prick testing and a history of type I symptoms on exposure to latex. The majority also underwent serum-specific IgE measurement. We determined a date of onset of symptoms by several mechanisms. During the interview and initial examination, health care workers were asked to recall the earliest year that symptoms with latex exposure began. We also reviewed medical records for the earliest date that latex allergy was listed on the allergy section of the patient-provided information forms, the earliest year that latex allergy was diagnosed by a Mayo Clinic physician, or in the cases of transfer from other medical centers, the first

year that the patient was employed at the Mayo Clinic, even if onset of symptoms was earlier. Fig 4 shows the number of new-onset cases per year from 1985 to 1999. There were very few new cases of latex allergy before 1985, followed by a striking rise in new cases starting in 1988. Using an estimate of 12,000 workers per year who regularly use gloves, we calculated a crude incidence rate of 0.15% for the years 1985 to 1993. As shown in Fig 4, the number of new-onset cases of latex allergy at the Mayo Clinic fell abruptly after the December 1993 intervention measures were implemented, from a rate of 0.15% to 0.027%, suggesting that the medical center-wide modification of the latex glove supply was effective in reducing the number of new cases of latex allergy.

Latex-allergic health care workers reported at our institution had all experienced symptoms with latex exposure at work, and several had problems with surgical and dental procedures and delivery of infants.⁴⁸ A review of the medical records of 187 latex-allergic health care workers in December 2000 showed that after the December 1993 intervention measures were implemented, these workers collectively made 299 urgent care visits and underwent 60 endoscopic procedures, 294 dental and surgical procedures, and 34 infant deliveries without any symptoms or complications that could be attributed to latex allergy. In 3 instances one of these persons presented to the urgent care center because of urticaria, rhinoconjunctivitis, or asthma related to latex exposure outside of the workplace. Exposure items in these individuals were toy balloons in two and a rubber raincoat in one. Further, there has been a dramatic reduction in reports of work-related symptoms by employees, and there have been no new reports of change of work area

because of latex allergy to the Employee Health Department since the onset of the intervention measures.

DISCUSSION

Data on incidence of latex allergy, like data on prevalence, vary according to the methods used. Kajala⁴⁹ calculated an incidence rate of latex allergy of 1.9 per 10,000 health care workers per year as determined by questionnaires. Jolanki et al⁵⁰ estimated the incidence to be between 1.3 and 11.8 per 10,000 employed worker-years as determined by skin prick testing. Turjanmaa et al⁵¹ reported an incidence rate of 0.12% as determined by skin prick testing of patients scheduled for surgery. Sussman et al⁵² found an incidence rate of 1% in health care workers who were followed up for a period of 1 year.

We have shown that removal of latex gloves of high allergen content from our medical center alone can reduce the number of new cases of clinical latex allergy. Further studies with this cohort of patients are under way to assess the effect of this intervention measure on symptom reduction and size of skin prick test reaction to a latex skin test extract.

Little other information exists as to whether incidence rates can be modified by latex avoidance methods. Sussman⁵² removed powdered latex gloves from designated areas of a hospital and compared the symptoms and skin test results with those of areas in which powdered latex gloves were used. In the powder-free areas, there was probably a reduction of new cases of latex sensitivity. Two skin test conversions in the powder-free group were subsequently thought to be either negative or weak positive responses that rapidly converted to negative responses.⁵³ Regardless of whether these were borderline positive skin test responses, the 2 subjects in the powder-free group had no symptoms and thus did not have clinical latex allergy. This study also suggested that the incidence of new cases of latex allergy after changing to powder-free gloves as the only environmental modification is probably very low.

Several other studies involving latex-sensitive health care workers suggest that symptoms can also be reduced with environmental modification. The data suggest that when powdered latex gloves are removed from a medical environment, symptoms from latex aeroallergen are prevented. In 1994 Tarlo et al¹⁴ successfully demonstrated that a latex-sensitized laboratory technician had no symptoms when coworkers changed from powdered latex gloves to powder-free latex gloves and latex aeroallergen levels were undetectable without any other environmental modification. Although symptoms were not assessed in their study, Heilman et al⁸ found that when latex gloves were replaced with powder-free or very low-allergen-content gloves, with no other modifications, aeroallergen levels in operating rooms were reduced to levels similar to those seen in operating rooms on days when nonlatex gloves were used or on days when surgery was not performed. Laoprasert et al,⁹ by exposing health care workers with latex-induced asthma to large amounts of latex aeroallergen in an exposure chamber, showed that symp-

toms could be prevented by having the subjects use low-allergen powder-free gloves, nonlatex gloves, or a HEPA filter to remove latex aeroallergen. Rather than substituting powderless non-latex gloves, Vandenplas et al³⁷ were able to prevent symptoms in allergic health care workers by exposure challenge with low-protein latex gloves.

Our study was not designed to assess the effect of reducing latex allergen exposure on the degree of sensitivity to latex. Allmers et al⁵⁴ examined skin test response size and latex-specific IgE measurements in sensitized employees before and after removal of powdered latex gloves from work areas. Seven health care workers had positive skin prick test responses and symptoms with latex exposure. Over the observed year, all had reduction in their skin test response size and latex-specific IgE values. There was a reduction of symptoms with the removal of powdered gloves, as well as a reduction in medication use to treat symptoms.⁵⁴ When we repeated air sampling in areas where the concentrations had been high before intervention, we found less than detectable levels (3 ng/m³). Hamilton et al⁵⁵ reported that 14 of 16 subjects with positive serology for latex and 6 of 18 subjects with a positive latex skin prick test response had reduced values after 10 to 15 months of latex avoidance. It is obvious that further work in this area is needed, and now that several cohorts of health care workers have been identified, whether these results can be confirmed will be of interest.

