

Prospective study of risk factors in natural rubber latex hypersensitivity

Denise-Anne Moneret-Vautrin, MD,^a Etienne Beaudouin, MD,^a
Simone Widmer, MD,^a Claudie Mouton, MD,^b Gisèle Kanny, MD,^a
Frédérique Prestat, MD,^a Chantal Kohler, MD,^a and Luc Feldmann, MD^c
Nancy, France

Five hundred sixty-nine subjects routinely underwent skin prick tests for latent sensitization to latex. The study of risk factors included skin tests to inhalant allergens, to diagnose atopy, and a questionnaire aimed at revealing frequent exposure to latex such as the wearing of gloves, multiple surgical procedures, or urinary catheterization. The subjects were categorized into five groups: group I, subjects with no risk factor ($n = 272$); group II, nonatopic subjects exposed to latex ($n = 73$); group III, atopic subjects not exposed ($n = 180$); group IV, exposed atopic subjects ($n = 44$); and group V, subjects with a history of intraoperative anaphylactic shock caused by latex ($n = 13$). Twenty-five subjects had spina bifida and were in either group II (14 subjects) or group IV (11 subjects). The questionnaire identified a probable allergy to latex in 18 subjects: 16 cases were confirmed by skin test, but responses were not informative in 23 patients who were sensitive to latex. Positive prick tests to latex were obtained in 0.37% of group I, 6.85% of group II, 9.44% of group III, and 36.36% of group IV. Of the children with spina bifida, 32% had positive skin test results. As risk factors, atopy and exposure were synergistic. We recommend predictive prick tests not only in children with spina bifida but also in any atopic subject or in any patient with a history of frequent exposure to latex. Latex could be considered a habitual allergen. The use of latex urinary catheters should be avoided in patients who are catheterized on a daily basis. (J ALLERGY CLIN IMMUNOL 1993;92:668-77.)

Key words: Latex allergy, risk factors, spina bifida, intraoperative anaphylaxis, atopy, exposure

Immediate allergy to latex was first described in 1979 as contact urticaria to gloves.¹ A large variety of clinical reactions such as urticaria, edema, angioneurotic edema, conjunctivitis, rhinitis, and bronchospasm have been encountered clinically. In 1987 Axelsson et al.² predicted the possibility of anaphylactic shock, particularly during gynecologic examinations,² as a consequence of latex allergy.² After the first report of systemic reactions during childbirth,³ the number of cases of anaphylactic shock occurring during surgery and

Abbreviations used

FA: Food allergy
SB: Spina bifida

gynecologic procedures has increased.⁴⁻¹³ Currently eight of 10 anaphylactic reactions occurring during surgery in children are due to latex allergy.¹⁴ The high frequency of sensitization to latex in children with spina bifida (SB) is now well known.¹⁵ Indeed, numerous cases of intraoperative anaphylaxis caused by latex have occurred in these patients.¹⁶⁻²⁰ It is certain that dermatomucosal or serous membrane contact with latex in latex-sensitive persons carries with it a relatively high risk of death.^{21, 22}

The frequency with which these accidents occur has led some authors to recommend predictive allergy testing.^{10, 17} This recommendation, however, is still controversial.²³ The problem is to ascertain which subjects would benefit from routine predictive testing. As a first approach to this problem, the risk factors for latex allergy should

From "The Service de Médecine "D," Immunologie Clinique et Allergologie, Centre Hospitalier Universitaire de Nancy, ^bDépartement d'Anesthésie-Réanimation Hôpital Central, and ^cService d'Informatique Médicale Université de Nancy I, Faculté de Médecine de Nancy.

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Reprint requests: Pr. Denise Anne Moneret-Vautrin, Service de Médecine "D," Immunologie Clinique et Allergologie, Centre Hospitalier Universitaire de Nancy, Rue du Morvan, 54511 Nancy Vandoeuvre, France.

