

Endotoxin: a role in latex allergy?

The advent of latex allergy as a generalized and even epidemic problem is a singular event. There appears to be no obvious precedent for the transformation of a seemingly innocuous product in common usage into a potent type I allergen. Inasmuch as latex gloves are the most widely distributed of all regulated medical devices, provide direct contact to both health care workers and patients, and are sources of measurable aeroallergen levels in healthcare facilities, suspicions have increasingly focused on latex gloves as the primary source of allergen exposure.

Latex gloves were in general use in autopsy procedures in Germany already by the latter half of the 19th century. In Britain and America patents for latex surgical gloves were obtained by Thomas Forster in 1878. The true impetus for wide adoption of gloves came only after Joseph Bloodgood, partner of the noted surgeon William Halsted, convincingly demonstrated their benefit in a double-blind study.¹

Early gloves were heavy and thick and were re-used following autoclave sterilization, a technique that probably served both to denature and to leach extractable allergen from glove surfaces. In the early part of this century, problems with stickiness and difficulties with donning led to the introduction of talc powder dry lubricant, a practice later discarded with the appreciation of its propensity to cause granuloma and intraabdominal adhesions.

As a result of these perceived shortcomings, two major changes in latex glove manufacture and marketing occurred some time after the mid century. First, cornstarch was introduced as a substitute dry powder lubricant beginning at about the mid-century mark. The aim of this change was to eliminate the incidence of powder-re-

lated operative complications, a goal only incompletely realized. On the other hand, cornstarch absorbs latex proteins and thus provides a ready vehicle for aerosolization of latex proteins. The importance of this property was not appreciated until recently when several studies showed that significant levels of latex aeroallergen present in medical facilities were closely related to the use of high allergen latex gloves.²⁻⁶ Second, disposable, thinner, and consequently "more responsive" gloves, introduced in the 1960s, replaced the older heavier gloves. The gamma-radiation sterilization techniques used in the manufacture of these new gloves obviated the need for repeated washing and autoclaving, but at the same time ensured consistently high levels of exposure to both patients and healthcare workers in any facility supplied with high allergen gloves.

Most attempts to explain the epidemic of latex allergy ascribe the cause to increased exposure to latex, especially due to more frequent and prolonged glove use, which resulted from the institution of universal precautions. Even agreement about the central role of high allergen gloves fails to explain much of the "Why?" of latex allergy and leaves many troubling questions unanswered. As pointed out in an earlier *Annals* editorial,⁷ the temporal relationship of latex sensitization agrees poorly with the initiation of universal precautions. Evidence for significant sensitization in healthcare workers in Europe antedates universal precautions by several years. Many of the cases of fatal anaphylaxis associated with latex retention balloons used in barium enema procedures occurred in patients lacking an extensive prior occupational or medical latex exposure due to universal precautions. Further, even in pa-

tient groups with significant historical and on-going exposure, such as the children with spina bifida, identifiable allergic reactions began rather abruptly about 1987 in North America, suggesting a possible contribution of another factor or factors in the pathogenesis of these reactions.

The nature of the allergic response to latex proteins raises several additional questions. It has been appreciated for some time that some substances, such as cat dander and ragweed pollen, have an intrinsic propensity to elicit an atopic immune response even at low doses. In the large majority of cases, allergic responses to these substances has been restricted to only one or two distinct constituent allergenic proteins, such as Fel d. 1 in cat dander and Amb a. 1 in ragweed pollen. The nature of this atopic response does not generalize to other constituent proteins even after long-term exposure. In contrast, allergy to latex rubber commonly involves sensitization to multiple constituent proteins of natural latex rubber (Table 1).⁸⁻¹⁰ Presumably, these proteins were always present in latex products and medical devices, hence, it is not immediately evident why any one of these should have become so allergenic after many years of uneventful use. It is even less obvious why not just one, but so many of these constituent proteins now provoke atopic responses. Even more puzzling is the fact that different groups of patients appear to be sensitized to different groups of latex proteins.¹¹⁻¹⁴ If provocation of atopic responses is due only to increased glove use, why should responses stratify depending on whether glove exposure occurs as a patient or as a glove wearer?

Changes in rubber harvesting, aging, and processing have all been advanced

as possible malefactors contributing or responsible for the recently recognized antigenicity of latex rubber, but the case against any or all remains at best circumstantial. In some respects, the allergic response to latex is reminiscent of that of penicillin which has both a "major" and several "minor" protein determinants. Inasmuch as penicillin allergy may result from haptenation of the drug by other proteins, there has been ongoing speculation that either a contaminant or chemical used in the manufacture of latex might play the role of a "hapten" in the generation of allergic responses. The experiences with L-tryptophan and with contaminated olive oil in Spain (which resulted in eosinophil-myalgia syndrome in the former instance and a poorly defined connective tissue syndrome in the latter) demonstrate that even trace contamination of ingestants can result in the stimulation of a vigorous immune response. There is, however, no obvious historical precedent for such responses to be primarily expressed as atopic phenomena as in the case with latex rubber. Alternatively, the capacity of several chemicals used in rubber manufacture, such as thiuram and mercaptobenzothiazole, to generate immunologically specific cell-mediated reactions raises thus far unanswered questions regarding their potential contribution to atopic sensitization to latex proteins.

