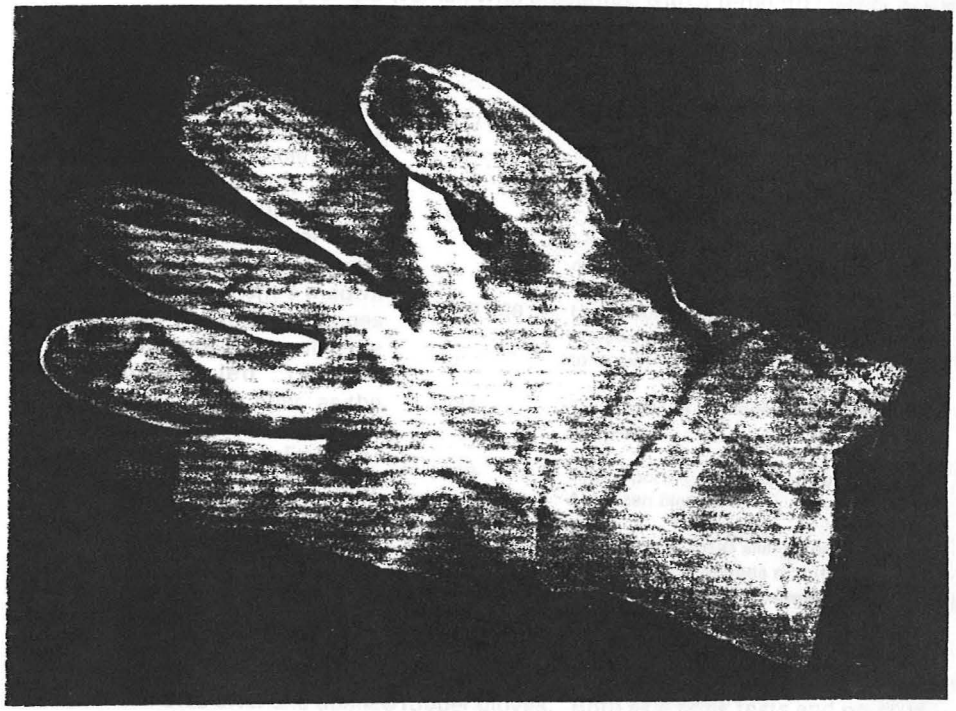
LATEX ALLERGY:
A GROWING RISK FOR HEALTH CARE WORKERS IN THE 1990'S



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HISTORY

In 1933, Downing [1] provided the first description of a hypersensitivity reaction to a rubber product. The reaction was a Type IV, delayed-type hypersensitivity reaction and consisted of a dry, scaly eczematous exantham, typical of contact dermatitis, that appeared 48 to 72 hours after the use of rubber gloves. In addition to Type IV reactions, immediate, IgE-mediated (Type I) hypersensitivity reactions to latex also have been described (Figure 1). The first published report in 1927 described a 48-year-old woman who presented with a 6-month history of daily urticaria and oral angioedema. Her symptoms had begun within three hours after the insertion of a dental prosthesis that consisted of gold and porcelain on a rubber plate. Upon removal of the device the symptoms disappeared but resumed three days later when the prosthesis was again placed in the patient's mouth. Skin tests and oral challenges with components of the prosthesis led to the identification of rubber as the inciting allergen [2].

LATEX ALLERGY - HISTORY

1927	Urticaria and oral angioedema caused by a dental prosthesis made of gold and porcelain on a rubber plate
1979	Contact urticaria from rubber gloves in a housewife with a history of contact dermatitis
1979 - 88	Numerous reports in the European literature of immediate allergic reactions to latex
1984	Two cases of intraoperative anaphylaxis in nurses
1989	First reports of latex allergy in the North American literature
1988 - 94	Greater than 1100 allergic or anaphylactic reactions reported

Figure 1.

The first English-language report of latex allergy was provided by Nutter [3] in 1979. He described a case of contact urticaria in a 34-year-old housewife who had a history of atopic dermatitis. The patient would note that during a flare of her hand eczema she would develop intense itching of her hands within minutes after she donned rubber gloves. Both skin prick tests and patch tests performed with a 5% rubber extract were positive thus indicating the presence of both rubber-specific IgE antibodies and T lymphocytes.

Between 1979 and 1988 numerous reports of immediate hypersensitivity reactions to latex appeared in the European literature. Most of the reactions consisted of contact urticaria, often in association with nasal and ocular symptoms [4, 5, 6] Also appearing during this period was one of the first descriptions of latex allergy in a healthcare worker. In 1980, Forstrom [7] described a 24-year-old operating room nurse who had a history of atopic dermatitis and allergic rhinitis who subsequently developed urticaria on her hands whenever she used latex surgeon's gloves. Skin

tests performed with a small piece of the glove yielded a strong wheal and flare response within 20 minutes.

The first cases of intraoperative anaphylaxis caused by latex gloves were described by Turjanmaa et al [8] in 1984 and both of the patients involved were female nurses. The first patient developed generalized urticaria and bronchospasm during both a cesarian delivery as well as a subsequent vacuum-assisted vaginal delivery. The second patient underwent two uneventful deliveries but then experienced an episode of anaphylaxis after a sterilization procedure. Skin tests and RAST (radioallergosorbent) tests were performed to detect rubber-specific IgE and each was positive when both latex surgical gloves and natural rubber served as the antigen in the assays.

Other reports of anaphylaxis also appeared during this period. While many of the episodes were associated with exposures that occurred in a medical environment, such as catheter placement, vaginal exams and dental manipulations, anaphylaxis also was associated with contact with condoms [9, 10], balloons [9, 11, 12] and other natural rubber-containing products. In addition, it became apparent that many of the reactions occurred in individuals who previously had experienced contact urticaria with latex exposure as well as in children with spina bifida who had undergone multiple surgical procedures [13].

Reports of latex allergy in the North American literature began to appear in 1989. Slater [14] provided the first report and in it he described two children with spina bifida and a history of contact urticaria to rubber products who went on to experience intraoperative anaphylaxis. Rubber-specific IgE antibodies were demonstrated both by skin testing as well as by histamine release from basophils after they were incubated in a latex antigen extract.

Since 1988, more than 1100 allergic, often severe, reactions associated with latex-containing medical devices have been reported to the Food and Drug Association (FDA). These have occurred in both patients and health care workers and have involved primarily latex gloves and barium enema catheters. The association of anaphylaxis and barium enema catheters was first presented in a report by Ownby and colleagues [15] in 1991. There they described six patients who experienced anaphylaxis between January 1989 and March 1990 following barium enema procedures. The initial case involved a 49-year-old atopic female who underwent a barium enema for the evaluation of occult blood found in her stool during a routine exam. Within minutes after the catheter was placed and the balloon was inflated the patient complained of warmth, itching, and chest tightness. The symptoms progressed rapidly and, ultimately, the patient arrested and died despite aggressive resuscitative efforts. Autopsy results confirmed that anaphylaxis was the cause of death. Upon analyzing one of the catheter manufacturer's databases, Gelfand [16] found that between December 1988 and September 1990, 148 incidents of allergic reactions associated with barium enema procedures had been reported and that in five fatal reactions the symptoms occurred following the insertion of the balloon-tipped catheter prior to the infusion of barium.

REASONS FOR THE INCREASE IN LATEX REACTIONS

Immediate hypersensitivity reactions to latex have been increasing and there are several theories as to why this is happening. One of the most important causes of this rise in reaction rate is secondary to the tremendous increase in the use of latex gloves and condoms. Because of the increased incidence of hepatitis B and human immunodeficiency virus (HIV) infections, universal precautions for barrier protection from blood and body fluids were established [17]. With the establishment of these precautions increased exposure to latex-containing products inevitably has occurred as well.

Another factor contributing to the increased number of reactions may be related to alterations in manufacturing. Due to the increased demand for latex-containing products "short-cuts" may have been taken in the manufacturing process [18]. It is known that the antigens in latex gloves are easily elutable. Therefore, with the implementation of shorter wash times the concentration of protein antigen in the final product may have increased significantly.

Other possible explanations that may account for the recent increase in Type I reactions to latex are presented in Figure 2 [19].

REASONS FOR THE INCREASE IN LATEX REACTIONS

- Universal precautions resulting in increased glove usage.
- Increased recognition and reporting.
- General increase in allergic sensitivities in the population.
- Sudden increase in poor-quality gloves from new companies.
- Geographic changes of latex source.
- Change in site of the manufacturing location that may decrease total storage time.
- Changes in manufacturers' practices to comply with environmental and occupational health concerns.
- Irritant and allergic contact dermatitis from added attention to scrubbing, with possibly insufficient rinsing, which results in breached epidermal protection and increased transdermal routes for endotoxin, chemical and protein entry.
- Use of barrier creams for dermatitis relief, which extract protein allergens from the gloves and may aid in dermal penetration.
- Aerosolized glove powder providing increased endotoxin available to contact the lung's mucosal lining and predisposing the area for exaggerated susceptibility to Type I sensitization.
- Increase in hospital environmental exposure to latex protein allergen-bound cornstarch in the air.
- Changes in exposure to cross-reacting allergens due to increased amounts of protein by stimulation and augmented allergenicity potential due to ethylene, or ethylene oxide hapten conjugate from avocados, bananas, chestnuts, kiwis and other fruits.
- Increased use of ethylene oxide-sterilized custom packs.
- Environmental or agricultural concerns altering the harvest in an as-yet-unforeseen manner.
- An increase in the survival rate in the spina bifida population of approximately 40% over the last 15 years.