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be carefully studied. Two prospective studies showed that latex allergy is fairly frequent in persons having regular contact with latex at work. Moreover, people allergic to latex are atopic in more than 60% of the cases.^{24, 25} The present study aims at an exact evaluation of the risk of sensitization in atopic subjects, in patients with frequent exposure to latex either occupationally or through having undergone repeated surgical procedures, and in patients with SB.⁶ The study includes 569 subjects of all ages and confirms the importance of atopy and frequent exposure as risk factors for allergy to latex. It shows that a combination of these two factors increases the risk of sensitization considerably. SB must be considered to be a major risk factor, and systematic screening for sensitization to latex before each surgical procedure for children with this condition is highly recommended.

METHODS

Patients

This study was authorized by the ethics committee, and all patients or parents gave their informed consent to participate in the study. The study lasted for 1 year, from June 1990 to June 1991, and included 569 patients (226 male, 343 female) from 7 to 67 years of age, who were seen in the Immuno-Allergology Department, University Hospital, Nancy, France, for various reasons (e.g., rhinitis, asthma, nasal polyposis, recurring respiratory infections, various types of eczema, urticaria, history of an anaphylactic reaction, diseases of the eye, iatrogenic disease) and patients seen for preoperative examination. The latter were referred to us for a variety of reasons, including a history of atopy, asthma, drug allergy, a previous anaphylactic reaction, a previous undiagnosed incident that had occurred under anesthesia, and anxiety before surgery. Other categories of subjects included patients about to undergo chemonucleolysis and children with SB, all of whom we have skin tested with latex routinely since 1989.¹⁵

Finally, 13 subjects (five men, eight women) were referred for evaluation of anaphylactic shock that had occurred during surgery, within 15 minutes to 1 hour after induction of anesthesia. Assessment of these patients was carried out within 3 months of the shock so as to eliminate the possibility of anaphylaxis to muscle relaxants and anesthetic agents.

Questionnaire

Subjects answered a questionnaire revealing antecedents of atopic disease: atopic dermatitis, infantile asthma, allergic rhinitis, and authenticated food allergy (FA). Systemic drug reactions suggestive of allergy were not considered as diagnostic of atopy, but their existence was recorded. The number and type of pre-

vious surgical procedures was noted, as was exposure more than three times per week to latex gloves (surgical or household) or rubber contraceptives. In children with SB we tried to establish whether latex urinary catheters had been used. Last, the questionnaire dealt with the appearance of pruritus, erythema, or a feeling of intolerance when wearing gloves or on contact with other articles containing latex.

Skin tests

Atopy was investigated by skin tests. Prick tests were done with the use of 15 inhalant allergenic extracts as references: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat and dog epithelia, and eight pollens (Bermuda grass, timothy grass, birch, mugwort, *Parietaria officinalis*, plantain, cypress, olive) and three molds (*Penicillium*, *Alternaria*, and *Aspergillus*) (Stallergènes S.A., Fresnes, France). The latex prick tests were carried out (1) with an ammoniated natural rubber latex emulsion, which had been centrifugated twice, with an intermediary wash. Its final concentration was 60% rubber particles and 0.5% of ammonia, and its density was 0.95 (information provided by Porges S.A., Sarlat, France), (2) with a commercial extract of ammoniated latex at 1:100 wt/vol (Stallergènes), and (3) by pricking through a latex surgical glove (Gammex-Ansell, Cergy-Pontoise, France). A negative control was made with the allergen diluent, and a positive control with codeine phosphate solution. The diameter of the resulting wheals was compared with that of the codeine control. A test result was considered positive when the diameter was greater than 66% of the size of the codeine control. When the latex prick test result was positive and if the patient consented, a RAST (Pharmacia Phadebas Cap-System) was carried out. The threshold of positivity was set at 0.35 kU/L. Allergy to muscle relaxants and anesthetic agents was ruled out by skin tests and specific IgE antibody assays.²⁶ Statistical analysis of latex skin test results was done with the chi-square test. Evaluation of the interaction between groups was done with an additive model with the method of Bernard and Lapointe.²⁷

RESULTS

At the end of the study the 569 subjects were sorted into four groups (groups I to IV) according to the presence or absence of the two selected risk factors, atopy and exposure, to latex either isolated or combined, on the basis of the results of skin tests with the inhalant allergens and their responses to the questionnaire. The 13 patients with a history of anaphylaxis to latex were classified separately in a fifth group (group V). The groups may be classified as follows:

