

The puzzle of latex allergy: some answers, still more questions

As evidence for significant prevalence of natural rubber latex (NRL) allergy has accumulated, investigation of the nature of this problem has burgeoned over the last 5 years. The depth and extent of this effort is impressive: nearly 50 abstracts were presented during the most recent annual meetings of the American College of Allergy and Immunology and the American Academy of Allergy and Immunology—and important information on both the clinical manifestations and underlying immunologic mechanisms of NRL allergy has been elucidated. In this issue of the *Annals*, three additional significant contributions address the nature of NRL allergens. Despite these real advances, many crucial questions regarding the origin, etiology, epidemiology, diagnosis, and management of NRL allergy remain unanswered.

ORIGIN OF NRL ALLERGY

For the better part of this century, NRL products have been used in a wide range of medical applications due to the unique combination of strength, flexibility, elasticity, tear resistance, and barrier qualities of natural rubber. Until recently, complications were thought limited to contact dermatitis due to irritant phenomena and sensitivity to certain rubber additives. Only isolated reports of phenomena consistent with NRL IgE-mediated sensitivity appeared before 1984.

The perceived acute increase in incidence in cases of NRL allergy since 1988, expressed most dramatically in the incidents of fatal anaphylaxis occurring during barium enema procedures and intra-operative anaphylaxis among children

with myelodysplasia, is a real, unanticipated, global phenomenon. There is no evidence demonstrating a "silent epidemic" in prior years and the origin of this phenomena remains unknown. The abrupt rise in incidence suggests the effect of some change in rubber processing or manufacturing. No such agent has yet been identified, although cornstarch dry lubricant has been considered a possible cause of latex sensitization. Studies confirm that cornstarch powders bind NRL antigen and appear to provide carriage for measurable levels of latex in ambient circulating air.¹⁻⁴ Since use of cornstarch in glove manufacture began before 1980, the temporal link between its widespread utilization and the onset of NRL sensitization is tenuous.

The rapid increase in rubber demand due to "universal precautions" coupled with the removal of a major supplier, Liberia, due to internal conflicts in that nation, disrupted NRL markets in the late 1980s. It has been suggested that insufficient washing and leaching of the rubber product by new and inexperienced manufacturers led to distribution of products appreciably higher in latex antigen content that in turn led to extensive NRL sensitization. The report by Jones et al in this issue of the *Annals* showing high levels of extractable antigen in gloves from both major and minor producers in samples taken as late as 1993, vitiates the claim that NRL sensitivity is due only to past actions of some marginal producers.⁵

It may well be that no one factor is causal, but rather it is heightened levels of cumulative exposure via direct contact of skin and mucous

membranes and by aerosol inhalation that explains the dramatic rise in NRL allergy in both patients and health care workers. This rationale, however, both fails to offer a tenable explanation for fatal anaphylaxis associated with barium enemas in low-risk patients and fails to account for the complete absence of sensitization of highly exposed patients, such as children with spina bifida, during the years prior to the current epidemic. Furthermore, while the appearance of NRL allergy does begin after the advent of universal precautions in the USA in 1987, reports from Europe do not describe such helpful sequential behavior. Already by early 1987, a 5% prevalence in one group of operating room personnel was found in Finland, an observation that does not seem well explained by a "cumulative exposure" hypothesis.⁶

ETIOLOGY

Significant research efforts directed toward identifying the antigens in NRL have shown that crude ammoniated and nonammoniated latex extracts appear to have similar antigenic repertoires. Using a variety of methods, over 15 polypeptides have been identified that bind IgE antibodies from individual or pooled sera obtained from sensitive patients; a majority of descriptions include both a 14-kD and larger 30-kD binding protein.⁷ Czuppon and co-workers identified this 14-kD protein as rubber elongation factor (REF), and on the basis of its ability to generate symptoms and inhibit IgE binding, have proposed REF as the major allergen of NRL.²

This claim appears controversial in light of multiple other findings

that emphasize the complex nature of NRL as an antigen source.⁸ While previous work has demonstrated sensitive and consistent results of IgE antibody binding tests using either crude or finished latex extract sources, the work of Alenius and colleagues which appears in this issue of the *Annals* demonstrates that more detailed analysis of glove extract reveals marked variance in the constituent antigens expressed; indeed, some gloves have no detectable 14-kD binding protein.⁹⁻¹⁰ Further, it has been shown that finished glove extracts may express at least one additional antigen not found in crude latex.¹¹ The significance of this protein and its source—whether due to protein cleavage occurring during vulcanization, emergence of a previously concealed antigen, or formation of a neo-antigen—remains to be determined.

Observations that serologic specificities have identifiable characteristics for different patient groups and that group findings may vary according to country of origin, make it likely that more than one antigenic protein has immunologic relevance.¹²⁻¹⁴ Whether the mode of sensitization, ie, via mucosal or skin contact, or via aerosol inhalation, may create a characteristic pattern of IgE response awaits further investigation.