Figure 2.

EPIDEMIOLOGY OF LATEX ALLERGY

Sensitivity to natural rubber latex develops as a result of repeated exposure and, in this day and age, it is almost impossible to escape contact with the variety of articles that contain latex (Figure 3). Since our exposure to latex is so widespread it would be interesting to know the prevalence of latex allergy in the general population. While this figure is not known, it is believed that the prevalence of latex allergy in nonatopic individuals is less than 1%. In contrast, however, the prevalence in health care workers and in patients who have undergone multiple surgical procedures is markedly higher.

COMMON SOURCES OF LATEX

Medical/anesthetic products

Adhesive tape	Fluid-circulating warming blankets
Balloon/urinary catheters	Head straps
Breathing circuits	Hemodialysis equipment
Condom urinary collection devices	Injection ports on IV tubing
BP cuffs	Nasopharyngeal airways
Plastic tracheal tubing	Oropharyngeal airways
Dental devices	Reservoir breathing bags
Elastic bandages	Rubber pads
Electrode pads	Stomach/intestinal tubing
Endotracheal tubing	Tourniquets
Enema tubing tips	Tympanometers
Epidural catheter injection adapters	Ventilator bellows/hoses
Face mask and straps	Wound drains

Personal and household items

Balloons	Rubber bands
Condoms	Rubber plants
Contraceptive sponges	Scuba face masks
Diaphragms	Swim caps and goggles
Dishwashing gloves	Toys
Hot water bottles	

Figure 3.

Health care workers

Turjanmaa [20], in 1987, reported the prevalence of latex allergy, as determined by skin test positivity, in a group of 512 hospital personnel. Of 145 individuals who worked in various operating areas (surgery, ophthalmology, otolaryngology, gynecology and obstetrics), 6.2% were allergic to latex, in contrast to only 1.6% of the 367 persons who worked in other areas of the hospital.

More recently, Lagier and colleagues [21] conducted a study in 268 operating room nurses in several hospitals in Marseille. Two hundred forty eight (96%) completed a questionnaire and 197 (73.1%) underwent skin testing with a latex extract. Skin tests were positive in 21 (10.7%) of those tested. While 102 of the nurses, many of whom were atopic, complained of local symptoms (itching and/or urticaria) upon wearing gloves, only 19 (18.6%) of these individuals had a positive latex skin test. These results suggest that latex allergy may be more common than previously recognized in operating room nurses, especially those with an atopic history. In addition, it appears that a questionnaire alone is not reliable to detect those with latex sensitivity. In order to make a definitive diagnosis, a skin test must be performed as well.

In 1994, Yassin et al [22] investigated the incidence of latex allergy in 224 hospital employees. These individuals were interviewed and prick tests were performed to six common aeroallergen extracts, one non-latex glove extract and four

different latex glove extracts. The subjects consisted of 136 nurses, 41 laboratory technicians, 13 dental staff, 11 physicians, 6 respiratory therapists, and 17 housekeeping and clerical workers. While all of individuals tested negative for the nonlatex glove extract, 38 (17%) tested positive to one or more of the latex extracts used. A comparison between the latex skin test positive and latex skin test negative in-hospital employees is presented in Figure 4. The variables with statistical significance included a history of asthma, symptoms (associated with latex glove use) of anaphylaxis, urticaria, rash, itching, sneezing, nasal congestion, itchy, watery eyes and cough. While a history of seasonal allergic rhinitis was not significantly different between the two groups, 68.4% of the subjects in the latex-positive group tested positive to two or more aeroallergens as compared with 31% in the skin test negative group. There was no difference between the two groups in the type of employment (full-time versus part time), number of years of employment, gender, frequency of latex glove use at home, symptoms when using condoms or diaphragms, or history of seasonal allergic rhinitis, eczema, or sinus disease.

	Latex Skin Test Negative	Latex Skin Test Positive	Two-Tailed *P* Value
Subjects tested	186	38 (17%)	
Full-time employees	145 (78%)	28 (74%)	ns
Sex F/M	164/22	33/5	ns
No. of years of hospital employment	928/186 (4.98 yr)	198/38 (5.2 yr)	
History of hay fever	51 (27%)	16 (42%)	ns
History of sinus disease	97 (52%)	21 (55%)	ns
History of bronchial asthma	14 (7.5%)	8 (21%)	$P < .05$
History of eczema	17 (9%)	8 (21%)	ns
No. of surgical procedures	266/186 (1.43)	50 ÷ 38 = 1.3	
Use of latex gloves at work	170 (91%)	38 (100%)	
"always"	70 (41%)	20 (53%)	
most of the time	57 (33.5%)	17 (45%)	
occasionally	43	1 (3%)	
Daily use of household latex gloves	39 (21%)	3 (8%)	ns
Symptoms when using latex gloves	71 (38%)	38 (100%)	$P < .000001$
Anaphylaxis	0 (0%)	4 (10.5%)	$P < .000001$
Hives (urticaria)	1 (0.5%)	21 (55%)	$P < .000001$
Rash	31 (17%)	26 (68%)	$P < .000001$
Itching	54 (29%)	32 (84%)	$P < .000001$
Sneezing	13 (7%)	13 (34%)	$P = .0000069$
Nasal congestion	13 (7%)	15 (39%)	$P < .000001$
Itchy watery eyes	11 (6%)	17 (45%)	$P < .000001$
Cough	3 (2%)	7 (18%)	$P = .0000346$
Symptoms when using latex condoms or diaphragms	10 (5%)	4 (10.5%)	ns
Subjects who tested positive to two or more aeroallergens tested	58 (31%)	26 (68%)	$P = .0000352$
Subjects tested for latex antigens	0 (0%)	38 (100%)	
Subjects tested positive for vinyl extract	0 (0%)	0 (0%)	

ns = not significant.

Figure 4. Comparison between latex skin test positive and latex skin test negative in-hospital employees [22].

Figure 5 depicts the number of skin test positive individuals in each of the groups. Of the 136 nurses tested, 24 (17.6%) were skin test positive to latex. In the other employees studied, skin test positivity to latex ranged from 0% in housekeeping and clerical personnel to 38% in the dental assistants and dental residents. In this study only one of eleven (1%) physicians demonstrated a positive skin test.

SKIN TEST REACTIVITY IN 224 HOSPITAL EMPLOYEES [22]

Subject (#)	Latex ST Negative	Latex ST Positive
Subjects tested (224)	186	38
Nurses (136)	112	24
Laboratory techs (41)	34	7
Dental assistants (13)	8	5
Resp. therapists (6)	5	1
Physicians (11)	10	1
Housekeeping/clerks (17)	17	0

Figure 5.

In other studies, the percentage of latex-sensitive physicians has been found to be higher. Of 31 latex-sensitive hospital employees evaluated by Pecquet [23] seven were nursing aides and nine were physicians (including four surgeons and two anesthesiologists). Similarly, Jaeger et al. [24] found that 37% of the 70 latex-sensitive individuals he evaluated were physicians or medical students while 54% were nurses or technicians.

Patients with spina bifida

In addition to healthcare personnel, children with spina bifida are at increased risk of developing latex allergy [14, 25, 26, 27, 28, 29]. In a study of 187 families, Meeropol and colleagues [29] found that up to 28% of spina bifida children are allergic to latex and Slater et al. [26] reported that as many as 34% of such children have detectable latex-specific IgE by RAST. It is thought that this increased risk is due to the high levels of exposure to latex that occur during the multiple surgical procedures that are performed in these individuals.

Hypersensitivity reactions to latex in spina bifida patients range from mild contact urticaria symptoms to anaphylaxis and death. From January 1990 through January 1991 a cluster of anaphylactic reactions occurred in patients during induction of anesthesia at the Children's Hospital of Wisconsin [30]. An epidemiologic study performed to identify risk factors for anaphylaxis revealed that the reactions occurred exclusively in patients with spina bifida or in patients with a congenital urinary tract anomaly. These patients were more likely than control patients (patients with spina bifida who underwent uneventful general anesthesia during the same period) to have a history of asthma, rubber contact allergy, food allergy, rash caused by adhesive tape, daily rectal disimpaction, or nine or more prior surgical procedures (Figure 6). In addition, case patients were more likely to have latex-specific IgE as determined by skin prick testing (SPT), ELISA or RAST as well as elevated total IgE (Figure 7).