- Group I consisted of 272 nonatopic, nonexposed subjects (129 male, 143 female). Atopy was eliminated by the absence of a previous

TABLE I. Clinical features and biologic findings in 13 cases of intraoperative anaphylaxis caused by latex

Patient No.	Sex	Age (yr)	Reason for surgery	Atopy	Previous reactions to chemicals	Work exposures
1	F	16	SB	+		
2	M	14	SB	0		
3	F	10	SB	0		
4	M	10	SB	0	CD to iodinated PVP	
5	F	20	SB	+		
6	F	35	Ileitis, Crohn's disease	+, FA		
7	F	27	Ileitis, Crohn's disease	+	SR to ICM	
8	M	16	Urinary malformation	+, FA		
9	F	47	Obstetric purposes	0	Urticaria to paracetamol	+ (nurse)
10	F	30	Unknown	+		+ (nurse)
11	F	30	Unknown	0	CD to glutaraldehyde	+ (nurse)
12	M	8	Otoplasty	+		
13	M	50	Arthroscopy	+		

1+, Reaction size 66% to 100% of codeine control; 2+, reaction size equal to codeine control; 3+, reaction size greater than codeine control; CD, contact dermatitis; EO, ethylene oxide; ICM, iodinated contrast medium; ND, not done; PVP, polyvinylpyrrolidone.

history of atopic disease and negative prick tests to all the inhalant allergens. They had not had frequent exposure to latex, and had no more than occasional wearing of latex gloves and fewer than three surgical procedures on the abdomen and/or thorax, or fewer than five operations in all.

- Group II consisted of 73 nonatopic, exposed subjects (21 male, 52 female). Sixteen of these subjects were exposed to latex occupationally (e.g., surgeons, nursing staff, dentists, housewives, cooks), 43 through multiple surgical procedures, and 14 (children) because of SB.
- Group III consisted of 180 atopic subjects (64 male, 116 female) with no history of exposure to latex. Atopy was diagnosed on the basis of an atopic disease confirmed by prick tests, or by at least one positive prick test confirmed by RAST.
- Group IV consisted of 44 atopic, latex-exposed subjects (12 male, 32 female). Fifteen of them were exposed at work, 18 through multiple operations, and 11 because of SB.
- Group V consisted of 13 subjects (five male, eight female) with a history of anaphylaxis caused by latex (Table I). We included this to see whether the risk factors examined in the four other groups were actually present in these persons. Prick tests and RAST for IgE antilatel antibodies were done in all these patients.

The manner in which the subjects were recruited (through the immunoallergy depart-

ment) explains the high proportion of atopic subjects (39.3%). Regular or repeated contact with latex was found in 20.6% of the subjects. The notion of intolerance to the wearing of gloves was recorded in 18 subjects (3.16%).

Of the 569 patients skin tested with the two latex extracts, 39 subjects (6.85%; 10 men, 29 women) had a positive response. Both extracts gave similar results except that the ammoniated latex was slightly more reactive. Of the 39 latex-sensitive persons, 33 (84.5%) were atopic, and 10 of them had a history of FA (six to banana and avocado, also to chestnut and tomato in some of them; one to chestnut alone; one to egg; one to shellfish; one to peanut and potato). Of the 39 subjects, 21 had had frequent exposure to latex. Sixteen (41%) had a history of intolerance to latex goods. RAST was done in 27 patients with a positive prick test result; it was positive in 17 (63%) (Table II).

As shown in Table III, sensitization to latex was detected in only one (0.37%) of the 272 nonatopic, nonexposed subjects. The incidence rose to 6.85% in the 73 nonatopic patients with repeated exposure to latex, and to 9.44% in the 180 atopic, nonexposed subjects. The combination of an atopic background and frequent exposure (group IV) resulted in an incidence of 36.4%. In general, when the risk resulting from exposure and to preexisting disease was equal (groups II and IV), atopy greatly increased the likelihood of sensitization to latex (from 6.85% to 36.4%;

