

A history of latex allergy

Dennis R. Ownby, MD Augusta, Ga

Archaeologists have found that latex items were used as early as 1600 BC, but it took until approximately 1900 AD before surgical gloves were commonly used. Descriptions of apparent allergic reactions to natural rubber appeared in the medical literature in 1927, and irritant and delayed-contact reactions were reported in 1933. Although irritant and delayed-contact reactions to rubber products were increasingly recognized, immediate-type allergic reactions were not reported again until 1979. However, after 1980, increasing numbers of contact urticarial reactions to latex were reported, and investigations suggested that many of these reactions were IgE-mediated. In 1984, the first anaphylactic reactions caused by latex surgical gloves were reported, followed in 1991 by the first report of a fatal anaphylactic reaction to latex. Increasing recognition of latex allergy led to divergent paths of investigation. Critical early questions were whether the observed reactions were truly IgE-mediated, and if they were IgE-mediated, what was the source of the allergen? If the allergen was present in latex products, where did it come from? Was it present in raw latex or was it added during processing? As knowledge about the allergens improved, efforts were made to develop and test materials for skin testing and for allergen-specific IgE assays. Now more than 10 unique proteins are recognized as major latex allergens. Although much has been learned about latex allergy, important unanswered questions remain, including the sources of latex exposure that led to sensitization, why latex allergy increased dramatically during the 1980s, and the prevalence of latex allergy in diverse populations. This review concentrates on the history of latex use in medicine and the dramatic emergence of immediate-type latex allergy. (J Allergy Clin Immunol 2002;110:S27-32.)

Key words: Latex allergy, natural rubber, surgical gloves

There are many ways to examine the history of latex allergy. A history could examine the increasing use of latex from prehistoric times to the present or it could examine the introduction and changing patterns in the medical use of latex gloves and other latex devices. A history could also consider how latex allergy was first recognized and how knowledge about latex allergy has advanced from early recognition to the molecular identification of IgE-

binding epitopes. A hope of historical analysis would be to better understand why latex allergy suddenly appeared and progressed from a rare to a common medical problem. Finally, it is important to consider whether there have been any substantial changes in latex production or use that may alter the risk for latex allergy in the future.

EARLIEST USES OF LATEX

The use of latex items in ancient Mesoamerica can be documented as early as 1600 BC.¹ The oldest rubber artifacts are from the Manati site in Veracruz, Mexico and consist of 12 solid rubber balls that range from 13 cm to 30 cm in diameter and from 0.5 kg to 7 kg in weight. Radiocarbon dating shows the 2 oldest of these balls to be from 1600 BC. Additional rubber artifacts from other Mesoamerican sites include wooden tool handles wrapped with rubber, human figurines, casts of human hands, a hollow human head, and a stone tool hafted with a rubber band.¹

Fig 1 shows the Mayan site of Altun Ha in northern Belize. This center is typical of many Mayan ceremonial centers in Central America that contained stone courts used for playing a game with rubber balls. The common presence of ball courts in Mayan sites suggests that the ability to process latex into useful rubber balls was widespread hundreds of years before Europeans first arrived in Central America.

Early Mesoamerican rubber artifacts were made with latex from the *Castilla elastica* tree, indigenous to the tropical lowlands of Mexico and Central America. When dried, *Castilla* latex is too brittle to retain its shape. *Castilla* latex was processed by mixing it with juice from a morning glory vine (*Ipomoea alba*) to improve its qualities.¹ A recent study has shown that processing *Castilla* latex with *I alba* juice enhances the physical properties of the rubber, allowing it to be formed into various objects while retaining significant elasticity. The principal effects of the *I alba* juice result from two factors. The first factor is a relative purification of the cis-1,4-polyisoprene from the crude latex by separation from the aqueous phase and a corresponding relative reduction in the concentration of natural plasticizing compounds. The second factor is an increase in both covalent and noncovalent, interchain interactions caused by reactions with compounds present in the *I alba* vine.¹ Today nearly all commercial natural rubber comes from latex of the *Hevea brasiliensis* trees, commercially grown in a number of tropical countries including Malaysia, Thailand, and India. Smaller quantities are produced in Central and South America. Another potential commercial source of latex is the guayule bush (*Parthenium argentatum*). Importantly, latex from the guayule bush does not appear to contain proteins cross-

From the Section of Allergy and Immunology, Medical College of Georgia.