	Case patients (n = 11)	Control patients (n = 64)	Odds ratio (95% CI)	p Value
Age (yr) (mean ± SD)	7.8 ± 3.3	5.6 ± 4.5		>0.1
Sex (M : F)	6 : 5	28 : 36		>0.1
Race				
White	8 (73%)	52 (81%)		>0.1
Black	2 (18%)	8 (12.5%)		
Other	1 (9%)	4 (6.5%)	-	
CIC	7 (64%)	42 (66%)	1.0 (0.6, 1.6)	>0.1
Duration CIC-years (mean ± SD)	3.4 ± 3.1	3.0 ± 3.9		>0.1
Rhinitis	5 (45%)	12 (18%)	2.4 (1.0, 5.4)	>0.1
Eczema	0 (0%)	6 (9%)	NC	>0.1
Tracheostomy	2 (18%)	5 (8%)	2.3 (0.5, 10.5)	>0.1
Prior surgeries (number ± SD)	12.1 ± 5.9	7.2 ± 4.8		0.008
≥9 Surgical procedures	9 (82%)	19 (30%)	2.8 (1.7, 4.4)	0.002
Midazolam given intraoperatively	4 (36%)	6 (9%)	3.9 (1.3, 11.6)	0.045
History of anaphylaxis	11 (100%)	4 (6%)	16.0 (6.2, 41.3)	<0.001
Asthma	7 (64%)	10 (16%)	4.1 (1.98, 8.4)	0.002
Rubber contact allergy	6 (55%)	3 (5%)	11.6 (3.4, 39.8)	<0.001
Food allergy	5 (45%)	1 (2%)	29.1 (3.8, 226)	<0.001
Rash from adhesive tape	5 (45%)	11 (17%)	2.6 (1.1, 6.1)	0.05
Daily rectal disimpaction	6 (55%)	5 (8%)	7.0 (2.6, 19.0)	<0.001
Drug allergy history	5 (45%)	14 (22%)	2.1 (0.9, 4.6)	<0.1

CIC, Clean intermittent catheterization; *NC*, not calculable.

Figure 6. Comparison of potential risk factors for anaphylactic reactions among case and control patients, CHW, January 1, 1990 to January 31, 1991 [30].

	Case patients			Control patients			
Test	No. positive	No. tested	%	No. positive	No. tested	%	p Value
Latex SPT	10	10	100	19	39	46	0.01
Latex ELISA	10	10	100	27	42	62	0.02
Latex RAST	10	10	100	21	41	51	0.017
Latex sensitivity*	11	11	100	33	49	67	0.027
ETO	3	9	33	15	44	34	>0.1
Aeroallergen SPT	3	8	38	9	33	27	>0.1
Banana SPT	2	8	25	5	33	15	>0.1
IgE > 84 IU	7	9	78	9	44	20	0.002
IgE mean IU + SD	476 ± 606 IU			75 ± 155 IU			<0.001

*Latex sensitivity = any one of the following positive: latex SPT, latex ELISA, or latex RAST.

Figure 7. A comparison of immunologic evaluation of case and control patients, CHW, January 1, 1990 to January 1, 1991 [30].

In another large-scale study, Moneret-Vautrin et al [31] evaluated the risk of sensitization to latex in several different groups: atopic individuals; individuals frequently exposed to latex either occupationally or through having undergone repeated surgical procedures, and patients with spina bifida. Five hundred sixty-nine subjects were evaluated and categorized into one of five groups. Group I consisted of 272 subjects with no history of atopy or frequent exposure to latex. Group II was composed of 73 nonatopic, subjects who had a history of frequent latex exposure. Sixteen of these individuals had occupational exposure (surgeons, nurses, dentists, housewives, cooks), 57 had exposure through multiple surgical procedures and included 14 (children) with spina bifida. Group III consisted of 180 atopic subjects with no history of latex exposure and group IV consisted of 44 latex-exposed, atopic subjects. Fifteen of these individuals were occupationally exposed, and 29 were exposed through multiple surgical procedures (11 of these had spina bifida).

The 569 patients underwent latex prick skin testing and 39 subjects (6.85%) were skin test positive. Of these 39, 33 (84.5%) were atopic, 21 (54%) had previous frequent exposure to latex and 16 (41%) had a history of intolerance to latex goods. When each of the above four groups was analyzed individually (Figure 8), sensitization to latex was detected in: one (0.37%) of the 272 nonatopic, nonexposed individuals; 5 (6.85%) of the 73 nonatopic subjects repeatedly exposed to latex; and 17 (9.44%) of the 180 atopic, nonexposed subjects. Interestingly, the combination of atopy and frequent exposure (group IV) resulted in an incidence of 36.4%. Of the 25 children with spina bifida, 8 (32%) were skin test positive to latex and 6 of these were also atopic. Thus, as has been shown in other studies [21], atopy appears to increase the likelihood of sensitization to latex in individuals with histories of previous exposure.

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.

Figure 8. Hypersensitivity to latex in 569 subjects [31].

Rubber manufacturers

It is not surprising that workers in a glove-manufacturing plant also have an increased risk of developing sensitivity to latex. Tarlo and colleagues [32] evaluated 81 workers in one plant for for prevalence of latex sensitivity. Sixty-seven workers completed a questionnaire to address work-related respiratory symptoms, 63 underwent prick skin testing to latex and 50 underwent spirometry during their work

shift. Seven (11%) of the workers tested demonstrated a positive latex skin test and three of the 50 (6%) who underwent spirometry were considered to have latex-related occupational asthma. These findings, along with those described previously, reveal that latex is an important cause of occupational allergy.

Other risk factors

An association has been made between latex hypersensitivity and certain fruit allergies and the existence of cross-reactivity has been shown through RAST inhibition [33, 34, 35, 36, 37]. Crossreacting fruits include banana, chestnut, avocado, kiwi and papaya. A recent evaluation of 25 latex-allergic individuals (all skin test positive to latex) with associated food hypersensitivities was performed by Blanco et al. [38]. The subjects were predominately females and included nine greenhouse workers, six hospital workers (four nurses, one surgeon, and one cleaner), four housewives and six miscellaneous individuals. Forty-two food allergies were diagnosed in 13 of the patients (52%), and 23 of the reactions demonstrated were anaphylaxis. The most frequent foods implicated were avocado (9), chestnut (9), banana (7), kiwi (5) and papaya (3) (Figure 9).

No.*	Avocado			Chestnut			Banana			Other Food Allergies			
	CM	SPT†	IgE‡	CM	SPT†	IgE‡	CM	SPT†	IgE‡	Food	CM	SPT†	IgE‡
1	A	4 x 4	13.1	A	6 x 5	0.0							
2	A	18 x 17	3.8	AE	4 x 4	0.0	U/AE	11 x 9	0.4	Papaya	U	6 x 4	nd
										Peanut	AE	9 x 9	0.0
										Mustard	AE	10 x 9	nd
										Pepper	AE	15 x 12	nd
3	AE	4 x 4	0.0	AE	4 x 4	0.0	U	3 x 3	0.0				
4	A	5 x 3	2.4				A	3 x 3	0.4	Walnut	U/AE	7 x 6	0.0
										Kiwi	RC	3 x 3	0.0
5	A	6 x 5	2.7	AE	7 x 5	0.0				Kiwi	RC	3 x 3	0.0
6				RC	3 x 3	0.0							
7				A	9 x 9	0.0							
8	A	12 x 12	15.2	A	11 x 7	20.6	A	10 x 10	5.1	Papaya	A	15 x 8	0.6
										Pineapple	A	5 x 4	0.0
9	A	9 x 8	0.4	A	3 x 3	0.0	A	5 x 5	0.0	Kiwi	AE	4 x 4	0.6
										Fig	A	5 x 5	nd
10	AE	5 x 5	0.4										
11										Kiwi	A	4 x 4	0.0
12				U/AE	12 x 11	0.5	A	4 x 4	0.0				
13	A	7 x 7	3.9				A	3 x 3	2.0	Kiwi	A	8 x 8	0.0
										Papaya	A	4 x 4	1.9
										Peach	AE	4 x 4	0.0
										Fig	A	5 x 4	nd
										Potato	AE	6 x 5	2.5

* No., patient number; CM, clinical manifestations; nd, not done; RC, rhinoconjunctivitis; U, urticaria; AE, angioedema; A, systemic anaphylaxis.
† Skin prick test in mm.
‡ IgE in kU/L.

Figure 9. Associated food immediate hypersensitivities in latex-allergic patients [38]

In addition to positive prick tests to latex extract, specific IgE also could be demonstrated in the sera of all 25 individuals by RAST assay. Upon incubating pooled sera (containing latex-specific IgE) with various fruit extracts, significant RAST inhibition was demonstrated, especially with the extracts from chestnut and avocado (Figure 10).

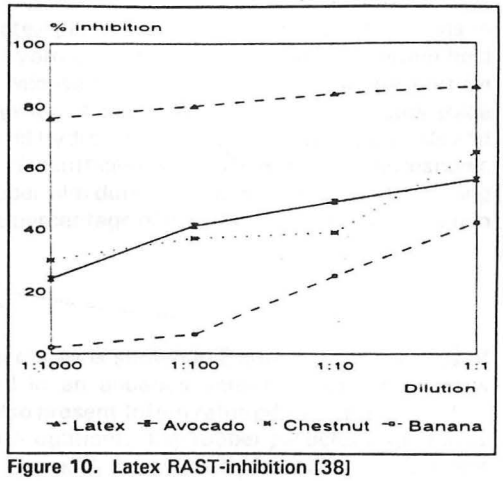

Figure 10. Latex RAST-inhibition [38]

Another risk factor for the development of latex sensitivity (Type I, IgE mediated) may be pre-existing contact dermatitis (caused by the nonlatex components in rubber gloves) on the hands. A Finnish survey found that 60% of the latex-sensitive persons they evaluated had a history of hand eczema, while 17.4% of nonsensitized persons had such a history [20]. Charous et al. [39] also found an increased incidence of contact dermatitis in their patients with latex allergy. In contrast, positive skin test reactions to latex were not higher among patients with a history of contact dermatitis in the Marseille survey [21] described previously. These data indicate that while contact dermatitis may be a potential risk factor for the development of latex allergy further investigation is needed to determine its importance.