No. of operations	Urinary catheterization	Contact urticaria	Associated sensitivities	Prick test	RAST (kU/L)
4	+	+	EO	3+	0.65
24	+	-	EO	3+	1.46
10	+	+	EO	2+	2.4
10	+	+	CD	2+	+
9	-	+	Gelatins	3+	3
8	-	-	Muscle relaxant	3+	1.6
10	-	-		1+	ND
10	?	+		3+	0.68
2	-	-	Muscle relaxant	3+	ND
1	-	+		3+	3.6
1	-	+		1+	ND
2	-	-		1+	-
2	-	-		3+	ND

$p < 0.001$). Conversely, frequent exposure raised the likelihood of sensitization from 0.37% to 6.85% in nonatopic subjects and from 9.44% to 36.4% in atopic subjects. The incidence of sensitization to latex was not significantly different in men and women (4.4% vs 8.5%). Subjects with a history of a systemic drug reaction were no more sensitized to latex than those without such a history, whether they were atopic (9.1% vs 10%) or not (0% to 0.5%) (Table IV). When atopy and exposure were present, the differential risk reached 36.4%. If the effect of the two risk factors was simply additive, then the differential risk would have been 16.29% rather than 36.4%. The greater differential risk value observed shows a synergistic effect of atopy and exposure to latex. When atopy and exposure are considered separately (groups II and III), the risk of sensitization is not significantly different (6.85% vs 9.44%). SB was an especially high risk factor if the child was atopic: six of 11 atopic subjects (54.4%) were allergic to latex, whereas only two of 14 nonatopic subjects (32%) were sensitized. Nevertheless, the overall incidence of sensitization in these children (32%) was not different from that in patients sensitized through occupational exposure (29%). The role of multiple operations in non-SB patients was significantly less important ($p < 0.01$), with only 6.5% of these subjects being sensitized (Table V).

Group V (Table I) includes 13 subjects (eight female, five male) who had had an anaphylactic reaction during surgery before being seen in our department. Allergy to latex was documented by

a positive prick test result in all 13 patients and by a positive RAST (in eight of nine). Eight of the 13 were atopic, seven of 13 had had multiple previous surgical procedures (eight or more), three (nurses) had a history of occupational exposure to latex, and four had had mucosal contact with latex through a urinary catheter. Five of these patients had SB. Nine of the 13 had a history of some sensitivity to a chemical or other substance.

The degree of cutaneous reactivity was to a great extent correlated with the intensity of the clinical manifestation of the latex sensitivity. Indeed, the prick test response was strongly positive ($\geq 3+$) in eight of the 13 (61.5%) subjects with a history of intraoperative anaphylaxis (Table I) compared with only three strongly positive reactions among the 39 latex-sensitive subjects in groups I to IV, a rate of 7.7% (Table I). This correlation is better than the correlation between the level of serum IgE antibody and the intensity of the allergic reactions (data not shown).

DISCUSSION

IgE-dependent allergy to natural rubber latex has been linked to various proteins, which range in mass from 10 to 67 kd.^{28, 29} A 14.6 kd peptide seems to be a major allergen.^{29, 30} A 10 kd polypeptide seems to be a frequent allergen and could correspond to hevein.^{31, 32} It has been shown that numerous allergens found in natural latex are also present in aged ammoniated latex, the normal source material for medical-use latex goods, and in different vulcanized lattices. Slight