Dr Ownby has provided expert advice to legal firms representing Allegiance Healthcare and Safeskin, evaluated or reviewed individual cases related to latex allergy for both defendants and plaintiffs, and has given depositions on behalf of both patients and defendant health care institutions regarding latex allergy. All fees from such activities have been donated to the Medical College of Georgia Foundation. He has also reviewed data on a candidate latex extract for Greer Laboratories. Dr Ownby has no direct financial interest in any company involved in the production, distribution, or sale of latex products.

Reprint requests: Dennis R. Ownby, MD, Section of Allergy and Immunology, BG 1019, Medical College of Georgia, Augusta, GA 30912-1790.

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FIG 1. By the time this Mayan center of Altun Ha reached its developmental zenith in 400 to 800 AD, indigenous people of Mesoamerica had been producing and using natural rubber items for over 2000 years. Nearly all Mayan centers had stone courts where games were played with a natural rubber ball made of latex from the *Castilla elastica* tree.

reactive with the allergens of *Hevea* latex.² Other closely related materials that have been reported to be potentially cross-reactive with *Hevea* latex are gutta-percha and gutta-balata from Sapotaceae trees.³

INTRODUCTION OF THE SURGICAL GLOVE

It is difficult to credit a single individual with discovering the value of rubber surgical gloves; rather, the use of rubber surgical gloves appears to have been a developing idea that was gradually adopted by surgeons between 1890 and 1910.

The first suggestion of using gloves to reduce the risk of infection was made by Adam Elias von Siebold in 1813. Von Siebold suggested that physicians use swine or horse bladders as gloves or fat-impregnated linen gloves during delivery of infants to women with infections to reduce the risk of the physician acquiring infection from the patient.⁴ In a series of lectures from 1840 to 1842, Sir Thomas Watson suggested that it should be possible and valuable to invent a "pliant" glove that physicians could use to protect their hands.⁴ Thomas Hancock received patents for clothing items, including gloves, made of rubber as early as 1830, but the instability of rubber remained a problem until 1843 when Charles Goodyear and Nathaniel Hayward in the United States and Thomas Hancock in England almost simultaneously discovered the process of vulcanization. By 1852, a French surgical catalogue listed rubber anatomic gloves to prevent infection.⁴ In 1878 the first patent for rubber surgical gloves

was granted to T. Forster. One of the pioneers in the study of surgical infections was Dr William S. Halsted at Johns Hopkins Hospital. Because of the dermatitis produced by the mercuric chloride solutions used to disinfect hands and instruments, Dr Halsted was in danger of losing one of his operating room nurses. He therefore requested two pairs of thin rubber gloves with gauntlets for his nurse from the Goodyear Rubber Company in 1889. However, the first doctor at Johns Hopkins reported to regularly use rubber gloves was Joseph Bloodgood, an intern of Dr Halsted in 1892. In 1899, Dr Bloodgood reported a case series demonstrating a reduction in postoperative infections when all members of the surgical team wore rubber gloves.⁴ The first written document suggesting that all members of a surgical team should wear rubber gloves to prevent infection was authored by Zoege von Manteuffel of Dorpat in 1897. In the United States, Dr Charles McBurney presented a paper on the value of surgical gloves to the New York Surgical Society on March 9, 1898. By the early 1900s, surgeons in both Europe and the United States were beginning to adopt the use of rubber gloves.⁴ Although the use of latex gloves in surgery became routine after World War I, gloves were not consistently used in other areas of patient care until the onset of the AIDS epidemic. The Centers for Disease Control—proposed universal precautions of 1987 and 1989 produced a dramatic increase in the use of latex gloves in all areas of patient care.^{5,6} The use of latex gloves in other areas of everyday life, such as food handling, also appeared to increase after 1987.