CHEMISTRY OF NATURAL RUBBER LATEX

Latex collection

As many as 2000 shrubs, trees and vines produce latex from which a rubbery polymer can be obtained. However, despite the large number of latex-producing plants, only the latex from *Hevea brasiliensis* has been commercially exploited [40].

Latex is located in latex vessels contained in the cortex of the tree and it is obtained from these vessels by the process of tapping. A cut is made into the bark and the latex flows from the cut along a spout and into a receptacle. Within a few hours after tapping, the receptacle containing the latex is removed, a stabilizer is added and the material is taken to a processing center. The stabilizer used may be sodium sulfite, formaldehyde or ammonia plus a mixture of zinc oxide and tetramethylthiuram disulfide (most widely used), and its addition prevents bacterial contamination which would lead to premature coagulation of the latex. The collected latex is termed *field latex* [40].

The ammonia stabilizer in field latex performs several additional functions in addition to killing bacteria. It also: a) hydrolyzes the rubber particle-adsorbed lipid layer, causing fatty acid soaps to be released which then adsorb to the particle surface, increasing the mechanical stability of the latex [41]; b) deactivates trace metals by sequestration or precipitation; c) hydrolyzes proteins and phospholipids and d) degrades proteins and peptides [19]. If insufficient stabilizer is added, microscopic latex particle aggregates form in the rubber film during glove manufacturing resulting in uneven strength and an increase in the percentage of insufficiently degraded protein in the final product.

Composition of latex

The composition of natural rubber latex is shown in Figure 11. It consists of rubber hydrocarbon particles dispersed in an aqueous serum phase. Numerous nonrubber particles termed *lutoids* are also present (often referred to as the *B-fraction* since they fall to the bottom during centrifugation). The rubber particles themselves consist of rubber hydrocarbon surrounded by a protective layer of proteins and lipids [40]. Rubber hydrocarbon is cis-1,4-polyisoprene and its molecular weight ranges from 200 to 600 kD. The rubber content of latex varies greatly, from 25% to 45%, depending upon the environmental conditions. In addition, intensive tapping causes reduction in the rubber content of latex.

COMPOSITION OF LATEX [40]

Component	Percentage
Rubber hydrocarbon	25-45
Protein	1-1.8
Carbohydrates	1-2
Neutral lipids	0.4-1.1
Polar lipids	0.5-0.6
Inorganic constituents	0.4-0.6
Amino acids, amines, Water	0.4

Figure 11.

Aside from rubber hydrorcarbon and water, protein and carbohydrates occur in the largest concentration in latex. Approximately 25% to 30% of the proteins are located in the rubber phase, 45% to 50% are in the serum phase and approximately 25% are found in the B-fraction in a typical latex sample [40]. The protein composition in latex is very complex consisting of greater than 200 individual proteins (See latex antigens below). The other nonrubber substances in latex include: lipids (predominately neutral lipids), carbohydrates (predominately quebrachitol or 1-methyl inositol) and inorganic constituents (predominately potassium and magnesium).

Latex processing and the production of latex concentrate

Upon arrival at the factory field latex is sieved and blended. Subsequently, it is processed into dry rubber that will be used for making products such as tires or into a latex concentrate that will be used for making latex products such as dipped gloves, condoms etc. The production of dry rubber and the manufacturing of dry rubber

products will not be discussed. Field latex is concentrated to approximately 60% rubber by a process called centrifugation. In addition to concentrating the latex, centrifugation also cleans it by removing 50% of the water content and reducing the nonrubber solids (proteins, fatty-acid soaps, salts, minerals). Centrifugation causes latex to separate into two phases: a rubber-rich concentrate phase and a skim latex phase with a rubber content of 3% to 5%. The concentrate is collected and bulked in storage tanks until it is shipped to consumers. This process is performed usually by the plantation or a third-party processor and is not under the glove manufacturer's direct control.

A single centrifugation step is usually performed and is responsible for approximately 95% of all dipping latex. During a single pass through the centrifuge the protein content is decreased by 50%. While a second centrifugation results in an additional decrease in protein content, the tensile strength of the final product is reduced and the cost is markedly increased.

Latex glove manufacture from latex concentrate

The manufacturing of products from latex concentrate involves several steps [42]. The first is **stabilization** whereby agents are added to prevent premature coagulation, maintain rubber particle integrity and help in keeping the dispersion homogeneous. Saturated fatty acid soaps and unsaturated fatty acid soaps are the most effective stabilizers.

Stabilization is followed by the **preparation and mixing of compounding ingredients with latex.** The first compounding ingredient is a vulcanization agent which is used to crosslink the rubber molecules to yield an elastic material. Elemental sulfur is often used for this purpose. The cross-linking process is relatively slow and therefore, an accelerator is also used. The accelerators, which are categorized into three groups (dithiocarbamates, thiazoles and thiurams) are responsible for most of the cases of contact dermatitis due to natural rubber gloves [43, 44, 45, 46, 47]. Other compounding ingredients that are added include antioxidants, gelling agents, foaming agents, thickeners, softeners, fillers, and pigments [19, 40].

The next stage is the **fabrication or shaping process** that is necessary to convert the latex into a solid product. During this step, the latex is destabilized allowing it to undergo a phase change into solid rubber. The two processes used are dipping or gelation (used to make natural rubber latex thread and thicker articles such as teats, pacifiers and foam toys). Dipping (either straight or coagulant dipping) involves the immersion of a clean, dry former made of glass, steel, or glazed porcelain into the latex compound and subsequent slow withdrawal. In most instances, two or more dips are done in order to increase the thickness of the product. Condoms, finger cots and some surgical gloves are made in this way (Figure 12). In coagulant dipping, the former is first dipped into a coagulant solution prior to slow and smooth immersion into the latex compound. The coagulant rapidly diffuses through the latex coating, converting the liquid latex into a gel. Balloons and dipped gloves are made by this process. In both straight dipping and coagulant dipping the article is stripped from the

former after drying and vulcanization [40].

Following the shaping process, a **leaching** procedure is performed. Leaching in water is done for most latex products made by the dipping process and for latex thread and molded foam. The purpose of leaching is to allow the removal of water-soluble materials, the presence of which may cause decreased clarity, discoloration or excessive water absorption in the product. If done properly, most of the unbound chemical additives and proteins are removed while the physical characteristics of the glove are increased. Leaching may be performed on either the dry product (dry film leaching) or on the wet get before it is dried (wet gel leaching). It is followed by **drying** and repeat **vulcanization.**

The final stage prior to stripping is **surface treatment.** Products that are made of natural rubber latex have a tendency to stick together due to self-tack. In addition, high surface friction causes rubber gloves to be difficult to don. In order to solve these problems, the product is surface treated. Powders are advantageous in that they reduce both tack and friction. While talc was popular in the past it is now against the regulations of the FDA to use talc on surgeon's gloves because of talc-induced granulomas and adhesions that were reported after numerous surgeries [48, 49]. For medical gloves, talc has been replaced with cornstarch, and powdering is carried out in the dry state or by dipping the gloves in a wet powder slurry.

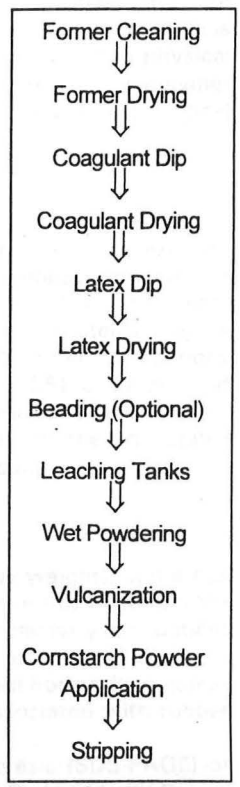

Figure 12. Flowline for production of examination gloves [40].

Powder is a vehicle for the various chemicals and proteins that are pushed to the surface of the glove during the drying process. Not only may it cause irritation, but also allergic contact dermatitis (Type IV), or a Type I, IgE-mediated allergic reaction due to the agents that are carried. The conversion from talc to the use of cornstarch in surgeons' gloves occurred in the 1970's and in the 1980's it began to be used as the donning agent in examination gloves. While the cases of postoperative granulomas decreased, other problems arose. Cornstarch is an excellent vehicle for latex protein allergens and chemicals [50]. In addition, cornstarch may support bacterial growth. Oven drying and sterilization by gamma irradiation destroys any viable organisms. However, the endotoxin in gram-negative cell walls, if inhaled in the form of endotoxin-laden powder, may amplify the rate of sensitization to latex proteins and may potentiate asthma-like symptoms associated with glove use. If deposited on the skin, endotoxin may enter the dermis through abrasions or fissures leading to the development of dermatitis upon repeated exposure [19, 51].

Other methods may be used instead of powdering in order to reduce tack and friction. Liquid detackifiers such as silicone oil and silicone emulsions are the most

common agents used for gloves. Another method is to modify the surface of the product by treatment with a solution of chlorine or bromide. Gloves that are chlorinated have low friction and no tack. However, a problem with halogenation is that it must be carefully controlled so as not to cause deterioration in the physical properties of the product. A third method is to dip the product in a synthetic polymer latex, thus providing a tack-free, low friction film. Hydrogel or Biogel [52] surgical gloves use this technique.