TABLE II. Characteristics of 39 patients with a positive prick test to latex

Group	Sex	Age (yr)	Latex prick test	RAST (kU/L)	No. of surgeries	SDR	FA	Cath	Glove-wearing	SB	Symptoms to latex
I											
1	F	40	1+	—	2	GAP		—	—	—	—
II											
2	F	11	2+	—	20			+	—	+	—
3	M	18	2+	3	10			—	—	+	—
4	F	48	2+	ND	5			—	—	—	—
5	M	21	1+	—	0			—	+	—	—
6	F	27	1+	—	0			—	+	—	+
III											
7	F	30	2+	17.2	0		Av, Ba	—	—	—	+
8	F	30	2+	13.3	—		BY	—	—	—	+
9	F	32	2+	11.4	2		—	—	—	—	+
10	F	38	3+	ND	0		Av, Ba	—	—	—	+
11	F	47	3+	ND	3		—	—	—	—	—
12	F	67	1+	ND	3		Shrimp	—	—	—	—
13	F	47	1+	ND	2			—	—	—	+
14	F	14	1+	ND	1			—	—	—	—
15	F	51	3+	1.2	1	Pen		—	—	—	+
16	F	15	2+	—	1	Peni Vécür		—	—	—	—
17	F	34	1+	ND	4	Pen		—	—	—	+
18	F	42	1+	ND	0	Amoxycillin		—	—	—	+
19	M	50	1+	ND	2	Peni GAP		—	—	—	—
20	F	21	1+	0.36	2			—	—	—	—
21	M	45	1+	ND	0			—	—	—	—
22	M	56	1+	—	3			—	—	—	—
23	F	28	2+	2.44	2	Peni	Peanut, Potato	—	—	—	—
IV											
24	F	39	1+	—	4	Sulfamides		—	—	—	+
25	F	35	1+	3.6	—		Av, Ba	—	*	—	+
26	F	24	2+	24	—		Av, Ba	—	*	—	+
27	F	36	1+	12.3	2	Glut	Av	—	*	—	+
28	M	31	2+	ND	—		Ba, nuts	—	*	—	—
29	F	44	1+	4,3	1	Alcuronium	Av, Ba	—	*	—	—
30	F	28	1+	—	7			—	—	—	+
31	M	23	1+	—	5			—	—	—	—
32	F	28	1+	ND	5			—	*	—	+
33	F	10	1+	0.76	7			—	—	+	—
34	M	7	1+	1.9	5			—	—	+	—
35	F	7	1+	2.45	6			—	—	+	—
36	F	11	1+	0.8	6			—	—	+	—
37	M	*	ND	4.6	6			—	—	+	—
38	M	*	ND	0.36	17			—	—	+	—
39	F	28	1+	—	4	Sulfamides		—	*	—	+

1+, Reaction size 66% to 100% of codeine control; 2+, reaction size equal to codeine control; 3+, reaction size greater than codeine control; Av, avocado; Ba, banana; BY, baker's yeast; Cath, previous urinary catheterization; GAP, glycerylaminophenamine; Glut, glutaraldehyde; ND, not done; Pen, penicillin; SDR, systemic drug reaction.

*Unknown.

conformational changes in latex proteins might be produced by ammonia and prolonged storage.^{29, 32} These water-soluble polypeptides, however, are thermostable because latex is heated to at least 130° C for 30 minutes in the final phase of glove

manufacturing. Moreover, they are easily leached from the finished product, because they can be detected in glove-rinsing liquid.^{12, 21} They are also found in the cornstarch powder that is present in medical-use gloves. Results of prick tests with

TABLE III. Hypersensitivity to latex in 569 subjects*

Group	Atopy	Exposure	n	M/F ratio	Positive prick tests		Latex positivity (%)
					n	M/F ratio	
I	0	0	272	129/143	1	0/1	0.37
II	0	+	73	21/52	5	1/4	6.85
III	+	0	180	64/116	17	4/13	9.44
IV	+	+	44	12/32	16	5/11	36.36
Total			569	226/343	39	10/29	6.85

* $p < 0.001$ for group I to II, group I to III, and for group IV compared with group I, or II, or III.

TABLE IV. Sensitization to latex, related to previous systemic drug reactions

	With SDR		Without SDR		p
	n	Latex positivity (%)	n	Latex positivity (%)	
Nonatopic patients	51	0	221	0.45	NS
Atopic patients	60	10	120	9.1	NS

NS, Not significant; SDR, systemic drug reaction.

TABLE V. Incidence of hypersensitivity to latex, according to type of exposure

Exposure to latex	Total	Positive cases	Positivity (%)
SB	25	8	32
Occupational exposure	31	9	29
Repetitive surgery (non-SB)	61	4	6.5
Total	117	21	17.9

glove powder have been reported to be positive in latex-sensitive persons.²⁸ This powder becomes airborne easily, which explains how it is possible for asthma to develop where gloves are being manipulated.^{32, 33}

The symptoms are varied and correspond to contact with diverse articles, such as respiratory manifestations (rhinitis, asthma) linked to inhalation^{32, 33}; contact urticaria to the use of gloves,³⁴ condoms,^{35, 36} or items such as adhesives, shoes, or stretch textiles²⁸; angioedema through blowing up a toy balloon^{6, 9, 16, 17}; and perineal edema through contact with a urinary catheter.¹³