In this issue of the *Annals*, Williams and Halsey present intriguing and provocative evidence implicating a new suspect—endotoxin.¹⁵ Endotoxin possesses several properties that appear relevant for a potential role as co-factor in the pathogenesis of latex allergy and occupational asthma. Endotoxin has pro-inflammatory properties and can elicit significant toxic reactions such as fever and rhinoconjunctivitis on its own. Endotoxin in irradiated latex gloves has previously been reported as a cause of contact dermatitis.¹⁶ Of more interest is its ability to act as mitogen that can stimulate B cells to divide and begin to make and secrete immunoglobulin and as an adjuvant for IgE responses in some mu-

Table 1. Allergen Designation by the International Union of Immunological Societies (IUIS)

Allergen	Common Name	Molecular Weight, kD	% Reactivity
Hev b 1	Rubber Elongation Factor (REF)	14.6, 58	~22%
Hev b 2	β -1-3-gluconase	34–36	?
Hev b 3	prenyltransferase	24–27	?
Hev b 4	microhelix	100, 110, 115	?
Hev b 5	acidic protein	16–24	~62%
		20 (6.01)	
Hev b 6	hevein protein	14 (6.03)	~60%
		5 (6.02)	
Hev b 7	patatin homologue	43–46	~23%

rine systems. These effects might serve as plausible explanations for the presence of IgE antibodies directed at such a wide range of latex constituent proteins found in many patients. Aerosolized endotoxin increases airflow obstruction and bronchial hyperreactivity in cases of occupational asthma. The levels of endotoxin generated by snapping multiple gloves as determined by Williams and Halsey appears in the range of that reported in other cases of pulmonary disease resulting from chronic endotoxin exposure. The presence of endotoxin may help explain the complaints of persistent cough and bronchial irritability voiced by many latex-allergic workers which seem at times out of proportion to the degree of airflow obstruction found in formal measurements. Furthermore, the recent report by Michel and co-workers demonstrating that the severity of asthma in mite sensitive asthmatic patients correlates with the concentration of endotoxin in inhaled house dust strengthens the argument that endotoxin may potentiate latex antigen-induced occupational asthma.¹⁷

The preliminary nature of this communication requires tempering interest with caution and demands completion of a substantial amount of additional work to confirm this hypothesis. In this regard, the authors detract from the strength of their arguments by making unnecessary claims. Endotoxin effects appear notable only in people with pre-existing allergies to relevant allergens.^{18,19} Thus the assertion that "powder is most likely relevant . . . not as a carrier of allergens, but as a growth source for bacteria" appears both pre-

mature and ultimately unconvincing especially in view of the substantial body of research indicating its central role in the carriage of latex as an aeroallergen.^{5,20,21} The authors contend that endotoxin reactions are important because they can explain the "high number of latex skin tests [that] are positive in individuals with negative clinical histories." We are unaware of this problem with latex skin testing.^{22,23}

In an industrial setting, endotoxin exposure may be fairly constant over the work shift of four to eight hours. Most healthcare settings offer a substantially different occupational environment where ventilation and air quality are better. Endotoxin liberation is not constant but more likely varies with the types and antigen levels of gloves used and the frequency of glove change. Additional data concerning the amounts of endotoxin present in hospitals and operating rooms must be collected and shown to reach significant levels. We need to have a much better idea of how much of the glove-associated endotoxin gets into the air, how this varies with glove use, and how much inhaled endotoxin reaches areas where it can excite a reaction. Dose-response challenges of endotoxin with and without latex allergen will help delineate their various contributions to pulmonary responses.

While the adjuvant and pro-inflammatory effects of endotoxin seen in in vitro murine systems are of interest, they cannot be assumed uncritically to have direct relevance for human in vivo responses. In humans, endotoxin is not a B cell mitogen, its ability to act as an immune adjuvant is unknown,

and its ability to augment atopic responses remains to be demonstrated. The nature, extent and length of exposure required to generate these putative effects must be carefully worked out.

Abundant reasons have already been outlined in the American College of Allergy, Asthma, and Immunology position statement issued in 1995 for restricting procurement and use of latex gloves to low allergen, non-powdered, latex gloves.²⁴ Elimination of powder from surgical gloves has been estimated to reduce the incidence of post-operative wound granuloma by as much as 5%.²⁵⁻²⁸ Latex aeroallergen levels fall to nearly undetectable levels when only non-powdered low allergen gloves are used.^{5,29} Although cost considerations are frequently cited as an objection to adapting such policies, one major midwest medical center achieved a substantial savings in glove expenditures after instituting appropriate programs designed to reduce latex aeroallergen levels.³⁰

Williams and Halsey provide an additional valuable service by underlining still another reason to avoid use of powdered high allergen gloves—endotoxin contamination. In their series, the five most allergenic gloves had a mean level nearly 400 times the level of allergenic protein of the five least allergenic. This same group of high allergen gloves also contained about 16 times the amount of endotoxin. Inasmuch as no data concerning endotoxin levels are commonly available, it appears prudent to continue to use glove antigen level data as a guide to glove purchases. This information, updated as new data are available, can be obtained from the latex home page located on the American College of Allergy, Asthma & Immunology website (<http://allergy.mcg.edu>).

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