Sterilization

Sterilization may occur in several ways. Initially, gloves were sterilized by boiling. Subsequently, steam sterilization and ethylene oxide sterilization were the methods employed. In regards to dermal compatibility, both boiling and steam treatment have been shown to markedly reduce the concentration of protein allergens [19]. In contrast, ethylene oxide sterilization actually augments potential reactions by creating residues that cause chemical burns, irritation [53, 54, 55], and enhanced allergenicity of latex [55, 56, 57, 58]. Today sterilization is performed predominately by irradiation, a technique that has been shown to have no effect on the extractable protein levels or allergenicity content of the finished latex product.

LATEX ANTIGENS

Rubber products may contain as much as 3% protein (by weight), and it has been shown that over 200 individual peptides exist [59]. Despite this large number of potential allergens, characterization of these proteins by their reactivity with patient serum antibodies has revealed that only approximately 25% of them (ranging in molecular weight from 2 to 100 kD) actually react with IgE antibodies from latex-allergic individuals [60]. Some of these, particularly those associated with rubber synthesis, have been purified and characterized.

Sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) of nonammoniated latex reveals major proteins at 46, 29, and 14kD. Hevein (5kD) and hevamine (29kD) are two latex proteins that have been isolated, cloned and sequenced [61, 62]. In addition, rubber particles contain bound proteins prenyltransferase (38kD) and rubber elongation factor (REF), an integral protein necessary for the biosynthesis of the polyisoprene chains in latex [63, 64]. Both prenyltransferase and REF have been isolated, characterized and sequenced.

REF has a molecular weight of 14.6 kD, and it has been found as a 58 kD noncovalent homotetramer in both raw latex and latex gloves [65] (Figure 13).

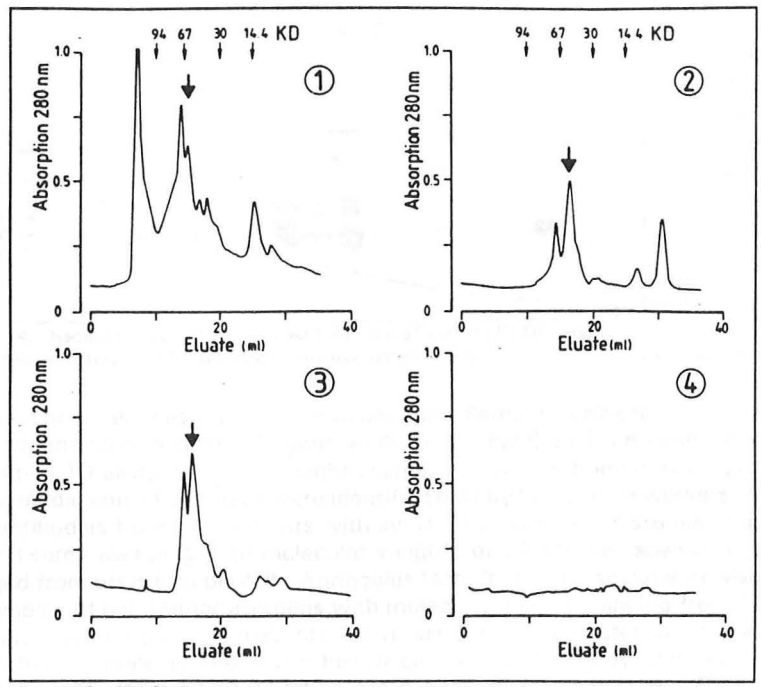

Figure 13. FPLC of raw latex (1), extract of starch powder on gloves (2), glove extract (3), extract of native starch powder (4) [65].

Slater and Chhabra [66] demonstrated that upon separating and staining nonammoniated latex (NAL) by SDS-polyacrylamide gel electrophoresis under nonreducing conditions four major bands at 45, 28, 21 and 14 kD, along with numerous minor bands could be identified. Immunoblotting of electrophoresed, reduced NAL with sera from 14 latex-RAST positive spina bifida patients revealed IgE binding to several of these bands. While protein binding varied from patient to patient, all sera demonstrated binding to the 14 kD peptide (Figure 14). Because of its ability to bind to specific IgE antibodies in the sera of a majority of latex-sensitive individuals [66], REF is thought to be a major latex allergen.

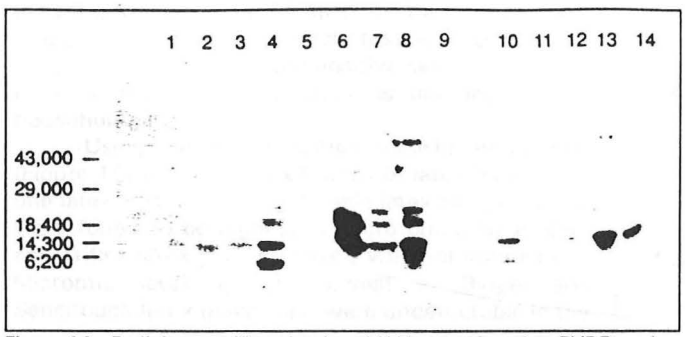

Figure 14. Radioimmunoblot of reduced NAL, transferred to PVDF, and incubated with sera of 14 latex-RAST positive patients [66]

More recently, Alenius et al. [60] showed by immunoblotting, that 57 latex proteins bound to IgE antibodies from seven latex-allergic health care workers and 10 latex-allergic patients with spina bifida. Interestingly, the binding pattern of IgE antibodies to latex proteins differed between these two groups of patients. Serum samples from the patients with spina bifida identified 46 allergens while serum samples from health care workers identified 19 allergens. Thirty-eight allergens were identified only by patients with spina bifida, and 11 allergens were identified only by health care workers. In addition, IgE antibodies from all 5 patients with spina bifida who had histories of anaphylaxis bound three allergens with molecular weights of 27 kD and isoelectric points that ranged from pH 4.6 to pH 4.8. Antibodies from four of these patients also identified a complex of eight other allergens with molecular weights ranging from 13 kD to 27 kD and isoelectric points from pH 4.4 to pH 5.6. This cluster of 11 allergens was identified by none of the seven health care workers and by only one of the five patients with spina bifida who had not experienced anaphylaxis. Thus, it may be found that certain groups of patients possess characteristic anti-latex IgE profiles depending upon type of allergic reaction experienced as well as the type of underlying disease process.

VARIATION IN ANTIGENICITY OF LATEX PRODUCTS

As described previously, dipped latex products are made by dipping a former into compounded liquid latex. Products made in this way include medical gloves and condoms. While only approximately 10% to 12% of the world's production of natural rubber latex is in the form of liquid latex [67], dipped products are widely used in the health-care industry and are responsible for most of the allergic reactions seen in latex-allergic patients and health care workers [68].

Disposable medical gloves

Both the protein concentration and the allergen concentration of medical gloves varies markedly depending on the brand being analyzed. In 1988, Turjanmaa et al. [69] evaluated the allergenicity of 19 different brands of gloves in 40 latex-allergic

individuals. Extracts of each of the gloves were prepared and used for prick testing. Of the 17 surgical gloves, six elicited positive skin tests in over 87% of the allergic subjects as did one of two household gloves.

Using a nitrocellulose membrane fingerprint test (Figure 15) to analyze six brands of latex gloves and one latex-free glove, transferable latex allergen levels were found to be highest in Microtouch, Neutralon, and Triflex latex gloves. Levels were intermediate in Microptic latex gloves; lowest in Biogel and Sensitouch latex gloves and were undetectable in the nonlatex (Sensicare) glove tested [70] (Figure 16).

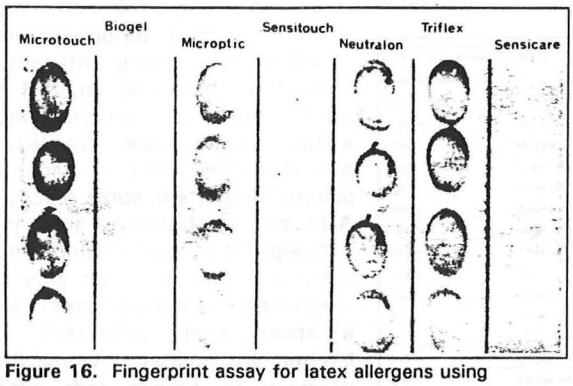

Figure 16. Fingerprint assay for latex allergens using nitrocellulose membranes and anti-latex antiserum [70].

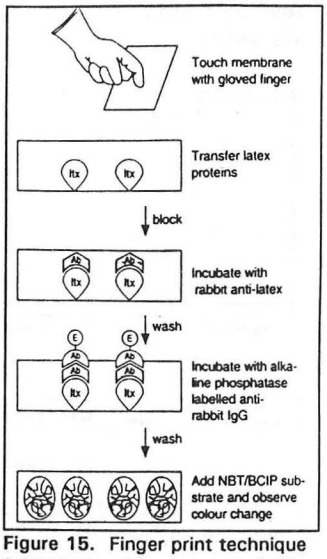

Figure 15. Finger print technique for transfer of latex protein [70].

Jaeger and colleagues [24] challenged seven latex-allergic individuals by performing a glove use test (see Diagnosis of the Latex-Allergic Patient) with six different brands of sterile latex gloves including three "hypoallergenic" brands and two latex-free brands. While the latex-free gloves were well-tolerated, the regular latex gloves and the "hypoallergenic" latex gloves were not.