Anaphylactic shock has been described during gynecologic examinations,³ on the introduction of an intestinal catheter,⁷ during dental surgery and barium enema examinations,^{21, 37} and on contact with a squash racket handle.³⁸ The most serious cases are those which occur during surgery, typically with a delayed onset of 15 minutes to 2 hours after anesthetic induction, during the surgical act itself.¹¹ For example, during orthopedic surgery in which a tourniquet was used, shock occurred when the tourniquet was taken off the patient,

because the allergens probably entered the bloodstream at the point of incision.³⁹ This delayed onset is highly characteristic of latex allergy, in contrast to anaphylaxis caused by synthetic curarizing agents and anesthetic agents, which begin within a few minutes of their being injected intravenously.⁴⁰ Allergy to latex now probably constitutes the main cause of anaphylactic shock during surgery in the pediatric population,^{10, 14} because anaphylaxis to curarizing agents is not frequently reported in children.⁴⁰ Localized allergic manifestations may occur intraoperatively; for example, angioedema of the face can begin after application of an anesthetic mask, bronchospasm after intubation, and edema of the larynx after removal of an intubation cannula, if these devices are made of latex.

The methods generally used to diagnose this allergy are the prick test and the RAST. The prick test possesses ideal specificity and sensitivity, as established by various studies.⁴¹⁻⁴³ In a previously reported preliminary study we used the latex extracts described previously in prick tests on 907 physicians, surgeons, and nurses, 18 (1.98%) of

whom reported clinical intolerance to latex goods. Results of the latex prick test were positive in 13 of 18. In contrast, of the 883 who had no clinical intolerance to latex, the prick test results were positive in only four (0.45%), supporting the outstanding specificity and the good sensitivity of prick tests to latex. Consequently we regard the prick test as a valuable means for predicting allergy to latex; this opinion is shared by other authors.¹³ Latex emulsion, the prick test made through a latex surgical glove, and the use of glove-rinsing liquid or glove powder have been reported to give equivalent results.^{28, 43, 44} RAST is also specific, but because only 60% to 83% of skin test-positive persons have a positive RAST, it is not a very sensitive diagnostic method. Therefore the prick test was chosen for the present study.

The results we obtained with the prick test allow the reliability of the questionnaire to be examined, because it has been proposed for use as an instrument for the prediction of anaphylaxis to latex.^{19, 23} In fact, intolerance to contact with toy balloons, gloves, or catheters has been noted by parents of children with SB, in 18% to 28% of cases.¹⁹ Some authors repeatedly noted this intolerance during retrospective questioning of subjects having a history of latex-induced anaphylaxis.^{13, 42} Indeed, we noted it in seven of our 13 subjects (group V). In one of these subjects perineal edema had occurred during a urinary catheterization just before the surgery. However, pruritus induced by sweating, or cholinergic urticaria, could account for intolerance to contact with gloves and must be taken into account.

The present study thus confirms the high specificity of a positive history of intolerance to latex articles. Of 18 subjects with such a history, 16 had a positive prick test to latex (Table I), supporting a specificity of 88.8%. Of these 18 subjects, seven underwent RAST; seven had positive results. Conversely, 23 of the 39 skin test-positive subjects did not have a history of intolerance. Of 23 patients, 14 underwent a RAST; 10 had positive results. This fact questions the meaning of the positivity of prick tests to latex. This positivity reflects an IgE-dependent sensitivity but does not necessarily indicate a clinical allergy. This issue cannot be solved because blinded challenges were not performed.

Atopy multiplied the risk of latex sensitization by 25 in a sample of nonexposed subjects: 9.44% (in group III) vs 0.37% (in group I). In a random sample of atopic women the incidence of latex hypersensitivity reached 15%.⁴⁵ Two previous studies, in which latex allergy was systematically investigated among nursing staff, revealed that

64% of the sensitized subjects were atopic.^{24, 25} In our series of 39 the frequency was 84.6%. Consequently it was hardly surprising to discover that eight subjects among the 13 with intraoperative anaphylaxis were atopic.

