

A previous study of the prevalence of sensitization to aeroallergens in California found mesquite to be the second most commonly positive tree pollen skin prick test result, in 36.4% of those tested (olive tree pollen was most common, at 42.4%).¹ Another study specifically in Southern California found mesquite to be the most common positive pollen skin prick test result, at 42% (in the same study, olive tree was 28%).² The authors of this second study found positive RASTs, but only if the mesquite pollen extract was concentrated, and positive nasal challenges in those with positive skin tests. They acknowledged that the nearest mesquite trees were 50 miles away from the study site, but found pollen resembling mesquite in local air samples. Published reports of air sampling in San Diego, Calif, show olive tree pollen but no mesquite pollen.³ Another possible route of sensitization is inhalation of mesquite wood smoke or the ingestion of food cooked over burning mesquite wood.⁴ However, regardless of the route or method of sensitization, if a positive skin test result to mesquite represents the presence of IgE antibody, this antibody should be demonstrable *in vitro*. The frequency of isolated positive skin test results to mesquite pollen, and their lack of confirmation by ImmunoCAP, in the present study suggest that these positive skin test results represent non-IgE-mediated reactions. A previous animal study demonstrated "...the histamine-releasing activity of extracts of ... pollens in the skin of guinea pigs which are not sensitized with the pollens. ..."⁵ The pollen extract most capable of causing this direct mast cell degranulation was mesquite. Mesquite pollen also contains unique peptidases (peptidase IIms),⁶ which could possibly alter mast cell biology.

In summary, despite the fact that there is olive tree pollen but no mesquite pollen in the air in San Diego, as many people have positive skin test results to mesquite pollen as to olive tree pollen, and mesquite comes up as an isolated positive skin test result much more often than olive tree. Most such isolated positive skin tests to mesquite pollen are not substantiated by a positive *in vitro* specific IgE (ImmunoCAP) to mesquite pollen. We conclude that when mesquite tree pollen results in an isolated positive skin test result, it likely represents a false-positive result. In some patients, this allergen extract apparently has the ability to cause direct mast cell degranulation. Whether by an IgE-mediated mechanism or by direct mast cell degranulation, in areas of the country or world where mesquite pollen is actually present in the air, contact could presumably result in mast cell-mediated symptoms.

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The Chief, Navy Bureau of Medicine and Surgery, Washington, DC, Clinical Investigation Program sponsored this study (S-03-084) as required by NSHSBETH 6000.41B. The views expressed in this article are those of the author and do not reflect the official policy or position of the Department of the Navy, the Department of Defense, or the US Government.

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doi:10.1016/j.jaci.2004.05.011

Latex allergens are not detectable in reconstituted smallpox vaccine or vaccine vial stoppers

To the Editor:

In December 2002, plans to immunize military personnel, first responders, health care workers, and public health workers against smallpox were released. The Centers for Disease Control and Prevention (CDC) developed smallpox vaccination guidelines stating that smallpox vaccine should not be administered to individuals with a history of latex allergy because of possible release of latex allergens from rubber vial stoppers into smallpox vaccine (<http://www.bt.cdc.gov/agent/smallpox/vaccination/pdf/smallpox-vax-clinic-guide.pdf>; accessed May 2004). Concerns have been expressed about the potential for latex allergen exposure from natural rubber stoppers in vaccine vials, including smallpox vaccine, and the possibilities of latex sensitivity after vaccine administration. Because no information is available regarding the actual composition of smallpox vaccine vial stoppers (natural rubber vs synthetic rubber) and because we were unable to find any data relating to latex allergy and smallpox vaccine, we investigated whether such latex allergens could be identified in reconstituted smallpox vaccine.

Smallpox vaccine (Dryvax; Wyeth Laboratories, Marietta, Pa) is provided as a lyophilized multidose vaccine (100 dose vials) that must be reconstituted. The vaccine diluent is a 50% glycerol and 0.25% phenol solution that contains trace amounts of neomycin, streptomycin, polymyxin B, and chlortetracycline. The vaccine is ideally stored at 2°C to 8°C and, once reconstituted, should be used within 15 days. Reconstitution is performed by drawing up the vaccine diluent provided with the vaccine and injecting the diluent into the vaccine vial after cleaning the vial stopper with an alcohol wipe and allowing it to dry.