EPIDEMIOLOGY

On the basis of skin test results, the prevalence of NRL allergy has been estimated at a range of 10% to 17% among health care workers with latex exposure in studies from several countries and 40% to 65% of children with myelodysplasia.^{7,15-17} Given these findings, there is a striking and disappointing lack of adequate epidemiologic studies observing the longitudinal trends and natural history of NRL allergy. It is generally accepted that along with the groups named above, patients who have undergone multiple operations or instrumentations, and individuals who have chronic latex

exposure either by virtue of glove use or work in the rubber industry are also at high risk.

The large percentage of children with spina bifida with both atopy and NRL allergy has suggested the interesting possibility of a unifying neuro-immunologic abnormality underlying these disorders. Preliminary reports correlating the risk of latex sensitization in children with spina bifida with the number of previous major medical procedures raise the alternate possibility that the presumed excess of cases among this group is due only to their very early and high level of exposure.¹⁸ Studies utilizing a case-control group of patients with similar NRL mucosal exposure occurring early and frequently thereafter are needed to clarify these issues.

The risk for NRL allergy among health care workers appears to vary with the frequency and intensity of exposure. Among those presumably most exposed, operating room personnel, prevalence rates are higher, but other employees, such as housekeepers, may have substantial rates of sensitization—8% of tested housekeeping personnel were prick skin test positive at a Toronto hospital according to a recent preliminary report.¹⁹ A prior history of inhalant atopy is frequently found and should be considered a risk factor based on the weight of previous reports. Other reports have highlighted the frequent history of contact dermatitis in glove wearers that precedes the onset of IgE sensitization.^{20,21} Some individuals, who have used gloves uneventfully for years, may experience a rapid "march" of symptoms commencing with contact dermatitis and progressing to systemic reactions. The recent finding that most latex proteins do not appear to pass through intact skin is consistent with speculation that disruption of the skin barrier by contact dermatitis may facilitate passage of sensitizing NRL proteins.²² The substantial base rate of contact dermatitis in this popu-

lation requires careful longitudinal epidemiologic studies for confirmation.

Cross-reactivity between NRL proteins and certain foods, particularly banana, avocado, and chestnut have been appreciated for some time. More recently, the scope of cross-reactive foods has widened to include fruits such as kiwi, papaya, fig, passion fruit, nectarine, plum, cherry, melons, and tomato and the vegetable, celery. In this issue of the *Annals of Allergy*, Blanco and co-workers report some cases in which severe food reactions, including anaphylaxis, preceded the onset of recognizable NRL reactions.²³

The existence of NRL allergy among individuals with no identifiable risk factors has also been noted in a variety of reports. Ownby and co-workers found that 2.5% of a large group of blood donors were strongly seropositive.²⁴ The source of NRL exposure in these individuals is uncertain, but the ubiquity of NRL antigen was emphasized by work of Williams and colleagues who demonstrated high numbers of rubber particles capable of inhibiting latex-specific IgE in urban air samples.²⁵

DIAGNOSIS

The clinical variability in presentation of NRL allergy is notable; perhaps the most striking feature is the exquisite degree of sensitivity and severe reactions experienced by a substantial proportion of sensitized individuals. Contact urticaria and angioedema can result from casual contact with donning, powder residue on furniture surfaces or clothing; respiratory difficulties may be elicited by a "snap test"; and anaphylaxis has resulted from exposure to trace amounts of latex in intravenous tubing or from needle passage from a latex port.^{26,27} Natural rubber latex allergy should be considered in all cases of presumed topical anesthetic reactions, especially those occurring in dental offices where mucosal exposure to NRL

antigen is considerable. Suspected allergic reactions to parenteral drugs or any case of intra-operative anaphylaxis may well be due to inadvertent latex exposure in a sensitive patient. It does not appear unreasonable to include NRL allergy in the differential diagnosis of any unexplained anaphylaxis or severe food reaction.

The clinical evaluation of NRL allergy has received a very complete treatment recently by Kelly et al.²⁸ Their recommendations of sequential use of serologic, use, and prick skin tests appear to offer reasonable degrees of safety, diagnostic sensitivity, and specificity with the caveat that negative prick or serologic testing done shortly after an acute latex reaction might reflect a "false negative" such as that encountered during the "refractory period" after a bee sting.

Previous reports of anaphylactic reactions resulting from prick skin tests emphasize the extreme degree of sensitivity generated in some patients and have led to justifiable reticence in pursuing skin test diagnosis. Where initial serologic and use testing is non-revealing, commercial non-standardized extracts for prick testing available outside of the United States (eg Bencard, Stallergenes) have proved effective and safe diagnostic agents, especially if initial testing is done with a 10- or 100-fold dilution. American allergists who wish to prick skin test should follow experimental protocols.