RECOGNITION OF LATEX ALLERGY

The first recorded immediate-type reactions to natural rubber appear to be two cases in the German literature from 1927.⁷ The first, reported by Stern,⁸ involved urticaria and laryngeal edema after dental exposure to natural rubber. The second report involved asthma that was provoked by the fumes given off by a rubber-coated electrical cable when the wire warmed from current passing through it.⁹ Although these cases do not meet current standards for a diagnosis of latex allergy, they are certainly suggestive. The concept of immediate-type allergic reactions to natural rubber latex was then dormant until 1979, with the exception of a mention of rubber allergy in an allergy textbook by K. Hansen in 1957.⁷ Dr J. G. Downing reported delayed-type reactions to rubber gloves in 1933, not in medical personnel but in electrical company linemen.¹⁰ Downing's report is interesting and frustrating. Seven cases of skin reactions are described in linemen who were wearing heavy rubber gloves to insulate them from the electrical wires they worked around. Three of the cases were related to a particular brand of "chocolate-colored" gloves. In these 3 cases, the symptoms could have been due to chemical irritation or toxicity, judging from the relatively rapid onset of symptoms. In other cases, a 24-hour patch test produced no reaction at 24 hours but a marked reaction at 72 hours, a finding highly suggestive of delayed-contact reactions. This report also contains an interesting quotation, attributed to the chief chemist at a rubber glove company. In part the quotation reads, "...some individuals are so hypersensitive that they will get a marked reaction from the protein materials in the rubber as it comes from the tree. With other individuals there is no reaction except with certain of the vulcanizing agents used in the manufacturing process." The first part of this quotation, that some individuals will react to proteins in the rubber as it comes from the tree, suggests that immediate-type allergy to the proteins in raw latex was already known, but the quotation does not give enough information from which to draw a firm conclusion. The second part of the quotation would appear to refer to either toxic reactions to chemicals or to delayed-type hypersensitivity reactions to added chemicals.¹⁰ The first, clear, immediate-type allergic reaction to natural rubber was reported by A. F. Nutter, in 1979.¹¹ This report concerned a 34-year-old housewife with long-standing atopic dermatitis, mainly involving her hands. When the patient attempted to wear a new pair of rubber gloves during a flare of her hand eczema, she experienced intense itching within 5 minutes. Dr Nutter found that an open patch test with a small piece of a rubber glove caused a wheal to form on unbroken skin within 15 minutes. A skin prick test with an extract of a rubber glove provoked an immediate wheal in the patient but not in 4 control subjects. Dr Nutter went on to confirm the reactivity to components of the native, natural rubber by testing the patient with an extract of a leaf from a *Hevea brasiliensis* tree. Consistent with the hypothesis that the allergen was present in the latex as it

came from the tree, this woman had an immediate reaction to the leaf extract.¹¹ Less than a year later, Dr L. Förström described a nurse with a history of atopic dermatitis and allergic rhinitis who had immediate urticaria along with rhinitis and edema of the eyelids every time she wore latex surgical gloves.¹² The patient had a strong local urticarial reaction, along with swelling of her face, within 20 minutes of exposure to a small piece of a surgical glove. Cutaneous exposure to chlorinated cornstarch, used as dusting powder on surgical gloves, produced no reaction in this nurse.

The first report of anaphylactic reactions to surgical gloves was in an abstract by Dr Kristina Turjanmaa in 1984.¹³ In this report Dr Turjanmaa describes two female nurses with systemic allergic reactions. The first patient had generalized urticaria, bronchial obstruction, and hypotonia during cesarean delivery of her first child. The same patient had similar symptoms 4 years later during the delivery of her second child, which was assisted by suction. The second patient had an anaphylactic reaction minutes after a surgical sterilization was performed after her third pregnancy. Both of these patients were evaluated for sensitivity to anesthetic agents, but no sensitivity was found. When they were evaluated for latex allergy, RAST and skin test results were positive, and the IgE-mediated nature of the skin test responses was confirmed with positive Prausnitz-Küstner test results.¹³ In the same year, additional reports of contact urticaria caused by latex exposure came from Sweden and Germany.^{14,15}