After obtaining permission from the CDC to use only one recently outdated and reconstituted vial of smallpox

vaccine, we tested the vaccine for evidence of measurable latex allergens. We tested the following: (1) one sample of reconstituted smallpox vaccine (Dryvax; control no. 4008284); (2) one sample of reconstituted and expired rubella and mumps single-dose virus vaccine that contains approximately 25 µg of neomycin and trace amounts of sorbitol and hydrolized gelatin (Biavax II; Merck, West Point, Pa; lot no. 0968H, expiration March 23, 1999); and (3) a diluent for live virus vaccines (Merck; lot no. 1467E, expiration August 2002). In addition, we prepared PBS extracts of vial stoppers from smallpox vaccine, rubella and mumps vaccine, and rubella and mumps vaccine diluent. Individual stopper extracts were prepared by dicing them into 10–12 small pieces and extracting them 1:4 (weight/volume) in PBS for 2 hours at 37°C and then overnight at 4°C. The resulting extracts were isolated by means of centrifugation and tested for latex allergens with the reconstituted vaccines and diluent.

Smallpox vaccine, rubella and mumps vaccine, the diluent for virus vaccine, and the 3 stopper extracts were tested in an inhibition immunoassay for latex allergens, as previously described.¹ The solid-phase allergen was prepared by covalently coupling a natural rubber latex glove extract to cyanogen bromide-activated microcrystalline cellulose particles. Briefly, the assay was performed by mixing solid-phase allergen (0.5 mL), latex-specific IgE antibodies pooled from several individuals with latex allergy (1:5 dilution, 0.1 mL), assay buffer (0.35 mL), and several 3-fold dilutions of latex standard (FDA E8 latex reference; arbitrarily assigned an allergen potency of 100,000 allergy units [AU]/mL) or test analytes (vaccines, diluent, or stopper extracts; 0.5 mL) overnight at room temperature. The solid-phase latex allergen was then isolated by means of centrifugation, washed with assay buffer, and incubated with radiolabeled anti-IgE.

After identical incubation and washing steps, the solid-phase complex was counted in an automatic gamma spectrometer. The latex allergen contents of the various analytes were calculated by means of interpolation from this standard curve. The sensitivity of the assay in our laboratory is 100 AU/mL.

We were unable to detect quantifiable levels of latex allergen in any analyte, including reconstituted vaccines, vaccine diluent, and stopper extracts from vaccine and vaccine diluent vials. An internal standard (positive control) included in the same assay was markedly positive at 79,000 AU/mL.

Despite warnings advising against the use of smallpox vaccine in persons with a history of latex allergy, we were unable to find any data concerning allergic reactions to latex in human subjects or studies identifying the presence of latex allergens in smallpox vaccine or diluent. Our limited study failed to find evidence of measurable latex allergens. We suspect that the general warning against administering smallpox vaccine to such persons is empiric; that is, given the use of a “rubber” stopper in smallpox vaccine vials, there is legitimate concern about the possibility of latex contamination of the vaccine.

In this study a solid-phase inhibition immunoassay was used to detect latex allergens. However, intradermal skin testing is at least 100-fold more sensitive than inhibition immunoassays for the detection of latex allergens.² Using vial stoppers of synthetic, natural, or mixed rubber composition that were manufactured especially for their study (not commercially available), Primeau et al³ demonstrated that natural rubber vial stoppers might release sufficient quantities of allergenic latex proteins to elicit positive intradermal skin reactions in individuals with latex allergy. However, smallpox vaccine is bioreactive (contains live virus), and thus an inadvertent vaccination could have been elicited in persons skin tested with the vaccine or rubber stopper extract. Because of these human subject concerns, we did not skin test latex-sensitive individuals to verify the results of the *in vitro* tests. Neither our study nor that by Primeau et al offers data on the safety of injections from rubber-stoppered vials in latex-sensitive persons.

The strength of this study is that we used a well-accepted assay method to detect latex allergens. In addition, the smallpox vaccine we tested was contained in the same vial for a minimum of 20 years, was then reconstituted with diluent, and was tested some 60 days later. The limitations of this study are that the CDC gave permission to study only one vial of outdated smallpox vaccine and that the immunoassay used might be insufficiently sensitive to identify trace quantities of natural rubber latex allergens. Because the number of vial stoppers tested was limited and because the total amount of extractable latex allergen might have been less than the sensitivity level of our assay, we cannot make any statement about the risk of anaphylaxis in latex-sensitive persons who receive immunizations from vials with natural rubber stoppers.

Nonetheless, because of concern regarding the use of smallpox as a bioweapon and the desire of many health care workers and others to receive the smallpox vaccine, we hope our initial observations will stimulate additional *in vitro* testing of a larger number of smallpox vaccine lots. The current stores of vaccine were manufactured more than 20 years ago, and little information is available. Any available production records should be reviewed to determine whether the stoppers on smallpox vaccine vials were made with natural rubber latex or from a synthetic elastomer.

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We thank Kim Zabel for editorial assistance.