Apparently, the atopic person is preferentially sensitized by frequent contact with gloves. Of 15 glove-wearing atopic subjects, 7 (46.7%) had become allergic to latex compared with only 3 of 18 (16.7%) atopic subjects with a history of multiple surgical procedures. One explanation for this tendency may be the existence of contact dermatitis caused by other substances (e.g., penicillin, streptomycin, and glutaraldehyde). The atopic nurses in our study population often had a history of contact dermatitis. Lesions might facilitate the transcutaneous passage of latex proteins and consequently sensitization.²⁴ What is certain is that for an atopic member of an occupational group having regular contact with natural rubber latex goods, the risk of sensitization is multiplied greatly, by a factor of 129 in our study, compared with the nonexposed, nonatopic person.

FA to certain fruits and vegetables has often been reported in persons sensitized to latex.^{9, 43, 46, 47} In the present series a third of the sensitized atopic subjects had an FA, but this allergy concerned only bananas and avocados in only 18% of cases. Cross-reactivity has been shown to exist between these fruits and latex.^{48, 49} It is not clear which allergy, latex or FA, appears first.

Since Slater described the first cases, several publications have confirmed the high frequency of latex-induced anaphylactic shock in children with SB.^{8, 11, 12} We observed in this study that 11 of 25 children (44%) with SB who had not had an anaphylactic reaction were atopic. In contrast, using the same diagnostic methods described here, we previously found that only 29% of a group of 907 nursing personnel were atopic.²⁵ Thus a privileged relationship seems to exist between SB and atopy that is as yet inexplicable because SB is not a genetic disorder.

Frequent exposure to latex is known to be a risk factor because the frequency of sensitization to latex has been found to be 2.6% to 2.9% among general nursing personnel,^{24, 25} and 5.6% to 9% among operating room nurses and surgeons, respectively.^{24, 50} This factor can be further analyzed with our present data. In our nonatopic subjects the risk of sensitization was found to be 19 times greater when a history of frequent exposure to latex existed (group II vs group I) and four times greater in exposed atopic subjects than in nonexposed atopic subjects (group IV vs group III). The

risk of sensitization linked to occupational exposure to gloves is equal to the risk in children with SB who undergo frequent surgery and catheterization, 29% and 32%, respectively. The incidence of latex sensitization detected by prick test in these children is also the same as the rate of positive RAST in a recent survey of 32 patients with SB.⁵¹ Because the risk is much lower in patients without SB who undergo surgery frequently (6.5%), the main sensitizing factor in children with SB appears to be the dermatomucous membrane contact with latex catheters and with the latex gloves used in caring for these children. Questioning often reveals signs of local intolerance to latex, such as pain, burning, and difficulty with urination. These symptoms have been attributed to the neurologic abnormalities associated with the malformation, to urinary infection, or to urethritis caused by the toxicity of the chemical additives in latex.⁵² Therefore these symptoms should be suspected of indicating mucosal edema caused by latex allergy. It is also interesting that of the 13 patients who had had an intraoperative anaphylactic reaction (group V), three types of exposure were reported: seven subjects had had repeated surgical procedures, three (all nurses) had had occupational exposure, and four had had daily mucosal contact through a urinary catheter.

Finally, it is worth noting that although atopy and frequent exposure to latex are independent risk factors for sensitization to latex, they also act synergistically, so that the cumulative risk is very high (36.4%).

CONCLUSIONS

The importance of atopy and frequent exposure to latex as risk factors for hypersensitivity is supported by this study. Prophylaxis appears essential. A first step could be a systematic ban on the use of latex catheters in children with SB or genitourinary malformations. Neoprene gloves and nonlatex plastic catheters should be used until truly hypoallergenic natural rubber latex substitutes are marketed.^{53, 54} A second step would be to carry out, before any surgical procedure, predictive prick tests to latex on all high-risk subjects, including children with SB, nursing staff, other persons who are highly exposed or who have undergone multiple surgical procedures, patients having had repeated urinary catheterization (e.g., children with a genitourinary malformation), and atopic subjects.^{24, 25, 50, 55, 56} Even if the prick test to latex is negative before one operation, it must be repeated before each subsequent operation in these high-risk patients.

