REPORT OF A SCIENTIFIC MEETING

Carol A. Hirshman, M.D., Editor

International Latex Conference: Sensitivity to Latex in Medical Devices November 5–7, 1992 Baltimore, Maryland

In 1993, the U.S. Food and Drug Administration (FDA) will issue regulations requiring manufacturers of latex-containing medical devices to label their products, advising of their "natural latex" content. In addition, the FDA will bar manufacturers from using the term "hypoallergenic" in connection with latex gloves. These two FDA actions were the tangible outcomes of the International Latex Conference: Sensitivity to Latex in Medical Devices, held in November 1992 in Baltimore, Maryland. Cosponsored by the FDA's Center for Devices and Radiological Health (FDA-CDRH), the Centers for Disease Control (CDC), and the National Institute of Allergy and Infectious Diseases. The conference brought together health-care workers, scientists, manufacturers, and government officials to discuss the growing problem of allergic reactions to latex-containing medical devices. More than 400 participants from 15 countries met for 3 days to review the chemistry, immunology, and regulatory issues raised by latex allergy.

Representatives of the rubber industry provided background on the manufacturing of latex products. Thomas Pendle, of the Malaysian Rubber Producers' Research Association, described living latex in the rubber tree, a cytoplasmic fluid that contains hundreds of proteins, including enzymes that are involved in the biosynthesis of the rubber molecules. Rubber producers concentrate the latex, and the total protein content is estimated to be between 1.4% and 1.7% of the weight of the concentrated latex. According to Zakaria Karim, of Revertex Malaysia, only about 0.5% of the total proteins in this latex concentrate are water-extractable. Water-extractable proteins have been implicated in the production of type 1 hypersensitivity or anaphylactic reactions. To reduce the amount of water-extractable proteins by up to 50%, manufacturers employ various leaching treatments. However, Theodore Wendt, Ph.D., of Johnson and Johnson Medical, Inc., cautioned that the total protein content is not analogous to either anaphylactic or allergic risk. Indeed, during the manufacturing process, chemicals used as sterilizers, accelerators, or antioxidants can provoke type 4 hypersensitivity reactions or contact dermatitis.

Traditionally, manufacturers have used the term "hypoallergenic" for gloves that have reduced levels of chemical residues capable of triggering allergic contact dermatitis. Specifically, F. Alan Andersen, Ph.D., of the FDA-CDRH's Office of Device Evaluation, noted that the FDA allowed glove manufacturers to make a claim of hypoallergenicity if the gloves passed the modified human Draize test for dermal toxicity. Andersen emphasized that this "hypoallergenic" label never referred to a glove's potential for causing an anaphylactic reaction.

Thomas Tillotson, of the Tillotson Rubber Company, hypothesized about the sudden increase in the incidence of latex allergy in the late 1980s despite its recognition as a clinical entity as early as 1979. In 1987, the CDC published its recommendations for universal precautions, which led to a worldwide shortage of gloves by 1988. Hundreds of new glove factories opened abroad, and a worldwide glut of 10 billion gloves occurred by 1989. Lengthy periods of product storage ensued as the industry worked off this inventory. This unprecedented combination of new factories, inexperienced in glove manufacturing, and unusual storage periods may have lead to the increased sensitization of individuals to latex.

Robert Hamilton, Ph.D., an immunologist at the Johns Hopkins University's Asthma and Allergy Center, discussed the diagnostic methods available to test a patient for latex allergy. These include *in vivo* skin provocations such as skin-prick testing for type 1 IgE-mediated hypersensitivity and patch testing for type 4 cell-mediated reactions. *In vitro* serologic tests include IgG/IgM/IgA immunoassays examining exposure to latex and latex-specific IgE immunoassays showing sensitization to latex. Serologic testing has been limited by its clinical sensitivity. Hamilton found a sensitivity ranging from 67% to 82% for latex-specific IgE radioallergosorbent tests in a series of 64 patients who experienced systemic reactions to latex. *In vivo* tests have been limited by both the lack of a standardized, FDA-approved skin-testing reagent and the potential for adverse reactions from skin-testing for latex allergy. Kevin Kelly, M.D., an allergist at the Medical College of Wisconsin, reported nine adverse reactions, including five anaphylactic reactions, from skin-testing 118 patients for latex allergy.