Using both a RAST inhibition immunoassay and a monoclonal antibody-based ELISA assay, Slater and Trybul [71] also found variation in allergen as well as protein content in seven different medical gloves evaluated. While the RAST inhibition immunoassay was found to be more sensitive than the ELISA, allergen levels were measurable in four of the five rubber gloves using both assays.

Recently, Yunginger and colleagues [72] evaluated 71 lots of examination gloves, surgical gloves, or chemotherapy gloves for their allergenicity. Extracts of each were prepared and tested for total latex allergen content by an inhibition immunoassay employing pooled sera from five latex-sensitive health care workers. The allergen concentrations were reported in allergen units (AU), calculated by using

a standard curve produced by an FDA reference extract of raw latex that was arbitrarily assigned a potency of 100,000 AU/ml. The results of the study are summarized in Figure 17. Latex allergen levels varied by greater than 3000-fold among all of the gloves tested. Surgical gloves and chemotherapy gloves had lower allergen contents than examination gloves. In addition, more allergen could be extracted from powdered than powder-free gloves. While 24 of the lots of gloves were labeled "hypoallergenic" 11 of them contained measurable latex antigens. This finding is not surprising since the hypoallergenic label claim granted by the FDA applies only to Type IV allergenicity and was not intended to address Type I reactions to protein antigens.

Glove Type	Range (AU/mL)*
Examination gloves:	
Powdered (n = 15)	< 5–16,300
Powder-free (n = 7)	< 5–151
Surgical gloves:	
Powdered (n = 37)	< 5–12,100
Powder-free (n = 9)	< 5–61
Chemotherapy gloves (n = 3)	All < 5
Above gloves labeled "hypoallergenic" (n = 24)	< 5–12,800

Figure 17. Extractable latex allergen levels in 71 lots of disposable medical gloves [72]

Presently, there exists a controversy regarding the optimal assays that should be used to determine the protein content and latex allergen content in latex gloves. For this reason, the FDA has not mandated that this information be included in the product label. Figures 18 and 19 list the immunogenic latex protein content of several widely used examination and surgical gloves. The LEAP (Latex ELISA for Antigenic Protein) assay was used in the analysis of the latex protein concentration. This is an indirect ELISA technique in which latex proteins are immobilized by adsorption to plastic and reacted with rabbit anti-latex antisera, HRP-labelled anti-rabbit IgG and a color development reagent. The amount of color produced is proportional to the amount

Glove Manufacturer	Brand	Weight,g	LEAP	Total µg protein	Protein, µg/g
Surgical gloves					
Smartpractice	Tactylon*	12.3	b.d.	b.d.	b.d.
Deseret	Neolon*	15.5	b.d.	b.d.	b.d.
Ansell	Medigrip	11.8	0.098	0.98	0.08
Fugi	Surgeonplus	10.1	0.32	3.2	0.31
Perry	Whitelix 47	7.1	0.57	5.7	0.80
Regent	Biogel M	13.2	1.14	11.4	0.86
Regent	Biogel	12.9	1.65	16.5	1.3
Baxter	Triflex L.P.	8.6	1.34	13.4	1.6
Ansell	Sensi-touch	12.0	3.05	30.5	2.5
Fugi	Pristine	9.0	2.84	28.4	3.2
B-D	Dextren Ortho	17.3	12.2	122	7.9
B-D	Eudermic	8.8	6.93	69.3	7.9
B-D	Integron	13.6	10.9	109	8.0
B-D	Dextren HA	13.6	16.9	169	12.4
Perry	Whitelix 42	9.4	11.87	118	2.6
Perry	Dermaguard	8.6	20.5	205	23.8
Baxter	Ultraderm	7.9	21.09	210	26.7
J & J	Neutralon	9.9	31.66	316	32.1
Baxter	new Ultraderm	10.2	36.15	361	35.4
Ansell	NuTex	2.1	45.9	459	37.9
J & J	Microtouch	8.9	36.26	362	40.7
Baxter	new Triflex	12.8	58.0	580	45.2
Perry	Microptic	8.1	47.3	473	58.5
J & J	Orthopaedic	16.5	132.0	1320	80
Deseret	Tradition	11.7	185.0	1850	158
Baxter	Triflex	10.1	178.4	1784	177
Travanol	Triflex	9.9	467.5	4675	471

*=Latex free glove.

Figure 18. Latex protein content of surgical gloves [70]

of latex antigen present. This assay uses a preparation of latex proteins as an internal standard and is both sensitive and specific.

Glove Manufacturer	Brand	Weight,g	LEAP	Total µg protein	Protein, µg/g
Examination gloves					
Baxter	Flexam	9.7	0.162	1.62	0.17
Ansell	E.P.	12.8	0.77	9.8	0.77
Regent	Biogel D	12.9	1.26	12.6	0.97
Delta	Powder F.	7.5	2.03	20.3	2.68
AHP	Glovetex P.F.	6.4	1.98	19.8	3.1
AHP	Glovetex	8.2	34.6	346	42.1
AHP	Dermasafe	7.9	40.7	407	51.6
Mydent	Defend	7.5	65.6	656	86.9
Ansell	Conform	8.1	132.5	132	164
Delta	Low.P.	6.6	116.7	1167	177
Baxter	Pharmaseal	6.4	206.3	2063	322
Baxter	Dent exam	11.3	567.8	5768	502
J & J	MicrotouchXP	10.1	2835	28350	2806
Surgikos	5741	7.3	2961	29610	4001

Figure 19. Latex protein content of examination gloves [70].

Latex condoms

When prick tests were performed with extracts from 16 different brands of condoms, four of these elicited positive wheal and flare skin test responses in 52% to 67% of latex-allergic individuals [10]. The fact that three of the four of the allergenic brands were produced by the same manufacturer suggests that the manufacturing process is important in determining the presence of latex allergens in condoms.

Other rubber-containing products

Only one death has been attributable to latex allergy from a latex-containing medical device. It occurred when a rubber balloon-cuffed rectal catheter was used during a barium enema procedure [15]. Latex allergens were demonstrated by immunoassay to be present in catheter balloon extracts. These catheters have since been removed from the market. Measurable levels of latex allergens have also been found in anesthesia rebreathing bags and toy balloons [72].

MANIFESTATIONS OF LATEX ALLERGY

The manifestations of latex allergy are variable and are influenced by the type of immunologic sensitivity, the route of exposure, the quantity of exposure, and the variability in the sensitivity of shock organs between individuals [73]. Two types of immunologic reactions, Type I, IgE-mediated reactions and Type IV, contact hypersensitivity reactions are produced, in addition to nonimmunologic irritant reactions (Figure 20).

Irritant reactions

Irritant reactions commonly occur with latex exposure [74]. These often occur in those who are occupationally-exposed and they result from contact with a material that causes physical or chemical damage to the skin. Manifestations of irritant reactions include erythema, chapping, cracking, dryness, scaling and vesicle or blister formation. Normally innocuous substances may produce irritant reactions if they come in contact with the skin for prolonged periods. Thus, any material found under a glove has a good chance of producing an irritant reaction. The most common

Type of Reaction	Time of Onset	Clinical Signs	Immune Mechanism
Irritant	Usually gradual, over days	Erythema, scalded or parched appearance, chapped, cracked, fissured, scaling, sometimes vesicles or blisters	None
Immediate or Type I	Within minutes, rarely more than 2 hours	Swelling, pruritus, urticaria, rhinoconjunctivitis, asthma, hypotension, anaphylaxis	IgE-mediated release of mast cell mediators. Antigens are natural proteins found in latex.
Delayed contact or Type IV	6–48 hours after contact	*Acute:* erythema, pruritus, vesicles or blisters, cracking, crusting, desquamation *Chronic:* dryness, scaling, fissuring, thickening, and darkening	Delayed or cell-mediated immunity, T cell response to small rubber chemicals acting as haptens

Figure 20. Manifestations of latex allergy [73].

offenders are defatting agents [73]. Temperature extremes and age may also influence the development of irritant dermatitis.

While irritant reactions are not immunologically mediated, they may play a role in the development of hypersensitivity reactions. Irritant reactions perturb the barrier properties of the skin, thus allowing chemicals and proteins to penetrate.

Delayed contact hypersensitivity reactions

Contact hypersensitivity reactions involve the sensitization of specific T lymphocytes. The substances that most commonly elicit reactions of this nature are low molecular weight haptenic chemicals. These agents, which are often highly reactive, readily bind to autologous proteins forming an immunogenic complex. Some of these immunogens may elicit a reaction within a short time after exposure (within one week). However, most, including natural rubber latex, elicit sensitivity only after repeated exposure that occurs over weeks to months. Exogenous factors that increase the likelihood of sensitization include: increasing concentrations of the sensitizer, increasing the area of exposed skin, applying the sensitizer to inflamed skin, placing an occlusive dressing on the skin where the sensitizer is applied, and repeated exposure to the sensitizer [74].