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doi:10.1016/j.jaci.2004.05.058

Chronic idiopathic urticaria exacerbated with progesterone therapy treated with a novel desensitization protocol

To the Editor:

Chronic idiopathic urticaria and angioedema (CIU) is a more common skin disorder that is usually responsive to inhibitors of mast cell mediators, such as histamine type I (H1) antagonists alone or in combination with H2 antagonists, leukotriene inhibitors, and corticosteroids. This disorder has an autoimmune component, with approximately 45% of patients demonstrating evidence of circulating IgG autoantibodies directed against the α subunit of the high-affinity IgE receptor or antibodies to the α subunit of IgE.^{1,2} CIU has also been observed with other autoimmune diseases, such as Hashimoto and Graves thyroid disease.^{1,3}

In comparison, progesterone-induced urticaria and angioedema is a rare disorder characterized by cyclic skin eruptions 10 to 14 days before the onset of menses. This disorder is related to a spectrum of diseases termed *autoimmune progesterone dermatitis* that is characterized by erythema multiforme, papulovesicular eruptions, eczematous lesions, urticaria, and angioedema. Whereas history is usually sufficient for diagnosis, confirmation by means of positive intradermal skin test results to progesterone or a provocative progesterone challenge can be performed. Treatment is aimed at reducing levels of serum progesterone or suppressing ovulation. In the 1950s, desensitization with corpus luteum extracts by means of serial injections was used.⁴ Today, treatment options have included cyclic norethisterone and ethinyl estradiol, conjugated estrogens, 17- α -alkylated steroids, gonadotropin releasing hormones, and bilateral oophorectomy.⁵

We report a patient with CIU exacerbated by progesterone with laboratory evidence of autoantibodies to the high-affinity IgE receptor who clinically responded to a novel progesterone desensitization protocol. The patient is a 28-year-old woman with a history of chronic urticaria and angioedema since puberty at age 13 years. Symptoms initially occurred monthly approximately 10 to 14 days before menses, with complete resolution of hives at the onset of menses. Episodes were under good control with antihistamines. During the pregnancy of her only child in 1997, she had complete resolution of urticaria and angioedema. She underwent bilateral oophorectomy in

April 2001 for serous ovarian carcinoma detected during exploratory laparoscopy for chronic abdominal pain. Surgical margins were free, and there has been no recurrence of carcinoma detected to date through appropriate screening measures.

Immediately after oophorectomy, she had symptoms of menopause, including hot flashes, vaginal dryness, and irritability, which were alleviated by estrogen replacement therapy. However, supplementation with progesterone caused severe life-threatening recurrence of urticaria and angioedema, including throat swelling, wheezing, and shortness of breath. She required multiple emergency department visits for rescue treatment with subcutaneous epinephrine, steroids, and antihistamines. Frequent prednisone burst tapers were also prescribed. Multiple agents tried for hormone replacement therapy included Orthonovum, Premarin plus Provera, Yasmin, and micronized progesterone. A low-dose challenge with micronized progesterone at 25 mg caused immediate urticaria, followed by angioedema, necessitating rescue treatment at a local emergency department. The patient strongly desired *in vitro* fertilization, and therefore she refused a hysterectomy. Her obstetrician-gynecologist referred her to our center for possible desensitization to progesterone because progesterone replacement therapy was necessary for future *in vitro* fertilization plans.

Otherwise, her medical history was unremarkable and without evidence of allergic rhinitis, asthma, or food allergy. There was no family history of eczema, atopy, asthma, autoimmune disorders, chronic urticaria-angioedema, or immunodeficiencies. Her initial physical examination revealed urticarial lesions on the left forearm and antecubital fossa.

Laboratory data showed a normal complete metabolic panel and complete blood count. Both the erythrocyte sedimentation rate and C-reactive protein levels were increased at 30 mm/h and 2.8 mg/dL, respectively. The results of complement studies were normal, as follows: C4, 29.5 mg/dL; C5a, 9.2 ng/mL; and CH50, 358 U/mL. Results of thyroid function studies, including antithyroid antibodies (antithyroglobulin and antimicrosomal), were normal. There was no evidence of cryoglobulinemia. Serum IgE levels were increased at 405 kU/L. Basophil histamine release assay for indirect determination of detecting antibodies to the high-affinity IgE receptor were positive (Allen Kaplan, MD, Laboratory testing, Charleston, SC).

The patient underwent a 2-day progesterone desensitization protocol, as shown in Table I. Treatment with Benadryl and prednisone was given throughout the desensitization. After desensitization, she was able to tolerate micronized progesterone at 100 mg daily. Her additional daily medications included cetirizine and Estrace. She initially reported significant improvement in symptoms of urticaria. Follow-up has now been extended to 1 year, with occasional flares of urticaria-angioedema noted but overall good tolerance of progesterone.