We also did not assess outcome with regard to modification of the host response. Immunotherapy has been successful in modification of the host response for many identified allergens, resulting in reduction of both rhinoconjunctivitis and asthma symptoms.⁵⁶ Although they are experimental and require further study, 3 reports suggest that immunotherapy might be successfully performed in patients with latex allergy. Pereira et al⁵⁷ immunized a single patient to a dose of 40 µg. At the patient's request, the build-up phase was performed by rush immunotherapy. One systemic reaction occurred during the build-up phase, but generally, the series was well tolerated. The latex skin prick test response size was reduced, and the patient tolerated a glove use challenge. Toci et al⁵⁸ reported on the treatment of 3 subjects with oral immunotherapy to a dose of 2 mg. The treatment was well tolerated, and there was a reduction of latex skin prick test response size in all. Leynadier et al⁵⁹ performed a double-blind, placebo-controlled study for 1 year with 9 patients in the treatment group and 8 in the placebo-treated group. Those in the treatment group had significantly reduced eye and nasal symptoms but no asthma symptoms. Also, medication scores decreased, and conjunctival reactivity to latex allergen challenge was reduced.

There are conflicting reports as to whether intervention measures, particularly as they relate to change in glove purchasing patterns, are cost-effective. It has been estimated that to convert an entire dental school to use of powder-free latex gloves would cost almost \$14,000 per year, a 32% increase.⁶⁰ By contrast, when low-allergen gloves were substituted for powdered high-allergen gloves at the Mayo Clinic at the end of 1993, there was a cost saving of

about \$200,000 per year.⁴⁶ Phillips et al⁶¹ calculated that when costs of disability of health care workers were taken into consideration, it would be cost-effective to change to nonlatex gloves at a medical center. The cost-effectiveness was based on a break-even point of a disability rate of 1% for complete disability and 2% for partial disability.

In conclusion, these studies suggest that latex-allergic health care workers, although they need to use nonlatex glove alternatives for their personal use, can continue to work in their medical environments if their coworkers use either nonpowdered latex gloves, latex gloves with the lowest protein content, or latex gloves of very low allergen content. With these modifications, symptoms from latex aeroallergen exposure are prevented, and new cases of latex allergy are reduced.^{8,14,37,46,52,54,55,60} Allergists are doing health care workers a disservice if they inform patients that they cannot return to work or are disabled because they are allergic to latex. Latex allergy should be a manageable condition if proper environmental control measures are taken. Several groups have published data on glove allergen content, and medical centers and hospitals can use this information to modify purchasing patterns accordingly. Collectively, our data and those of others suggest that selecting only nonpowdered, lowest protein, or lowest allergen content latex gloves will effectively reduce aeroallergen concentrations in working environments and symptoms in allergic workers^{37,54,55} and that eliminating latex gloves with high allergen content will reduce the incidence of new-onset cases of latex allergy.

SUMMARY

The outcome of health care workers who have become sensitized to NRL is dependent on several variables. Policies for a latex-safe working environment are essential for reducing the number of workers who become sensitized, as well as for controlling or eliminating symptoms in those who are allergic. These policies should include institution-wide intervention measures aimed at controlling the amount of latex allergen protein exposure and efforts to modify the individual's sensitivity to latex protein.

We sought to determine whether eliminating latex gloves of high allergen content from our entire medical center would be effective in reducing the number of new cases of clinical latex allergy.

Using latex allergen quantification methods, we eliminated all latex gloves with high allergen content from our institution by December 31, 1993, and substituted latex gloves that had an allergen content that was below detectable limits in our assay. No other medical center-wide latex allergen reduction measures were undertaken. By means of skin prick testing, we identified 187 latex-allergic health care workers at the Mayo Medical Center from 1989 to 1999. By interviewing the health care worker or reviewing the medical records, we were able to identify a year of onset of symptoms in all subjects. Crude incidence rates were calculated based on an estimate that 12,000 workers per year regularly use disposable medical gloves on a daily basis. In grouping the number of new

symptomatic cases by year, we could determine whether intervention measures implemented at the end of 1993 were effective in reducing the number of new cases.

Intervention measures resulted in a dramatic reduction in onset of new symptomatic cases of latex allergy at our institution after 1993. There has also been a reduction in the number of workers presenting to the allergy, dermatology, or employee health divisions because of symptoms related to latex allergy. Further, a review of the medical records of these health care workers revealed that collectively, since the implementation of medical center-wide intervention measures, they had 294 dental and surgical procedures, 299 urgent care visits, 60 endoscopic procedures, and 34 infant deliveries, all without any complications or symptoms related to latex allergy.

Elimination of latex gloves with high allergen content from an entire medical institution and substitution of latex gloves with an unmeasurable allergen content can alone successfully reduce the number of new cases of latex allergy.

These studies were made possible through the efforts of many colleagues at the Mayo Medical Center, including Mark Swanson, Richard Jones, Dr Mark Warner, Dr Loren Hunt, Dr Dann Heilman, Dr Nan Laoprasert, the nurses in the Allergy Testing Laboratory, the members of the institutional Latex Allergy Task Force, and several latex-sensitive employees who contributed plasma samples or volunteered for the challenge studies described.

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