Contact hypersensitivity reactions to latex-containing gloves and condoms are not uncommon [45, 75]. However, the relevant antigens in these types of reactions are the rubber additives, not the latex component. Conde-Salazar and colleagues [76] patch tested 4680 individuals who had occupationally-induced contact dermatitis and found that 686 (14.7%) were positive to one or more rubber additive. The agent to which most demonstrated a positive reaction was a thiuram-mix which included tetramethylthiuram monosulfide, tetraethylthiuram disulfide and tetramethylthiuram disulfide. These data further support the studies by others demonstrating that thiurams are a very common rubber sensitizer [45, 74].

IgE-mediated hypersensitivity reactions

The manifestations of latex-induced IgE-mediated hypersensitivity reactions are typical of those caused by other allergens. The most common symptoms include: pruritus, urticaria, angioedema, bronchospasm and anaphylaxis. Skin manifestations are most frequent, followed by nasal, ocular and pulmonary symptoms. While not common, gastrointestinal and cardiovascular symptoms may occur as well [77, 78].

Cutaneous symptoms - Frequently, the skin is involved in latex-allergic reactions, especially in health-care workers, most likely because of the repeated and prolonged exposure to latex-containing medical gloves. Symptoms may first consist of mild itching and erythema, but as exposure and/or sensitivity increases, urticaria and angioedema may develop. Symptoms occur approximately fifteen minutes after exposure, but may appear more rapidly. In addition, while urticaria usually is limited to areas of direct exposure initially, it may spread and ultimately become generalized [79, 80, 81].

Latex exposure of the oral, vaginal or rectal mucosa of latex-allergic persons results in symptoms similar to those described for skin. However, mucous membrane exposure more often leads to the development of systemic symptoms [78, 82]. Individuals who develop latex allergy without occupational exposure often develop sensitivity because of mucosal latex exposure [82, 83]. When questioned, these individuals commonly have symptoms of swelling or itching when they blow up balloons or when they undergo dental, vaginal or rectal exams.

Oral Symptoms - Oral symptoms may occur when a latex-allergic individual eats a cross-reacting food such as bananas, avocados, kiwis or chestnuts [38, 84]. Symptoms may be as mild as itching of the palate or excess mucous in the throat or they may be more severe and include throat tightness and difficulty swallowing. In some individuals, allergic reactions to cross-reacting foods may precede the recognition of latex allergy [73].

Ocular and Nasal Symptoms - The most common ocular symptoms are pruritus and conjunctival injection followed by increased tearing, chemosis and conjunctival and/or lid edema [78]. Nasal symptoms include sneezing, itching, rhinorrhea and congestion. Hoarseness may occur with prolonged exposure. In some individuals, nasal, ocular and respiratory symptoms occur within a short time after they arrive at work before any direct latex contact has occurred. This finding demonstrates that the amount of latex antigen exposure that occurs by inhalation alone may be sufficient enough to trigger symptoms [78, 85, 86].

Pulmonary symptoms - Pulmonary symptoms due to latex allergy vary from mild coughing to life-threatening asthma. Individuals without a history of asthma may not recognize any chest symptoms or may describe only a vague sensation of chest tightness. Monitoring peak flow values in these individuals may help in diagnosis. During latex-exposure periods peak flow values should fall compared to baseline, but then should normalize when exposure ceases. Monitoring peak flow values may be very valuable in the occupational setting [32, 87].

Cardiovascular, Gastrointestinal, and Genitourinary Tract Symptoms - The most common cardiovascular manifestations of latex allergy are hypotension and tachycardia associated with anaphylaxis. Gastrointestinal symptoms include nausea, vomiting, abdominal pain and diarrhea [88, 89, 90]. These reactions occur after variable routes of exposure and, interestingly, they usually are not manifested when an oral reaction occurs to a cross-reacting food [38, 84]. Both local and systemic genitourinary symptoms have been reported with condoms and rubber catheters [9, 10, 78, 83, 91].

Anaphylaxis - The most severe manifestation of latex allergy, anaphylaxis, is characterized by a constellation of the symptoms described above [9, 73, 78, 83]. In most cases of latex-induced anaphylaxis there is very short interval between the time of exposure and the onset of symptoms, and it depends both upon the patient as well as the route of exposure as to which symptoms predominate, respiratory or cardiovascular. In some instances, anaphylaxis is preceded by mild symptoms, such as sneezing or pruritus, while in others there may be no warning signs or symptoms. Anaphylaxis may result from latex exposure through the skin, mucous membranes, inhalation, intravenous infusion or intraoperative contact and, despite prompt resuscitative treatment, it may be fatal.

DIAGNOSIS THE LATEX-ALLERGIC PATIENT

In order to establish a diagnosis of latex allergy a thorough history must be obtained and questions should include the following (Figure 21) [104]:

Questionnaire for Identification of Possible Latex Allergy [104]

- **Medical history**
  - Presence of atopy including hayfever, food allergy (especially reactions to banana, avocado, chestnut, kiwi, and papaya), childhood or adult eczema, and asthma
- **Surgical history**
  - Multiple surgeries
  - Intraoperative events consistent with anaphylaxis (episodes of urticaria or angioedema, respiratory distress, difficulty with ventilation hypotension, reactions during dental procedures, and radiologic procedures (barium enema)
- **Occupational history**
  - History of latex exposure; type of latex device, nature, duration of exposure
  - Work-related symptoms of possible latex allergy
    - Cutaneous symptoms including hand dermatitis, eczema, and urticaria
    - Upper respiratory symptoms including nasal rhinorrhea, pruritus, and sneezing
    - Lower respiratory symptoms including cough, wheeze, and shortness of breath
  - Other symptoms including itchy hands, localized angioedema, possible systemic anaphylactic symptoms with use of household latex cleaning gloves, balloons, condoms, and diaphragms

Figure 21.

Both *in vivo* and *in vitro* diagnostic tests have been used in the diagnosis of latex allergy; however, none of these tests are without problems. Therefore, presently, there is no consensus regarding the methods that should be used.

In vivo diagnostic techniques

The *in vivo* methods that have been employed include skin testing and provocation testing. Skin testing with natural rubber latex is the diagnostic procedure of choice for IgE-mediated rubber allergy in Europe and Canada, where a commercial extract is available. Despite the fact that in the U.S. no standardized latex skin test extract has been approved by the FDA, useful information is being obtained using extracts from latex gloves and from raw latex sap. Turjanmaa and colleagues [92] compared several diagnostic methods in 15 hospital employees who carried a diagnosis of latex allergy. Skin prick testing using an extract from one brand of latex glove yielded positive skin test responses in all of the allergic individuals, while prick tests using rubber tree sap were positive in 12 of 15 (80%). Using a scratch-chamber technique and crushed rubber tree leaves as the antigen, skin test responses were positive in 13 of the 15 (87%) tested.

Kelly et al. [93] evaluated the reliability of two latex extracts in 118 subjects consisting of patients with spina bifida, health care workers and other patients with symptoms of latex allergy as well as ten control subjects. Forty-nine percent of the patients with spina bifida, 73% of the health care workers with symptoms of latex allergy and 86% of patients with symptoms of latex allergy demonstrated positive wheal and flare skin test responses to both antigen extracts. None of the control subjects demonstrated positive skin test responses. During the skin test procedure, nine patients experienced adverse reactions, including anaphylaxis in four.

In addition to skin testing, the use test is another *in vivo* technique that may be used in the diagnostic evaluation of the latex-allergic individual. This technique, which was popularized by Dr. Kristiina Turjanmaa, a dermatologist in Finland [20], involves placing one finger of a glove on the wet hands of a person suspected of having contact urticaria to natural rubber. After 30 minutes, the glove finger is removed and the reaction is graded. As with the skin test, caution must be exhibited when performing this test, especially in the highly latex-sensitive individual.

In vitro diagnostic techniques

In vitro techniques also may be useful in the diagnosis of latex allergy. Turjanmaa and colleagues [92] compared the results obtained from skin testing to RAST results in which latex allergen was bound to cyanogen-bromide activated paper disks. In 15 latex-allergic individuals who were positive by skin prick testing using a glove extract, latex-specific IgE could be detected by RAST in only 8 (53%). Other studies as well demonstrated decreased sensitivity with *in vitro* assays [15, 27, 80, 94, 95]. More recently, Kelly et al. [93] developed an ELISA assay that appears to be more sensitive than previous *in vitro* tests. Eighty-seven percent of patients with

positive prick tests to latex had demonstrable latex-specific IgE by ELISA and latex ELISA titers were significantly higher in patients with positive skin test results and a history of anaphylaxis compared to patients with negative skin tests. In addition to this group, others too have been successful at developing more sensitive *in vitro* assays for latex-specific IgE [96, 97].

It has been recommended that until a standardized, safe latex extract is available, the clinician should rely on medical history, physical examination and serologic tests performed by reliable laboratories to confirm the diagnosis of latex allergy. Any skin tests that are performed should be done by a board-certified allergist/immunologist in a setting where there is immediate access to resuscitative equipment and a very dilute antigenic extract should be used (< 1 ng/ml) in the initial testing. A use test may be performed in the case of a negative serologic assay result and a compelling history [98]. An algorithm of diagnostic testing steps is provided in Figure 22.