B. Lauren Charous, M.D., an allergist at the Milwaukee Medical Clinic, suggested a relationship between latex-induced contact dermatitis and systemic anaphylaxis. Charous observed that a large percentage of health-care workers in his practice who developed systemic reactions from latex and were positive for latex-specific IgE antibody have a history of localized reactions including contact dermatitis and contact urticaria syndrome. In a murine model, contact sensitization with a variety of chemicals has engendered antigen-specific IgE antibodies. Therefore, contact dermatitis in atopic individuals may portend future systemic allergic sensitivity. Kristiina Turjanmaa, M.D., a dermatologist at Tampere University Hospital, in Finland, agreed with Charous, noting that 75% of the 57 latex-allergic health-care workers she has seen have a history of atopy and hand dermatitis. Gordon Sussman, M.D., an allergist at the University of Toronto, disagreed with Charous, stating that, of the 101 latex-exposed physicians he has studied, ". . . the presence or absence of hand sensitivity to latex gloves did not predict latex allergy."

Besides atopic health-care workers, meningomyelocele patients were identified as being at particular risk for latex allergy. Michele Pearson, M.D., of the CDC's Hospital Infections Program, examined reports of anaphylactic reactions during general anesthesia from 29 U.S. children's hospitals. She concluded that meningomyelocele patients with a history of allergies, asthma, and multiple surgical procedures were at increased risk of developing intraoperative anaphylaxis from latex. Kelly stated that spina bifida patients were at a 1,000-fold greater risk of intraoperative anaphylaxis from latex than were patients without spina bifida. He quantified their rate of anaphylaxis as 1 in 12.6, using 1990 statistics from the Children's Hospital of Wisconsin.

Complete epidemiologic data on the incidence of anaphylaxis from latex may be unobtainable, according to Sharon Dillard, of the FDA-CDRH's Office of Compliance and Surveillance. Though manufacturers must submit to the FDA any information they receive suggesting that a death or serious injury resulted from one of their products, health-care workers are not subject to any mandatory reporting requirements. Between October 1, 1988, and September 30, 1992, the FDA received 1,118 reports of adverse reactions to latex, including 15 anaphylactic fatalities. All 15 fatalities were caused by latex components of barium-enema retention catheters. The FDA received no reports of intraoperative deaths from anaphylaxis to latex.

Evidence was presented at the conference that latex can act as an aeroallergen. Kelly cited three patients who experienced anaphylaxis by merely walking into a room where latex gloves were stored. Furthermore, he stated that up to 70% of the latex-allergic health-care workers in Milwaukee continue to have inhalational symptoms despite avoiding latex products in their environment.

Beyond avoiding the use of latex gloves when caring for latex-allergic patients, specific recommendations provided for anesthesiologists in creating a "safe" operating-room environment were contradictory. James Taylor, M.D., a dermatologist at the Cleveland Clinic, suggested manually ventilating the lungs of all latex-allergic patients until a ventilator with a non-latex bellows could be obtained. Robert Holzman, M.D., an anesthesiologist at Boston Children's Hospital, indicated that washing the rubber bellows of a ventilator prior to use was sufficient. John Yunginger, M.D., an allergist at the Mayo Clinic, presented data that washing the disposable anesthesia rebreathing bag reduced the amount of extractable latex allergen from 20 U/ml to nondetectable levels (<10 U/ml). Yunginger also examined saline aliquots withdrawn from a 10-ml rubber-stoppered multiple-dose vial. Only after 40 punctures of the rubber stopper could he detect a latex allergen level (19 U/ml) in the saline.

The issue of pharmacologic prophylaxis for latex-allergic patients was raised during a panel discussion of physicians. All panel members agreed that there was no scientific evidence to suggest that pretreatment with steroids and antihistamines could prevent type 1 IgE-mediated anaphylactic reactions from latex.

The meeting concluded with the identification of three goals for future investigations: (1) the description of the exact chemical nature of the latex allergen(s), (2) the determination of the latex-concentration thresholds for inducing sensitivity and eliciting reactions, and (3) the development of standardized latex extracts for diagnostic tests.

Eric Lon Shampaine, M.D.
Assistant
Department of Anesthesiology and Critical Care Medicine
The Johns Hopkins University School of Medicine
The Johns Hopkins Hospital
600 North Wolfe Street
Baltimore, Maryland 21287