Because latex objects have become part of our every day environment, and because the rate of sensitization among atopic persons is nearly 10%, we recommend that prick tests to latex should be done routinely not only before surgery, but also during any allergy workup when a diagnosis of atopy is established. This highly predictive test should at least be performed in every atopic patient who is frequently exposed to latex, because the incidence of sensitization reaches 36% in this group of patients. It is likely that early detection of this latex hypersensitivity could prevent the subsequent development of respiratory allergy to latex.³³ Similarly, the high risk of sensitization in atopic subjects who undergo daily exposure to latex at work, for example, operating room personnel, should be taken into account by those responsible for occupational and industrial hygiene. By reducing exposure of these persons to latex, we might expect to see a decrease in the number of latex-induced clinical reactions in the coming years.

A positive prick test to latex does not mean that an anaphylactic reaction is inevitable, although its occurrence becomes highly likely if a previous intolerance to latex exists. In the absence of signs of intolerance, a use test is suggested,²⁴ the aim of which is to check the actual onset of latex allergy. If the wearing of a glove finger for 15 to 30 minutes brings on local or regional allergic signs, anaphylaxis during subsequent surgery may be expected. There is a real possibility, however, that subjective symptoms such as pruritus can be induced by stress alone or that a cholinergic urticaria can be induced by heat or sweating, thereby reducing the reliability of the test. As far as we are aware, the specificity of such a challenge has not yet been established, so if the prick test is positive, it is prudent to eliminate any contact with latex-based materials during surgery. The possible interest of such challenge testing deserves to be studied in more detail, for the exact relationship between latent sensitization and clinical allergic risk is at the very heart of our present preoccupation.

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Troleandomycin in the treatment of difficult asthma

Andrea Siracusa, MD, Giuliana Brugnami, MD, Tiziana Fiordi, MD,
Stefano Areni, MD, Carla Severini, MD, and Alessandra Marabini, MD
Perugia, Italy

Background: For difficult asthma, treatment is aimed at improving airway obstruction and minimizing adverse effects of systemic corticosteroids. The combination of troleandomycin (TAO) with methylprednisolone (MP) reportedly has a beneficial steroid-sparing effect on difficult asthma.

Methods: To test the steroid-sparing effect of TAO, 14 subjects with severe corticosteroid-dependent asthma were studied before and during treatment with MP and TAO.

Results: Treatment with MP and TAO resulted in a clear reduction in respiratory symptoms, asthmatic attacks, corticosteroid and hospitalization requirements, improvement in pulmonary function tests, and a remarkable decrease in peak expiratory flow rate circadian variability when compared with the period before TAO treatment (with corticosteroids). Treatment with MP and TAO was fairly well tolerated. Only a reduction (-5.2% , $p < 0.01$) in bone mineral content and an increase in plasma glucose levels (from 81.7 to 94.3 mg/dl, $p < 0.05$) were found, in comparison with pre-TAO values. One subject discontinued MP-TAO treatment because of a mild but persistent increase in serum alanine aminotransferase. In an evaluation of the clinical and pulmonary function test results, eight of the 14 subjects were responders and six were nonresponders. During follow-up three subjects discontinued TAO and consequently had an asthmatic attack after 4, 7, or 15 days, respectively.

Conclusions: This study confirms that treatment with MP and TAO has a beneficial effect in a subgroup of severely steroid-dependent asthma patients. (*J ALLERGY CLIN IMMUNOL* 1993;92:677-82.)

Key words: Difficult asthma, corticosteroid-dependent asthma, troleandomycin, methylprednisolone, steroid-sparing effect, side effects of corticosteroids, bone mineral content

From the Institute of Occupational Medicine, University of Perugia.

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Reprint requests: A. Siracusa, MD, Institute of Occupational Medicine, Via E. dal Pozzo, 06100 Perugia, Italy.

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Most patients with asthma benefit from treatment with inhaled β_2 -agonists and corticosteroids (CS). In a substantial group of subjects asthma is difficult to control;¹ poor drug compliance, oropharyngeal reflux, and sinusitis are some of the contributing factors. In a minority of asthmatic patients the condition can be controlled only with oral CS (steroid-dependent asthma), whereas in some the asthma is difficult to control.