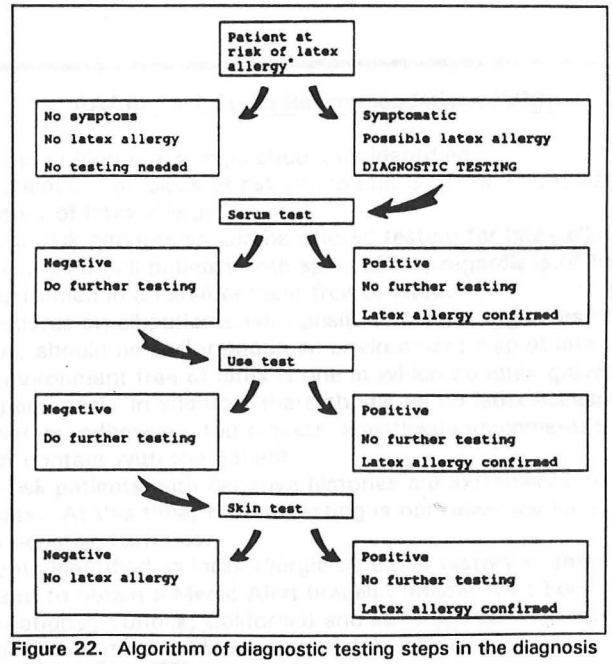

Figure 22. Algorithm of diagnostic testing steps in the diagnosis of latex allergy [98]

MANAGEMENT OF THE LATEX-ALLERGIC PATIENT

Patients with irritant latex reactions should eliminate all unnecessary glove use. The use of cotton liners or barrier creams may alleviate the irritation. Individuals with Type IV contact hypersensitivity reactions to rubber gloves should be patch tested to confirm the diagnosis and to determine which rubber additive is the culprit allergen. A different glove, lacking that allergen, subsequently should be used.

The only treatment for the patient with an IgE-mediated latex allergy is avoidance. While premedication protocols have been proposed, their utility is unclear at this time and conflicting reports regarding their benefit in latex allergy exist. Although effective in the prevention of radiocontrast media reactions, premedication regimens have not been shown to block IgE-mediated reactions. Preliminary data suggest that the use of corticosteroids and H_1 and H_2 blockers with or without an alpha agonist lessens the severity of intraoperative reactions but does not alter their frequency [99].

Recently, the Task Force on Allergic Reactions to Latex in the American Academy of Allergy, Asthma and Immunology [100] have published guidelines that should be considered for any individual in whom latex exposure is anticipated (Figure 23) :

AAAAI Task Force Recommendations [100]

- Patients in high risk groups should be identified.
- All patients, regardless of risk group status, should be questioned about a history of latex allergy.
- All high-risk patients should be offered testing for latex allergy.
- Procedures on all patients with spina bifida, regardless of history, should be performed in an environment free of latex.
- Procedures on all patients with positive history, regardless of risk group status, should be performed in an environment free of latex.
- An environment free of latex is one in which no latex gloves are used by any personnel. In addition, there should be no latex accessories (catheters, adhesives, tourniquets, anesthesia equipment) that come into direct contact with the patient.
- Low-risk patients with negative histories are extremely unlikely to react to latex. At this time, routine testing is not recommended for persons with negative histories.
- Patients identified as latex allergic by either history or testing should be advised to obtain a Medic Alert bracelet (Medic Alert Foundation International, Turlock, California) and self-injectable epinephrine. Medical records should be appropriately labeled.

Figure 23

LATEX AVOIDANCE IN THE HOSPITAL

It is important that all hospitals develop institutional guidelines for the care of the latex-allergic individual. At the Children's Hospital of Wisconsin, a multidisciplinary task force was established to develop policies and procedures for the detection, care and education of the latex-sensitive patient [99]. Manufacturers of all equipment were contacted using a standard letter inquiring about the content of latex protein in each product and a database of all latex and nonlatex products was developed. The list is upgraded on a regular basis and is distributed to each department. A review of glove usage is performed regularly as well and there has been a movement towards the purchasing of low-allergenic gloves. It must be realized that it is highly unlikely that every product containing latex can be eliminated. Therefore, it is more important that hospitals work toward a latex-"safe" environment and not a latex-"free" environment [99]. A list of nonlatex alternatives for patients allergic to latex is shown in Figure 24.

Item	Manufacturer	Composition
Sterile surgical gloves		
Allergard, Tactyl 1 and 2	Johnson & Johnson	Synthetic copolymer
Dermaprene	Ansell	Neoprene
Elastyren	ECI	Styrene
Neolon	Becton Dickinson	Neoprene
Examination and procedure gloves		
Sensicare	Becton Dickinson	Vinyl
Tactyl 2	SmartPractice	Synthetic copolymer
Tactyl 1 and 2	SmartPractice	Synthetic copolymer
Elastyren	Baxter Corporation	Styrene-butadiene
N-Dex	Best Glove	Nitrile
N-Dex Long Cuff	Best Glove	Nitrile
Tru-touch	Becton Dickinson	Vinyl
Royal Shield/Vinylite	SmartPractice	Vinyl
Safe+Touch	A. R. Medicom	Vinyl
Sime Vinyl	Sime Darby Canada	Vinyl
Baxter	Baxter Corporation	Vinyl
Fisherbrand	Fisher Scientific	Vinyl
MediTouch	AMG Medical	Vinyl
Dispos-a-glove	Johnson & Johnson	Polyethylene/methyl Acrylate copolymer
Tape		
Micropore	3M	
Blenderm	3M	
Dressings		
Tegaderm	3M	
Steri-strips	Johnson & Johnson	
Catheters		
Silicone foley	Sherwood	
Malecot	Cook Urological	
Drains		
Jackson Pratt (with silicone)		

* For complete list consult: *Compendium of Non-Latex Gloves*. Medical Devices Bureau, Health Protection Branch, Health Canada; July 1994.

Figure 24. Nonlatex alternatives for patients allergic to latex

LATEX PRECAUTIONS IN THE OPERATING ROOM

The most intense exposure to latex in the hospital occurs in the operating room. Here, both the patient and the medical personnel come into contact with multiple latex-containing products. As stated previously, almost any route of exposure can lead to anaphylaxis. While the majority of reactions have been due to direct glove contact, intravascular exposure from injection ports or tubing and buretrol valves may lead to life-threatening reactions [99, 101]. In addition, while the cornstarch powder in gloves is not allergenic, it acts as a carrier of latex protein. In fact, it contributes significantly to the aerosol exposure to latex. Swanson and colleagues [105] recently quantified the amount of aerosolized latex antigen in several areas of Mayo Medical Center and they found that cystoscopy suites and surgical suites had the highest latex aeroallergen levels (Figure 25). More recently, they found that rubber gloves are the major contributor to latex aeroallergen levels in the operating room and that avoidance of their use can greatly lessen latex allergen exposure [102].

The optimal situation would be to eliminate all latex glove use in the health care setting. However, at this time no other synthetic polymers exist that have the same barrier qualities and tactile sensitivity as latex [103]. Therefore, it is imperative that the manufacturing industry strive to reduce the allergen content of latex while at the

Air samples	Aeroallergen level (ng/m³)
Extensive glove use areas	
Urology – Cystoscopy	121.8
In-patient surgical suites (n = 5)	111 ± 25
Orthodontics – Outpatient Surgery	99.8
Mohs Dermatology – Outpatient Surgery	78.5
Blood Bank Drawing Room	46.3
Blood Bank Components – Separation Lab	38.4
Surgical Pathology – Lab	37.4
Venipuncture – Room	29.6
Blood Bank Cross Match – Lab	16.4
Hematopathology – Lab	14.3
Allergy Research – Lab	13.8
Minimal glove use areas	
Allergy Clinic	1.8
Spirometry	0.6
Bone Marrow Transplant*	0.6
Blood Bank – Virus Serology Lab†	0.3
Personal	
Hematopathology Tech	8.4
Venipuncture Tech	25.9
Venipuncture Tech	136.9
Anesthetists (n = 9)	419 ± 292

tech, Technician.
*Powder-free gove use.
†Vinyl glove use.

Figure 25. Latex aeroallergen levels in various areas within Mayo Medical Center [105]

same time striving to improve the barrier and tactile quality of other polymers.

Most hospital latex-containing products have nonlatex substitutes available. All airway equipment can be substituted with silicone and polyvinyl chloride polymer materials. However, the inner working valves, tubing, and the high pressure gas tubing from the wall insert to the ventilator may be made of or lined with latex. While it is unlikely that these devices contribute to allergen contact, this possibility can not be ruled out. Syringe plungers often contain latex, but there is little data available to suggest that these are a source of soluble protein. Since many vial tops of injectable medications are made of latex, the top should be removed and the medication drawn up directly in order to avoid dispersal of protein into the fluid which may occur when the top is punctured. Also, if possible intravenous tubing without latex injection ports should be used in latex-sensitive individuals. If the only tubing available has latex ports, injections should be given through a stopcock system [99].

Again, it must be stressed that it is impossible to make an operating room 100% latex free. However, it is possible to reduce latex exposure significantly.

CONCLUSIONS

In spite of the increasing awareness of latex allergy in both the medical and lay communities, a large number of health-care personnel lack sufficient knowledge regarding this condition. These individuals, as well as patients, latex industry employers, parents, advocacy groups and the government, must be educated. Also, it is necessary that further research be performed to more clearly elucidate the relevant latex allergens and to determine optimal ways to measure them. Finally, there should be a better labeling system for natural rubber-containing products. Hopefully, the National Institutes of Health, the Federal Drug Administration and other governmental agencies will lead the way in helping to remedy this growing problem.

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