In 1987, Axelsson et al¹⁶ reported more systemic reactions to rubber gloves in 5 women, only one of whom was a health care worker. In the same year, Turjanmaa¹⁷ published the first study on the prevalence of immediate-type allergic sensitivity to latex in hospital employees. Overall, 2.9% of the employees had positive skin test responses to an extract of a latex glove. The prevalence of sensitivity was higher in employees in the surgical departments, 6.2%, compared with that in employees in examination and laboratory units, 1.6%. An association between latex allergy and atopy was suggested by the fact that 67% of the latex-sensitive employees also demonstrated sensitivity to other allergens. A year later, Seaton et al¹⁸ published the first case report of occupational asthma caused by gloves. A potentially latex allergy-related finding in 1985 was a report of occupational allergy to weeping fig trees (*Ficus benjamina*) in two persons working for a business that maintained ornamental plants in office buildings.¹⁹ The report does not mention whether the workers wore latex or rubber gloves as part of their plant-tending work. A second report in 1987 identified weeping figs as a source of indoor allergen in Sweden; 13 of 395 office workers with allergic-type symptoms demonstrated IgE antibodies to weeping fig extracts. Ten of these 13 individuals also had food allergies.²⁰ Weeping figs are one of the hundreds of plant species that produce forms of latex. Weeping figs do not usually produce pollen by flowering; however, they do "weep" or drip a sticky material from their leaves. In 1998, Brehler et al²¹ demonstrated that allergens from

the weeping fig cross-react with allergens in *Hevea* latex and with edible figs (*Ficus carica*). Others have noted cross-reactivity between weeping fig and papain.²² It is tempting to speculate that the recognition of sensitivity to both weeping figs and natural rubber latex, at about the same time in Scandinavian countries, may have resulted from increasing sensitization to latex and the cross-reactivity between the allergens from these two trees.

Two reports of latex-related anaphylaxis in children who had previously undergone multiple operations related to spina bifida were published in 1989. The first, by Slater,²³ demonstrated that latex exposure during surgery was the most probable cause of anaphylaxis in two children. The report by Slater demonstrated both skin test sensitivity and basophil histamine release caused by latex in these children. The second 1989 report, by Gerber et al,²⁴ confirmed the increased risk of latex anaphylaxis in children who had undergone multiple surgeries and pointed out the risk of multiple reactions in these children if the diagnosis was not promptly made. Anaphylaxis caused by exposure to a latex condom was also reported in 1989 along with more cases of latex-induced anaphylaxis from multiple countries.²⁵⁻²⁸ A possible relationship between latex allergy and food allergy was first reported by Leynadier et al²⁹ in 1989. They found that 3 of 5 women with latex allergy were also allergic to fruits and suggested that there might be an association between the two problems. The association of latex and fruit allergy was again noted in a report by M'Raihi et al³⁰ in 1991. In this report, a woman with latex allergy was also found to be allergic to bananas. Many reports have since confirmed cross-reactivity between latex and allergens in multiple foods including avocados, chestnuts, potatoes, figs, and kiwi fruit.³¹⁻³⁵ Although the first case of occupational asthma caused by gloves was published in 1989,¹⁸ Tarlo et al³⁶ expanded this area by conducting a survey of occupational asthma in workers employed by a surgical glove manufacturing plant. In the study by Tarlo et al,³⁶ 3 (6%) of the 81 workers had latex-related occupational asthma, and 11% of the workers had positive skin test responses to latex. Six severe anaphylactic reactions, including one fatal reaction, during administration of barium enemas were reported by Ownby et al³⁷ in 1991. The cause of these anaphylactic episodes was identified as the latex balloons found on enema catheters. The relationship of these reactions to mast cells was demonstrated by the finding of elevated serum tryptase levels in 3 patients. Consistent with many previous reports of severe allergic reactions to latex, all of the patients in this report were women, even though approximately one half of the barium enema procedures during the period of observation had been performed on men. In 1991, Sussman et al³⁸ reported a series of 14 patients who had allergic reactions to latex in a variety of medical settings including surgery, administration of barium enemas, and dental procedures. Because of the growing concern about latex allergy and the number of severe reactions, an *FDA*

Medical Bulletin warned physicians about the risks of latex allergy.³⁹ This bulletin suggested that physicians routinely question all patients about reactions to rubber products, especially persons in high-risk groups before surgical or radiologic procedures are performed.

Czuppon et al⁴⁰ identified the first latex allergen as rubber elongation factor in 1993. Since then, 10 more allergens have been isolated. Research with these isolated allergens has explained some of the cross-reactions noted with fruits and other foods and also provided information for improving tests for latex-specific IgE.³³⁻³⁵

WHY DID LATEX ALLERGY SUDDENLY INCREASE?

Many theories have been proposed to explain the sudden increase in the number of persons affected by latex allergy, starting in the 1980s and extending into the 1990s.⁴¹ Even in retrospect, this key question has been difficult to answer because many essential bits of information are missing.