The significance of a positive prick or serum test in the absence of systemic symptoms is as yet unknown. In the context of a history of contact dermatitis or urticaria, or of a previous reaction to a cross-reactive foods, these findings must be regarded as a marker of potential NRL reactivity.

In patients with only contact dermatitis or urticaria, patch testing with a standard battery of rubber additives may provide useful diagnostic information.

MANAGEMENT

Antigen avoidance remains the cardinal principal guiding management of NRL allergy. In their study in this month's *Annals*, Jones and colleagues report measurements of extractable antigen from a variety of glove and other NRL sources.⁵ It appears reasonable to hope that procurement decisions based on this information will reduce workplace antigen exposure and thus may lead to a decrease in the incidence of sensitization. Since only minute amounts of antigen can elicit severe reactions in sensitive individuals, any product containing NRL must still be considered as a potential "trigger," especially when in contact with mucosal surface or coated with dry powder lubricant.

Sensitive patients need to be aware of the multitude of sources of NRL exposure at home, at work, and while receiving medical and dental care. Since this problem is of recent origin, patient requests regarding this subject may be met with disbelieving or superfluous reactions at work or even by some medical providers; it is essential that supervising physicians be available to intercede on a patient's behalf.

Treatment of patients with NRL allergy requires careful adherence to procedures designed to avoid inadvertent exposure. Appropriate signage, labeling, and identification are mandatory. Alternative NRL-free devices must be available and in certain areas—the emergency room and on crash carts—should be used as exclusively as possible. The considerable difficulties attendant on maintaining lists of NRL-free supplies should end with the advent of promised FDA regulations mandating content labeling of medical supplies. All medical and dental procedures performed on these patients should take place "first of the day" in a carefully cleaned room as free of NRL-containing devices as possible. Multi-use vials and preloaded syringes that utilize rubber-topped plungers are but two additional ex-

amples of NRL sources implicated in anaphylactic events.

The utility of pre-operative regimens patterned after those used successfully in the prophylaxis of radiocontrast dye reactions remains unclear. Reports of anaphylactic reactions occurring despite such treatment has resulted in a waning of initial enthusiasm.^{29,30} In the absence of case-control studies, it is impossible to determine whether pretreatment results in reduction of acute responses. Given the low rate of pretreatment complications, however, its use among highly sensitive patients would appear an elective, but justified, procedure.

Due to the possibility that glove-associated irritant dermatitis or allergic contact dermatitis may favor the onset of IgE sensitization, affected employees should be encouraged to switch brands of gloves. Patch testing sensitivity profiles for rubber additives may suggest particular types of gloves to avoid. Local care, including topical moisturizers, corticosteroids, and periods of glove avoidance may be helpful. New symptoms of contact urticaria or of allergic rhinoconjunctivitis strongly suggest NRL allergy; complete avoidance of NRL gloves is mandatory. To minimize aerosol exposure, geographic areas where only non-powdered NRL products are used may need to be established. Care must be taken to ensure that filtration and ventilation systems provide adequate fresh/recirculating air ratios and avoid recirculating air from areas with high levels of latex aerosols (eg, operating rooms).

More severely affected employees may present with typical symptoms of occupational asthma, complaints of hyperreactive airway phenomena similar to reactive airways dysfunction syndrome (RADS) or anaphylaxis. Many of these highly skilled employees are understandably resistant to change duties even in the face of severe symptoms and thus provide significant dilemmas for their physicians in terms of disabil-

ity issues. Peak flow monitoring or spirometry before, during and after work place exposure may provide useful data to guide decisions. Symptomatic progression despite personal and institutional measures of avoidance discussed above suggests that assignment or even career changes may be necessary.

Natural rubber latex-allergic patients should be cautioned concerning the consumption of foods known to cross-react, particularly if these are not consumed regularly. It would appear safer for those with a history of anaphylaxis to avoid these foods entirely. Individuals presenting with a history of anaphylactic or severe reactions to these same foods must be considered at risk for future reactions to NRL and appropriate avoidance measures should be followed.

With the emergence of natural rubber latex, a substance in common usage, as a potent antigen that frequently causes sensitization, we are confronted with an apparently new medical problem.

We can hope that research of this phenomenon will yield not only specific information about this particular allergic reaction, but will broaden our appreciation concerning the nature and causes of allergic sensitization. Meanwhile it is the duty of the allergy/immunology community to take an active role in educating our physician colleagues, allied health workers, and others with occupational exposure on the risks, clinical presentations and management of this disorder. In the coming months, an educational slide program funded by a grant to the American College of Allergy and Immunology from Becton-Dickinson Corporation will be made available for allergists and other specialists for use in educational programs designed to meet this new challenge.

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