One important factor related to the increasing recognition of latex allergy was the discovery that it existed. Once a new disease has been identified and criteria for diagnosis have been formulated, it is much easier for others to recognize similar cases, a phenomenon termed *a bias of ascertainment*. This clearly developed during the 1980s and almost certainly contributed to the increasing number of cases recognized. Also important was the dissemination of information about latex allergy to health care workers and to the general public through a variety of media sources. This information allowed many affected persons to recognize their problem and seek a diagnosis. An alternate view is that it is highly unlikely that so many reactions could have gone unrecognized in the past.

Another factor that developed in the 1980s was increasing concern about AIDS and other transmissible infectious diseases. As these concerns increased, the importation of latex gloves dramatically increased in the United States and other developed countries. The use of latex gloves was further increased by the policy of universal precautions formally proposed by the Centers for Disease Control and Prevention in 1987.⁵ The implementation of universal precautions increased the exposure of both health care workers and the general public to latex gloves. Even in retrospect, it is impossible to tell whether the increased use of latex gloves increased the rate of sensitization to latex, the prevalence of symptoms in persons already sensitized, or the rate of recognition of latex allergy. Few data are available to answer this question, but it seems most likely that widespread exposure to latex increased sensitization, symptoms, and recognition simultaneously.

A commonly expressed theory about latex allergy is that the increased demand for latex gloves, brought on by universal precautions, led to a decline in the quality of latex gloves. The decline in quality is attributed to either established manufacturers cutting corners to increase production or to the proliferation of new companies with less manufacturing skill. This theory also requires the

assumption that a decline in glove quality was associated with an increase in the average allergen content of gloves. Unfortunately, no one has reported results of allergen assays on large numbers of gloves manufactured before 1987, making it impossible to refute or substantiate this theory.

Another theory, suggesting that the allergen content of gloves increased in the 1980s, is based on the shift in glove manufacturing from industrial, glove-using countries, to latex-producing countries. This shift in manufacturing locations started in the 1970s and continued into the 1980s. As latex is collected from rubber trees, it drips into cups containing liquid solutions of ammonia. Mixing with ammonia is used to prevent autocoagulation of the latex and to prevent bacterial and other forms of contamination. The ammonia remains in the liquid latex while the latex is collected, centrifuged, transported to a port city, loaded on an ocean tanker, and shipped to the country where glove manufacturing will take place. This process commonly takes several months. During the time that the latex is in transit, ammonia accelerates hydrolysis of the proteins present in the raw latex. The result of this hydrolysis is fewer intact proteins and therefore, presumably, fewer intact allergens by the time the latex is manufactured into gloves. As glove manufacturing moved to latex-producing countries, the time interval between latex collection and glove manufacturing was reduced to as little as 4 to 6 weeks. This rapid movement from collection to manufacturing significantly reduced the time for ammonia-augmented protein hydrolysis to take place, potentially resulting in higher levels of intact proteins (allergens) in finished gloves. Again as mentioned previously, there are no published studies comparing allergen content of gloves manufactured before and after the shift of plants to latex-producing countries.

Two other factors that could have played a role in increasing the allergen content of gloves are the selective growth of higher latex-yielding trees and the use of chemical agents on trees to enhance their yield. The continuing selection of trees for higher latex yields may have also selected for trees producing latex with higher protein content, but this possibility has not been carefully evaluated. The use of yield enhancers is also interesting, but again, little scientific information is available. Some yield enhancers used on rubber trees are ethylene compounds, and similar ethylene compounds are used to artificially ripen fruit. If ethylene covalently coupled to proteins or if ethylene caused similar conformational changes in proteins from latex and from fruits, then ethylene compounds might become or produce cross-reactive epitopes, recognizable by human IgE, in both latex and fruit.⁴¹

In summary, the history of increasing use of latex from prehistoric times to the present is associated with an increasing recognition of adverse reactions to latex products. One illustration of the increasing interest in latex allergy is the number of publications concerning latex allergy found per year. The number of publications has risen from 1 in 1979 to an average of 130 to 160 per year

in the late 1990s. At present, it is impossible to find strong data supporting any single theory explaining the apparent sudden increase in latex allergy seen during the 1980s and early 1990s. It seems most likely that both the recognition of latex allergy and the increased use of latex gloves for control of transmissible diseases were major factors in the increase, but the roles of other factors cannot be completely dismissed.

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